

# HEMATOLOGY

Dr. I. Quirt

Adriana Cipolletti, Jeremy Gilbert and Susy Hota, chapter editors  
Leora Horn, associate editor

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Hereditary			
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# APPROACH TO THE BLOOD FILM

## Size

- macrocytic
  - increased size
  - e.g. low B<sub>12</sub>, low folate
- microcytic
  - reduced size
  - e.g. iron deficiency, thalassemia

## Colour

- hypochromatic
  - increase in the size of the central pallor (normal = less than half of the diameter of RBC)
- increased polychromasia (blue cells) indicates increased RBC production by the marrow

## Shape

- normal = discocyte (biconcave)
- spherocyte = spherical RBC
  - e.g. hereditary spherocytosis, immune hemolytic anemia
- fragmented cells (schistocytes) = split RBC
  - e.g. microangiopathic hemolytic anemia (TTP, DIC, vasculitis, glomerulonephritis), prosthetic heart valve
- elliptocyte (ovalocyte) = oval, elongated RBC
  - e.g. hereditary elliptocytosis, megaloblastic anemia
- sickle cell = sickle-shaped RBC
  - e.g. sickle cell disorders, HbSC, HbSS
- target cell = bell-shaped, looks like target on dried film
  - e.g. liver disease, hemoglobin S and C, thalassemia, Fe deficiency
- teardrop cell (dacrocyte) = single pointed end, looks like a teardrop
  - e.g. myelofibrosis

## Distribution

- rouleaux formation = aggregates of RBC resembling stacks of coins
  - e.g. artifact, paraprotein (multiple myeloma, macroglobulinemia)

## Inclusion

- nuclei
  - immature RBC
  - indicates serious medical disease
  - e.g. severe anemia, leukemia, bone marrow metastases
- Heinz bodies
  - denatured hemoglobin
  - e.g. G6PD deficiency
- Howell-Jolly bodies
  - small nuclear remnant with the colour of a pyknotic nucleus
  - e.g. post-splenectomy, hyposplenism, hemolytic anemia, megaloblastic anemia
- basophilic stippling
  - deep blue granulations of variable size and number, pathologic aggregation of ribosomes
  - e.g. lead intoxication, thalassemia

- Investigations** (see Table 1)

**Table 1. RDW (Red Cell Distribution Width)**

Normal	Increased
anemia of chronic disease	iron deficiency
thalassemia	dual deficiency (e.g. iron and folate)
	myelodysplastic syndrome
	AIHA
	liver disease
	pernicious anemia
	folate deficiency

# ANEMIA

## CLINICAL APPROACH TO ANEMIA

- acute vs chronic
- decreased production vs increased destruction
- anemia vs pancytopenia
- based on MCV
- rule out dilutional anemia (low Hb due to increased effective circulating volume)

**Table 2. Differential Diagnosis of Anemia Based on MCV**

Hypochromic microcytic (MCV<80)	Normochromic normocytic (80<MCV<100)		Macrocytic (MCV>100)
<ul style="list-style-type: none"> <li>• Fe deficiency</li> <li>• Thalassemia</li> <li>• Lead Poisoning</li> <li>• Sideroblastic</li> <li>• Chronic disease (some cases)</li> </ul>	<p>Low Reticulocytes:</p> <ul style="list-style-type: none"> <li>• Myelodysplasia</li> <li>• Infiltration (leukemia, myeloma, mets, infection)</li> <li>• Myelofibrosis</li> <li>• Aplasia</li> <li>• Chronic Disease (some cases)</li> <li>• Liver Disease</li> <li>• Uremia</li> <li>• Endocrine (hyper/hypothyroid, Addison's)</li> </ul>	<p>High Reticulocytes:</p> <ul style="list-style-type: none"> <li>• Hemolytic anemia</li> <li>• Post-hemorrhagic anemia</li> <li>• Treated nutritional deficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Megaloblastic               <ul style="list-style-type: none"> <li>• B<sub>12</sub></li> <li>• Folate</li> <li>• Drugs</li> </ul> </li> <li>• Myelodysplasia</li> <li>• Liver Disease</li> <li>• Alcohol</li> <li>• Reticulocytosis</li> </ul>

### Hematological History

- ID: background: Mediterranean, Asian, black (thalassemia), black (sickle cell)
- presenting symptom & HPI: depend on how rapidly the anemia develops
  - fatigue, malaise, weakness, palpitations, syncope, dyspnea, headache, vertigo, tinnitus
- PMH: past anemias, therapies, past blood loss (GI/GU), blood donation history, menstrual history, signs/symptoms of renal, liver, endocrine disturbances, AIDS and other chronic diseases, malignancies
- family Hx: important in hereditary anemia; ask about anemia, jaundice, gallbladder disease, splenectomy
- medications: drugs may cause aplasia, macrocytic/megaloblastic states, hemolysis, blood loss
- diet: iron, folic acid, vitamin B12 supplementation: amount, frequency, duration, reason
- alcohol consumption: quantify amount and duration (toxic effect on bone marrow or anemia due to liver disease)

### Physical Exam

- HEENT: pallor: mucous membranes, conjunctivae (Hb < 90 g/L), icterus, cervical lymphadenopathy, ocular bruits (Hb < 55 g/L), glossitis
- CVS: tachycardia, postural changes, systolic flow murmur, wide pulse pressure, CHF
- GI: hepatomegaly, splenomegaly, rectal (occult blood)
- skin: pallor, jaundice, skin creases (Hb < 75 g/L), telangiectasia as in hemolytic anemia, koilonychia (spoon-shaped nails) as in iron deficiency anemia

# IRON METABOLISM

## IRON INTAKE (Dietary)

- "average" Canadian adult diet = 10-20 mg Fe/day
- absorption = 5-10% (0.5-2 mg/day)
- males have a positive Fe balance
- menstruating females have a negative Fe balance

## PHYSIOLOGIC CAUSES OF INCREASED FE REQUIREMENTS

- infancy-growth spurt 2x basal need
- puberty-growth spurt, menarche 3x basal need
- pregnancy-maternal RBC, fetus 4x basal need
- blood donation 4x basal need
  - 500 mL blood = 250 mg Fe
  - 4 donations/year = 1 g

# IRON METABOLISM ... CONT.

## IRON ABSORPTION

- in duodenum iron combines with apoferritin to form ferritin that is absorbed through villi

**Table 3. Intraluminal Factors in Absorption of Non-Heme Iron**

Promoters	Inhibitors
Gastric HCl	Achlorhydria Antacids
Reducing agents • ascorbic acid	Oxidants
In Fe <sup>2+</sup> form	In Fe <sup>3+</sup> form
Inorganic form	Organic form
Soluble chelators • amino acids • sugars • alcohol	Non-absorbable chelators • phosphate (milk)      • oxalate (spinach) • phytates (cereals)    • tannin (tea)

## IRON TRANSPORT

- majority of non-heme Fe in plasma is bound to transferrin
- transferrin
  - beta-globulin
  - carries Fe from mucosal cell to RBC precursors in marrow
  - carries Fe from storage pool in hepatocytes and macrophages to RBC precursors in marrow

## IRON STORAGE

- Fe is stored in two forms: ferritin and hemosiderin
- ferritin
  - ferric Fe complexed to a protein called apoferritin
  - hepatocytes are main site of ferritin storage
  - minute quantities are present in plasma in equilibrium with intracellular ferritin
- hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monocyte system is main source of hemosiderin storage

## IRON INDICES

- bone marrow aspirate is the gold standard test for iron stores
- serum ferritin
  - single most important blood test for iron stores
  - falsely elevated in inflammatory disease, liver disease (from necrotic hepatocytes), neoplasm and hyperthyroidism
- serum iron
  - varies significantly daily
  - a measure of all non-heme Fe present in blood
  - virtually all serum iron is bound to transferrin
  - only a trace of serum Fe is free or complexed in ferritin
- total iron binding capacity (TIBC)
  - high specificity for decreased iron, low sensitivity
  - measure of total amount of transferrin present in blood
  - normally, one third of the TIBC is saturated with Fe, remainder is unsaturated
- saturation
  - serum Fe divided by TIBC, expressed as a proportion or a %

## INTERPRETING IRON INDICES

**Table 4. Interpreting Iron Indices**

	Ferritin	Serum Iron	TIBC	RDW	Saturation
Iron Deficiency	↓↓	↓	↑	↑	↓↓
Chronic Disease	↑/N	↓/N	↓/N	N	N
Sideroblastic Anemia	↑	↑	N	No (dimorphic picture)	—
Iron Overload	↑	↑	N	—	↑

## IRON METABOLISM . . . CONT.

### LABORATORY FEATURES

- Fe stores diminished
  - decreased stainable iron in marrow
  - serum ferritin decreased
- Fe stores absent (in order of increasing Fe deficiency)
  - serum Fe falls
  - TIBC increases
  - hemoglobin falls
  - microcytosis (Hb levels of 100-110 g/L or 10-11 g/dL)
  - hypochromia (Hb 90-100 g/L or 9-10 g/dL)

## IRON DEFICIENCY

- most common cause of anemia in Canada
- imbalance of intake vs. requirements or loss
- may indicate the presence of serious GI disease

### PHYSIOLOGIC CAUSES

- increased need for iron in the body

### PATHOLOGIC CAUSES

- in adult males and post-menopausal females, Fe deficiency is usually related to chronic blood loss
- dietary deficiencies (rarely the only etiology)
  - cow's milk (infant diet)
  - "tea and toast" (elderly)
- absorption imbalances
  - post-gastrectomy
  - malabsorption
- hemorrhage
  - obvious causes - menorrhagia
  - occult - peptic ulcer disease, aspirin, GI tract cancer
- intravascular hemolysis
  - hemoglobinuria
  - hemosiderinuria
  - cardiac valve RBC fragmentation

### CLINICAL PRESENTATION

- iron deficiency may cause fatigue before clinical anemia develops
- brittle hair
- dysphagia (esophageal web, Plummer-Vinson ring)
- nails
  - brittle
  - koilonychia
- glossitis
- angular stomatitis
- pica (appetite for bizarre substances e.g. ice, paint, dirt)

### DIAGNOSIS

- major diagnostic difficulty is to distinguish from anemia of chronic disease
- serum
  - ferritin < 20 is diagnostic of iron deficiency anemia
  - iron deficiency anemia unlikely if ferritin > 22-322
  - platelet count may be elevated
- peripheral blood film (**see Colour Atlas H3**)
  - hypochromic microcytosis: RBCs are under hemoglobinized due to lack of Fe
  - pencil forms
  - target cells (thin)
- bone marrow
  - intermediate and late erythroblasts show micronormoblastic maturation
  - Fe stain (Prussian blue) shows decreased iron in macrophages
  - decreased normal sideroblasts

### TREATMENT

- treat the underlying cause
- different preparations available: tablets, syrup, parenteral (if malabsorption)
- dose: ferrous sulphate 325 mg PO TID or ferrous gluconate 300 mg PO TID until anemia corrects and then for 3 months after

## IRON DEFICIENCY ... CONT.

### RECOVERY TIME

- reticulocytes begin to increase after one week
- Hb normalizes by 10 grams per week
- if serum ferritin is normal then discontinue iron therapy

### ANEMIA REFRACTORY TO TREATMENT WITH ORAL IRON

- medication
  - poor preparation (e.g. expired)
  - drug interactions
- patient
  - poor compliance
  - continued bleeding
  - malabsorption (rare)
- physician
  - misdiagnosis

## THE ANEMIA OF CHRONIC DISEASE

### Etiology

- infections
- cancer
- inflammatory and rheumatologic disease
- renal disease
- endocrine disorders (e.g. thyroid)

### Pathophysiology

- a mild hemolytic component is often present
- red blood cell survival modestly decreased
- erythropoietin levels are normal or slightly elevated but are inappropriately low for the degree of anemia
- iron cannot be removed from its storage pool in hepatocytes and reticuloendothelial cells

### Diagnosis

- a diagnosis of exclusion, biochemically rule out Fe deficiency
- serum
  - serum iron, TIBC, and % saturation all normal or slightly reduced
  - serum ferritin is normal or increased
- peripheral blood
  - usually normocytic and normochromic if the anemia is mild
  - may be microcytic and normochromic if the anemia is moderate
  - may be microcytic and hypochromic if the anemia is severe but rarely < 90 g/L)
- bone marrow
  - normal or increased iron stores
  - decreased "normal" sideroblasts

### Management

- resolves if underlying disease is treated
- erythropoietin may normalize the hemoglobin value
- dose of erythropoietin required higher than for patients with renal disease
- only treat patients who can benefit from a higher hemoglobin level

## LEAD POISONING

**L:** Lead Lines on gingivae and epiphyses of long bones on X-ray

**E:** Encephalopathy and Erythrocyte basophilic stippling

**A:** Abdominal colic and microcytic Anemia

**D:** Drops: wrist and foot drop. **D**imercaprol and **EDTA** as first line of treatment

# SIDEROBLASTIC ANEMIA

- ❑ group of disorders with various defects in the porphyrin biosynthetic pathway leading to a reduction in heme synthesis resulting in an increase in cellular iron uptake
- ❑ characterized by presence of abnormal erythroid precursors in marrow

## Types of Sideroblasts

- ❑ "normal" sideroblasts
  - aggregates of ferritin, diffusely spread throughout the red blood cell cytoplasm
  - small
  - found in normal individuals
- ❑ "ring" sideroblasts
  - iron deposited in the mitochondria forms a ring around the red blood cell nucleus
  - large
  - abnormal finding

## Etiology

- ❑ hereditary
  - rare
  - X-linked (defective D-aminolevulinic acid synthetase – rate-limiting enzyme in heme synthesis)
  - median survival is 10 years
- ❑ acquired
  - primary
    - may be a preleukemic phenomenon (10%)
  - secondary
    - toxins
    - drugs (isoniazid), ethanol
    - neoplasms and consequent chemotherapy (alkylating agents)
    - collagen vascular disease

## Diagnosis

- ❑ serum
  - iron overload: increased serum iron, normal TIBC, increased ferritin
- ❑ peripheral blood
  - dimorphic picture (normal and hypochromic population)
- ❑ bone marrow
  - required for diagnosis
  - bizarre megaloblastic changes
  - ring sideroblasts
  - increased iron stores

## Management

- ❑ treatment of underlying cause
- ❑ oral pyridoxine (vitamin B6)
  - hereditary and secondary acquired forms usually responsive
  - myelodysplastic sideroblastic anemia not responsive

# HEMOGLOBIN AND HEMOGLOBINOPATHIES

## Hemoglobin Structure and Production

- ❑ 4  $\alpha$  genes are located on chromosome 16
- ❑ 2  $\beta$  genes are located on chromosome 11
- ❑ heme group in centre with iron
- ❑ fetal hemoglobin, HbF ( $\delta$  2) switches to adult forms HbA ( $\beta$ 2) and HbA2 ( $\delta$  2) at 3-6 months of life
- ❑ HbA constitutes 97% of adult hemoglobin
- ❑ HbA2 constitutes 3% of adult hemoglobin
- ❑ beware of the possibility of mixed defects e.g.  $\beta$ -thalassemia minor and sickle cell trait

## THALASSEMIA

- ❑ defects in production of Hb  $\beta$  that leads to microcytosis

### I. HETEROZYGOUS: $\beta$ -Thalassemia Minor

- ❑ common among people of Mediterranean and Asian descent

## Clinical Presentation

- ❑ depends on extent of disease
- ❑ mild or no anemia
- ❑ possible palpable spleen
- ❑ may be masked by Fe deficiency

## Diagnosis

- serum
  - Hb 90-140 g/L, MCV < 70
- peripheral blood
  - microcytosis +/- hypochromia
  - target cells and increased poikilocytosis ("fish RBC") may be present
  - basophilic stippling usually present
- Hb electrophoresis
  - specific: Hb A2 increased to 0.025-0.05 (2.5-5%) (normal 1.5-3.5%)
  - non-specific: 50% have slight increase in HbF

## Management

- not necessary to treat
- patient and family should receive genetic counselling

## II. HOMOZYGOUS: $\beta$ -Thalassemia Major

### Pathophysiology

- autosomal recessive
- ineffective chain synthesis leading to ineffective erythropoiesis and hemolysis of RBC
- increase in HbF

### Clinical Presentation

- initial presentation at 3-6 months due to replacement of HbF by HbA
- severe anemia develops in the first year of life
- jaundice
- stunted growth and development (hypogonadal dwarf)
- gross hepatosplenomegaly (extramedullary hematopoiesis)
- changes (expanded marrow cavity)
  - skull x-ray has "hair-on-end" appearance
  - pathological fractures common
- evidence of increased Hb catabolism (e.g. gallstones)
- death from
  - untreated anemia (transfuse)
  - infection (treat early)
  - hemochromatosis (late, secondary to transfusions), usually 20-30 years old

### Diagnosis

- CBC
  - hemoglobin 40-60 g/L
- peripheral blood
  - hypochromic microcytosis
  - increased reticulocytes
  - basophilic stippling, target cells
  - postsplenectomy blood film shows Howell Jolly bodies, erythroblasts, and thrombocytosis
- Hb electrophoresis
  - Hb A: 0-0.10 (0-10%) , (normal > 95%)
  - Hb F: 0.90-1.00 (90-100%)

### Management

- transfusion
- Fe chelation to prevent iron overload (e.g. desferal)
- bone marrow transplant

## III. ALPHA THALASSEMIA

- similar distribution to thalassemia but a higher frequency among Asians

### Pathophysiology

- autosomal recessive
- deficit of  $\alpha$  chains
- 4 grades of severity depending on the number of defective alpha genes
  - 1 - silent
  - 2 - trait
  - 3 - HbH Disease (presents in adults due to excess  $\beta$  chain production)
  - 4 - Hb Bart's (hydrops fetalis, not compatible with life)

### Diagnosis

- peripheral blood film
  - microcytes, hypochromia, occasional target cells
  - screen for HbH inclusion bodies
- Hb electrophoresis not diagnostic
- DNA analysis using alpha gene probe



## Management

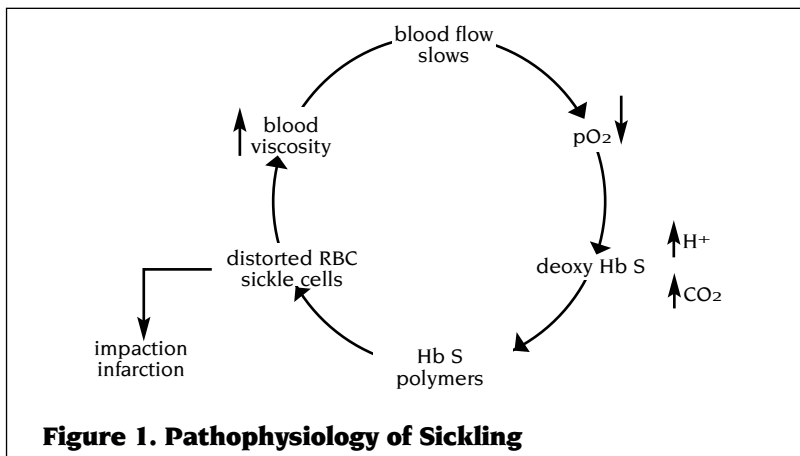
- ☐ same as  $\beta$  thalassemia

## SICKLE CELL ANEMIA

- ☐ autosomal recessive
- ☐ amino acid substitution of valine for glutamate in position 6 of beta globin chain

## Mechanisms of Sickling (see Figure 1)

- ☐ at low  $pO_2$ , deoxy Hb S polymerizes, leading to rigid crystal-like rods that distort membranes = SICKLES
- ☐ the  $pO_2$  level at which sickling occurs is related to the percentage of Hb S present
  - in heterozygotes (Hb AS) sickling occurs at a  $pO_2$  of 40 mmHg
  - in homozygous (Hb SS), sickling occurs at a  $pO_2$  of 80 mmHg
- ☐ sickling is aggravated by
  - increased  $H^+$
  - increased  $CO_2$
  - increased 2,3-DPG
  - increased temperature and osmolality



**Figure 1. Pathophysiology of Sickling**

## Heterozygous: Hb S Trait

- ☐ clinical presentation
  - patient will appear normal except at times of extreme hypoxia and infection
- ☐ diagnosis
  - serum: Hb normal
  - peripheral blood: normal except for possibly a few target cells
  - Hb electrophoresis (confirmatory test): Hb A fraction of 0.65 (65%); Hb S fraction of 0.35 (35%)

## Homozygous: Hb S Disease

- ☐ clinical presentation
  - chronic hemolytic anemia
  - jaundice in the first year of life
  - vaso-occlusive crises (infarction) leading to pain, fever and leukocytosis e.g. acute chest syndrome (pulmonary infarct) associated with infection, such as parvovirus, leading to aplastic anemia, acidosis, dehydration, and hypoxia
  - susceptibility to infections by encapsulated organisms due to hyposplenism
  - retarded growth and development +/- skeletal changes
  - spleen enlarged in child and atrophic in adult
- ☐ diagnosis
  - peripheral blood: sickled cells (**see Colour Atlas H6**)
  - screening test: sickle cell prep
  - Hb electrophoresis (confirmatory test): Hb S fraction > 0.80

## Management

- ☐ prevention of crises is the key
  - establish diagnosis
  - avoid conditions that favor sickling (hypoxia, acidosis, dehydration, fever)
  - vaccination in childhood e.g. pneumococcus, meningococcus
  - consider prophylaxis - penicillin V 250 mg PO bid
  - good hygiene and nutrition
- ☐ genetic counselling
- ☐ folic acid to avoid folate deficiency

## HEMOGLOBIN AND HEMOGLOBINOPATHIES . . . CONT.

- hydroxyurea to enhance production of HbF
  - causes depression of the gene for HbF or by initiating differentiation of stem cells in which this gene is active; presence of HbF in the SS cells decreases polymerization and precipitation of HbS
  - Note: hydroxyurea is cytotoxic and may cause bone marrow suppression

**Table 5. Organs Affected by Vaso-Occlusive Crisis**

Organ	Problem
brain	seizures, hemiplegia
eye	hemorrhage, blindness
liver	infarcts, RUQ syndrome
lung	chest syndrome
gall bladder	stones
heart	hyperdynamic flow murmurs
spleen	enlarged (child); atrophic (adult)
kidney	hematuria; loss of renal concentrating ability
intestines	acute abdomen
placenta	stillbirths
penis	priapism
digits	dactylitis
femoral head	aseptic necrosis
bone	infarction, infection
ankle	leg ulcers

### Treatment of Vaso-Occlusive Crisis

- oxygen
- hydration (reduces viscosity)
- antimicrobials
- correct acidosis
- analgesics/narcotics (give enough)
- magnesium (inhibits potassium and water efflux from RBCs thereby preventing dehydration)
- exchange transfusion for CNS crisis
- experimental anti-sickling agents

### MEGALOBLASTIC ANEMIA

- failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm
- non-megaloblastic anemia reflects membrane abnormality with abnormal cholesterol metabolism
- megaloblast = large, nucleated RBC precursor; macrocyte = large RBC

### Causes of Megaloblastosis

- folate deficiency (seen after 4 months of decreased intake)
- B<sub>12</sub> deficiency (seen after 10-15 years decreased intake)
- antimetabolite drugs
  - methotrexate
  - folate analogues (sulpha drugs)
  - purine/pyrimidine analogues (6-MP, 5-FU)
- nitrous oxide
- myelodysplasia/some cases of AML

### B<sub>12</sub> DEFICIENCY

#### Etiology

- if intake stops abruptly body stores last 3-4 years
- diet
  - strict vegetarian (rare)
- gastric
  - mucosal atrophy of pernicious anemia
  - post-gastrectomy
- intestinal absorption
  - malabsorption (e.g. Crohn's, celiac sprue, pancreatic disease)
  - stagnant bowel (e.g. blind loop, stricture)
  - fish tapeworm
  - resection of ileum as in Crohn's and celiac sprue
- rare genetic causes

## HEMOGLOBIN AND HEMOGLOBINOPATHIES ... CONT.

### Pernicious Anemia

- auto-antibodies produced against gastric parietal cells leading to achlorhydria and no intrinsic factor secretion
  - intrinsic factor is required to stabilize B<sub>12</sub> as it passes through the bowel
  - decreased intrinsic factor leads to decreased ileal absorption of B<sub>12</sub>
- female:male = 1.6:1
- may be associated with other autoimmune disorders e.g. thyroid and adrenal deficiency
- often > 60 years old

### Neurological Lesions in B<sub>12</sub> Deficiency

- cerebral (common; reversible with B<sub>12</sub> therapy)
  - confusion
  - delirium
  - dementia
- cranial nerves
  - optic atrophy (rare)
- cord (irreversible damage)
  - subacute combined degeneration
  - posterior columns - paresthesias, disturbed vibration, decreased proprioception
  - pyramidal tracts - spastic weakness, hyperactive reflexes
- peripheral neuropathy (variable reversibility)
  - usually symmetrical
  - affecting lower limbs more than upper limbs

### Diagnosis

- serum
  - anemia often severe +/- neutropenia +/- thrombocytopenia
  - MCV > 120
  - low reticulocyte count relative to the degree of anemia
- serum B<sub>12</sub> and RBC folate
  - caution: low serum B<sub>12</sub> leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of B<sub>12</sub>
- blood film
  - oval macrocytes (**see Colour Atlas H2A**)
  - hypersegmented neutrophils (**see Colour Atlas H2B**)
- bone marrow
  - differentiates between megaloblastic and myelodysplastic anemias
  - hypercellularity
  - failure of nuclear maturation
  - elevated unconjugated bilirubin and LDH due to marrow cell breakdown
- Schilling test to distinguish pernicious anemia from other causes
  - Schilling test: part 1
    - tracer dose (1 µg) of labelled B<sub>12</sub> (cobalamin (Co<sup>\*</sup>)), PO
    - flushing dose (1 mg) of cold B<sub>12</sub>, IM to saturate tissue binders of B<sub>12</sub> thus allowing radioactive B<sub>12</sub> to be excreted in urine
    - 24 hour urine Co<sup>\*</sup> measured
    - normal → > 5% excretion
  - Schilling test: part 2
    - tracer dose B<sub>12</sub> (Co<sup>\*</sup>) plus intrinsic factor, PO
    - flushing dose of cold B<sub>12</sub>, injected IM
    - 24 hour urine Co<sup>\*</sup> measured
    - normal test result (> 5% excretion) = pernicious anemia
    - abnormal test result (< 5% excretion) = intestinal causes (malabsorption)

### Management

- B<sub>12</sub> 100 µg IM monthly for life or oral B<sub>12</sub>
- watch for hypokalemia (due to return of potassium to intracellular sites) and thrombocythemia

### FOLATE DEFICIENCY

- more common than B<sub>12</sub> deficiency because folate stores are depleted in 3-6 months
- folate complexes with gastric R binder
- R binder is replaced by intrinsic factor in the duodenum
- this complex is absorbed in the jejunum

### Etiology

- diet (folate is present in leafy green vegetables)
  - most common cause
  - e.g. infancy, poverty, alcoholism
- intestinal
  - malabsorption

## HEMOGLOBIN AND HEMOGLOBINOPATHIES . . . CONT.

- drugs/chemicals
  - alcohol
  - anticonvulsants
  - antifolates (MTX)
  - birth control pills
- increased demand
  - pregnancy
  - prematurity
  - hemolysis
  - hemodialysis
  - psoriasis, exfoliative dermatitis

### Clinical Presentation

- mildly jaundiced due to hemolysis of RBC secondary to ineffective hemoglobin synthesis
- glossitis and angular stomatitis
- rare
  - melanin pigmentation
  - purpura secondary to thrombocytopenia
- folate deficiency at time of conception and early pregnancy has been linked to neural tube defects

### Management

- never give folate alone to individual with megaloblastic anemia because it will mask B<sub>12</sub> deficiency and neurological degeneration will continue
- folic acid 15 mg PO/day x 3 months; then 5 mg PO/day maintenance if cause not reversible
- folic acid supplementation 1 mg PO/day will protect against elevated homocysteine levels (risk factor for CAD)

## HEMOLYTIC ANEMIAS (HA) (see Colour Atlas H4)

### Classification

- hereditary causes (intrinsic)
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)
- acquired causes (extrinsic)
  - immune
    - hemolytic transfusion reaction
    - idiopathic immune HA
    - drugs
    - cold agglutinins
    - secondary autoimmune HA
  - non-immune
    - RBC fragmentation syndromes
    - paroxysmal nocturnal hemoglobinuria
    - liver disease
    - hypersplenism
    - march hemoglobinuria

### Clinical Presentation

- jaundice
- cholelithiasis
- splenomegaly
- skeletal abnormalities
- leg ulcers
- regenerative crisis
- folic acid deficiency
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

### Diagnosis

- indirect - not specific to hemolytic anemias
  - increased reticulocyte count
  - reduced haptoglobin
  - increased unconjugated bilirubin
  - increased urine bilinogen
  - increased LDH
- tests exclusive for intravascular hemolysis
  - serum free hemoglobin present
  - methemalbuminemia (heme + albumin)
  - hemoglobinuria (immediate)
  - hemosiderinuria (delayed)

## Antiglobulin Tests (Coombs' Tests)

- direct Coombs' test (direct antiglobulin test)
  - purpose: detect antibodies or complement on the surface of RBC
  - by adding anti-antibodies to the RBC; the RBC agglutinate in a positive test
  - indications
    - hemolytic disease of newborn
    - hemolytic anemia
    - AIHA
    - hemolytic transfusion reaction
- indirect Coombs' test (indirect antiglobulin test)
  - purpose: detect antibodies in serum that can recognize antigens on RBC
  - by mixing serum with donor RBC and then anti-antibodies; RBCs agglutinate in a positive test
  - indications
    - cross-matching of recipient serum with donor's RBC
    - atypical blood group
    - blood group antibodies in pregnant women
    - antibodies in AIHA

## I. HEREDITARY HEMOLYTIC ANEMIAS

### STRUCTURAL ABNORMALITIES IN CYTOSKELETON

#### Hereditary Spherocytosis

- autosomal dominant with variable penetrance
- incidence 22 per 100,000
- most common type of hereditary hemolytic anemia
- abnormality in spectrin (compound in RBC membrane)
- blood film shows spherocytes (**see Colour Atlas H8**)
- increased osmotic fragility
- sometimes confused with immune hemolytic anemia
- treatment: splenectomy (immunize against pneumococcus first); avoid in childhood

#### Hereditary Elliptocytosis

- autosomal dominant
- incidence 20-50 per 100,000
- abnormality in spectrin interaction with other membrane proteins
- 25-75% elliptocytes
- hemolysis is usually mild
- treatment: splenectomy for severe hemolysis (immunize against pneumococcus first)

### ENZYMATIC ABNORMALITIES IN RBC

#### G6PD Deficiency

##### Clinical Presentation

- X-linked recessive
- oxidant drug-induced hemolysis
  - sulfonamides
  - primaquine
  - nitrofurantoin
  - acetanilid
- favism (fava beans)
- neonatal jaundice
- chronic hemolytic anemia
- infection

##### Diagnosis and Management

- high index of suspicion
- G6PD assay
  - should not be done when reticulocyte count is high in acute crisis, PBF shows Heinz bodies (granules in red blood cells due to damaged hemoglobin molecules) and features of intravascular hemolysis
- transfusion in severe cases
- stop offending drugs or food

## II. ACQUIRED HEMOLYTIC ANEMIAS AUTOIMMUNE HEMOLYTIC ANEMIA

**Table 6. Classification of autoimmune hemolytic anemia**

	Warm	Cold
<b>Antibody Coating RBC</b>	• IgG	• IgM
<b>Temperature Detect by Coomb's</b>	• 37°C	• 4-37 °C
<b>Direct Coombs Test</b>	• positive for antibodies	• positive for complement
<b>Etiology</b>	<ul style="list-style-type: none"> <li>• idiopathic</li> <li>• secondary to lymphoproliferative disorder                             <ul style="list-style-type: none"> <li>• e.g. CLL, Hodgkin's</li> </ul> </li> <li>• secondary to autoimmune disease                             <ul style="list-style-type: none"> <li>• e.g. SLE</li> </ul> </li> <li>• drug induced                             <ul style="list-style-type: none"> <li>• penicillin</li> <li>• quinine</li> <li>• methyldopa</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• idiopathic</li> <li>• secondary to infection                             <ul style="list-style-type: none"> <li>• e.g. mycoplasma, EBV</li> </ul> </li> <li>• secondary to lymphoproliferative disorder                             <ul style="list-style-type: none"> <li>• e.g. macroglobulinemia, CLL</li> </ul> </li> </ul>
<b>Blood Film (see Colour Atlas H5)</b>	• spherocytes	• agglutination
<b>Management</b>	<ul style="list-style-type: none"> <li>• treat underlying cause</li> <li>• corticosteroids</li> <li>• splenectomy</li> <li>• immunosuppression</li> </ul>	<ul style="list-style-type: none"> <li>• treat underlying cause</li> <li>• warm patient</li> <li>• plasmapheresis</li> <li>• immunosuppression</li> </ul>

## RBC FRAGMENTATION SYNDROMES

### Classification

- cardiac and large vessel abnormalities (macroangiopathic)
- small vessel disease (microangiopathic) (**see Colour Atlas H7**)
  - thrombotic thrombocytopenic purpura (TTP)/ hemolytic uremic syndrome (HUS)
  - DIC
  - metastatic carcinoma
  - eclampsia
  - malignant hypertension
  - vasculitis
- infection (malaria, clostridia)
- drowning
- thermal injury

### Diagnosis

- evidence of hemolysis, schistocytes, hemosiderinuria, hemoglobinuria

### Management

- treat underlying disease, replace iron if indicated

## THROMBOTIC THROMBOCYTOPENIC PURPURA AND HEMOLYTIC UREMIC SYNDROME

**Table 7. Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)**

TTP	HUS
<ul style="list-style-type: none"> <li>• predominantly adult</li> <li>• <b>neurological symptoms (90%)</b> <ul style="list-style-type: none"> <li>• H/A, somnolence, confusion, focal neurological findings, convulsion, stupor, coma</li> </ul> </li> <li>• purpura (90%) due to severe <b>thrombocytopenia</b> <ul style="list-style-type: none"> <li>• epistaxis, hematuria, hemoptysis and GI bleed</li> </ul> </li> <li>• epistaxis, hematuria, hemoptysis and GI bleed</li> <li>• microangiopathic hemolytic anemia</li> <li>• <b>fever (90-100%)</b></li> <li>• GI           <ul style="list-style-type: none"> <li>• N/V, abdominal pain</li> </ul> </li> <li>• <b>renal (40-80%)</b> <ul style="list-style-type: none"> <li>• abnormal UA, oliguria, ARF</li> </ul> </li> <li>• etiology           <ul style="list-style-type: none"> <li>• idiopathic</li> <li>• familial</li> <li>• secondary TTP               <ul style="list-style-type: none"> <li>• infection                   <ul style="list-style-type: none"> <li>• enterobacteriaceae</li> <li>• viral: flu, HIV</li> </ul> </li> <li>• systemic diseases                   <ul style="list-style-type: none"> <li>• SLE and other CVD</li> </ul> </li> <li>• cancer and chemotherapeutic drugs</li> </ul> </li> </ul> </li> <li>• diagnosis           <ul style="list-style-type: none"> <li>• by clinical picture</li> <li>• CBC: anemia, thrombocytopenia</li> <li>• PT, PTT: normal</li> <li>• ESR: normal</li> <li>• negative Coombs'</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• predominantly children</li> <li>• <b>purpura (90-100%) due to severe thrombocytopenia</b></li> <li>• microangiopathic hemolytic anemia</li> <li>• <b>renal symptoms (90%)</b> <ul style="list-style-type: none"> <li>• abnormal UA, oliguria, ARF</li> </ul> </li> <li>• etiology           <ul style="list-style-type: none"> <li>• <i>E. coli</i> serotype O157:H7 virotoxin</li> </ul> </li> <li>• diagnosis           <ul style="list-style-type: none"> <li>• by clinical picture</li> <li>• same as TTP</li> <li>• stool C+S</li> </ul> </li> </ul>
*Key characteristics bolded	

### Management

- plasmapheresis is the treatment of choice
- steroid is treatment of choice only in mild disease

## APLASTIC ANEMIA

- destruction of hematopoietic cells of the bone marrow

### Etiology

- radiation
- drugs
  - anticipated (chemotherapy)
  - idiosyncratic (chloramphenicol, phenylbutazone)
- chemicals
  - benzene and other organic solvents
  - DDT and insecticides
- post viral e.g. hepatitis B, parvovirus
- idiopathic
  - often immune (T-cell mediated)
- paroxysmal nocturnal hemoglobinuria
- marrow replacement
- congenital

### Clinical Presentation

- occurs at any age
- slightly more common in males
- can present acutely or insidiously
- anemia or neutropenia or thrombocytopenia (any combination) +/- pancytopenia
- thrombocytopenia with bruising, bleeding gums, epistaxis
- anemia with SOB, pallor and fatigue

## APLASTIC ANEMIA ... CONT.

- presentation of neutropenia ranges from infection in the mouth to septicemia
- absence of splenomegaly

### Diagnosis

- serum
  - neutrophil count  $< 5.0 \times 10^9/L$
  - platelet count  $< 20 \times 10^9/L$
  - corrected reticulocyte count  $< 1\%$
- blood film
  - decreased normal RBC
- bone marrow
  - aplasia or hypoplasia of marrow cells with fat replacement

### Management

- removal of offending agents
- supportive care (red cell and platelet transfusions, antibiotics)
- antithymocyte globulin (50-60% patients respond)
- cyclosporine
- allogeneic bone marrow transplantation
  - minimize blood products on presentation
  - only irradiated, leuko-depleted blood products should be used
  - CMV negative blood for CMV negative patients

## HEMOSTASIS

### THREE PHASES OF HEMOSTASIS

#### Primary Hemostasis

- goal is to rapidly stop bleeding
- vessel injury results in collagen and subendothelial structure exposure and release of vasoconstrictors
- blood flow is impeded and platelets come in contact with vessel wall
- platelets adhere to collagen and are activated resulting in change of shape and release of ADP and thromboxane A<sub>2</sub>
- these factors further recruit and aggregate more platelets resulting in formation of hemostatic plug

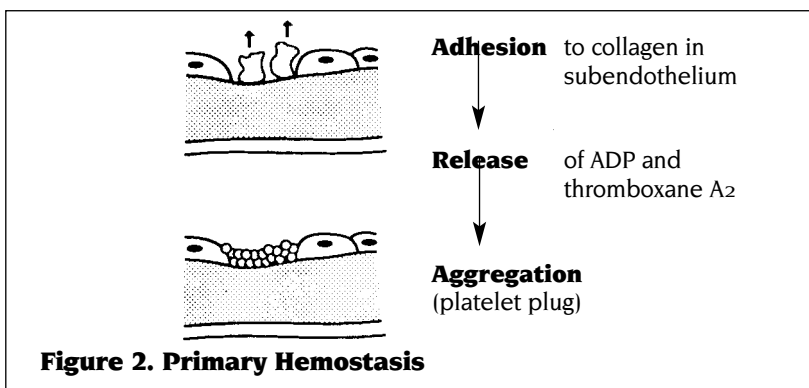


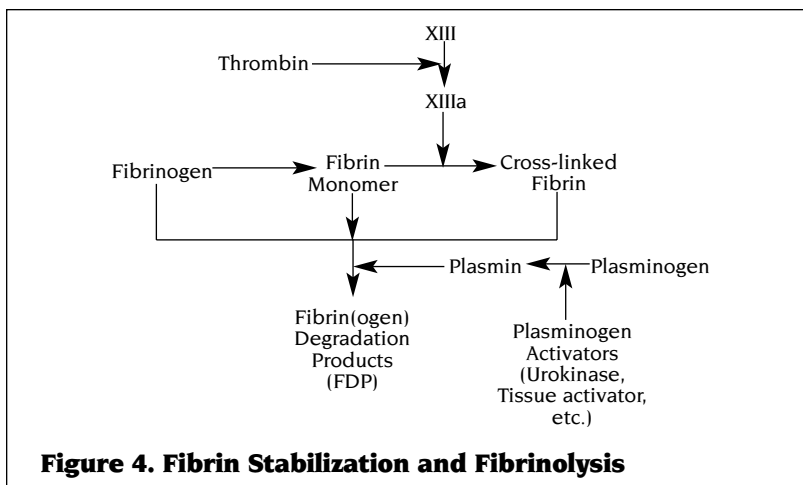
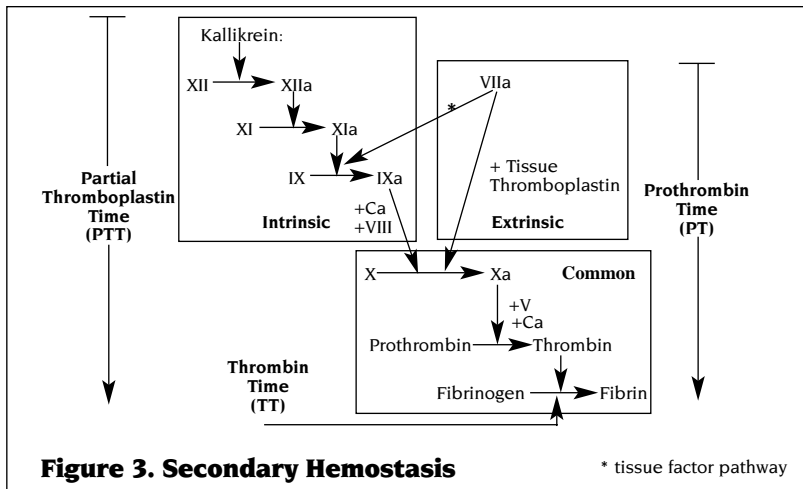
Figure 2. Primary Hemostasis

#### Secondary Hemostasis

- platelet plug formed through primary hemostasis is reinforced through process of secondary hemostasis and a stable plug is formed
- secondary pathways involved in the activation of coagulation factors include
  - intrinsic
    - activated when vessel wall remains intact
    - slow pathway
  - extrinsic
    - activated when there is injury to vessel wall
    - fast pathway



# HEMOSTASIS ... CONT.



## TESTS OF HEMOSTASIS

<b>Table 8. Commonly Used Tests of Hemostasis</b>			
Type of hemostasis	Test	Reference Range	Purpose
<b>Primary</b>	platelet count	2-12 mins	<ul style="list-style-type: none"> <li>• to quantitate platelet number</li> <li>• platelet function</li> <li>• platelet function</li> </ul>
	bleeding time		
	platelet aggregation		
<b>Secondary</b>	PTT - depends on lab	22-35 s	<ul style="list-style-type: none"> <li>• measures intrinsic pathway factors VIII, IX, XI, XII</li> <li>• measures extrinsic pathway factor VIII in particular</li> <li>• measures deficiency of fibrinogen</li> <li>• inactivation of prothrombin</li> <li>• permits determination of coagulation status independent of laboratory performing measurement</li> </ul>
	PT - depends on lab	11-24 s	
	TT - depends on lab	14-16 s	
	INR	1 is normal	
<b>Fibrinolysis</b>	euglobulin lysis time		
<b>Other</b>	<ul style="list-style-type: none"> <li>• fibrinogen</li> <li>• fibrinogen degradation products (FDPs)</li> <li>• specific factor assays</li> <li>• tests of physiological inhibitors (antithrombins, protein S, protein C, hereditary resistance to APC)</li> <li>• tests of pathologic inhibitors (e.g. lupus anticoagulant)</li> </ul>		

**Table 9. Signs and Symptoms of Disorders of Hemostasis**

	<b>Primary (Platelet)</b>	<b>Secondary (Coagulation)</b>
<b>Surface Cuts</b>	excessive, prolonged	normal/slightly prolonged
<b>Onset After Injury</b>	immediate	delayed
<b>Typical Type and Site of Bleeding</b>	superficial i.e. mucosal (nasal, gingival, GI tract, uterine), petechiae	deep i.e. into joints, muscles, GI tract, GU tract, excessive, post-traumatic

## THROMBOCYTOPENIA AND OTHER DISORDERS OF PRIMARY HEMOSTASIS

- inability to form an adequate platelet plug due to
  1. disorders of blood vessels
  2. disorders of platelets
    - abnormal function
    - abnormal numbers

### Classification

#### Vascular (Non-Thrombocytopenic Purpura)

- hereditary
  - hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)
  - connective tissue disorders
- acquired
  - purpura simplex (easy bruising)
  - senile purpura
  - dysproteinemias
  - Henoch-Schonlein Purpura
  - scurvy
  - Cushing's syndrome
  - infections
  - drugs

#### Platelets

- dysfunction
  - hereditary
    - von Willebrand's disease, others (rare)
  - acquired
    - drugs eg. ASA, EtOH, NSAIDs
    - uremia
    - myeloproliferative disorders
    - dysproteinemias
- thrombocytopenia (usually acquired)
  - decreased production
    - drugs, toxins
    - radiation
    - marrow infiltrate or failure
    - ineffective production
    - megaloblastic anemias
    - myelodysplasia
    - vitamin B<sub>12</sub>, folic acid or iron deficiency
    - viral infections eg. varicella, mumps, HIV, EBV, CMV, parvo
  - increased destruction
    - drugs eg. quinidine, sulfas, thiazides, heparin
    - ITP
    - allo-antibodies
    - HIV positive
    - sepsis
  - increased consumption
    - DIC
    - microangiopathies (TTP)
  - sequestration
    - splenomegaly
  - dilutional
    - massive transfusion with stored blood

**IDIOPATHIC (AUTOIMMUNE) THROMBOCYTOPENIC PURPURA (ITP)****Table 10. Idiopathic Thrombocytopenic Purpura**

Features	Acute ITP	Chronic ITP
<b>Peak Age</b>	2-6 years	20-40 years
<b>Sex Predilection</b>	none	F > M (3:1)
<b>History of Recent Infection</b>	common	rare
<b>Onset of Bleed</b>	abrupt	insidious
<b>Platelet Count</b>	< 20 x 10 <sup>9</sup> /L	30-80 x 10 <sup>9</sup> /L
<b>Duration</b>	usually weeks	months to years
<b>Spontaneous Remissions</b>	80% or more	uncommon

**CHRONIC (ADULT-TYPE) ITP**

- most common cause of isolated thrombocytopenia
- diagnosis of exclusion

**Pathophysiology**

- IgG autoantibody
- spleen
  - site of antibody production and platelet destruction
  - usually not palpable (enlarged in ~ 10%)

**Clinical Presentation**

- insidious onset
- may be seen after mild viral illness or after immunization
- mucosal or skin bleeding
- petechiae and easy bruising
- hematuria
- melena
- epistaxis
- female with menorrhagia

**Laboratory Results**

- peripheral blood film: decreased platelets, large platelets
- bone marrow: plentiful megakaryocytes
  - critical test to rule out other causes of thrombocytopenia
- anti-platelet antibodies present in most
- increased bleeding time
- PT and PTT normal

**Management**

- conservative if mild
  - platelet count > 30,000, no mucosal bleeding
- steroids: moderate dose, then taper (80% responsive)
  - platelet count < 20-30,000 or evidence of mucosal bleeding
- splenectomy if steroids fail
- IV gamma globulin if steroids and splenectomy fail or if rapid response is required
- other: immunosuppressives, platelets, plasma exchange, Danazol

**Prognosis**

- fluctuating course
- overall relatively benign, mortality 1-2%
- major concern is cerebral hemorrhage at platelet counts < 5 x 10<sup>9</sup>/L

**DISORDERS OF SECONDARY HEMOSTASIS****Classification****I. Hereditary**

- Factor VIII: Hemophilia A, von Willebrand's disease
- Factor IX: Hemophilia B (Christmas Disease)
- Factor XI
- other factor deficiencies are rare

**II. Acquired**

- liver disease
- DIC
- vitamin K deficiency
- circulating anti-coagulants (inhibitors)
- other e.g. primary fibrinolysis

**HEREDITARY****I. Hemophilia A (factor VIII)**

- X-linked, 1/5,000 males
- mild (> 5%), moderate (1-5%), severe (< 1%)

**Clinical Presentation**

- hemarthroses, hematomas, GI and GU bleeding
- bleeding in response to trauma (mild and moderate disease)
  - intracranial hemorrhage following head injury
- spontaneous bleeding (severe disease)

**Laboratory Results**

- prolonged PTT, normal INR (PT)
- decreased factor VIII (< 40% of normal)
- vWF usually normal or increased

**Management**

- minor but not trivial bleeding (eg. hemarthroses)
  - heat treated Factor VIII concentrate
- major potentially life-threatening bleeding (eg. multiple trauma)
  - heat treated Factor VIII concentrate
- prophylaxis (eg. multiple dental extractions, surgery)
  - heat treated Factor VIII concentrate
- DDAVP in mild or moderate hemophilia A

**II. Von Willebrand's Disease**

- heterogeneous group of defects
- usually autosomal dominant
- qualitative or quantitative abnormality of vWF
  - vWF needed for platelet adhesion and acts as carrier for factor VIII
  - vWF exists as a series of multimers ranging in size
    - the largest ones are most active in mediation of platelet adhesion
    - both large and small complex with factor VIII
- both primary and secondary hemostasis affected
- usually mild to moderate in severity

**Classification**

- type I: decreased vWF in platelets and plasma (will see prolonged bleeding time, decreased factor VIII)
- type IIA: decreased large and intermediate sized multimers in plasma and platelets (will see prolonged bleeding time, normal levels of factor VIII)
- type IIB: largest multimers are missing from plasma but not from platelets

**Clinical Presentation**

- mild
  - asymptomatic
  - mucosal and cutaneous bleeding, easy bruising, epistaxis, menorrhagia, gingival bleeding
- moderate to severe
  - as above but worse, occasionally soft-tissue hematomas, petechiae (rare), GI bleeding, hemarthroses

**Course**

- may fluctuate, often improves during pregnancy and with age

**Laboratory Results**

- prolonged bleeding time and PTT
- decreased factor VIII (5-50%)
- normal platelet count (except in Type IIB)
- decreased ristocetin cofactor activity
- analysis of multimers

**Management**

- DDAVP is treatment of choice except in Type IIB
  - causes release of vWF and plasminogen activator from endothelial cells
  - in type IIB, the appearance of the large multimers in the circulation can cause thrombocytopenia
- Hemate P in selected cases
- conjugated estrogens

### III. Factor IX Deficiency

- Christmas disease, Hemophilia B
- X-linked recessive, 1/30,000 males
- clinical and laboratory features identical to Hemophilia A
- main treatment is Factor IX concentrate

### IV. Factor XI Deficiency (Rosenthal syndrome)

- autosomal recessive inheritance
- usually mild, often diagnosed in adulthood
- treatment: fresh frozen plasma

## ACQUIRED

### I. Liver Disease

- deficient synthesis of all factors except VIII
- aberrant synthesis: fibrinogen
- deficient clearance of hemostatic "debris" and fibrinolytic activators
- accelerated destruction due to dysfibrinogenemias: increased fibrinolysis, DIC
- thrombocytopenia: hypersplenism, folate deficiency, EtOH intoxication, DIC
- platelet dysfunction: EtOH abuse
- miscellaneous: inhibition of secondary hemostasis by FDPs
- peripheral blood smear: target cells
- diagnosis
  - factor V because it has the shortest half-life
  - elevated INR (PT), PTT and bleeding time
- treatment: fresh frozen plasma, platelets

### II. Vitamin K Deficiency

#### Etiology

- poor diet (especially in alcoholics)
- biliary obstruction
- chronic liver disease
- malabsorption e.g. celiac disease
- drugs
  - oral anticoagulants produce inhibition of factors II, VII, IX, X, Protein C & S
  - antibiotics eradicating gut flora which is 50 % of vitamin K supply
- hemorrhagic disease of newborn

#### Diagnosis

- INR (PT) is elevated out of proportion to the elevation of the PTT
- decreased factors II, VII, IX and X (because vitamin K-dependent)

#### Management

- vitamin K 10-20 mg SC (not IM)
- Note: PT should improve within 24 hours, if not search for other causes

### III. Disseminated Intravascular Coagulation (DIC)

- massive uncontrolled intravascular coagulation resulting in depletion of platelets, coagulation factors and fibrinogen
- not a primary disorder but a syndrome that complicates a number of other conditions

#### Clinical Conditions Associated with DIC

- activation of procoagulant activity
  - anti-phospholipid antibody
  - intravascular hemolysis (incompatible blood, malaria)
  - tissue factor
  - tissue injury (obstetric catastrophes, leukemia, tumours, liver disease, trauma, burns)
  - snakebite
  - fat embolism
  - heat stroke
- endothelial injury
  - infections
  - vasculitis
  - metastatic disease (adenocarcinoma)
  - aortic aneurysm
  - giant hemangioma
- reticuloendothelial injury
  - liver disease
  - splenectomy

## HEMOSTASIS ... CONT.

- vascular stasis
  - hypotension
  - hypovolemia
  - pulmonary embolus
- other
  - acute hypoxia/acidosis
  - extracorporeal circulation

### Signs of Microvascular Thrombosis (Early DIC)

- neurological: multifocal, delirium, coma, seizures
- skin: focal ischemia, superficial gangrene
- renal: oliguria, azotemia, cortical necrosis
- pulmonary: ARDS
- GI: acute ulceration
- RBC: microangiopathic hemolysis

### Signs of Hemorrhagic Diathesis (Late DIC)

- neurologic: intracranial bleeding
- skin: petechiae, ecchymosis, oozing from puncture sites
- renal: hematuria
- mucosal: gingival oozing, epistaxis, massive bleeding

### Diagnosis

- clinical picture
- laboratory
  - primary hemostasis: decreased platelets
  - secondary hemostasis: prolonged INR (PT), PTT, TT, decreased fibrinogen and other factors
  - fibrinolysis increased FDPs, short lysis time
  - extent of fibrin deposition: urine output, urea, RBC fragmentation

### Management

- recognize early
- TREAT UNDERLYING DISORDER
- life support measures, O<sub>2</sub>, blood transfusion, fluid therapy
- replacement of hemostatic elements with platelet transfusion, FFP, cryoprecipitate

## THROMBOSIS

### Virchow's Triad

- stasis
- hypercoagulable state
- endothelial injury

### Etiology

- endothelial damage
- blood flow
  - stasis
  - turbulence
  - hyperviscosity
- blood components
  - platelets
  - contact factors
  - thrombin
  - Factor VIII
  - fibrin
- hypercoagulable state due to
  - cancer
  - pregnancy
  - birth control pills
  - DIC
  - lipids
  - decreased physiological inhibitors (antithrombin-III, protein C, protein S)
  - hereditary resistance to activated protein C (Factor V Leiden mutation)
  - prothrombin variant 20210A
  - nephrotic syndrome

## Management (acute and prophylaxis)

- hyperhomocysteine anticoagulants
  - low molecular weight heparin
    - no test required
    - reduced incidence of HIT
  - unfractionated heparin
    - maintain PTT 1.5-2.5 x the normal control
  - coumadin (see Table 11)
  - hirudin
- thrombolytics
  - snake venom enzymes (ancrod)
  - plasminogen activators (streptokinase, urokinase, tPA)
- antiplatelet agents
  - ASA
  - sulfinopyrazone
  - dipyridamole

**Table 11. Monitoring Coumadin (Warfarin) Therapy (therapeutic ranges)**

	INR	
	Range	Target
<ul style="list-style-type: none"> <li>• pre-operative                             <ul style="list-style-type: none"> <li>• surgery</li> <li>• hip surgery</li> </ul> </li> </ul>	1.5-2.5 2-3	2 2.5
<ul style="list-style-type: none"> <li>• prevention of venous thrombosis</li> </ul>	2-3	2.5
<ul style="list-style-type: none"> <li>• active venous thrombosis, pulmonary embolism and prevention of recurrent venous thrombosis</li> </ul>	2-4	3
<ul style="list-style-type: none"> <li>• prevention of arterial thrombo-embolism including mechanical heart valves</li> </ul>	3-4.5	3.5
<ul style="list-style-type: none"> <li>• INR should never exceed 5</li> </ul>		

## HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

### HIT-I

- non-immune
- decrease in platelet count usually seen early (48-72 hours post administration) but may take up to 1 week to appear
- transient thrombocytopenia, returns to normal once heparin discontinued
- no intravascular thrombosis
- likely due to platelet aggregation and sequestration

### HIT-II

- immune-mediated
- typically occurs at day 5-15 of heparin therapy and decline is gradual
- HIT can begin sooner in patients who have received heparin in the past three months
- delayed-onset HIT occurs several days after discontinuing heparin
- typical platelet count in patients with HIT ranges from 25 to 100 x 10<sup>9</sup>/L

### Pathogenesis

- immunoglobulin-mediated adverse drug reaction
- pathogenic antibody, usually IgG recognizes a multimolecular complex of heparin and platelet factor 4, resulting in platelet activation via platelet Fc receptors and activation of the coagulation system

### Clinical Complications

- cases of serious bleeding related to thrombocytopenia have been reported
- intravascular thrombosis
  - both venous (DVT, PE, venous gangrene) and arterial thrombi (MI, stroke, limb vessels) can form
- heparin-induced skin necrosis
- unusual thrombotic complications include mesenteric artery or vein occlusion, adrenal hemorrhage and infarction
- acute platelet activation syndromes
  - acute inflammatory reactions (eg. fever/chills, flushing, etc.),
  - transient global amnesia

### Laboratory Tests

- C-serotonin release assay
- ELISA
  - measures binding of antibody in patients serum to PF4:heparin complex

## HEMOSTASIS ... CONT.

### Management

- discontinuation of heparin
- platelet count should return to normal in a few days
- danaparoid (organon) is the preferred agent if anti-thrombotic therapy is indicated
- low-molecular-weight heparin is less likely to cause HIT in de novo use but still carries an increased risk if previously sensitized with unfractionated heparin
- other alternatives include ancrod and hirudin
- patient may be re-exposed to heparin only under careful supervision

## HEMATOLOGIC MALIGNANCIES

### OVERVIEW

#### Myeloid

- clonal stem cell neoplasms
  - i. acute myeloid leukemia (clonal proliferation of immature cells)
  - ii. myeloproliferative disorders (proliferation of mature cells)
    - polycythemia rubra vera
    - chronic granulocytic (myelogenous) leukemia
    - idiopathic myelofibrosis
    - essential thrombocythemia
  - iii. myelodysplastic syndromes (defective differentiation)

#### Lymphoid

- all cells arise from a single abnormal lymphoid precursor (B or T)
  - i. acute lymphoblastic leukemia (arise from stem cell)
  - ii. lymphomas (arise from maturing lymphoid cell)
    - Hodgkin's lymphoma
    - non-Hodgkin's lymphoma
  - iii. malignant clonal proliferation of B cells
    - chronic lymphocytic leukemia
    - plasma cell dyscrasias
    - light chain disease
    - monoclonal gammopathy of unknown significance
    - macroglobulinemia of Waldenstrom
    - macroglobulinemia-hyperviscosity syndrome

## MYELOID MALIGNANCIES

### ACUTE MYELOID LEUKEMIA (AML)

- failure of myeloid cell to differentiate beyond blast stage
- clonal proliferation of immature hematopoietic cells
- incidence increases with age
- associated with exposure to benzene, radiation and alkylating agents

### Pathophysiology

- uncontrolled growth of blasts in marrow leads to
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood
  - accumulation of blasts in other sites
  - metabolic consequences of a large tumour mass
- chronic myeloproliferative disorders and myelodysplastic syndromes can transform into AML

### Clinical Features of AML

- decrease in normal hematopoiesis
  - anemia
    - pallor, weakness, fatigue, dyspnea on exertion
  - thrombocytopenia
    - purpura
    - mucosal bleeding
    - associated with DIC (promyelocytic leukemia- a type of AML)
  - neutropenia → infections
    - septicemia
    - pneumonitis
    - skin and mucosal infections



## MYELOID MALIGNANCIES ... CONT.

- accumulation of blast cells in marrow
  - skeletal pain
  - bony tenderness, especially sternum
- accumulation of blast cells at other sites
  - lymphadenopathy
  - hepatosplenomegaly
  - gums
  - skin - leukemia cutis
  - CNS - N/V, H/A, papilledema +/- hemorrhage
  - gonads
  - eyes - Roth spots (oval retinal hemorrhages surrounding pale spot), blurred vision, diplopia
- metabolic effects - aggravated by treatment
  - increase in uric acid → uric acid nephropathy
  - release of phosphates → decrease in  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$
  - release of pro-coagulants → DIC

### Diagnosis

- peripheral blood film (**see Colour Atlas H11**)
  - decreased hemoglobin (usually normocytic, normochromic anemia) and platelets
  - variable leukocyte count
  - decrease in normal granulocytes
  - presence of blast cells (Auer Rods) – azurophilic granules within lysosomes
- bone marrow
  - usually hypercellular
  - increased blast cells - > 30% leukemic blasts for definitive diagnosis (normal < 5%)
  - decrease in normal erythropoiesis, myelopoiesis, megakaryocytes
- cytogenetics and molecular analysis
- INR (PT), PTT, FDP, fibrinogen in case of DIC
- increased uric acid, LDH and LFTs
- decreased  $\text{Ca}^{2+}$
- baseline urea and creatinine
- chest x-ray to r/o mediastinal compression and infection

### Management of AML

- cure - defined as survival that parallels age-matched population
- first step is complete remission- defined as normal peripheral blood smear, normal bone marrow with < 5% blasts, and normal clinical state
- leukemia will recur after complete remission if no further treatment given
- aims of treatment
  - eliminate abnormal clone - cytotoxic therapy
    - 1. Induction
    - 2. Consolidation or BMT
  - repopulation of marrow with normal hemopoietic cells
    - consider acceleration with hematopoietic growth factors
    - e.g. G-CSF, GM-CSF if increased incidence of severe infection
- supportive care
  - prophylaxis against infection via regular C&S of urine, feces, sputum, oropharynx, catheter sites, perianal area
  - antibiotics if fever with C&S of all orifices and chest x-ray
  - platelet and RBC transfusions - CMV negative products
  - prevention and treatment of metabolic abnormalities

### Prognosis

- achievement of first remission
  - 70-80% if < 60 years old, 50% if > 60 years old
  - median survival 12-24 months
  - 5 year survival 40%
- statistics may be improved by BMT – 50-60% cure rate

# CHRONIC MYELOPROLIFERATIVE DISORDERS

- clonal myeloid stem cell abnormalities leading to qualitative and quantitative changes to erythroid, myeloid, and platelet cells
- may develop marrow fibrosis with time
- all disorders may progress to acute myelogenous leukemia
- mainly middle-aged and older patients

## COMMON FEATURES

- increased
  - uric acid
  - LDH
  - serum B<sub>12</sub>
  - transcobalamin I
  - eosinophils
  - basophils
  - blood histamine (from basophils)
- pruritus
- bruising
- thrombosis
- peptic ulcer disease (histamine increases acid secretion)

**Table 12. Chronic Myeloproliferative Disorders**

	PRV	CGL (CML)	IMF	ET
<b>HCT</b>	↑↑	↓/N	↓	N
<b>WBC</b>	↑	↑↑	↑/↓	N
<b>PLT</b>	↑	↑/↓	↑/↓	↑↑↑
<b>LAP</b>	↑↑	↓	↑/N	↑/N
<b>marrow fibrosis</b>	±	±	+++	±
<b>splenomegaly</b>	+	+++	+++	+
<b>hepatomegaly</b>	-	+	++	-

PRV = polycythemia rubra vera  
 IMF = idiopathic myelofibrosis  
 LAP = leukocyte alkaline phosphatase

CGL = chronic granulocytic leukemia  
 ET = essential thrombocythemia

## POLYCYTHEMIA RUBRA VERA (PRV)

- autonomous overproduction of erythroid cells

### Clinical Features

- secondary to high red cell mass and hyperviscosity
  - headache, dizziness, tinnitus
  - congestive heart failure
  - thrombosis
- secondary to platelet abnormalities
  - cerebrovascular accident
  - myocardial infarction
  - phlebitis
  - bleeding, bruising
- secondary to high blood histamine (from basophils)
  - pruritus, especially post-bath or shower
  - peptic ulcer
- secondary to high cell turnover
  - gout (due to hyperuricemia)

### Management

- phlebotomy
  - if symptoms are due to erythrocytosis alone and platelet count normal or only slightly increased
- alkylating agents
  - if symptoms systemic or secondary to splenic enlargement
- antihistamines
- allopurinol
- <sup>32</sup>P

## Complications

- vascular complications (thrombosis, hemorrhage)
- myeloid metaplasia
- acute leukemia

## Causes of Secondary Polycythemia

- spurious (decrease in plasma volume)
- poor tissue oxygenation
  - high altitude
  - cyanotic congenital heart disease or pulmonary disease
  - hemoglobinopathies with increased O<sub>2</sub> affinity
  - carbon monoxide poisoning
- local renal hypoxia
  - renal artery stenosis
  - renal cysts
- ectopic production of erythropoietin
  - uterine leiomyoma
  - cerebellar hemangioma
  - hepatocellular cancer
  - pheochromocytoma
  - renal cell cancer

## CHRONIC GRANULOCYTIC (MYELOGENOUS) LEUKEMIA (CML)

- overproduction of myeloid cells, erythroid cells and platelets in peripheral blood
- marked myeloid hyperplasia in bone marrow

## Clinical Features

- disorder of middle age
- 40% asymptomatic
- secondary to splenic involvement
  - splenomegaly (most common physical finding)
  - shoulder tip pain due to splenic infarction
- secondary to high blood histamine
  - pruritus, peptic ulcer
- secondary to rapid cell turnover
  - fever, weight loss
- secondary to anemia
  - symptoms of anemia - most commonly fatigue
- secondary to gross elevation of the WBC (rare)
  - encephalopathy
  - priapism

## Diagnostic Features

- Philadelphia (Ph1) chromosome
  - translocation between chromosomes 9 and 22
  - the c-abl proto-oncogene is translocated from chromosome 9 to "breakpoint cluster region" (bcr) of chromosome 22 to produce bcr-c-abl fusion gene, an active tyrosine kinase
  - detection of this fusion gene is a diagnostic test for CML (present in over 90% of patients)
- leukocyte alkaline phosphatase (LAP)
  - normal constituent of secondary neutrophil granules
  - low or absent (normal or increased in other chronic myeloproliferative diseases and reactive states)
- peripheral blood film (**see Colour Atlas H10**)
  - leukocytosis with early myeloid precursors
  - eosinophils and basophils may be increased
  - hypogranular basophils
- bone marrow
  - myeloid hyperplasia with a left shift, increased megakaryocytes and increased reticulin or fibrosis

## Course/Outcomes

- chronic phase
  - normal bone marrow function
  - white blood cells differentiate and function normally
- accelerated phase
  - fever
  - marked increase in basophils
  - increased extramedullary hematopoiesis (unusual sites)
  - transformation → disease similar to idiopathic myelofibrosis
  - pancytopenia secondary to marrow aplasia

## CHRONIC MYELOPROLIFERATIVE DISORDERS ... CONT.

- acute phase (blast transformation)
  - 2/3 develop a picture similar to AML
    - unresponsive to remission induction
  - 1/3 develop a picture similar to ALL
    - remission induction (return to chronic phase) achievable
  - sepsis
  - bleeding
  - thrombosis

### Management

- symptomatic
  - allopurinol and antihistamines
- chronic phase
  - hydroxyurea or occasionally busulfan
  - interferon
  - STI 571
- only curative treatment is bone marrow transplantation

### IDIOPATHIC MYELOFIBROSIS (IMF)

- marrow replaced by fibrosis - abnormal megakaryocytes stimulate collagen deposition

### Clinical Features

- same as CML except no priapism or encephalopathy

### Diagnostic Features

- significant hemolysis due to hypersplenism and red cell fragmentation
- peripheral blood film (**see Colour Atlas H16**)
  - tear drop cells
  - red cell and megakaryocyte fragments
  - increased polychromasia
  - nucleated RBCs and poikilocytes
  - giant abnormal platelets due to early release from marrow
  - leukoerythroblastic changes i.e. due to the space occupying lesions in the bone marrow, a variable number of erythroid and myeloid cells are released into the circulation
- bone marrow
  - replaced with fibrosis, difficult to aspirate
  - megakaryocytes normal or increased

### Management

- transfusion
- erythropoietin
- androgens
- allopurinol and antihistamines
- folic acid if stores depleted
- desferoxamine for iron overload (iron and aluminum chelator)
- hydroxyurea in extremely small doses
- splenectomy in highly selected cases
- bone marrow transplant

### Complications

- refractory anemia
- pancytopenia
- transformation to AML
- thrombosis and bleeding

### ESSENTIAL THROMBOCYTHEMIA

- overproduction of platelets in absence of recognizable stimulus
- invariably above 400,000/mL

### Clinical Features

- asymptomatic most common
- bleeding - although plentiful, platelets are not working
- thrombosis
- symptoms 2° to splenic enlargement, high blood histamine, and rapid cell turnover - as per CML and IMF

### Laboratory Features

- defect in platelet function may be present
- elevation of phosphatase and potassium in plasma sample due to release of cytoplasmic content from aggregation of platelets

## CHRONIC MYELOPROLIFERATIVE DISORDERS ... CONT.

### Diagnosis

- exclude other myeloproliferative diseases and 2° thrombocythemia

### Management

- hydroxyurea
- <sup>32</sup>P
- plateletpheresis
- avoid splenectomy as spleen is removing unwanted platelets

### Complications

- bleeding
- thrombosis
- leukemic transformation
- transformation to myelofibrosis

### Clinical Pearl

- There is an asymptomatic "benign" form of essential thrombocythemia with a stable or slowly rising platelet count; treatment includes observation, ASA, sulfinpyrazone or dipyridamole.**

### Causes of Secondary Thrombocythemia

- infection
- inflammation (IBD, arthritis)
- malignancy
- hemorrhage
- Fe deficiency
- hemolytic anemia
- post splenectomy
- post chemotherapy

## MYELOYDYSPLASTIC SYNDROMES

- set of clonal disorders characterized by one or more cytopenias with anemia present
- ineffective hematopoiesis despite presence of adequate numbers of progenitor cells (bone marrow is usually hyper-cellular)
- considered preleukemic: 30-70% develop AML
- most common in elderly, post-chemotherapy, benzene or radiation exposure
- insidious onset
- clinical presentation
  - fatigue, weakness, pallor, infections, bruising and rarely weight loss, fever, and hepatosplenomegaly
- diagnostic triad
  1. anemia ± thrombocytopenia ± neutropenia
  2. bone marrow hypercellular or normocellular
  3. dysmyelopoiesis in bone marrow precursors
- hematological changes
  - RBC: variable morphology with decreased reticulocyte count
  - WBC: decrease in granulocytes and abnormal function
  - platelet: either too large or too small and thrombocytopenia

### FAB Classification

- refractory anemia (RA)
- refractory anemia with ring sideroblasts (RARS)
- refractory anemia with excess blasts (RAEB)
- refractory anemia with excess blasts in transformation (RAEB-T)
- chronic myelomonocytic leukemia (CMML)

### Management

- symptomatic: transfusion, antibiotics
- hematopoietic growth factors (G-CSF, GM-CSF) may decrease risk of infection
- erythropoietics
- AML induction chemotherapy: 50-60% remission, 90% relapse
- bone marrow transplant may be curative

# LYMPHOID MALIGNANCIES

## ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

### Pathophysiology

- develops from any lymphoid cell blocked at a particular stage of development

### Clinical Features

- see AML
- 50% present with fever

### Diagnosis

- see AML
- leukemic lymphoblasts lack specific morphological or cytochemical features, therefore diagnosis depends on immunophenotyping
- immunology (B or T lineage)
- cytogenetics

### Treatment

- see AML
- eliminate abnormal clone
  1. Induction
  2. Consolidation
  3. Intensification
  4. Maintenance
  5. Prophylaxis: CNS with XRT or MTX

### Prognosis

- depends upon response to initial induction or if remission is achieved following relapse
- achievement of first remission: 60-90%
- childhood ALL: 80% long term remission (> 5 years)
- adult ALL: 30-40% 5 year survival

**Table 13. To Differentiate AML From ALL – Remember Big and Small**

<b>AML (see Colour Atlas H11)</b>	<b>ALL (see Colour Atlas H13)</b>
big people (adults)	small people (kids)
big blasts	small blasts
lots of cytoplasm	little cytoplasm
lots of nucleoli (3-5)	few nucleoli (1-3)
lots of granules and Auer rods	no granules
big toxicity of treatment	little toxicity of treatment
big mortality rate	small mortality rate
myeloperoxidase, sudan black stain	PAS (periodic acid schiff)
maturation defect beyond myeloblast or promyelocyte	maturation defect beyond lymphoblast

# LYMPHOMAS

## HODGKIN'S DISEASE AND NON-HODGKIN'S LYMPHOMA STAGING

- Stage I
  - involvement of a single lymph node region or extralymphatic organ or site
- Stage II
  - involvement of two or more lymph node regions OR an extralymphatic site and one or more lymph node regions on SAME side of diaphragm
- Stage III
  - involvement of lymph node regions on BOTH sides of the diaphragm
  - may or may not be accompanied by single extralymphatic site or splenic involvement
- Stage IV
  - diffuse involvement of one or more extralymphatic organs including bone marrow

## Subtypes

- A = Absence of B symptoms
- B = Presence of B symptoms

## B Symptoms

- unexplained fever  $> 38^{\circ}\text{C}$
- unexplained weight loss ( $> 10\%$  of body weight in 6 months)
- night sweats

## HODGKIN'S DISEASE

- substantial number represents monoclonal B cell disorders
- bimodal distribution with peaks at the age of 20 years and  $> 50$  years

## Clinical Features

- lymphadenopathy (neck, axilla)
- B symptoms
- classical symptoms
  - pruritus
  - painful nodes following alcohol consumption

## Diagnosis

- nodal biopsy (**see Colour Atlas H15**)
- bone marrow biopsy for Reed-Sternberg cell – polynucleated cells derived from B-cells
  - nodular sclerosis is the most common histological subtype

## Work-up

- CBC
  - normocytic normochromic anemia
  - leukocytosis in  $1/3$  of patients
  - eosinophilia
  - platelet count is normal or increased in early disease but decreased in advanced disease
- biochemistry
  - RFTs to assess renal excretion of chemotherapeutics
  - LFTs to r/o liver involvement
  - uric acid
  - ESR to monitor disease progress
  - $\text{Ca}^{2+}$ , ALP, phosphate for bone metastasis
- chest x-ray to r/o mediastinal masses and lung metastases
- CT of chest, abdomen and pelvis

## Management

- high cure rate
- Stage I-II: radiation therapy or chemotherapy plus local field radiation (less risk of second malignancy)
- Stage III-IV: combination chemotherapy eg. ABVD or MOPP
- relapse: high dose chemotherapy, bone marrow transplant

## Complications of Treatment

- diminished fertility
  - consider oophoropexy/sperm banking before radiation
- post-splenectomy sepsis
  - immunize pre-splenectomy
- hypothyroidism
- secondary malignancies
  - $< 2\%$  risk of MDS, AML
  - usually within 4 years after exposure to alkylating agents and radiation
  - solid tumours in the radiation fields  $> 10$  years after exposure
- accelerated cardiovascular disease

## NON-HODGKIN'S LYMPHOMA

### Clinical Features

- painless superficial lymphadenopathy usually  $> 1$  lymph region
- usually presents as widespread disease
- constitutional symptoms (fever, weight loss, night sweats) not as common as in Hodgkin's disease
- cytopenia: anemia +/- neutropenia +/- thrombocytopenia if bone marrow fails
- abdominal symptoms or signs
  - hepatosplenomegaly
  - retroperitoneal and mesenteric involvement (2nd most common site of involvement)
- oropharyngeal involvement in 5-10% with sore throat and obstructive apnea

## Diagnosis

- lymph node biopsy
  - fine needle aspiration occasionally sufficient, core biopsy preferred
- bone marrow biopsy
- peripheral blood film sometimes shows lymphoma cells

## Work-Up

- CBC
  - normocytic normochromic anemia
  - autoimmune hemolytic anemia
  - advanced disease: thrombocytopenia, neutropenia, and leukoerythroblastic anemia
- biochemistry
  - increase in uric acid
  - abnormal LFTs in liver metastases
  - elevated LDH (rapidly progressing disease and poor prognostic factor)
- chest x-ray + CT for thoracic involvement
- CT for abdominal and pelvic involvement

## Revised European American lymphoma (REAL) Classification for Subtypes of NHL

- several classification systems exist and may be used at different centres
  1. plasma cell disorders
  2. Hodgkin's lymphoma
  3. indolent lymphoma/leukemia
    - good prognosis: median survival 10 years
    - not curable if stage III/IV
    - 8 subtypes of NHL
  4. aggressive lymphoma/leukemia
    - shorter natural history
    - 30-60% cured with intensive combination chemotherapy
    - 5 year survival 50-60%
    - 2 main subtypes of NHL

## Management of NHL

- localized disease (e.g. GI, brain, bone, head and neck)
  - surgery (if applicable)
  - radiotherapy to primary site and adjacent nodal areas
  - adjuvant chemotherapy
- indolent lymphoma
  - watchful waiting
  - radiation therapy
  - chemotherapy
- aggressive lymphoma
  - combination chemotherapy
  - aggressive consolidation with marrow or stem cell support

## NHL Complications

- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- Note: never give live vaccines e.g. MMR and oral polio

## Indicators of Poor Prognosis

- > 60 years old
- poor response to therapy
- multiple nodal regions
- elevated LDH
- > 5cm nodes
- previous history of low grade disease or AIDS



# MALIGNANT CLONAL PROLIFERATIONS OF B CELLS

## CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

- indolent disease characterized by the clonal malignancy of poorly functioning B cells
- accumulation of neoplastic lymphocytes in blood, bone marrow, lymph nodes and spleen
- most common leukemia in western world
- mainly older patients
- up to 60% asymptomatic
- 9 year median survival, but varies greatly

### Investigations

- absolute lymphocytosis  $> 5.0 \times 10^9/L$  (usually  $> 10.0 \times 10^9/L$ )
- lymphocytes small and mature
- smudge cells (**see Colour Atlas H12**)
- diffuse or focal infiltration of marrow by lymphocytes

### Complications

- bone marrow failure
- bulky lymphadenopathy
- hypersplenism
- immune hemolytic anemia
- immune thrombocytopenia
- hypogammaglobinemia
- monoclonal gammopathy (often IgM)
- hyperuricemia with treatment
- transformation to histiocytic lymphoma

### Management

- the gentlest treatment that will control symptoms
  - observation if early, stable, asymptomatic
  - intermittent chlorambucil
  - corticosteroids
  - radiotherapy
  - chemotherapy
- no cure

## PLASMA CELL MYELOMA (MULTIPLE MYELOMA)

- monoclonal malignancy of plasma cells engaged in the production of a specific protein (paraprotein) characterized by replacement of bone marrow and bone destruction
- incidence: 3 per 100 000
- increasing frequency with age
- the protein produced is monoclonal i.e. one class of heavy chains and one type of light chains ("M" protein)
- light chains only: 15% (light chain disease)
- IgD (1%) and IgE are rare

### Clinical Features

- onset between 40-70 years
- bone pain, tenderness, deformity
- weakness, fatigue (due to anemia)
- weight loss, night sweats with advanced disease
- abnormal bleeding (epistaxis, purpura)
- infection eg. pneumococcal diseases
- renal failure
- on exam: pallor, bone deformity, pathologic fractures, bone tenderness, hepato/splenomegaly, petechiae and purpura

### Laboratory Features

- peripheral blood film (**see Colour Atlas H14**)
  - rouleaux
  - rare plasma cells
  - normocytic anemia, thrombocytopenia, leukopenia
- bone marrow
  - focal or diffuse increase in plasma cells (**see Colour Atlas H9**)
  - primitive plasma cells
- biochemistry
  - hypercalcemia (N/V, apathy, weakness, polydipsia, polyuria)
  - increased creatinine
  - increased ESR
  - narrow anion gap (myeloma protein is a cation)
- monoclonal protein on serum protein electrophoresis
- heavy chain and light chain types identified by serum immunoelectrophoresis
- decreased normal immunoglobulins
- urine electrophoresis (Bence-Jones protein, a light chain dimer)

## Diagnosis

- bone pain, anemia, increased ESR or increased rouleaux suggests myeloma
- classic diagnostic triad: must show increased numbers of atypical immature plasma cells
  1. greater than 10% abnormal plasma cells in bone marrow
  2. lytic bone lesions
  3. monoclonal protein spike in serum or urine

## Complications

- bone abnormalities
  - osteoporosis, pathological fractures - common due to osteoclastic activating factor and PTHrp
  - lytic lesions are classical (skull, spine, proximal long bones, ribs)
  - osteoclast activating factor (hypercalcemia, normal ALP)
- renal failure secondary to
  - myeloma kidney (intratubular deposition of light chains)
  - hypercalcemic nephropathy
  - pyelonephritis
  - amyloidosis from chronic inflammation
  - obstructive uropathy
  - renal infiltration by plasma cells
  - hyperuricemia
  - hyperviscosity compromising renal blood flow
- recurrent bacterial infections
- anemia
- hyperviscosity syndrome (caused by M protein)
- amyloidosis (CHF, nephrotic syndrome, joint pain, carpal tunnel syndrome)
- transformation to acute leukemia

## Management

- melphalan, cyclophosphamide or other alkylating agents
- corticosteroids
- radiotherapy to local painful lesions
- bisphosphonates
- follow serum or urine M protein as indicator of response
- early identification and treatment of complications
- treatment of renal failure
  - hydration
  - corticosteroids
  - plasmapheresis
- autologous stem cell transplant
- thalidomide

## Prognosis

- median survival 24-30 months

## LIGHT CHAIN DISEASE

- plasma cells produce only light chains
- 15% of patients with myeloma
- diagnosis
  - urine immunoelectrophoresis
  - serum studies often non-diagnostic as light chains can pass through glomerulus
- renal failure a MAJOR problem
- prognosis: survival kappa > lambda light chains

## MONOCLONAL GAMMOPATHY OF UNKNOWN SIGNIFICANCE (BENIGN MONOCLONAL GAMMOPATHY)

- incidence: 0.15% in general population, 3% of people > 70 years of age
- diagnosis
  - exclude myeloma
  - < 10% plasma cells in bone marrow
  - no rise in the M protein with time
- 10% of patients develop multiple myeloma each year in the first 3 years

## MACROGLOBULINEMIA OF WALDENSTROM

- uncontrollable proliferation of lymphoplasmacytoid cells (a hybrid of lymphocytes and plasma cells)
- monoclonal IgM para protein is produced
- symptoms: weakness, fatigue, bleeding (oronasal), recurrent infections, dyspnea, CHF, weight loss, neurological symptoms peripheral neuropathy, cerebral dysfunction)
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, retinal lesions

## MALIGNANT CLONAL PROLIFERATIONS OF B CELLS ... CONT.

- bone marrow shows plasmacytoid lymphocytes
- bone lesions usually not present
- cold hemagglutinin disease possible
- normocytic anemia, rouleaux, high ESR if hyperviscosity not present
- watch for hyperviscosity syndrome

### MACROGLOBULINEMIA-HYPERVISCOSITY SYNDROME

#### Clinical Features

- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms: headache, vertigo, ataxia, stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
  - due to impaired platelet function, absorption of soluble coagulation factors e.g. nasal bleeding, oozing gums
- ESR usually very low

#### Management

- chlorambucil or melphalan
- corticosteroids
- plasmapheresis for hyperviscosity

**Table 14. Characteristics of B Cell Malignant Proliferation**

	CLL	Macroglobulinemia	Myeloma
<b>Cell Type</b>	lymphocyte lymphocyte	plasmacytoid	plasma cell
<b>Protein</b>	IgM if present	IgM	IgG, A, D or E
<b>Lymph Nodes</b>	very common	common	rare
<b>Hepatosplenomegaly</b>	common	common	rare
<b>Bone Lesions</b>	rare	rare	common
<b>Hypercalcemia</b>	rare	rare	common
<b>Renal failure</b>	rare	rare	common
<b>Immunoglobulin Autoimmune Complications</b>	common	infrequent	rare

### BONE MARROW TRANSPLANTATION

- allows even more intensive therapy for hematologic malignancies
- high doses of chemo +/- whole body radiation
- "marrow rescue"
  - autologous: from self
  - allogeneic: HLA identical sibling (donor must be < 55 years)
- complications
  - cytopenias - especially neutropenia and thrombocytopenia
  - infections - especially opportunistic
  - drug toxicity

# TUMOUR LYSIS SYNDROME

- more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, leukemia)
- metabolic abnormalities
  - hyperuricemia
  - hyperkalemia
  - hyperphosphatemia
  - hypocalcemia
- complications
- lethal cardiac arrhythmia
- acute renal failure

## Management

- prevention
  - aggressive IV hydration
  - alkalinization of the urine
  - allopurinol
  - correction of pre-existing metabolic abnormalities
- dialysis

# WBC DISORDERS

## NEUTROPHILIA

### Definition

- absolute neutrophil count (ANC)  $> 7.5 \times 10^9/\text{liter}$

### Mechanism

- increased mitosis/proliferation e.g. response to chronic infection
- decreased marrow storage pool e.g. acute response to infection
- decreased marginal pool e.g. acute response to infection
- decreased egress from circulating pool e.g. chronic steroids

### Etiology

- acute infections especially bacterial
- inflammation
- metabolic derangement e.g. uremia, acidosis, gout
- acute hemorrhage or hemolysis
- malignant neoplasm and myeloproliferative disorders
- steroid therapy (due to poor migration)

## LEUKEMOID REACTIONS

- blood findings resembling those seen in certain types of leukemia with immature WBC in the peripheral blood film
- myeloid leukemia mimicked by
  - pneumonia
  - other acute bacterial infections
  - intoxications
  - burns
  - malignant disease
  - severe hemorrhage or hemolysis
- lymphoid leukemia mimics (see [Infectious Diseases](#) Chapter)
  - pertussis
  - TB
  - infectious mononucleosis
- monocytic leukemia mimics
  - TB

## NEUTROPENIA

### Definition

- ANC  $< 2.5 \times 10^9/\text{liter}$

### Mechanisms

- decreased stem cells e.g. aplastic anemia
- decreased mitosis e.g. marrow hypoplasia secondary to alkylating agents
- increased ineffective mitosis e.g. megaloblastic anemia
- increased peripheral destruction e.g. hypersplenism
- combinations e.g. lymphoma
- increased marginal pool or decreased storage pool egress e.g. viremia

## WBC DISORDERS ... CONT.

### Etiology

- overwhelming infection
  - viral: HIV, hepatitis, EBV
  - bacterial: typhoid, miliary TB
- drugs and chemicals
  - examples: ionizing radiation, benzene, chemotherapeutic drugs, anti-inflammatory drugs
  - dose-dependent predictable e.g. anticonvulsants
  - dose-dependent idiosyncratic e.g. ASA, phenothiazine, indomethacin
  - dose-independent hypersensitivity
  - antibody-mediated eg. penicillins
- marrow disease
  - low B<sub>12</sub>/folate
  - bone marrow infiltration (hematologic malignancies > solid tumours)
  - aplastic anemia
- hereditary: cyclic neutropenia
- hypersplenism

### Clinical Features

- fever, chills
- infection by opportunistic organisms
- painful ulceration on skin, anus, mouth and throat by opportunistic organisms
- septicemia in later stage

### Diagnosis

- CBC
- bone marrow biopsy to rule out marrow failure

### AGRANULOCYTOSIS

- virtually complete disappearance of granulocytes from the blood and granulocyte precursors from the marrow; drugs often implicated
- abrupt onset of
  - fever, chills and weakness
  - oropharyngeal ulcers
- drug induced (eg. clozapine)
- highly lethal without vigorous treatment

### Management

- discontinue offending drug
- antimicrobial therapy e.g. TMP-SMX, ciprofloxacin, antifungal
- Filgrastim (G-CSF) - growth factor that stimulates neutrophil production

## APPROACH TO SPLENOMEGALY

### Etiology

- infections
  - subacute bacterial endocarditis, TB, salmonella, EBV, CMV, histoplasmosis, malaria, toxoplasmosis, schistosomiasis, HIV/AIDS
- hematologic disorders
  - hemolytic anemia, hemoglobinopathies, Fe deficiency anemia
- congestive splenomegaly, portal hypertension: secondary
  - secondary to portal or splenic vein obstruction
  - secondary to intrahepatic disease
  - secondary to CHF
- infiltrative or metabolic diseases
  - lipid storage disease, mucopolysaccharidosis, glycogen storage disease, amyloidosis, tyrosinemia
- immunological
  - SLE, sarcoidosis
- neoplastic
  - leukemia, lymphoma, Hodgkin's disease
- epidermal cysts
- other
  - serum sickness, Felty's syndrome, osteoporosis

### Mild Spleen Enlargement

- 0-4 cm below costal margin
- CHF, SBE, SLE, RA, thalassemia minor, acute malaria, typhoid fever

## WBC DISORDERS ... CONT.

### Moderate Spleen Enlargement

- 4-8 cm below costal margin
- hepatitis, cirrhosis, lymphomas, infectious mononucleosis, hemolytic anemias, splenic infarct, splenic abscess, amyloidosis, acute leukemias, hemolytic anemias

### Massive Spleen Enlargement

- > 8 cm below costal margin
- chronic leukemias, lymphoma, myelofibrosis, hairy cell leukemia, leishmaniasis, portal vein obstruction, polycythemia vera (end-stage), primary thrombocythemia, lipid-storage disease, sarcoidosis, thalassemia major

## BLOOD PRODUCTS AND TRANSFUSIONS

### BLOOD GROUPS

Group	Antigen	Antibody
O	H	anti-A, anti-B
A	A	anti-B
B	B	anti-A
A B	A and B	nil

Product	Indication
<b>Packed Cells</b>	symptomatic anemia bleeding with hypovolemia
<b>Frozen Red Cells</b>	rare blood groups multiple alloantibodies

- group compatible uncrossmatched blood is safer than O-negative uncrossmatched blood - there is no universal donor

### RED CELLS

#### Packed Cells

- stored at 4°C
- transfuse within 35 days of collection, otherwise hyperkalemia due to cell lysis
- transfuse within 7 days of collection if renal failure or hepatic failure is present to reduce solute load
- each unit will raise hematocrit by about 4% or hemoglobin by 10 gm/L (1 g/dL)

#### Selection of Red Cells for Transfusion

- donor blood should be crossmatch compatible (by mixing recipient serum with donor RBC)
- donor blood should be free of irregular blood group antibodies
- the donor blood should be the same ABO and Rh group as the recipient

### PLATELETS

Product	Indication
<b>Random Donor (pooled)</b>	thrombocytopenia with bleeding
<b>Single Donor Platelets</b>	potential BMT recipients
<b>HLA Matched Platelets</b>	refractoriness to pooled or single donor platelets

- each unit of random donor platelets should increase the platelet count by approximately  $10 \times 10^9/L$
- single donor platelets should increase the platelet count by  $40-60 \times 10^9/L$
- if an increment in the platelet count is not seen, alloantibodies, bleeding, sepsis or hypersplenism may be present

**COAGULATION FACTORS**

<b>Product</b>	<b>Indication</b>
<b>Fresh Frozen Plasma</b>	Depletion of multiple coagulation factors
<b>Cryoprecipitate</b>	Factor VIII deficiency Von Willebrand's disease Hypofibrinogenemia Hemate P
<b>Factor VIII Concentrate</b>	Factor VIII deficiency
<b>Factor IX Concentrate</b>	Factor IX deficiency

**Special Considerations**

- irradiated blood products
  - potential BMT recipients
  - immunocompromised patients
- CMV negative blood products
  - potential transplant recipients
  - neonates

**GROUP AND RESERVE SERUM**

- an alternative to holding crossmatched blood for individuals who may require transfusion
  - recipient's ABO and Rh group is determined
  - recipient's serum is tested for the presence of irregular blood group antibodies
  - serum is kept frozen
- compatible blood can be issued immediately in an emergency or within 30 minutes electively

**ACUTE COMPLICATIONS OF BLOOD TRANSFUSIONS****Febrile Nonhemolytic Transfusion Reactions**

- due to antibodies stimulated by previous transfusions or pregnancies against antigens on donor lymphocytes, granulocytes, platelets or to lymphokines that are released with storage of the cells
- signs and symptoms: chills, fever
- management and prevention
  - stop transfusion
  - acetaminophen
  - steroids
  - filtered blood
  - washed blood

**Allergic Reactions**

- usually due to interaction between donor plasma proteins and recipient IgE antibodies
- signs and symptoms: a spectrum from urticaria and generalized itching to wheezing to anaphylaxis
  - Note: anaphylaxis is rare, usually in IgA deficient patients reacting against IgA in donor plasma
- management and prevention
  - antihistamines
  - slow infusion
  - steroids
  - washed blood
  - anaphylaxis may require IV epinephrine and IgA deficient blood components in future

**Acute Hemolytic Transfusion Reactions**

- most commonly due to incorrect patient identification
- intravascular hemolytic reaction due to complement activation
- signs and symptoms
  - muscle pain, back pain
  - fever, N/V, chest pain, wheezing
  - dyspnea, tachypnea (acute respiratory distress syndrome)
  - feeling of impending doom
  - hemoglobinemia
  - renal failure - DIC
  - hypotension and vascular collapse
  - patient under general anesthetic may present with bleeding

## BLOOD PRODUCTS AND TRANSFUSIONS . . . CONT.

- investigations
  - repeat crossmatch and donor and recipient blood groups
  - direct antiglobulin test (direct Coombs' test)
- management
  - stop transfusion
  - hydrate aggressively
  - transfuse with compatible blood products

### **Citrate Toxicity**

- seen with massive transfusion and with liver disease
- toxicity secondary to hypocalcemia
- prevented by giving 10 mL of 10% calcium gluconate for every 2 units of blood

### **Hyperkalemia**

#### **Circulatory Overload**

- signs: dyspnea, orthopnea, cyanosis, sudden anxiety, hemoptysis, crackles in lung bases
- with prior CHF and in elderly patients
- minimize the amount of saline given with the blood

#### **Hemorrhagic State due to Dilutional Coagulopathy**

- with massive transfusion
- packed cells contain no Factor VIII or V or platelets
- correct with fresh frozen plasma and platelets

#### **Bacterial Infections**

- never give blood > 4 hours after a bag has been entered!
- signs and symptoms: chills, rigors, fever, hypotension, shock, DIC (profound symptoms with Gram negatives)
- management: blood cultures, IV antibiotics, fluids

#### **DELAYED COMPLICATIONS IN TRANSFUSIONS**

- days to weeks
- viral infection risks
  - HIV < 1:500,000
  - HBV < 1:250,000
  - HCV < 1: 10,000

#### **Delayed Hemolytic Transfusion Reaction**

- may be delayed up to 5 to 10 days
- extravascular hemolysis due to alloantibodies that are too weak to be detected by indirect antiglobulin test or by crossmatch
- may be confused with autoimmune hemolytic anemia
- signs and symptoms: anemia, fever, history of recent transfusion, jaundice, positive direct Coombs' test
- further transfusion should be avoided

#### **Iron Overload**

- often with repeated transfusion for long periods of time, e.g. beta-thalassemia major
- use of iron chelators after transfusion can reduce the chance of iron overload
- complications include secondary hemochromatosis
  - dilated cardiomyopathy
  - cirrhosis
  - DM, hypothyroidism, delayed growth and puberty

#### **Transfusion Associated GVHD**

- transfused T-lymphocytes recognize and react against the "host" (recipient)
- between 4-30 days later
- most patients with this have severely impaired immune systems (e.g. Hodgkin's, NHL, acute leukemias)
- signs and symptoms: fever, diarrhea, liver function abnormalities, pancytopenia
- mortality about 90%
- prevention: gamma irradiation of blood components



# MEDICATIONS COMMONLY USED IN HEMATOLOGY

<b>Drug</b>	<b>Common Formulary</b>	<b>Mechanism of Action</b>	<b>Clinical Uses</b>	<b>Common Side Effects</b>	<b>Contraindications</b>
<b>iron</b>	iron gluconate iron sulphate iron fumarate	<ul style="list-style-type: none"> <li>for synthesis of hemoglobin</li> </ul>	<ul style="list-style-type: none"> <li>iron deficiency anemia treatment and prevention</li> <li>pregnancy</li> </ul>	<ul style="list-style-type: none"> <li>in children: acute iron toxicity as                             <ul style="list-style-type: none"> <li>necrotizing enterocolitis</li> <li>shock</li> <li>metabolic acidosis</li> <li>coma and death</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>iron overload</li> </ul>
<b>B<sub>12</sub></b>	cyanocobalamin hydroxycobalamin	<ul style="list-style-type: none"> <li>synthesis of folic acid and DNA</li> </ul>	<ul style="list-style-type: none"> <li>B<sub>12</sub> deficiency</li> </ul>	<ul style="list-style-type: none"> <li>no significant toxicity</li> </ul>	<ul style="list-style-type: none"> <li>N/A</li> </ul>
<b>folic acid</b>	folic acid	<ul style="list-style-type: none"> <li>synthesis of purines and thymidylate thus DNA</li> </ul>	<ul style="list-style-type: none"> <li>folic acid deficiency</li> <li>pregnancy</li> </ul>	<ul style="list-style-type: none"> <li>no significant toxicity</li> </ul>	<ul style="list-style-type: none"> <li>N/A</li> </ul>
<b>erythropoietin</b>	Epo	<ul style="list-style-type: none"> <li>stimulate RBC synthesis</li> </ul>	<ul style="list-style-type: none"> <li>renal failure</li> <li>marrow failure</li> <li>myelodysplastic syndrome</li> <li>autologous blood donation</li> </ul>	<ul style="list-style-type: none"> <li>no significant toxicity</li> </ul>	<ul style="list-style-type: none"> <li>N/A</li> </ul>

<b>Class</b>	<b>Example</b>	<b>Mechanism of Action</b>	<b>Common Toxicity</b>	<b>Examples of Clinical Use</b>
<b>alkylating agent</b>	<ul style="list-style-type: none"> <li>nitrogen mustard</li> <li>cyclophosphamide</li> <li>nitrosurea</li> <li>busulfan</li> <li>cisplatin</li> </ul>	<ul style="list-style-type: none"> <li>cell cycle non-specific drugs</li> <li>via alkylation of nucleophilic groups in base pairs</li> <li>leading to cross-linking of bases or abnormal base-pairing or DNA breakage</li> </ul>	<ul style="list-style-type: none"> <li>marrow suppression</li> <li>GI irritation</li> <li>change in gonadal function</li> <li>nitrogen mustard (cyclophosphamide): hemorrhagic cystitis</li> <li>busulfan: adrenal insufficiency and pulmonary fibrosis</li> </ul>	<ul style="list-style-type: none"> <li>cyclophosphamide                             <ul style="list-style-type: none"> <li>breast CA</li> <li>small cell lung CA</li> <li>NHL</li> </ul> </li> <li>busulfan</li> <li>CML</li> <li>cisplatin                             <ul style="list-style-type: none"> <li>advanced ovarian CA</li> <li>testicular CA</li> </ul> </li> </ul>
<b>antimetabolites</b>	<ul style="list-style-type: none"> <li>folic acid antagonist (methotrexate)</li> <li>purine antagonist (mercaptopurine)</li> <li>pyrimidine antagonist (5-FU)</li> <li>hydroxyurea</li> </ul>	<ul style="list-style-type: none"> <li>all are cell cycle specific drugs</li> <li>all inhibit DNA synthesis                             <ul style="list-style-type: none"> <li>methotrexate inhibits synthesis of tetrahydrofolate</li> <li>mercaptopurine inhibits purine synthesis</li> <li>5-FU inhibits thymidylate synthesis</li> <li>hydroxyurea inhibits nucleotide reductase</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>marrow suppression</li> <li>oral mucositis</li> <li>nausea and vomiting</li> </ul>	<ul style="list-style-type: none"> <li>methotrexate                             <ul style="list-style-type: none"> <li>breast CA</li> <li>gestational trophoblastic CA</li> <li>ovarian CA</li> </ul> </li> <li>mercaptopurine                             <ul style="list-style-type: none"> <li>AML</li> </ul> </li> <li>5-FU                             <ul style="list-style-type: none"> <li>breast CA</li> <li>GI CA</li> <li>hepatocellular CA</li> </ul> </li> <li>hydroxyurea                             <ul style="list-style-type: none"> <li>CML</li> </ul> </li> </ul>
<b>antibiotics</b>	<ul style="list-style-type: none"> <li>anthracyclines (doxorubicin)</li> <li>bleomycin</li> <li>mitomycin-C</li> </ul>	<ul style="list-style-type: none"> <li>anthracycline is cell cycle non-specific; intercalates between base-pairs and thus blocks DNA and RNA synthesis</li> <li>bleomycin is cell cycle specific (G<sub>2</sub>); produces free radicals leading to DNA breaks and inhibits DNA synthesis</li> <li>mitomycin-C is cell cycle non-specific; metabolized in liver to alkylating agent</li> </ul>	<ul style="list-style-type: none"> <li>anthracyclines                             <ul style="list-style-type: none"> <li>marrow suppression</li> <li>severe alopecia</li> <li>cardiomyopathies</li> </ul> </li> <li>bleomycin                             <ul style="list-style-type: none"> <li>pulmonary fibrosis</li> <li>pneumonitis</li> <li>hypersensitivity</li> <li>mucocutaneous reactions</li> </ul> </li> <li>mitomycin-C                             <ul style="list-style-type: none"> <li>myelo-suppression</li> <li>nephrotoxic</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>anthracyclines                             <ul style="list-style-type: none"> <li>breast CA</li> <li>AML</li> <li>lymphomas</li> </ul> </li> <li>bleomycin                             <ul style="list-style-type: none"> <li>testicular CA</li> <li>lymphomas</li> </ul> </li> <li>mitomycin-C                             <ul style="list-style-type: none"> <li>GI malignancies</li> </ul> </li> </ul>

## MEDICATIONS COMMONLY USED IN HEMATOLOGY ... CONT.

**Table 20. Chemotherapeutic Agents (continued)**

Class	Example	Mechanism of Action	Common Toxicity	Examples of Clinical Use
<b>alkaloids</b>	<ul style="list-style-type: none"> <li>• vinblastine</li> <li>• vincristine</li> <li>• podophyllotoxin (etoposide)</li> <li>• taxol</li> </ul>	<ul style="list-style-type: none"> <li>• all are cell cycle specific</li> <li>• vincristine and vinblastine inhibit assembly of microtubules therefore mitotic spindles and M phase</li> <li>• podophyllotoxin activates topoisomerase II therefore DNA breaks down</li> <li>• taxol inhibits disassembly of microtubules therefore cells are stuck in M phase</li> </ul>	<ul style="list-style-type: none"> <li>• all have marrow suppression</li> <li>• vincristine and vinblastine</li> <li>• neurotoxic with areflexia, peripheral neuritis and paralytic ileus</li> <li>• taxol</li> <li>• neurotoxic as above</li> </ul>	<ul style="list-style-type: none"> <li>• vincristine and vinblastine</li> <li>• lymphomas</li> <li>• Wilm's tumour</li> <li>• podophyllotoxin</li> <li>• small cell lung CA</li> <li>• prostate CA</li> <li>• testicular CA</li> <li>• taxol</li> <li>• advanced breast CA</li> <li>• ovarian CA</li> </ul>
<b>hormones</b>	<ul style="list-style-type: none"> <li>• glucocorticoids</li> <li>• tamoxifen</li> <li>• flutamide</li> <li>• aminoglutethimide</li> </ul>	<ul style="list-style-type: none"> <li>• tamoxifen                             <ul style="list-style-type: none"> <li>• as a partial E2 antagonist</li> </ul> </li> <li>• flutamide: androgen receptor antagonist</li> <li>• aminoglutethimide: aromatase inhibitor in E2 synthesis</li> </ul>	<ul style="list-style-type: none"> <li>• glucocorticoid                             <ul style="list-style-type: none"> <li>• refer to <u>Endocrinology</u> under Cushing's syndrome</li> </ul> </li> <li>• tamoxifen                             <ul style="list-style-type: none"> <li>• menopausal symptoms</li> <li>• long term: retinopathy</li> </ul> </li> <li>• aminoglutethimide                             <ul style="list-style-type: none"> <li>• menopausal symptoms</li> <li>• skin rashes</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• glucocorticoids</li> <li>• CML</li> <li>• lymphomas                             <ul style="list-style-type: none"> <li>• tamoxifen</li> </ul> </li> <li>• breast CA</li> <li>• flutamide                             <ul style="list-style-type: none"> <li>• prostate CA</li> </ul> </li> <li>• aminoglutethimide                             <ul style="list-style-type: none"> <li>• metastatic breast CA</li> </ul> </li> </ul>
<b>others</b>	<ul style="list-style-type: none"> <li>• carboplatin</li> <li>• mitoxantrone</li> </ul>	<ul style="list-style-type: none"> <li>• carboplatin                             <ul style="list-style-type: none"> <li>• DNA binding</li> </ul> </li> <li>• mitoxantrone                             <ul style="list-style-type: none"> <li>• ?DNA breaks</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• carboplatin                             <ul style="list-style-type: none"> <li>• myelo-suppression</li> <li>• nausea, vomiting</li> <li>• nephrotoxicity</li> </ul> </li> <li>• mitoxantrone                             <ul style="list-style-type: none"> <li>• cardiotoxicity</li> <li>• alopecia</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• carboplatin</li> <li>• ovarian CA</li> <li>• mitoxantrone</li> <li>• AML</li> <li>• NHL</li> <li>• breast CA</li> <li>• ovarian CA</li> <li>• lung CA</li> </ul>

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