HAEMATOLOGY

Definition;
This is the study of blood, its nature, function and diseases.

Blood consists of:

A. *RBC cells*
B. *WBC* cells
C. Platelet cells
D. Plasma

PLASMA.

It's the liquid component of blood (consists of soluble fabrinogen) in which the above cells are suspended.

SERUM.

This is what remains after the formation of blood cells.

HAEMATOPOIESIS

In early foetal life, blood is synthesized in the liver and spleen. Latter, before birth, formation of blood starts in the borne marrow. At birth, blood formation takes place in every bone. In adult life, *RBC* production is confined to the end of long bones and also to the flat bones e.g. Ribs, iliac bones, sternum, vertebrae.

All peripheral blood cells are derived from a single stem cell-primitive cells.

(A) RBC (Erythrocytes)

Derived from the stem cell. This cell divides into pronormoblasts. Pronormoblasts develop into a basophilic normoblast. This is where haemoglobin synthesis begins. The basophilic normoblast further develops into reticulocytes.

The reticulocytes nucleus is lost & the cell is usually small in size. It then matures into an adult blood cell within three days. After which there is mature *RBC* in circulation.

The red blood cell has no nucleus. It's shape is a biconcave disc.

NB: Normal reticulocyte count in the blood stream is usually less than 2%.

A high reticulocyte count in circulation suggests increase in formation; as it happens in excessive haemolysis.

Essentials for normal erythropoiesis

1. Erythropoietin – stimulates formation of *RBC*.
2. Iron.
3. Vitamin B_{12} and folic acid
   -for maturation

–for normal *DNA* synthesis.

Other vitamins include, riboflavin.

Elements - zinc, copper, pyridoxine.

Hormones – androgen, for formation of the *RBC.*

Functions of the RBC

1. Carry oxygen from lungs to body tissues & CO_2 from tissue back to the lungs.
2. Help maintain normal blood pH.

RBC INDICES

1. RBC count – Number of *RBC* in a given volume of blood.
2. Haemoglobin level- the amount of Hb in a given volume of blood.
3. Haematocrit – The percentage of blood made up of *RBC*.
4. Mean cell volume (mcv) – The volume of each individual *RBC*.
5. Mean cell Hb - This measures the average Hb content in each cell.
6. Mean cell Hb concentration - This is the amount of Hb in each individual *RBC*.

(B) WBC

There are five types of WBC.

1. Segmented granulocytes:

- Neutrophils - (PMNL).
- Eosinophils
- Basophils

  i.e. have granules in their cytoplasm.

2. Non – granulocytes:

- Lymphocytes
- Monocytes.

Development of granulocytes

Derived from the stem cell. Then develop to myeloblast, which Develop to metamyeloblast. Some will develop to Eosinophils, neutrophils, & basophils. They then mature before being released into blood stream.

Neutrophils.

Their function is to fight bacterial infection in the body by phacocytosis.

Causes of neutrophilia (leucocytosis) in the body

This is usually a figure of over 10 X 10^9/L.

These causes include:

1. Infections
   -Bacterial
   -Fungal
2. Trauma
   -Surgery
   -Burns
3. Infarction
   -myocardial infarction
   -Pulmonary embolus
   -Sickle cell crisis
4. Inflammation
   -Gout
   -Rheumatoid Athritis
   -Ulcerative colitis
5. Malignancy
   -Solid tumours
   -Hodgkin's disease
6. Physiological
   -Exercise
   -Pregnancy

<u>Causes of neutrophenia</u>

Cells are usually less $1.5X10^9$/l.

Causes include:

1. Infections
   i. viral
   ii. Bacterial salmonella
   iii. Protozoal malaria.
2. Drugs
3. Autoimmune
   i. Connective tissue diseases
4. Alcohol
5. Congenital
   i. Kostmann's syndrome
6. Drugs that cause bone marrow aplesia – salphanomides, chloramphenicol, cytotoxic drugs, phenytoin sodium, phenylbutazone, penicillamine, Noproxen, carbimazole, quinidine, captopril, enalapril, nifedipine, amitriptyline, pyremethamine, dapsone, sulfadoxine, chloroquine, phenytoin, sodium valproate, carbamazepine, Sulphonamides, penicillins, cephalosporins, cimetidine, chlorpropamide, zidovudine.

Eosinophils

The function of eosinophils is uncertain.

Causes of aosinophilia

1. Parasitic infections e.g.
   -askarias,
   -hook worm infections.
2. Allergic disorders
   -Hay fever
   -asthma
   -allergic rhinitis.
3. Skin disorders e.g.
   -eczema,
   -urticaria'
   -superficial inflammation
4. Pulmonary disorders e.g. bronchial asthma.
5. Neoplasms e.g. lymphomas, solid tumours
6. Drug hypersensitivity e.g. gold, sulphonamides
7. Connective tissue disorders e.g. polyarteritis nodosa

Basophils

- Its role in the body is unknown and its figure hardly changes.
- Capable of ingesting foreign particles.
- Contain histamine and Heparin
- Appro. 30-150 X 10^9/L

Causes of Basophilia

1. Myeloproliferative diseases
-Polycythaemia
-Chronic myeloid Leukaemia
2. Inflammation
-acute hypersensitivity
-Ucerative colitis
-Crohns disease
3. Iron deficiency anaemia.

Lymphocytes

- Derived from the stem cells in lymphoid tissue e.g. lymph nodes, spleen, adenoids, thymus gland, gut wall, as well as also in the BM.
- These cells divide from the primitive cells into lymphoblasts.
- The lymphoblasts further develop to lymphocytes.
- There are normally 1.5 - 4.5 X 10^9/L

- Subdivided into B-Lymphocytes (or B-Cells) and T-Lymphocytes (or T-Cells)
- They are primarily responsible for cell mediated immunity.
- B-lymphocytes make antibodies
- T-lymphocytes
    - Responsible for attacking viruses, fungi and some bacteria
    - T helper cells are central in orchestrating function of other immune cells
    - T killer cells are able to destroy infected cells

Causes of lymphocytosis

1. Infections.
    - Viral infections e.g Aids
    - Chronic bacterial infections e.g. TB, Bordetella pertusis

2. Lymphoproliferative diseases
   -Chronic lymphatic leukaemia
   -Lymphoma
3. Post-Splenetomy

causes of Lymphocytopenia

1. Inflammation
-Connective tissue disease
2. Lymphoma
3. Renal Failure
4. Sarcoidosis
5. Drugs
-Steroids
-Cytotoxics
6. Congenital
-severe combined immunodeficiency

Monocytes

Derived from the stem cell of the BM.

They divide producing monoblasts which develop into monocytes.

This cells migrate into tissues where they develop into macrophages.

Their function is phagocytosis of dead WBC, RBC, also microbes.

Macrophages are usually found in the blood stream.

Causes of Monocytosis

1. infection
   e.g. bacterial tuberculosis
2. Inflammation
   -acute hypersensitivity
   -Ucerative colitis
   -Crohns disease
3. Malignancy
   - Solid tumours

(C) PLATELETS (Thrombocytes)

They are derived from megakarryocytes in the BM. These cells are necessary for clotting of blood.

They are discoid in shape.

The cell surface invaginates to form a tubular network, the canalicular system. This provides a large surface area of phospholipids onto which clotting factors bind.

Three types are present in the cytoplasm

1. Alpha granules- Contain fibrinogen and Von Willebrand Factor
2. Dense (Delta) granules – Store adenosine Diphosphate (ADP) and 5-hydroxytryptamine (5-HT, serotonin)
3. Lysosomes contain acid hydrolases

When platelets are activated by ADP, thrombin, or collagen they contract to become spherical and extend pseudopodia which adhere to the subendothelium and other platelets.

Upon activation, platelet granules discharge their content, which encourages further platelet aggregation and fibrin formation.

At the same time, arachidonic acid is released from the platelet membrane and converted by cylo-oxydase to endoperoxides and the powerful platelet aggregating agent, thrombine A2.

Aspirin and other NSAIDs irreversibly inhibit platelet cyclo-oxygenase and impair platelet function.

Causes of thrombocytopenia

1. Bone marrow disorders
    - Hpoplasia

    -Idiopathic
    -Drug induced – cytotoxics, antimetabolites, thiazides

    - Infiltration
      -Leukaemia
      -Myeloma
      -Carcinoma
      -Myelofibrosis
      -Osteopetrosis
    - Vitamin B_{12} / Folate deficiency
2. Increased consumption of platelets
   -Disseminated intravascular Coagulation (DIC)
   -Idiopathic Thrombocytopenic Purpura
   -Viral infections e.g. Epstain-Bar virus, HIV
   -Baterial infections e.g. gram negative septicaemia
   -Hypersplenism
   -Thrombotic Thrombocytopenic purpura (TTP) / Haemolytic uraemic syndrome (HUS)
   -liver disease
   -Connective tissue diseases e.g. SLE

Causes of raised platelet count

1. Reactive thrombocytosis
   -Chronic inflammatory disorders
   -Malignant disease
   -Tissue damage
   -Haemolytic anaemias
   -Post-splenectomy
   -Post-haemorrhage
2. Malignant thrombocytosis
   -Essential thrombocythaemia
   -Polycythaemia rubra vera
   -Myelofibrosis
   -Chronic myeloid leukaemia

Causes of pancytopenia

1. Bone marrow failure
2. Hypoplastic/aplastic anaemia
   -inherited
   -Idiopathic
   -Viral
   -Drugs
3. Bone marrow infiltration
   -acute leukaemia
   -Myeloma
   -Lymphoma
   -Carcinoma
   -Haemophagocytic syndrome
   -Myelodysplastic syndromes
   -Acquired Immunodeficiency syndrome (AIDS)
4. Ineffective haematopoiesis
   -Megaloplastic Anaemia
5. Peripheral pooling / Destruction.
   -Portal hypertension
   -Feltys syndrome
   -Malaria
   -Myelofibrisis

Causes of a swollen leg

1. Venous thrombosis
2. Calf haematoma e.g. secondary to trauma
3. Skin inflammation e.g. cellulitis
4. Bakers cyst
5. Pelvic disease obstructing venous or lymphatic return
6. Congestive cardiac failure / corpulmonale
7. Hypoalbuminaemia

ANAEMIA

DEFINITION:

This is a state where by the level of circulating RBC, the amount of Hb or haematocrit (packed cell volume) is bellow the normal expected range, taking into account both age and sex.

The Hb in males is 13-18gm/dl. While in female is 12-16gm/dl.

The Hb of baby at birth is 15-18gm/dl.

NB: the presence of symptoms in anaemic patient depends how quickly the anaemia has developed i.e. in a sudden drop in Haemoglobin, the patient will present with S+S.

Anaemia developing slowly over a prolonged period may be asymptomatic.

CLASSIFICATION OF ANAEMIA AETIOLOGICALY

1.)Blood loss

- May be acute – onset is sudden.

- Chronic blood loss – prolonged persistent haemorrhage e.g. hook worm infestations. menorrhagia, recurrent epistaxis, peptic ulcers, haemorrhoids, oesophageal varices, ulcerative colitis, frequent blood donation.

2.) Anaemia due to inadequate production of red blood cells.

i) Deficient essential factors necessary for erythropoiesis e.g. iron, folic acid, vitamin B12, protein, ascorbic acid, nicotinic acid, riboflavin, copper.
ii) Chronic inflammatory diseases e.g. infections like TB, non infections diseases e.g. rheumatoid athritis, systemic lupus erythematosis.
iii) Chronic renal diseases – production of erythropoietin is reduced.
iv) Chronic liver diseases e.g. liver cirrhosis.
v) Endocrine abnormalities e.g. hypothyroidism, hypopituitarism, hypoadrenalism.

There will be low tissue absorption of O_2 > reduced metabolic activity in the bone marrow > reduction in RBC Production.

VI) Impairment of bone marrow activity e.g.

a) aplastic/hypoplastic anaemia.
b) BM infiltration with malignant cells e.g. leukemia, multiple mycloma, /metastasis of a malignant disease in BM.
c) Toxic effects resulting from chronic infections, malignancies, ureamia of collagen disorders.

3.) Excessive destruction of the red blood cells.

i) Defective RBC membranes e.g. spherocytosis, eliptocytosis – this are congenital abnormalities.
ii) Enzyme defects e.g. pyruvate kinase deficiency, glucose G6 phosphate dehydrogenize deficiency (*G6PD*). Also congenital.

i.e in this conditions there is no stability of RBC, so they are haemolysed easily.

iii) Defective haemoglobin synthesis e.g. sickle cell diseases, thalasaemia.

iv) Extra (*outside the cell*) erythrocytic abnormalies e.g.

a) Infections like malaria.
b) Physical trauma like burns.
c) Chemical agents e.g. phenacetine,pb,cu^{2+}
d) Antibody mediated destructions – occurs in incompatible transfusions.
e) Toxic agents e.g. septicaemia, uraemia.
f) Hyperspleenism – spleen enlarges, traps RBC, & destroys it.

MORPHOLOGY CLASSIFICATION

1) Normocytic normochromic anaemia.

The RBC are of normal size, shape, & contain normal amount of haemoglobin.

The index -*MCHC-Normal,*

-MCV-Normal

Causes

i) Chronic infections.
ii) Any chronic debilitating disease e.g. malignancies.

2) macrocytic normochronic anaemia.

RBC are too large but contain normal amount of Hb.

Blood for full haemoglobin- MCV is increased.

Causes

Deficiency of vitamin B12 and folic acid deficiency.

3) microcytic hypocromic anaemia.

The *RBC* will be small in size and contain less than Normal amount of pigment.(Hb)

Blood for full haemogram.

- *MCV* reduced.
- *MCH/MICHC* reduced.

Causes

- iron deficiency

GENERAL CLINICAL SYMPTOMS OF ANAEMIA

1. Fatigue.
2. Jaundice
3. Bone tenderness
4. Headache.
5. Dizziness.
6. Fainting.
7. Shortness of breath.
8. Palpitations
9. Angina of effort.
10. Interminent cluadiaction.—severe pain from the peripheral lymphs
11. Paleness
12. May or may not have Oedema.
13. Tachycardia.
14. Systolic flow murmurs.
15. Congestive cardiac failure.

Other features are those of specific causes of anaemia.

Investigation in anaemia

1. Take blood for full haemogram.

- Reduced RBC.
- Hb level reduced.
- Haematocrit will be reduced.
- *MCH &MCHC* are low.
- *MCV* will depend on the cause of anaemia.

-Reticulocyte count is high in excessive haemolysis or excessive blood loss.
-Reticulocyte is reduced in conditions where there is reduced BM functions eg in lack of erythropoietin requirements.

-Also reduced in bone marrow failure.

Erythrocyte sedimentation rate (*ESR*). Is high if the cause of anaemia is a chronic disease.

2. Bone Marrow Examination

i. Bone marrow aspirate – marrow is sacked out from the medullary space, stained, and examined under microscope

ii. Trephine biopsy – A core of protein may be removed, fixed, and decalcified before sections are cut for staining.

The following examinations may be made;

- Assess the composition and morphology of haematopoietic cells or abnormal infiltrates.
- Cell surface marker analysis (immunophenotyping), chromosome and molecular studies to assess malignant disease.

- Marrow culture for suspected tuberculosis.

A trephine Biopsy is superior for assessing

- Marrow cellularity
- Marrow fibrosis
- Infiltration by abnormal cells such as metastatic carcinoma.

4. Investigations of the coagulation system (mainly done for bleeding disorders).

Coagulation screen test is mainly used.

a. Platelet count
   -Normal range is 150-400X109/L
   -used in thrompocytopenia

b. Bleeding time
   -Normal range is <8minutes
   -used in; thrombocytopenia, abnormal platelet function, Deficiency of -Von Willebrand factor, vascular abnormalities

c. Prothrombin Time
   -Normal range is 12-15 seconds
   -used in deficiencies of factors II,V,VII or X

d. Activated partial thromboplastin time (APTT)
   -Normal range is 30-40 seconds
   -used in Deficiencies of factors II,V,VIII,IX,XI,XII, Heparin monitoring, antibodies against clotting factors, lupus anticoagulant

e. Fibrinogen concentration
   -Normal range is 1.5-4.0g/L
   -Used in Hypofibrinogenaemia

NB. International normalized ratio is not a coagulation screening test.

5. Investigations for thrombotic disorders (i.e. Thrombophilia screen)

i) Antithrombin

ii) Protein C

iii) Protein S

iv) Prothrombin G20210A

v) Factor V Leiden

vi) Thrompin /reptilase time (for dysfibrinogenaemia)

vii) Antiphospholipid antibody / lupus anticoagulant / anticardiolipin antibody

viii) Homocysteine

Indications for thrombophilia screen.

i) Venous thrombosis <45 years

ii) Recurrent venous thrombosis

iii) Family history of venous thrombosis

iv) Venous thrombosis at unusual site
-Celebral venous thrombosis
-Hepatic vein (Budd-Chiari syndrome)
-Portal vein

v) Arterial and venous thrombosis

Iron deficiency anaemia

Definition – this is a type of anaemia that occurs when the supply of iron is inadequate to support optimum erythropoiesis.

Iron metabolism

- The average daily diet contains about 10-20 mg of iron, but normal only about 10% of these is absorbed.
- Absorption is however increased in iron deficiency.
- Absorption of iron takes place in duodenum and jejunum
- Iron enters plasma & is bound to transferrin.
- In the BM trasferrin bound iron becomes attached to the erythroplast & becomes ready for use in synthesis of rbc.
- Iron is stored in body tissue mainly in the liver in amounts ranging from 1-1.5 g. Iron is mainly used in the synthesis of Hb
- Also used in synthesis of mylobin
- Iron contains enzymes e.g. cytochrome.

Sources of iron (*fe*)

1) Food rich in iron e.g. liver, eggs, red meat, & milk.
2) Others – Soya beans and green vegetables e.g. spinage and kales.

Causes of iron deficiency anaemia

1) Poor diet intake
   Ignorance
   Religion.
   Poverty.
   Economy
2) Increased demand for iron e.g. in pregnancy, during lactation, prematures and growing children.
3) Blood loss – e.g. menorrhagia, recurrent epistaxis, gut bleeding following hook worm infestations, peptic ulcers, haemorrhoids, oesophageal varices, ulcerative colitis, frequent blood donation.
4) Decreased absorption of iron e.g. gastrectomy, achlorhydria (reduced HCL), malabsorption syndrome due to crohns diseases, celiac diseases.

Clinical features

General symptoms of anaemia.

O/E

1) Pale.
2) Oral – angular stomatitis (cracking of mouth corners).
   - Glossitis (inflammation of tongue).
   - Papillary arthrophy – gives a smooth tongue.
3) Gut – dysphagia: associated with iron deficiency anemia & achlorhydria. This syndrome is called pattern **Pattenson *Kelley syndrome/plumer Vinson*** syndrome.
   The dysphagia occurs due to tongue atrophy which extends to upper oesophagus causing development of a stricture.

   Other features in Gut include;

   - Nausea, anorexia, Constipation, Flatulence, Pyrosis – heart burn, Eructation's.
   - Picar – bizarre craze for soil. Gastritis,
   - Latter they may have gastritis.
   - Splenomegaly may or may not be there.

4) Nails;
   - Brittle
   - Thinning
   - Restless
   - Koilonychia – spoon shaped.

Diagnosis

i) Based on good clinical history with information regarding diet or any evidence of bleeding.
ii) Take blood for a full haemogram.
iii) Take blood for o/c
iv) Stool for occult blood.
Other investigations depend on clinical History & investigations e.g. barium meal.

Treament

Aims:

i) Replace lost blood and any iron deficit.
ii) Treat the underlining cause.

Specific

i) Tabs $FeSO_4$ ii tds x 2/52
ii) IM Iron Dextran (inferon) 50-250 mg daily.
iii) Treat the cause.

DDx

- iron deficiency anaemia
- microcytic hypochronic anaemia
- thalasaemia.
- sideroplastic anaemia.

- Defects of haemoglobin synthesis due to drugs eg isoniazid, pyrazinamide.

Megaloblastic Anaemia

Definition: This is a type of anaemia characterized by presence in BM of erythrocytes with delayed nuclear maturation because of defective DNA synthesis. As a result, division of cell is delayed and eventually red blood cell division occurs rapidly. Normally red blood cell division occurs rapidly. Within this division, the RC has no time to re-grow to their full size and a progressive reduction in cell size occurs.

When DNA synthesis is reduced the time between cell division is increased and more cell growth occurs, thus the cells become larger. As this cell size grow, a larger number of erythrocytes fail to mature, and are destroyed in the BM.

A small proportion of normally developing cells are as well destroyed. Eventually if untreated cell production in the BM fails.

This anaemia occurs in **folic acid deficiency** & **vitamin B12 deficiency**.

A) Vitamin B12 deficiency anaemia

- Sources of Vitamin *B12* are animal products, e.g. eggs, meat, fish, milk, but not in plants.
- Vitamin B12 is synthesized by certain micro organisms in the small intestines.
- Vitamin B12 binds to intrinsic factor secreted from parietal cells of the stomach
- Then it is absorbed in the ileum but intrinsic factor remains in the gut lumen.
- Vitamin B12 becomes bound to a plasma protein *transcobolamin*.
- This protein transports Vitamin B12 to the liver where it is stored.

Causes of Vitamin *B 12* deficiency

1) Low dietary intake e.g. strict vegetarians

2) Impaired absorption.

i) stomach:
   (a) Pernicious anaemia – atrophy of the gastric mucosa leading to failure of intrinsic factor production.
   (b) gastrectomy - resection of part of stomach

ii) small intestines:
   a) Fish tape worm infestation – feed on v t B12
   b) Bacterial overgrowth: compete for Vitamin B12.
   c) Ileum disease infection

d) Celiac disease – causes malabsorption

e) crohns disease.

iii) pancreases

a) Chronic pancreatic disease – there is impaired secretion of bicarbonate which are necessary for Vitamin B12 absorption. Takes place equally in alkaline pH

Pathology

There is defective *DNA* synthesis.

Other cells will also be affected e.g. features in Git, BM, CNS.

Clinical Features

1) General s/s of anaemia.
2) Glossitis - privy red tongue.
3) Hepatosplenomegaly may or may not be there.
4) Peripheral neuropathy.
5) Sub acute combined degeneration of the cord.
   - Paraesthesia in the hands and feet.
   - There is numbness.
   - Burning sensations.
   - Absent ankle jerk
   - Positive Barbinisk's sign
   - Exaggerated knee jerk reflexes
   - Decreased vibration and loss of position sense
   - Abnormal Gait
6) Mental diseases/changes e.g.
   - irritability,
   - disorientation,
   - depression,
   - dementia,
   - memory and
   - Intellectual impairment.

Investigations

1) Take blood for a full haemogram: RBC, MCV, MCH.

2) Borne marrow aspirate:

- Nucleated RBC are large (*megaloplast*)
- The metamyeloblast are also large
- Megakaryocytes will be reduced and have an abnormal shape
- Erythroid hyperplasia – this means the RBC series are high in number above normal amounts.

3) Serum for Vitamin B12.

Serum Vitamin B12 is reduced

Normal is 160-925mg/l.

4) Absorption test:

Can be done using a schilling test.

Method: Fast the patient overnight, then give 1mg of cobalt labeled Vitamin B12 orally. At the same time give 100µg IM. This infected material saturates the binding protein size in the patient blood so that the vitamin B12 which is to be absorbed in the gut will be excreted in the gut. The urine is collected after 24 hours and the cobalt containing Vitamin B 12 is measured. Normal individuals will secrete about 15% of cobalt labeled Vitamin B12.

If excreted Vitamin B12 is low then the pt has either reduced intrinsic factor or disease of ileum.

Treatment

1) Vitamin B12 – (Hydroxycobalamine) or cyanocotalamin IM 1000mg once weekly until blood returns to normal.

Transfusion may or may not be given. If the pt patient has pernicious anaemia, give once in month for life.

B) Folic acid deficiency anaemia.

- Derived from many food stuffs e.g., green leafy vegetables, like spinage. Others are kidney, liver.
- They are broken down into simple forms by enzymes.
- Absorption takes place in the jejunum and duodenum.
- After absorption it is reduced by enzymes into tetrahydrofolic acid – essential for synthesis of nuclear protein. It is stored in the liver mainly.
- Folic acid is destroyed in cooking and body stores are relatively small, lasting for a few weeks after dietary deprivation.

Causes

1) Nutrition – poor intake due to poverty, negligence, excessive alcohol. OR due to anorexia e.g. In chronic diseases like TB
2) Excess utilization of folic acid
   i) Physiological like pregnancy, Lactation, pre-maturity.
   ii) Pathological e.g. conditions with excess RBC production e.g. haemolysis , inflammatory diseases, malignant ,metabolic diseases, haemodialysis
3) Malabsorption – due to disease of the upper small intestines e.g. coalic,tropical spruae, folic acid enzymatic process e.g.
   - Trimethoptim

- methotraxate
- pyrimethamine

Anti convulsant & isoniazide – These drugs interfere with absorption.

Clinical features

Are as those of Vitamin B12 deficiency. but neurological features are rare.

Investigation

- Blood for full haemogram.
- Bm aspirate
- Serum for folic acid -2-20mg/l.

Treatment

- Tabs folic acid 5mg

Prevention

- **G**ive prophylactic treatment usually with addition of iron.

Haemolytic anaemia

Red blood cells have a lifespan of 120 days.

In haemolytic state lifespan shortens causing anaemia.

However, the body has compensatory measure, thus the bone marrow increases the RBC production.

If the BM can cope up with the RBC destruction, then the haemolytic state can exist, without anaemia. Thus anaemia results when the BM can no longer compensate for lost cells.

This increased output of cells causes outpouring of high reticulocytes into the blood stream.

Abnormally rapid breakdown of RBC causes;

- Serum bilirubin level to increase
- Jaundice
- Increased urinary excretion of urobilinogen.

Sites of haemolysis

1). intravascular – RBC are rapidly destroyed in circulation & haemoglobin is released and becomes bound to haptoglobin forming a large complex which can not

be excreted by the kidneys instead it is taken to the liver for storage and removal. If all haptoglobin is released, then Haemoglobin is excreted in urine (*haemoglobinuria*) these leads to passage of black urine.

2) Extravascular – RBC are destroyed in liver, spleen & BM. If haemolysis is chronic the organ involved will hypertrophy. Consequently in long term haemolysis the liver& spleen enlarge.

Causes of haemolysis

1) Inherited, this includes;

i) Rbc membrane defects e.g. sperocytosis, erythrocytosis.

ii) Hb abnormalities e.g. sickle cell anaemia & thelassaemia.

ii) Metabolic defects e.g. G6PD, pyruvate kinase deficiency.

2) Acquired, this includes;

i) Immunological e.g.

a) auto immune disease

b) Iso immune disease

c) Drugs e.g. penicillin

ii) Non immunological e.g.

a) Rbc membrane defects e.g. paroxysmal nocturnal haemoglobinuria .

b) Renal & liver disease

c) Mechanical disorders e.g. damage to blood vessel, valve prosthesis.

iii) Miscellaneous causes e.g.

a) Infections like malaria.

b) Drugs & chemicals.

c) Hypersplenism.

<u>Clinical features of HA</u>

a) General symptoms of anaemia.

b) Jaundice.

Investigation

1) Blood for full haemogram.

- Hb level low
- Raised reticulocyte count.
- Cells are usually normocytic though there may be macrocytic.

2) Urinalysis: Haemoglobilirunogen (haemoglobinuria), Urobilirunogen

3) Serum – bilirubin elevated

4) BM aspirate - There is erythroid hyperplasia (*high RBC precursors*).

Haemoglobin abnormalities

This is manifested in **Sickle Cell Diseases** & **Thalassaemia**

Structure of Hb

Composed of protein (globin) + haem.

The globin consists of two pair of identical polypeptide chains i.e. gamma, alpha, beta, & delta. A normal adult has HbA which has two alpha and two Beta chains. What makes Hb to differ is sequence of amino acid in the chains. There are many other types of Hb e.g. x, c, e, s. etc.

SICKLE CELL DISEASE (SCD).

DEFINITION: This is a severe haemolytic condition resulting from the replacement of the 6th amino acid of the B chain i.e. glutamic acid by valine.

This condition is inherited from autosomol dominant mothers. This condition may give rise to homozygous sickle cell disease (ss) or heterozygous sickle cell trait (As).

Geographic distribution

In this country, it is common in;

a) Coast province,
b) Nyanza, &
c) Western province

Pathophysiology

The essential fault here is an abnormal Hb in the RBC (Hbss), which causes the red cell to become sickle shaped when the oxygen tension is reduced. De-oxygenation increases blood viscosity. As a result this Rbc become trapped in small blood vessels causing thrombosis with a poor blood flow.

This interference of blood flow through arterioles results in infarction and causes death of the tissue involved. Affected organs include spleen, liver.

Crisis

1) Thrombotic crisis (painful, vaso occlusive crisis) this results from occlusion of small blood vessels.

2) Sickle chest syndrome. This may follow on from a vaso-occlusive crisis and is the most common cause of death in adult sickle disease. Bone marrow infarction results in fat emboli in the lungs which cause sickling and infarction leading to ventricular failure if not treated.

3) Sequestration crisis – seen only in young patients. For unknown reasons large amounts of blood pull in spleen & liver. Thus patient presents with features of circulatory collapse.

The TX of sequestration is

i) Dehydration.

ii) Blood transfusion

iii) If untreated sequestration may lead to death.

4) Aplastic crisis – Patient with scd may have transient BM failure. Thus the patient has pancytopenia – this may cause death. The patient has very low Hb which may cause failure. There is low reticulocyte count compared to other sickling crises.

5) Haemolytic crisis- rare type of crisis but when a SCD patient who may not be having *GBPD* deficiency and at the same time injecting oxidative drugs e.g chloroquin, quinine, there will be massive haemolysis of red blood cells.

CLINICAL FEATURES.

Depend on what crisis the patient came with;

A) Therefore it will be characteristic i.e.

Thrombolitic crisis is characterized by:

i) Dactylitis – most in young people. Severe pain & swelling of the hands & feet.

ii) Acute abdominal pain because of occlusion of mesenteric artery.

iii) Painful bones & joints- this is due to plugging of small vessels in the bone.

iv) Stroke may occur due to cerebral vessel occlusion

v) Osteomyeclitis – inflammation bones due to salmonella

vi) Renal interacts – present with Painless haematuria

B) Acute chest syndrome

i) Chest pain

ii) Fever

iii) Tachypnoea

iv) Wheeze

v) cough

C) Sequestration crisis – there is

i) Circulatory collapse.

ii) Splenomogally

D) Aplastic crisis – There is

i) Bleeding tendencies – Low platelet count.

ii) Recurrent infections – low *WBC* e.g. pnemococcal meningitis.

iii) Anaemia – low *RBC*

iv) Fever and general malaise – due to recurrent infections.

Other features include the most general symptoms of anaemia and growth retardation with delayed puberty.

O/E

i) Sick looking

ii) Tachycardia, sweating and a fever – due to systemic response.

iii) Jaundiced.

iv) Anaemia – pale – haemolysis, sequestration

v) Spleenomegally – felt till the age of 6-8 years. The spleen is felt due to spleen autospleenectomy.

vi) Chronic leg ulcers.

vii) Bossing of the skull.

viii) Widened head – comes as a result of widening of parietal & frontal bones.

ix) *CNS* manifestation e.g. paralysis, mental retardation, focal epileptic fits. This is due to poor blood supply to the brain.

x) *CVS* manifestations e.g. tarchycardia, soft systolic murmur, cardiomegally with latter cardiac failure. This comes about as a result of anaemia.

xi) Priapism.

Nb The patients are prone to infections due to

i) Thrombotic changes usually leading to necrosis.

ii) Autospleenectomy

iii) They have a poor pharcocytic function.

iv) Common microbes are

a) salmonella

b) staph aurous.

c) Pneunococci

Diagnosis

On basis:-

i) Typical clinical features from the history

ii) Details of the geographical origin of the patient.

iii) Physical examination.

iv) Laboratory support e.g. blood for full haemogram, Hb range 6-8g/dl, Reticulocyte count.

v) Take blood for; liver function test. Buluribin level will be elevated.

vi) Blood for sick ling test will be positive

vii) Blood for Hb electrophoresis. This will confirm the diagnosis.

viii) In a skull x-ray – show widening of the cranial table.

Treatment

The Treatment is symptomatic, Treat the symptoms e.g.

i) Rehydrate with Intravenous fluids.

ii) Give oxygen by mask if P_aO_2 is low.

iii) Adequate Analgesics e.g. opiates., pethidine,

iv) Transfusion of cross-matched blood - in severe anaemia.

v) Infections – Give antibiotics.

vi) Others;

- Exchage transfusion - a patient is simultaneously venesected and transfused to replace Hbs and HbA. This is used in life threatening crises or to prepare patients for surgery.
- Allogeneic BM transplants from HLA-matched siblings have been performed but this procedure appears to be potentially curative.
- Oral cytotoxic agents e.g. hydroxycarbamide (hydroxyurea) – this drug increases synthesis of HbF. A high HbF Level inhibits formation of HbS, thus reducing sickling.

Note:- Painful crisis becomes precipited by: infections, dehydration, cold, acidosis, hypoxia. Thus should be treated or avoided.

Management of acute chest syndrome

i) Bronchodilators e.g salbutamol

ii) Antibiotics

iii) Oxygen if P_aO_2 is low

iv) Red cell transfusion- it improves oxygenation and is effective as exchange transfusion.

Maintenance treatment

- Folic acid 5mg. od->
- Paludrine 100mg. od->
- Pen v daily
- In a good set up - Vaccination against pneumococcus and where available Haemophilus and hepatitis B.

Prognosis

In Africa few children with sickle-cell anaemia survive to adult life without medical attention.

Even with standard medical care appr. 15% die by the age of 20 years and 50% by the age of 40 Years.

Prevention

- Genetic counseling.
- Prenatal Tests
- Parental education can help prevent 90% of deaths from sequestration crisis.

DDX

i) Rheumatoid arthritis.

ii) Osteomyelitis.

iii) Rheumatic fever.

iv) Leukemia – the patient has anaemia, bone pain, & bleeding tendencies.

Thalassaemia

Definition This is a condition in which there is a deficiency in the synthesis of globin chains of haemoglobin. Thus accumulation of abnormal globin chain within the red cells leads to its early destruction.

Alpha or beta chains may be affected hence giving rise to either alpha or beta Thalassaemia.

1. Beta Thalassaemia

There is failure to synthesize B chain. When the abnormality is heterozygous. Synthesis of haemoglobin is mildly affected *(thalassaemia minor*)

When the patient is homozygous, Hb synthesis is grossly impaired leading to early haemolysis with severe anaemia (thalassaemia major).

Clinical features *(children commonly affected)*

i) Growth failure.

ii) Severe anaemia.

iii) Intermittent infection

iv) A bossing of head

v) Hepatosplenomegaly.

vi) Blood for a full haemogram show:- low; Hb, MCV, MCH, & high reticulocyte count. WBC & Platelets are normal.

vii) Diagnosis's is confirmed by the electrophoresis.

Nb: these features are seen in thalassaemia major. Thelassaemia minor is usually asymptomatic. No Rx is given.

Rx – Thalassaemia major

Folic acid

Regular blood transfusion

2. Alpha Thalassaemia

This is reduction or absence of alpha chain synthesis.

a) Heterozygous alpha thalassaemia

b) Homozygous alpha thalassaemia.

Heterozygous alpha thalassaemia

-Alpha chains are adequate

-survives up to adult life.

Homozygous alpha thalassaemia

-The reduction or absence of alpha chain synthesis is common in S.E Asia.

- Alpha gene loci have four genes.
- If one is deleted there is no clinical effect
- If two are deleted the patient may have mild hypochromic anaemia
- If three are deleted the patient will have HbF disease
- If four are deleted the baby is stillborn (Hyrops Fetalis)

-it is Incompatable with life.

-Children born are still births or die shortly after they are born.

O/E

a) Pale

b) Oedematous

c) Large liver or spleen.

The above conditions are collectively called *hydrops fitalis*.

Treatment

Beta thalassaemia

- For erythropoietic failure
  Allogeneic bone marrow transplantation from human leucocyte antigen (HLA)-compatible sibling
  Transfusion to maintain Hb >10g/dl
- For iron over load
  Iron therapy is forbidden
  Give Desferrioxamine therapy

Alpha thalassaemia

- **For hydrops fetalis: No treatment available**
- **For Haemoglobin F: No specific therapy required; avoid iron therapy; give folic acid instead.**

Immune haemoltic anaemia

Are in two types:

a) Iso-immune.

b) Auto-immune.

1. Auto-immune haemolytic anaemia

This is an acquired disorder in which the body produces antibodies against its own cells. Antibodies binds to the patients RCs then are pharcocytosed & removed from circulation by macrophages.

Causes.

Idiopathic

Few secondary causes

a) Drugs e.g. methyldopa.

b) Autoimmune diseases e.g. rheumatoid arthritis and systematic lupus erythematosis.

c) Lymphomas and other malignancies

d) Chronic lymphocytic leukemia.

C/F

Signs and symptoms of anaemia.

O/E

i) pale

ii) jaundice

iii) splenolomgaly

iv) hepatomegaly may or may not be there

DX

i) Blood for comps test.

Direct coombs test

Coombs reagents is added to the blood. If the rbc surfaces was covered with Ab then agglutination will occur.

Indirect coombs

This help to detect free Ab in the blood serum. Usually this is done when direct coombs test is negative & still suspect the patient has autoimmune haemolytic anaemia.

Technique

Mix the blood of two individuals who have compatible blood. This will help to incubate antibodies. Then perform the test on the blood as in direct coomb's test. If agglutination occurs, then indirect coomb's test Is positive.

Treatment

1) Give steroids e.g. prednisone 60mg then taper.

2) Transfusion may or may not be done

3) If cause is identified then treat.

Iso-immune haemolytic anaemia

In this anaemia antibodies produced by one individual reacts with red cells of another.

Anemia due to BM Failure (*aplastic anaemia*)

Definition

This is aplasia of BM with subsequent peripheral pancytophenia (low WBC,RBC, platelets.)

Mechanism

Occurs due to destruction of primitive stem cells together with a fault in differentiation.

As a result all the peripheral blood cell components are reduced.

Causes

a) Idiopathic,

b) Congenital,

c) Acquired,

i) Drugs e.g. antibiotics; like chloramphenical, sulphanomides: cytotixic drugs, phenylbutazone: anti thyroid drugs:anticonvulsants:immunosuppressive drugs e.g. azathioprine

ii) Chemicals e.g. -benzene toluent solvent misuse – glue sniffing.
-Insecticides – chlorinated hydrocarbons (DDT),
-Organophosphates

ii) Infections like measles, viral hepatitis

d) pregnancy
e) radiations e.g. x-rays or radiotherapy
f) Paroxismal nocturnal haemoglobinuria

C/F

1. *features of anaemia*
2. *Frequent infections*
3. *Bleeding tendency – skin, mucus membrane*

O/E

1. may or may not have lymphodenopathy
2. ecchymosis
3. bleeding gums
4. mouth sores
5. oral candidiasis
6. throat infection
7. Evidence of infection in any other part of the body.

Investigation

1**) Blood for** a full haemogram – normocytic normochromic anaemia, low platelet count , low WBC , no reticulocyte.

2) Bone marrow aspirate and trephine – shows a hypocellular BM i.e. reduced cell in the Bm.

DDX

1. Other conditions that cause pancytopenia i.e. disseminated TB
2. hypersplenism

3. megaloplastic anaemia.
4. Bone marrow infiltration by malignant cells.

Treatment

Treat or remove the cause

a) Supportive care

- Frequent transfusion till remission.
- Treat any infection
- Steroids may be used to reduce the bleeding

b) Heamatopoiesis stimulants

Androgenic asteroids eg oxymetholone. Orally 100mg odx 6/12

androgen is able to raise erythropoietin to high serum level. Also may raise responsiveness of erythroid precursors to erythropoietin

S/E of oxymetholone

i) It is an androgenic predominant.

ii) Causes high lbids.

iii) Fluid retention.

iv) Gives abnormal LFT parameters

c). BM transplant if no remission to (a &b) treatment.

Prognosis

- Spontaneous remission with recovery.
- Progressive severe deficiency of all components of blood leading to death due to infections or haemorrhage.
- **Bad prognostic features**
    - neutrophil count < $0.4x10^9$ /l.
    - platelets count <$20X10^9$/l.
    - reticulocyte <0.1%.

Bleeding disorders

DEFINITION. This are conditions whereby there is abnormal bleeding due to impairment of haemostasis (ceasation of bleeding). Haemostasis is achieved by the following processes.

a) Vessel constriction: when blood vessel endothelium is injured, the blood vessel usually constrict e.g. small capillaries and arteries

b) Clumping of platelets – platelets adhere to the collagen tissue lying underneath the endothelium exposed during injury, and also to one another. This helps to plug the opening & bleeding stops if the injury was minimal.

c) Blood coagulation. This is the process involving a series of enzymatic reactions leading to the conversion of suitable fibrinogen to a fibrinogen clot. This mechanism can be triggered by two independent routes, namely

i) Extrinsic pathway &

ii) Intrinsic pathway

i) **Extrinsic pathway**

A tissue factor (iii) usually released from a damage cell with calcium and factor (vii). This (iii, vii,& ca) activate factor (x). Then this becomes Activated factor (xa).

ii) **Intrinsic pathway**

Following injury of a blood vessel, factor xii is activated with the injured blood surface to xiia. This activates factor xi to xia. This xia activates factor ix giving factor ixa. Factor ixa, vii & a phosphate lipid activate factor x giving xa.

Xa together with calcium and phospholipids activates factor ii giving iia. iia activates factor i i.e. fibrinogen, giving fibrin.

Factor iia and calcium activates factor xiii to xiiia. Xiiia stabilizes fibrin giving stable fibrin clot. This fibrin strands are laid on the platelet plug formed earlier forming a mesh, and binding together an injured tissue.

Fibrinolysis

Plasminogen becomes activated into plasmin which digests fibrin giving soluble fibrin degradation products.

Investigation of bleeding disorders

Full blood count and film;

- bleeding time (3 minutes)
- No. of platelets.
    - Blood diseases e.g. leukemia.
- Prothrombin time index (PTI)(n)13-14 seconds.
- Clotting time (n) 5-8 minutes.

Hemophilia (factor viii deficiency)

Definition.

This is a hereditary disorder of blood coagulation characterized by a live long tendency to excessive haemorrhage & a greatly prolonged coagulation time. Its inherited as a x linked trait (x linked recessive character).

NB. It appears only in males and is transmitted to them by clinically normal female carriers. Occasionally it affects women too e.g. when an infected man marries a carrier girl.

Clinical Features

- Persistent bleeding after cuts, abrasions or dental extraction or any form of trauma.
- Spontaneous bleeding into the joints mainly the knee joints (*haemarthroses*).
- joint pain
- fluids in joints

o/e

- The area is warm.
- Muscle spasm.
- Repeated episodes of haemarthroses causes damage to joints with wasting of surrounding muscles leading to deformity and crippling.
- Intracranial heamorrhage

Diagnosis

1) Is made on basis of typical Hx of heamathroses.

2) Sex – usually males.

3) Family Hx of similar illness.

Treatment

i) Intensive treatment is required.

ii) Fresh blood transfusion – and possibly refer.

iii) Fresh frozen plasma or factor viii concentrates.

Predisposed infections

i) Hepatitis B virus.

ii) Aids

iii) Syphilis

iv) Malaria.

Caution

a) Never stitch a cut wound of haemophilia patient.

b) No cutting.

C) Must be reviewed by a physician before going to theatre.

Vitamin *K* deficiency

This vitamin is necessary for synthesis of factors ii, vii, ix, & x.

Causes

a) Inadequate body stores e.g. in malnutrition, heamorrhrage, of the new bone.

b) Mal-absorption of vitamin k. often occurs in obstructive jaundice. The billiary duct becomes obstructed and bile is not poured in the GIT. Bile emulsifies fat. Vitamin k is fat soluble, so cant b e absorbed in to blood stream.

c) Use of oral anti coagulants antagonize the effects of vitamin k.

CF

- Bleeding tendencies.
- Cerebral bleeding

Tx

- Replace vitamin k inj IM vitamin k 10mg od.
- Identify and treat the cause**.**

Purpuras

Definition

This are a group of disorders associated with superficial capillary bleeding mainly in the skin and mucus membranes due to low plate let count, platelet function disorder or increased capillary permeability.

A purpura mesh consists of small purplish red spots which do not fate on pressure. When they are large, they are referred to as ecchymoses.

Types

a) Idiopathic thrombocytophenic purpura (*ITP*)

b) Secondary thrombocytophenic purpura (*STP*)

a) *ITP*

This is a rare auto immune disorder whereby the body forms antibodies against its own platelets. The platelets are coated with Ab and are destroyed by spleen at risk/high rates.

CF

Insidious onsets of bleeding tendency eg purpuric rush, superficial easy bruising, epistaxcis, haematuria, gut bleeding and menorrhagia.

O/E

- Evidence of bleeding in nose.
- Spleenomegally may or may not be there.
- Blood for full haemogram low platelet count.

Treatment

To lower level of antibodies that the body is developing.

To remove Ab sensitized cell.

a) Steroids: eg precision 60mg/1kg-day, then taper as remission occurs.

b) Spleenoctomy may or may not be done.

c) Some refractory cases respond to cytotoxic drugs eg vincristine, azathioprine.

b) STP

State with low platelet count and purpuric rush.

It includes:-

a) Sequestration eg hyperspleenism.

b) Bm infiltration by malignancies eg leukemia, multiple myloma, lymphomas etc.

c) Bm damage eg cytotoxin drugs, chemicals eg benzene, & excessive exposure to irradiation.

C/F

1) Easy bruising

2)Excessive bleeding tendency.

3) Purpuric rush on the skin.

4) Features of the underlying cause.

Treatment

Identify and treat the cause.

LEUKEMIAS

Definitions

A group of malignant disorders of the haematopoietic tissues characteristically associated with increased numbers of white blood cells in the Bone Marrow and /or peripheral blood.

The course of the disease may vary from a few days or weeks to many years, depending on the type.

Aetiology

-Unknown

Predisposing Factors

1. Ionizing radiation e.g.

- Radiotherapy (Like when used in ankylosing spondylitis and diagnostic radiogragh of foetus in pregnancy)
- Atomic bombs (e.g. as evidenced by bombing of Japanese cities – Hiroshima and Chernobyl)
- X-rays

2. Cytotoxic drugs particularly Alkylating agents e.g. cyclophosphamide, chlorambucil. Alkylating agents may induce Myeloid Leukaemia after a latent period of several years.

3. Chemical carcinogens
   - Benzene exposure – occurs in rubber industries- e.g. Firestone industry.
   - Aromatic hydrocarbons

4. Infections
   - Retroviral infection e.g. HIV especially AML
   - Human T cell leukaemia virus 1 (HTCLV-1)

5. Genetic exposure. Increased incidence has been noted in identical twins and certain chromosomal disorders e.g. Dawn syndrome, Fanconi's syndrome, Klinefelters syndrome, wiskott-Aldrich syndrome.

6. Immunological. Immune deficiency states e.g. Hypogammaglobulinaemia, are associated with an increase in haematological malignancy

Classification

1. Acute myeloid leukemia (AML)
2. Acute lymphoblastic leukemia (ALL)
3. Chronic myeloid leukemia (CML)
4. Chronic lymphocytic leukemia (CLL)

* **Chronic**
  - More mature cells
  - Adults
  - Have slow progression

***Acute**
  - More primitive cells
  - Children
  - Have rapid progression

1. ACUTE LEUKEMIAS

- Failure of maturation of WBC.
- Occurs in acute leukemia.
- Proliferation of cells which do not mature leads to accumulation of useless cells and congestion in BM at the expense of normal cells.
- This proliferation eventually spills into the blood.
- Normal immature cells should not exceed 5%.

Sub classification

1. Acute lymphoblastic leukemia
-common type (pre-B)
-T cell
-B cell
-Undifferentiated

2. Acute myeloid (French American British (FAB)
-M0-undifferented
-M1-minimal differentiation
-M2-differentiated
-M3- promyelocytic
-M4- myelomonocytic
-M5-monocytic
-M6- Erythrocytic
-M7- megakaryocytic

Clinical features

(1) BM failure features

- Anaemia-low RBC
  - Pallor

    - Constitutional features/ general features –sudden onset, fever, weakness/ fatigue.
    - Dyspnoea
- Bleeding-low platelets (thrombocytopaenia)
    - Purpura
    - Spontaneous bruises
    - Mucus membrane bleeding
    - Menorrhagia
    - Petechial haemorrhages
    - Ecchymoses
    - Fundal haemorrhage
    - Prolonged haemorrhage after surgery
- Infection-Low WBC
    - Common sites – mouth, throat, skin, respiratory system and perianal
    - Common organisms – gram negative microorganism, E. Coli, Pseudomonas SSP, proteus, Klebsiella, Candida.

(2) Hepatosplenomegaly-infiltration
(3) Lymphadenopathy -infiltration
(4) Chloromas-soft tissue masses
(5) Bone pains/tenderness especially in sternal bone.
(6) Renal abnormalities-infiltration
(7) Leukemic meningitis
-infiltration of Leukemic cells into the subarachnoid space especially AAL

Present with;

- -Third CN palsy
- -Papillaoedema
- -Seizures
- -Altered mentation
- Increased intracranial pressure
- Headache
- Nausea /vomiting
- Blurring of vision
- Diplobia

8. Gum hypertrophy – due to infiltration.
9. Chloromas – localized tumour forming masses in the skin or orbit due to infiltration by tumours.
10. Others – testicular swelling.
- Mediastinal compression in T- cell

Investigation

(1) FHG/PBF
(i) WBC – high leukocyte count – more than 100 X 10^9/ L. the leukocyte count may be as low as 1 x 10^9 /L or as high as 500 x 10^9/L
(ii) PBF may show blast cells or other primitive cells.
(iii) Thrombocypenia
(2) BM aspirate
Most valuable diagnostic investigation and will provide material for

- cytology – used in staining to check for the presence of enzymes e.g. Acid Phosphatase in ALL.
- cytogenetics
- Immunological phenotyping e.g. Auer rod in AML

  - the presence of Auer rods in the cytoplasm indicates Myeloplastic type of Leukaemia
- Will show – high cellularity, leukaemic cells, reduced erythropeiotic cells, reduced megakaryocytes,

(3) Trephine Biopsy

- Done incase BM aspirate dries up i.e. Biopsy of the bone itself.

(4) Other tests

(i) U/E + creatinine- kidney
(ii) LFTs-liver
(iii) Coagulation screen
(iv). Cell surface markers used in classification of ALL
(v). Serum uric acids increases due to rapid growing number of leukaemic cells.

Management

Aim of treatment is to destroy leukemic clone of cells without destroying the residual normal stem cell compartment from which repopulation of the heamatopoietic tissues will occur.

There are three phases of chemotherapy treatment

1. Remission induction

-This is the initial phase, where destruction of the bulk of tumour occurs.
-Severe BM hypoplasia occurs, requiring intensive support with in-patient care.
-The aim is to reduce blast cells to less than 5% in BM with normal peripheral film.

2. Remission consolidation

Since patients in remission induction phase still harbour leukemic cells further systemic treatment is required to prevent or delay leukemic relapse.

3. Remission main

If the pt is still in remission after consolidation phase a period of maintainance therapy is given consisting of a repeating cycle of drug administration usually upto 3 years.

Drugs commonly used in the treatment of Acute leukemia

	Phase	**ALL**	**AML**
1	**Induction**	vincristine. (iv) Prednisolone (oral) L-Asparaginase (iv) Daunorubicin (iv Methotrexate (intrathecal)	Daunorubicin (iv) Cytarabine (iv) Etoposide (iv) Tioguanine (iv
2	**Consolidation**	Daunorubicin (iv) Cytarabine (iv) Methotrexate	Cytarabine (iv) Amsacrine (iv) Mitoxantrone (mitozantrone) i.v.
3	**maintenance**	Prednisolone (oral) Vincristine (iv)	

		Marcaptopurine (oral) Methotrexate (oral)	

In patients with ALL CNS prophylaxis is necessary since the drug used poorly penetrate into the CSF.
These consist of a combination of cranial irradiation + methotrexate (TREATMENT)

Supportive treatment
These usually involve complication arising from BM failure.
1. Anaemia
   -packed Rbc infusion to maintain Hb>10 gm/dl
2. Bleeding
   -platelet concentrate infusion to maintain platelet count above 10 x 10^9/L
   -coagulation abnormalities
   -Fresh frozen plasma
3. Infection- parenteral broad spectrum Antibiotics
4. PCP prophylaxis with septrin may be necessary.
5. Systemic fungal infection or pulmonary aspergilosis may require IV amphotericin B
6. Herpes Simplex infection – Aciclovir 200mg x 5 per day.
7. Metabolic problems
   -Renal Hepatic FNX monitoring is necessary together with fluid balance measurement
8. Psychological support- an optimistic attitude from staff is vital
   -Delusions, Hallucinations and paranoia are very common during the stormy phase of TREATMENT.

Prognosi\s

Without treatment prognosis- 5 weeks to a few months.
With good support treatment -5 years in good set ups.

Poor prognostic factors include
1. increasing age
2. male sex
3. high leukocyte levels at diagnosis
4. Cytogenetic abnormalities
5. CNS involvement at diagnosis

Probable cure of AML has been achieved with BMT after successful remission in induction phase.

Allogenic Bone marrow Transplant.
- Health BM or stem cells from peripheral blood film are injected IV into a patient who has been suitably conditioned.

- The conditioning therapy commonly includes:-
  - i) High dose of cyclophosphamide
  - ii)Total body irradiation
- Conditioning destroys the malignant cells, haematopoeitic and immunological tissues of the patient.
- The injected donor cells engraft themselves into the BM and start producing erythrocytes, granulocytes and platelets.
- It takes 3-4/52 for the grafted stem cells to meet body cell and platelet needs.
- The donors immunological system can recognize residual malignant recipient cells and destroy them, this include nature killer cells etc.
- Preferred donors are histocompatible siblings with best results being obtained in patients below 20 years.

General indications for Allogenic BMT include;

i) Neoplastic disorders affecting totipotent or pluripotent stem cell compartment e.g.Leukemia
ii)Haematopoitic failure e.g. Aplastic anaemia
iii) Major inherited defect in RBC production e.g. Thalassaemia and possibly sickle cell anaemia and spherocytosis.
iv) Inborn error of metabolism e.g. pophyria caused by defective haemoglobin metabolism and G6PD deficiency

Haematological indications for Allogenic BMT:

i) Acute myeloid leukemia in 1st remission
ii) CML in chronic phase
iii) T- and B-cell lymphoblastic leukaemia in first remission
iv) Acute lymphoblastic leukaemia (common pre-B type) in second remission
v) Severe Aplastic anaemia
vi) Acute myelofibrosis
vii) Lymphoma
viii) Myeloma-plasma cell tumours

Complications of Allogenic BMT

i) Mucositis-inflammation of all body mucosa (conjuctiva , mouth, perinal , nose)
ii) Infection- especially during conditioning.
iii) Acute graft versus Host disease (AGVHD)
this affects mainly the skin, liver and the gut
iv) Chronic GVHD
-This presents like connective tissue disorder especially SLE
v) Infertility
vi) Secondary malignant disease.
vii) Cataract formation

2.Chronic Leukemias

(i). Chronic Myeloid Leukemia

i) This is a disorder that is characterized by restrained and excessive proliferation of myeloid series of WBC.
ii) It occurs mainly between 30-80 years of age
iii) Peak incidence -55 years.
iv) ~ 90% of patients with CML have a chromosome abnormality disorder called **Philadelphia chromosome.**
v) This is a shortened chromosome 22 and is the result a reciprocal translocation of material with chromosome 9. The break on chromosome 22 occurs in the break point cluster region (BCR). The fragment from chromosome 9 that joints the BCR carries the Abelson oncogenes, which form a chimeric gene with the remains of BCR. This chimeric gene codes for a 210 kDa protein with tyrosine kinase enzyme, which plays a causative role in the disease.

The disease has three phases
(1) Chronic phase
- This is responsive to treatment and is easily controlled.
- It is essentially a benign neoplasm.

(2) Accelerated phase
- Not responsive to TREATMENT
- Not easily controlled

(3) Blast crisis phase
- Refractory to TREATMENT relapse
- Main cause of death in majority of patients.
- Patients' survival is determined by detection timing of blast phase which cannot be predicted.
- The disease transforms into acute leukemia in either AML 70% or ALL 30%.

Clinical features of CML

Symptoms
- Fatigue
- Weight loss
- Breathlessness
- Abdominal pain and discomfort.
- Bleeding tendencies
- Gout due to high levels of uric acid from break down of nucleic acid in leukaemic cells
- Visual disturbances
- Neurological manifestation
- Priapism.

Signs
- Massive splenomegaly-90%
- Hepatomegaly-50%
- Lymphadenopathy -rare

Investigations

(1) FHG /PBF

- -Normocytic Normochromic anaemia
- -increase in WBC-10 x 10^9/L-800 x 10^9/L. (10-800 cells/mm^3)
- -platelet -162-2,000cells/mm^3
- -Full range of granulocytes precursors, from myeloblast to mature neutrophils in PBF.
- -In accelerated phase the % of primitive is more.
- -In Blast transformation there is a dramatic increase in the number of circulating myeloblast.

(2) BM aspirate

- This is usually taken for chromosome analysis to demonstrate the presence of Philadelphia chromosome.
- RNA analysis is also done to demonstrate the presence of chimeric
- BCR-ABL gene

(3) Biochemical Tests-serum

- Low alkaline phosphatase in the neutrophil leukaemic cells
- Raised B_{12} assay- due to increased B_{12} binding protein
- Elevated LDH
- Increased serum uric acid – Hyperuricaemia.

Management of CML

No specific therapy is required if the patient is asymptotic and the leukocyte count is not greatly elevated.

Treatment include:-

(1) Chemotherapy

- Hydroxycarbamide (Hydroxyurea) caps 500mg bd (or 2-4gm daily)

- is currently the most widely used oral agent to provide initial control of the disease

- Busulfan (myelvam) 2-4 mgs od

(2) Alpha interferon-1M 3-9 mega units od

- -Low % of Philadelphia positive cells.
- -ADR –flue like symptom
- The aim of the Treatment is to maintain leukocyte level between 5-10,000 cells/mm^3

(3) Allogenic BMT

- Provide long term remission if done in early phase
- ~80% of patients get probable cure
- Treatment of accelerated and blast phase is difficult in CML.

(4) Initab mesylate (STI 571)

- This is an inhibitor of BCR-Abl tyrosine kinase.
- It is active in Alpha-interferon resistance cases, accelerated phase and blast crisis.

(ii). CHRONIC LYMPHOCYTIC LEUKEMIA

Definition

- A neoplasm of activated B- cells.
- The CLL cells resemble mature small lymphocytes and accumulate in BM, blood, LN and spleen.
- Appro. Age of patients is >50 years.
- The B-cells which would normally respond to Antigens by transformation and Antibody formation fail to do so due to lowered immunity**.**

Clinical Features

- Features of Anaemia
- Painless lymphadenopathy – soft, rubbery, homogenous, non tender & have asymmetrical involvement. The nodal architecture is lost.
- Splenomegaly, Hepatomegaly
- Recurrent Infections e.g. HZ, Broncho-pneumonia
- Haemorrhagic manifestations – due to thrombocytopenia.

Investigation

(A) FHG/PBF

1. WBC are raised -50-200 x 10^9/L cells (WBC)
   95% of the cases.
2. NNA

(B) BM aspirate /trephine biopsy

- For Diagnosis and prognosis
- Will show the amount of lymphoblast

(C) Biochemical test

i. Total protein
ii. Immunoglobulin
-These two will establish the degree of immunosuppression.

(D) Monoclonal band may be seen on serum electrophoresis.
(E) Serum uric acid ± raised (rarely due to relatively reduced cell turnover).

Clinical staging of CLL

A-No anemia or thrombocytopenia
-less than 3 areas of lymphoid enlargement
B-No anaemia or thrombocytopenia
> or = 3 sites of LN enlargement.
C- Anaemia and /or thrombocytopenia regardless of the number of areas of lymphoid enlargement.

Management

This depends on the clinical stage of the disease.
1. Stage A

- No specific TREATMENT is required
- Life expectancy is normal in older patients
- The patient should be reassured.

2. Stage B

- Chemotherapy with chlorambacil 5mg OD

- ± Local radiotherapy to LN if causing discomfort.

3. Stage C
   - Anaemia-transfusion with red cell concentrate
   - BM failure-
     - If present initially should be treated with prednisolone 40mg daily for 2-4 weeks
     - Tabs oxymethalone 50mg bd
   - A degree of BM recovery is usually achieved.

Other TREATMENT modalities

1. Infection management -Gram negative
   -Gram positive
   -Anaerobes.
2. Splenectomy
   - -In Autoimmune haemolylic anaemia
   - -Gross splenic enlargement

Prognosis

- Median survival is ~ 6 years
- ~50% of patient will die of infection.
- CLL-rarely transforms to an aggressive high grade lymphoma called RITCHERS TRANSFORMATION.

MALIGNANT LYMPHOMA

- Neoplastic transformation of cell reciting in lymphoid tissue.
- The two major variants of Malignant lymphoma are:
    1) **Hodgkin's lymphoma-B cells**
    2) **Non Hodgkin's lymphoma – B and T cells**

- Although these two variants both infiltrate the RES organs, they biologically tend to be clinically distinct.
- The majority are of B-cell origin.
- NHL is divided into:-
    1) Low grade
    2) High grade } This is depending on basis of their proliferation rate.

- Low grade tumours divide slowly and may be present for months before their diagnosis.

1. HODGKIN'S LYMPHOMAS

- The Histological Hallmark of Hodgkin's disease is the presence of **Reed Sternberg cells**, which are large Malignant lymphoid cells of B cell origin.
- They are often present in small numbers but surrounded by a large number of reactive T-cells, plasma cells, and Eosinophils.
- Four types are recognized from the appearance of R-S cells and the surrounding reactive cells.

-p/Pathological classification of Hodgkin's Lymphoma is as follows:-

(i) Lymphocyte predominant
(ii) Nodular sclerosis
(iii) Mixed cellularity
(iv) Lymphocyte depleted.

Clinical features

(i) Lymphadenopathy

-Painless, discrete, and rubbery

-Mainly affects the following areas;

- Cervical
- Supraclavicular
- Mediastinal

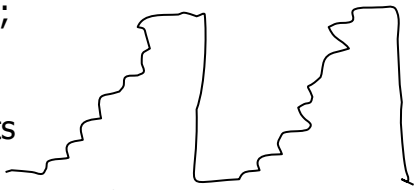
Pressure effects due to LN enlargement may occur. These effects include;

- Dysphagia

- Dyspnoea
- Venous obstruction e.g. Superior Vena cava Syndrome – presents initially as bilateral engorgement of the jugular veins and later as oedema affecting the face, neck and arms.
- Jaundice e.g. Porta Hepatis obstruction
- Paraplegia – due to cord compression

(ii) Hepatosplenomegaly
(iii) Constitutional symptoms;

- Progressive weakness
- Weight loss
- Drenching night sweats
- Fever; Pel-Stein Fever



(Bouts of pyrexia upto 39^0 C for several days alternating with apyrexial period.)

Investigations

1. FHG
- This is Normal however NNA may be present +/- Lymphopenia. Together is a bad prognostic factor.
- High ESR

1. Renal function Tests - U/E + Creatinine urinalysis
2. LFT
   - This may be abnormal in the absence of a disease or reflect hepatic infiltration.
   - An Obstructive may be caused by nodes at the porta Hepatis.
   - Useful in monitoring chemotherapy.
3. LDH
   - Levels are considered to be an adverse prognostic factor.
4. CXR
   - May show mediastinal masses
5. CT scan-chest and abdomen useful in clinical staging of the disease.
6. LN Biopsy-Histological Diagnosis. It may be undertaken surgically or by percuteneous needle biopsy under radiographic guidance.

Clinical staging of Hodgkin's disease (Ann Abbor classification)

Stage 1
- This is involvement of a single LN region (I) or Extra lymphatic sites (I_E).

Stage II
- Involvement of two or more LN region (II) or an extra lymphatic site and LN regions on the same side of the diaphragm. (II_E).

Stage III
- Involvement of LN regions on both sites of the diaphragm with (II_E) or without (III) extra lymphatic involvement of the spleen (III_S) or both (III_{SE}).

Stage IV

- -Diffuse involvement of one or more extra lymphatic tissues e.g. liver.

-Each stage is divided into A or B categories according to whether they have systemic symptoms or not.

A-No systemic symptoms
B-systemic symptoms - Weight loss, Drenching sweat, Un explained fever beyond 38^0.

- The lymphatic structures are defined as the LN, spleen, liver, Waldeyer's ring, appendix, thymus, and payer's patches.

Differential Diagnosis.

1. Tuberculous lymphadenopathy
2. Chronic pyogenic lymphadenitis
3. Chronic lymphocytic leukemia
4. Infectious mononucleosis
5. Secondary syphilis
6. Sarcoidosis
7. Generalised lymphadenopathy (PGL).

TREATMENT

Two main methods of treatment;

1. Radiotherapy
2. Chemotherapy
3. or a combination of the two.

Indications for Radiotherapy

- Stage I disease
- Stage IIA disease with less than or = 3 areas involved.
- After chemotherapy to sites where there was originally bulk disease.
- Lesions causing serious pressure problems.

Indications for chemotheraphy

- All patients with BM symptoms
- Stage II with more than 3 sites involved
- Stage III and IV disease

Chemotherapy drugs include

- Chlorambucil 6 mg/m^2 (upto 10mg total) days 1-14 orally.
- Vinblastine 6 mg/m^2 (up to 10 mg total) days 1 and 8 i.v.
- Procarbazine 100mg/m^2 days 1-14 orally.
- Prednisolone 40 mg/m^2 days 1-14 0rally.

80% Hodgkins lymphoma patient responds to chemotheraphy.
~90% of patients with stage I A disease are cured by radiotheraphy alone.

2. NON–HODGKIN'S LYMPHOMA

- Represents a monoclonal proliferation of lymphoid cells and may be of B-cells (70%) or T-cells (30%).
- The difficulties in establishing a reproducible and clinically useful Histological classification of NHL are reflected by large classification to date, than Hodgkin's Lymphoma.
- Clinically the most important factor is Grade; which is a reflection of proliferation rate.
- The same staging is used for Hodgkin's and non Hodgkin's.
- High grade has high proliferation rate and potentially treatable and is fatal if left untreated.
- Low grade NHL has low proliferation rates, may be asymptomatic for months before presentation, but is curable by conventional therapy.

Clinical Features

Compared to HL, NHL is often widely disseminated at presentation.

Clinical presentation;

I) LN compression symptoms
II) Weight loss, fever, and pruritus
III) Hepatosplenomegaly
IV) Extra nodal disease i.e. BM involvement, gut, thyroid, skin, testes, brain, bone.

Investigation

Same as for HL plus the following;

(i) Routine bone marrow aspirate
(ii) Immunophenotyping of surface antigens to distinguish B and T cell tumour.
(iii) Serum uric acid levels
-These are markedly elevated in every aggressive High grade NHL.
(iv) HIV screening
-This is a known risk factor of non Hodgkin's disease.

TREATMENT

(1) Low grade Non Hodgkin's lymphoma

(i) Radiotherapy in stage I disease.
(ii) Chemotherapy- chlorambucil is mainly used
–only to improve the quality of life, otherwise there is no cure.
(iii) Monoclonal antibody Therapy
-Humanized monoclonal antibody to target surface Antigen on tumour cells and deliver cytotoxic drugs or radiotherapy or induce tumour cell apoptosis directly. Such antibodies targeted to low grade lymphoma cells have been shown to induce durable clinical response in up to 60% of patients.
(iv)Transplantation

-Autologous stem cell transplantation are in progress.
-However no conclusive results have been made so far.

(2) High grade NHL

(i) Chemotherapy

- CHOP regime remains the mainstay of therapy i.e. cyclophosphamide (C) 500mg/m^2, +or- Doxorubucin (Adriamycin) (H) 50mg/m^2, Vincristine (Oncovin) (O) 1mg/m^2, prednisolone (P) 1-2mg/kg.
- Given in mg/SA
- Given in courses

Start 3 weeks interval for 6 courses.

(ii) Radiotherapy

This is indicated in:-

-A few stage I patients without bulgy disease may be suitable for radiotherapy.
-Residual localized site of bulky disease after chemotherapy.
-Spinal cord and other compressing symptoms.

(iii) Transplantation

-Autologous stem cell transplant have been tried, though still not monoclonal Antibody therapy.
-This is used in combination with CHOP regime to enhance results.

DDX of massive splenomegaly

1. Tropical Splenomegaly Syndrome (Chronic Malaria) (Hyperreactive malarial splenomegaly).
2. Kalaazar (visceral Leishmaniasis).
3. Chronic Myeloid Leukaemia
4. Sickle cell anaemia
5. Infiltrative conditions.