Haematology-1

Community Health Nursing (Kenya Medical Training College)

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HEMATOLOGY 2

Hours 12
Lecturer: B Onyango

Course objectives

By the end of the lesson the students will be able to:

- Define the term haematology
- Describe blood and its components
- Provide care to patients with anaemia using nursing process
- Manage patients with blood cancers using the nursing process
- Manage patients with infections related to blood such as agranulocytosis and hypoprothrombinaemia
- Manage patients with infection related to haemorrhagic conditions such as thrombocytopenia purpura, disseminated intravascular coagulopathy, sickle cell disease using nursing process

Course outline

Anaemia	02hrs
Blood cancer	04hrs
Infection related conditions	03hrs
Haemorrhagic conditions	03hrs

Teaching methods

Group discussions, lectures, demonstrations, role plays, flip charts, procedure mannuals and LCD projector and laptop, chalk and chalk board.

Definition;

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

Blood consists of:

Liquid component and cellular component.

- **Liquid component** consist of **plasma** which is 91%water mostly containing dissolved salts and proteins mainly albumin others are antibodies (immunoglobulins) and clotting factors (soluble fibrinogen), hormones, antibodies, electrolytes, fats, sugars, minerals and vitamins.

FUNCTIONS

- ✓ Transport blood cells, hormones, waste products, antibodies
- ✓ Provides reservoir of water for the body
- ✓ Prevents blood vessels from collapsing and clogging
- ✓ Helps maintain blood pressure and circulation throughout the body
- ✓ The antibodies contained in the plasma actively defend the body against foreign substances such as bacteria, viruses, fungi etc
- ✓ Clotting proteins control bleeding
- ✓ Plasma cools and warms the body.

❖ **Cellular component** of blood are the RBC, WBC and platelets which are all suspended in the plasma.

1. RBC (Erythrocytes) the most numerous of the three cellular components. Makes up almost half of the blood volume. They are filled with hemoglobin which enables them to carry oxygen from the lung to body tissues and then carry carbon dioxide from the tissues to the lungs.

2. WBC (Leukocytes) they are fewer in no. compared to the RBC to the ratio of about 1:660 (WBC: RBC). There are 5 main types:

- Neutrophils: (granulocytes) they contain enzyme-filled granules. Are the most prevalent white blood cell type. They protect the body against bacterial and fungal infections and ingest foreign debris. Two types are band (immature) and segmented (mature).
- Lymphocytes: T- lymphocytes which help protect against viral infections and can detect and destroy some cancer cells. B-lymphocytes which develop into cells that produce antibodies.
- Monocytes: ingest dead or damaged cells and provide immunologic defenses to many infective organisms.
- Eosinophils: kill parasites, destroy cancer cells and are involved in allergic responses.
- Basophils: also participate in allergic responses.

3. Platelets (thrombocytes) are cell-like particles smaller than red or white blood cells. They help in stopping bleeding. They gather at a bleeding where they are activated. Once activated they become sticky and clamp together to form a plug that helps seal the blood vessel and stop bleeding. They release substance that helps promote clotting.

SERUM.

This is what remains after the formation of blood cells. This is plasma without the clotting factors.

HAEMATOPOIESIS. This is the process of blood cell production. (haemopoiesis). The formation and maturation of blood cells.

In early foetal life, blood is synthesized in several tissues such as the liver, spleen, thymus and the lymph nodes. Later, before birth, formation of blood starts in the bone marrow. At birth, blood formation takes place in every bone. In adult life, *RBC* production is confined to the end of long bones (red bone marrow) and also to the flat bones e.g. Ribs, iliac bones, sternum, vertebrae and some white blood cells are produced in lymphatic tissues (lymph nodes and spleen and the thymus)

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

(A) RBC (Erythrocytes)

The process of formation of the RBC **- ERYTHROPOESIS**

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. (Erythrocyte)

The red blood cell has no nucleus. Its shape is a biconcave disc. They contain the protein hemoglobin which gives them the ability to carry oxygen.

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*. Hormone produced from the kidney.
2. Iron. Helps in the production of hemoglobin
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.*

Low oxygen levels in the body increase the RBC production by increasing the formation of glycoprotein, erythropoietin by the kidneys, erythropoietin stimulates the RBM to produce more RBC. When oxygen levels in the blood decreases the production of erythropoietin increases which increase RBC production. The increased NO. of RBC leads to increased oxygen transportation and delivery of oxygen to the tissues. Later the erythropoietin production reduces thus production reduces and vice versa. Life span 120 days then they die.

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 (granulocytes)

- Neutrophils - (PMNL- polymorphonuclear neutrophils)
- Eosinophils
- Basophils

  i.e. have granules in their cytoplasm.

2. Non – granulocytes (agranulocytes)

No granules in the cytoplasm

- Lymphocytes
- Monocyte

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.

Non neoplastic disorders of the WBCs

1. **Leukocytosis** is the increase in the number of WBCs
2. **Leukopenia** is the reduced number of WBCs
3. **Neutropenia** is the reduced No. of circulating neutrophils
4. **Agranuocytosis is** the absence of neutrophils

Neutrophils.

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

Causes of neutrophilia leukocytosis in the body include:

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

These causes include:

1. Acute 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

Causes of neutropenia: low no. of neutrophils

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

Causes include:

1. Infections
   i. viral
   ii. Bacterial salmonella
   iii. Protozoal malaria.
2. Radiation therapy
3. Autoimmune
   i. Connective tissue diseases
4. Alcohol
5. Congenital disorders
   i. Kostmann's syndrome: an inherited condition in infants where they present with no neutrophills shortly after birth.
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, clozapine(antipsychotic agent)

Eosinophils

The function of eosinophils is to detoxify foreign proteins and phagocytosis. They are important in allergic reactions and parasitic infections. They release chemicals that reduce inflamation and attack certain warm parasites.

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. Neoplasm e.g. lymphomas, solid tumours, non-hodgkin lymphomas
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.
- Releases histamine which promotes inflammation and Heparin (an anticoagulant which prevents blood clotting.
- 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 Bone Marrow.
- 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
    -

❖ Lymphocytes produce antibodies and other chemicals responsible for destroying microorganisms. They contribute to allergic reactions, graft rejections, tumor control and regulation of immune system.

Causes of lymphocytosis

This is related to disorders associated with chronic immunologic stimulation.

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 Bone Marrow.

They divide producing monoblasts which develop into monocytes.

These cells migrate into tissues where they develop into macrophages.

Their function is phagocytosis of dead WBC, RBC, microbes and cell fragments

Macrophages are usually found in the blood stream.

Causes of Monocytosis

1. Chronic infection
   e.g. bacterial tuberculosis, bacterial endocardiatis

2. Inflammation
   -acute hypersensitivity
   -Ucerative colitis
   -Crohns disease
3. Malignancy
   - Solid tumours

(C) PLATELETS (Thrombocytes)

They are derived from megakaryocytes in the BM through the process of megakaryocytopoiesis. These cells are necessary for clotting of blood.

They are discoid in shape. Thrombopoetin is a hormone produced by the liver that increases the rate of thrombocytes production.

The cell surface invalidates 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 Will brand 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 sub endothelium 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.

Some globulins are clotting factors which are necessary for the formation of blood clots. Fibrinogen is a clotting factor that constitutes 4% of plasma proteins. Activation of clotting factors result in the conversion of fibrinogen into fibrin, a threadlike protein that forms a blood clot.

Platelets are important for the formation of platelets plug which releases chemicals necessary for blood clotting. They work by

1. Formation of platelets plug which seal the holes in small vessels
2. Forms a clot which helps seal off larger wounds in the vessels.

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

Events of haemostasis.

_Haemostasis: is a sequence of responses that stops bleeding. Damage of the vasculature quickly leads to massive bruising and, if unrepaired, leads to extreme blood loss and *consequently organ failure. Haemostasis, the physiological processes that stop bleeding, is* critical for human health. The coagulation system is remarkably complex in both structure and function. Many proteins are involved, produced by different cell types of the body, with both inactive and active forms regulated in a fine balance.

The coagulation system provides for immediate activation when there is blood loss that needs to be stemmed but also confines its activity to the site of blood loss. The haemostatic system includes blood platelets, endothelial cells, and plasma coagulation factors, which work together to rapidly form a haemostatic plug in an injured blood vessel.

Whenever a vessel is severed or ruptured, haemostasis is achieved by several mechanisms: (1) vascular constriction, (2) formation of a platelet plug, (3) formation of a blood clot as a result of blood coagulation, and (4) eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently.

1. ***Vascular constriction.***

Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall itself causes the smooth muscle in the wall to contract; this instantaneously reduces the flow of blood from the ruptured vessel. The

contraction results from local myogenic spasm, local autacoid factors from the traumatized tissues and blood platelets, and lastly nervous reflexes.

2. Formation of platelet plug.

If the cut in the blood vessel is very small—indeed, many very small vascular holes do develop throughout the body each day—the cut is often sealed by a *platelet plug,* rather than by a blood clot.

Platelet repair of vascular openings is based on several important functions of the platelet itself. When platelets come in contact with a damaged vascular surface, especially with collagen fibers in the vascular wall, the platelets themselves immediately change their own characteristics drastically. They begin to swell; they assume irregular forms with numerous irradiating pseudopods protruding from their surfaces; their contractile proteins contract forcefully and cause the release of granules that contain multiple active; they become sticky so that they adhere to collagen in the tissues and to a protein called *von Willebrand factor* that leaks into the traumatized tissue from the plasma; they secrete large quantities of ADP; and their enzymes form *thromboxane A2*. The ADP and thromboxane in turn act on nearby platelets to activate them as well, and the stickiness of these additional platelets causes them to adhere to the original activated platelets. Therefore, at the site of any opening in a blood vessel wall, the damaged vascular wall activates successively increasing numbers of platelets that themselves attract more and more additional platelets, thus forming a *platelet plug.* This is at first a loose plug, but it is usually successful in blocking blood loss if the vascular opening is small. Then, during the subsequent process of blood coagulation, *fibrin threads* form. These attach tightly to the platelets, thus constructing an unyielding plug.

3. Clot formation.

The clot is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, and plasma. The fibrin fibers also adhere to damaged surfaces of blood vessels; therefore, the blood clot becomes adherent to any vascular opening and thereby prevents further blood loss.

4. Clot retraction.

Within a few minutes after a clot is formed, it begins to contract and usually expresses most of the fluid from the clot within 20 to 60 minutes. The fluid expressed is called *serum* because all its fibrinogen and most of the other clotting factors have been removed; in this way, serum differs from plasma. Serum cannot clot because it lacks these factors.

Platelets are necessary for clot retraction to occur. Therefore, failure of clot retraction is an indication that the number of platelets in the circulating blood might be low. Furthermore, platelets entrapped in the clot continue to release pro-coagulants substances, one of the most important of which is fibrin-stabilizing factor, which causes more and more cross-linking bonds between adjacent fibrin fibers. As the clot retracts, the edges of the broken blood vessel are pulled together, thus contributing still further to the ultimate state of haemostasis.

Aspirin and other NSAIDs irreversibly inhibit platelet cyclo-oxygenase and impair platelet function. They inhibit vasoconstriction and platelet aggregation by blocking the synthesis of thromboxane A2.

DISORDERS OF PLATELETS

Causes of thrombocytopenia. Reduced platelet count

Thrombocytopenia (less than 150,000)this is a deficiency of platelets which helps in blood clotting.

Low platelet count. Major causes are due to low production or increased breakdown of platelets.

1. Bone marrow disorders
    - Hypoplasia

    -Idiopathic
    -Drug induced – cytotoxic, antimetabolites, thiazides
    - Infiltration with cancer cells such leukemia or lymphoma which damages bone marrow
      -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(systemic lupus erythematosus)
3. Increased Use or destruction of platelets
   - Idiopathic thrombocytopenic purpura
   - Disseminated intravascular coagulation.
   - HIV infection
   - Purpura after blood transfutions
   - Drugs such as heparin, sulfa-based drugs
   - Lymphomas
   - Severe infections with blood poisoning
   - Systemic lupus erythematosus
4. Platelets become diluted
   - Massive blood replacement or exchange transfusion
   - Cardiopulmonary bypass surgery.
5. Hereditary disorders
6. Drug therapy (chemotherapy) or radiation therapy

Signs and symptoms

Bruising and bleeding, nose bleeding and petechial

Diagnosis:

- Platelet count,
- Prothrombin Time (PT),
- activated Partial Thromboplastin Time (aPTT)

Treatment

Is based on the cause

Administration of steroids

Platelets replacement/transfusion

Plasmaphoresis

splenectomy

Thrombocythemia –this is a disorder in which an excess of platelets is produced leading to abnormal blood clotting.

Causes of raised platelet count higher than 500,000 per microlitre

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
3. Rheumatoid arthritis.

Symptoms include: tingling sensations in the hands and feet, cold fingertips, headaches, weakness and dizziness, mild bleeding, spleen and liver may enlarge.

PANCYTOPENIA

This is a condition which occurs when one has low counts of all the three types of cells, white blood cells, red blood cells and platelets. It's normally due to a problem with the bone marrow that produces the blood cells.

Causes

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 ie DVT
2. Calf hematoma e.g. secondary to trauma
3. Skin inflammation e.g. cellulitis
4. Bakers cyst usually as a result of knee- joint conditions such as arthriris or torn cartillage that cause the knee to produce too much lubricating fluid
5. Pelvic disease obstructing venous or lymphatic return

6. Congestive cardiac failure / cor pulmonale – alteration in the structure and function of the right ventricle of the heart caused by a primary disorder of the respiratory system.

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 below the normal expected range, taking into account both age and sex. In anaemia there are too few erythrocytes or insufficient volume of erythrocytes in the blood or reduction of oxygen carrying capacity of blood. Anaemia is not a disease but an indication of some disease process or alteration in the body function.

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 sudden onset of signs and symptoms.

Anaemia developing slowly over a prolonged period may be asymptomatic.

CLASSIFICATION OF ANAEMIA AETIOLOGICALY

1.)Blood loss/excessive bleeding

- May be acute – onset is sudden ie accidents, surgery, child birth, ruptured blood vessels.

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

2.) Anaemia due to inadequate/decreased 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. (Iron deficiency anemia, Vit B12 deficiency, folic acid deficiency)
ii) Chronic inflammatory diseases e.g. infections like TB, non infectious diseases e.g. rheumatoid arthritis, systemic lupus erythematosus.
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 myelomas, /metastasis of a malignant disease in BM.
c) Toxic effects resulting from chronic infections, malignancies, uremia 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 these conditions there is no stability of RBC, so they are easily haemolysed.
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.

Autoimmune reactions against red blood cell

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

Acute blood loss

Chronic infections.

Any chronic debilitating disease e.g. malignancies.

2) Macrocytic normo-chromic anaemia.

RBC are too large but contain normal amount of Hb (normal in colour)

Blood for full haemoglobin- MCV is increased.

Causes

Deficiency of vitamin B12 and folic acid deficiency.

3) Microcytic hypochromic anaemia.

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

Blood for full haemogram.

- *MCV* reduced.
- *MCH/MCHC* reduced.

Causes

- iron deficiency

GENERAL CLINICAL SYMPTOMS OF ANAEMIA

1. Fatigue.
2. Headache.
3. Dizziness.
4. Fainting.
5. Shortness of breath.
6. Palpitations
7. Thirst and sweating
8. Angina of effort.
9. Interminent cluadiaction.
10. Paleness
11. May or may not have Oedema.
12. Tachycardia.

13. Systolic flow murmurs.
14. 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.(taken from the posterior iliac crest)

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 Hyperfibrinogenemia

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

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

i) Ant-thrombin 111

ii) Protein C

iii) Protein S

iv) Prothrombin G20210A

v) Factor V Leiden

vi) Thrombin /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. This presents with normal RBC count and normal hematocrit but the hemoglobin level will be low. Normally the body recycles iron, when the red blood cells die the iron in them is returned to the bone marrow to be used again in new red blood cells, The body losses large amount of iron only when red blood cells are lost through bleeding.

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 transferrin bound iron becomes attached to the erythroblast & becomes ready for use in synthesis of RBCs
- Iron is stored in body tissue mainly in the liver in amounts ranging from 1-1.5 g. in the form of ***ferritin*** 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/inadequate dietary 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.
5) hemolysis

Clinical features

✓ General symptoms of anaemia.

O/E

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

   Other features in Gut include;

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

4)Nails;

- Brittle
- Thinning
- Restless
- Koilonychias – 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/CBC
iii) Take stool for o/c
iv) Stool for occult blood.
Other investigations depend on clinical History & investigations e.g. barium meal.
Iron levels can be measured in the blood. Levels of iron of iron and transferrin are measured.
Bone marrow examination
Endoscopy and colonoscopy

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

- Thalassemia.
- 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 are fragile and easily destroyed.

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

Cobalamin/ pernicious anemia

- 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.

Vitamin B_{12} serves as a cofactor for two important reactions in humans:

i. It is essential for DNA synthesis and nuclear maturation, which in turn leads to normal red cell maturation and division.

ii. It is involved in a reaction that prevents abnormal fatty acids from being incorporated into neuronal lipids. This abnormality may predispose to myelin breakdown and produce some of the neurologic complications of vitamin B_{12} deficiency.

iii. vitamin B_{12} deficiency results from inadequate gastric production or defective function of intrinsic factor. Intrinsic factor plays a critical role in the absorption of vitamin B_{12}, a complex multistep process that proceeds as follows:

- **<u>Causes of Vitamin *B 12* deficiency</u>**

1) Low dietary intake e.g. strict vegetarians/ nutritional deficiency

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 loss of IF secretory cells.
   (c) chronic atrophic gastritis

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

<u>Pathology</u>

There is defective *DNA* synthesis.

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

Destruction of the gastric mucosa

<u>Clinical Features</u>

1) General s/s of anaemia.
2) Glossitis - sore 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 and confusion.

<u>Investigations</u>

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 cyanocobalamin 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, mush rooms, red beans, and fresh fruits.
- 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. colic, crohns disease, 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 (show megaloblasts)
- Bm aspirate
- Serum for folic acid -2-20mg/l.

Treatment

- Tabs folic acid 5mg
- Encourage the patient to take plenty of foods reach in folic acid like green leafy vegetables.

Prevention

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

Haemolytic anaemia

Red blood cells have a lifespan of 120 days.

In hemolytic state lifespan shortens causing anaemia.

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

If the BM cannot 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. The rate of destruction exceeds production.

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. hereditary spherocytosis, hereditary elliptocytosis.

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 (autoimmune hemolytic anaemia)

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. These may break up normal RBCs

iii) Miscellaneous causes e.g.

a) Infections like malaria.

b) Drugs & chemicals.

c) Hypersplenism. Enlarged spleen traps and destroy RBCs

Clinical features of HA

a) General symptoms of anaemia.
b) Jaundice.
c) Dark urine
d) Enlarged spleen.
e) Abdominal pains

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 an inherited condition characterized by sickle-shaped red blood cells and chronic hemolysis. 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) Acute 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;

Therefore it will be characteristic i.e.

A) Thrombotic crisis (painful 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) Splenomegaly

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 aimed at treatment of symptoms, prevention of sickling episodes and treatment of complications.

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 given prophylactically to prevent septicaemia.
- Hydroxyurea- Inhibition of DNA synthesis thus reduce pain in crisis and reduce anaemia.
- Immunization – H influenza, Hep B
- 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, DNA analysis in the fetal cells. (Amniocentesis.)
- Parental education can help prevent 90% of deaths from sequestration crisis.

Acute pain syndrome

Acute pain syndrome

Acute chest syndrome

Cholecystitis

Hand and foot syndrome

Priapism

Right upper hand quadrant syndrome

Splenic sequestration

EMERGENCY MANAGEMENT OF SICKLE CELL CRISIS

This is focused on support of airway,breathing,circulation,pain control and surveillance of complications.

1. Oxygenation ;especially for patients with hypoxia and SPO2 of <92%,supplement oxygen atleast at 2l/min.

2. Breathing;ensure the patient is breathing well by assessing the respiratory rates accurately and incase of respiratory failure,intubate

3.Hydration;with I.V.fluids like 0.9% normal saline and incase of difficulty in i.v access,oral hydration of the patient if can take well orally at 60mls/kg/24hrs.Ensure close input output monitoring.

4. Pain relief;within 30mins of entering the hospital.NSAIDS for mild pains and Morphine as the 1st-line analgesic for severe pain at a dose of 0.1mg/kg i.v

5. RBC transfusion in patients with ACS and hemolytic crisis

6. Antibiotics such as ceftriaxone 1g/2g i.v once daily for 5days incase of infection or fevers.

Chronic problems associated with SCD

1. Swollen joints, oedema occurs where clots form
2. Exertional dyspnoea, due to increased RBC hemolysis thus reduced oxygen
3. Leg ulcers, clots occlude circulation thus there is irritation of tissues
4. Fatigue, hemolyses of RBCs leads to decreased oxygen supply.

Complications of SCD

1. Chronic obstructive pulmonary disease
2. Heart failure
3. Retinopathy
4. Nephropathy
5. Major organ infaction.

DDX

i) Rheumatoid arthritis.
ii) Osteomyelitis.
iii) Rheumatic fever.
iv) Leukemia – the patient has anaemia, bone pain, & bleeding tendencies.

NURSING DIAGNOSIS

1.Impaired gas exchange Related To Decreased oxygen carrying capacity of blood As Evidenced By dyspnea, cyanosis spo2 of less than 98%

2.Ineffective tissue perfusion Related To Vaso-occlusive nature of the sickling As Evidenced By delayed capillary refill and diminished peripheral pulses.

3.Acute Pain Related To Occlusion As Evidenced By Facial grimancing or more generalizedpain and joint swellings

4.Knowledge deficit Related To lack of exposure As Evidenced By patient's request for information.

5.Risk for fluid volume deficit Related To increased fluid needs e.g fevers and inflammatory processes.

Thalassemia

Definition This is a condition in which there is a deficiency in the synthesis of globin chains of hemoglobin, Thus accumulation of abnormal globin chain within the red cells leads to its early destruction. It's an inherited disorder of haemoglobin synthesis leading to decrease synthesis of either a or b globulin chains.

Beta-Thalassemia are caused by deficient synthesis of the B chains and the a-Thelassaemia is deficient synthesis of the alpha chain.

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

Factors contributing to the anemia that occurs in thalassemia are:

i. low intracellular hemoglobin due to the decreased synthesis of the affected chain
ii. Continued production and accumulation of the unaffected globin chain.

The reduced hemoglobin synthesis results in a hypochromic, microcytic anemia, whereas the accumulation of the unaffected chain interferes with normal red cell maturation and contributes to membrane changes that lead to hemolysis and anemia.

Signs and symptoms

In thalassemia major the clinical manifestation is as shown:

i. At birth—no symptoms
ii. Infants ages 3 to 6 months—pallor; yellow skin and sclera
iii. Infants ages 6 to 12 months—severe anemia, bone abnormalities, failure to thrive, and life threatening complications
iv. Splenomegaly or hepatomegaly, with abdominal enlargement; frequent infections; bleeding tendencies (especially nose bleeds); anorexia
v. Small body, large head (characteristic features); possible mental retardation
vi. Facial features similar to Down syndrome in infants, due to thickened bone at the base of the nose from bone marrow hyperactivity

1. Beta Thalassaemia

The deficient is in the b chains of the hemoglobin. Also known as thalassemia major or cooleys disease. Its characterized by severe anemia, marked hemolysis and ineffective erythropoiesis. With regular blood transfusion therapy, growth and development through childhood is facilitated.

Clinical features *(children commonly affected)*

At birth there are no symptoms but appear later. Infants of age 3-6months presents with pallor, yellow skin and sclera.

i) Growth failure with mental retardation.
ii) Severe anaemia.
iii) Bone abnormalities
iv) Bleeding tendencies
v) Frequent infections
vi) Anorexia
vii) Abdominal enlargement
viii) Facial features similar to down syndrome in infants due to thickened bones at the base of the nose from bone marrow hyper activity.

ix) Intermittent infection

x) A bossing of head

xi) Hepatomegaly and splenomegaly.

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

xiii) Diagnosis's is confirmed by the electrophoresis.

Investigations

1. CBC and PBF

-Hb ranges from 2-8g/dl in severe form

-MCV and MCH are low

-WBCs elevated in Beta thalassaemia

2. HB electrophoresis

3. Iron studies ie serum ferritin level.

4. imaging sturdies

- CXR – cardiac size and shape

- MRI

- CT scan

-Skeleton survey- widening of the skull bones

4. Liver biopsy

5. Bone marrow aspiration

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

Rx – Thalassaemia major

Folic acid

Regular blood transfusion

Vitamin E supplement 1. iu/kg/day po

Ascorbic acid 3mg/kg/ day po

Vaccination with hemophillus and influenza

Pain management- acetaminophen 10-15mg

Counseling on the condition.

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) Edematous

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 is contraindicated
  Iron therapy is forbidden
  Give Desferrioxamine therapy
- Iron overload is a major complication of β-thalassemia. Excess iron stores, which accumulate from increased dietary absorption and repeated transfusions, are deposited in the myocardium, liver, and endocrine organs and induce organ damage. Regular blood transfusions to maintain hemoglobin levels at 9 to 10 g/dL improve growth and development and prevent most of the complications, and iron chelation therapy can reduce the iron overload and extend life expectancy

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 coombs test.

Direct coombs test

Coombs reagent 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 hemostasis (cessation of bleeding). Hemostasis is achieved by the following processes.

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

b) Clumping of platelets – platelets plug formation or clot. 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. The chemical clotting 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.

<u>Fibrinolysis/ clot retraction</u>

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

Bleeding disorder or impairment of blood coagulation can result from defects in any of the following factors that contribute to homeostasis:

1. platelets
2. coagulation factors
3. vascular integrity

the number of circulating platelets can be reduced (thrombocytopenia) or the platelet function can be impaired (thrombocytopathia). The impairement of blood coagulation can result from deficiencies of one or more of the known blood clotting factors. Deficiencies can also arise from defective synthesis ie in liver disease or Vit K deficiency, inherited diseases such as(hemophiliaor von-willebrand disease) or increased consumption of the clotting factors ie in DIC.

Investigation of bleeding disorders

Full blood count and film;

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

Treatment

Desmopressin acetate(DDAVP)

Replacement of factor viii and vwf

1. **Hemophilia A (factor viii deficiency)**

Definition.

This is a hereditary disorder of blood coagulation characterized by a live long tendency to excessive hemorrhage & a greatly prolonged coagulation time. It's inherited as an x linked trait (x linked recessive character). Also known as classic hemophilia

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.
- Bleeding from the soft tissues, GIT
- Spontaneous bleeding into the joints mainly the knee, elbow, ankle, shoulder 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

-Intensive treatment is required.

-Fresh blood transfusion – and possibly refer.

-Fresh frozen plasma

-factor viii concentrates.

Factor V111 replacement therapy

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.

2.Vitamin *K* deficiency

This vitamin is necessary for synthesis of factors ii, vii, ix, & x. the deficiency of vit k is common in malnourished patients and some antibiotics also decrease the intestinal flora that produce vit k.

Causes

a) Inadequate body stores e.g. in malnutrition, hemorrhage of the new born.

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 can't be absorbed into 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**.**

2. **<u>Purpuras</u>**

Definition

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

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

Thrombocytopenia – low platelet count.

This can be due to:

1. Decreased production of platelets such as in hematologic malignancy- in acute leukemia
2. Increased destruction of platelets ie in idiopathic thrombocytopenic purpura
3. Increased consumption of platelets ie in DIC

Types

a) Idiopathic (immune) thrombocytopenic purpura (*ITP*)

b) Secondary thrombocytopenic purpura (*STP*)

a. <u>ITP</u>

This is a rare auto immune disorder whereby the body forms antibodies against its own platelets. The platelets are coated with Antibodies and are destroyed by spleen at high rates thus shorten their life span. It affects all age groups but most common in children and young women.

Clinical features

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

O/E

- Evidence of severe bleeding in nose, gums
- Splenomegaly may or may not be there.
- Blood for full haemogram shows low platelet count.

Treatment

Aim is to:

-To lower level of antibodies that the body is developing.

-To remove Antibody sensitized cell.

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

b) Spleenectomy may or may not be done.

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

b) <u>STP</u>

- Present 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.

<u>C/F</u>

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.

4**. Von willebrand disease**

This in an hereditary bleeding disorder caused by the deficiency of or defect of vwf. It results in reduced platelet adhesions.vwf is a cofactor for the pro-coagulant factor viii, a defect in vwf will result in both platelet dysfunction and coagulopathy. There is mild to severe form. Because the vwf carries factor viii Its deficiency may also be caused by reduced levels of factor viii, resulting in defective clot formation.

Signs and symptoms

Bruising

Bleeding from the nose, mouth and GIT

Excessive menstrual flow

Treatment

Desmopressin acetate DDAvP)

Replacement of factor viii and vwf

4. **Disseminated intravascular coagulopathy**

This is a disorder in the haemostatic sequence characterized by wide spread intravascular coagulation and bleeding, its not a primary disease but occurs as a complication of a wide variety of conditions. It begins with massive activation of coagulation sequence as a result of unregulated generation of thrombin, resulting in systemic formation of fibrin, the levels of all the major anticoagulants are reduced, the generation of micro thrombin results in vessel occlusion and tissue ischemia, multiple organ failure may come in. clot

formation consumes all the available coagulation proteins and platelets and severe bleeding occurs.t
The normal hemostatic mechanism are altered so that a massive amount of tiny clots in the micro circulation. The platelets and clotting factors are consumed to form the micro thrombin thus coagulation fails, thus excessive clotting leads to excessive bleeding.

Clinical features

Bleeding from the mucous membranes, venipuncture sites, GIT and urinary tract

Risk factors

- Sepsis
- Obstetric complications
- Acute hemolysis eg transfusion reaction
- Trauma
- Shock
- Cancer
- Allergic reaction

NEOPLASTIC PROLIFERATION OF WBCS

BLOOD CANCERS

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.
It's a malignant disease/cancer of the blood cells characterized by unregulated proliferation of one cell type: the WBCs. The malignant cells are derived from precursor myeloid or lymphoid tissue cells.
The WBCs develop from stem cells in the bone marrow. Leukemia results when the process of maturation from stem cells to white blood cells go awry and produces a cancerous change, the change often involve a rearrangement of pieces of chromosomes: the cells complex genetic material. Because the chromosomal rearrangement disturbs the normal control of cell division the

affected cell multiply without restraint becoming cancerous. They ultimately occupy the bone marrow, replacing the cells that produce normal blood cells. Thus there is;

- Failure of maturation of WBC.
- 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%.

The course of the disease may vary from a few days or weeks to many years, depending on the type.
Leukemia is the most common cause of cancer in children and adolescents.

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 leukemia 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 hematological malignancy

Classification

Commonly classified according to their predominant cell type ie lymphatic or myelocytic and whether the condition is acute or chronic.

Two broad classes:

A. Acute in which the onset is insidious. It's more aggressive and mostly involves the immature cells: the blasts.

B. Chronic in which the onset is more slowly, less aggressive and usually involve well differentiated cells (the mature cell). The four major classifications include:

1. Acute myeloid leukemia (AML)
2. Acute lymphoblastic (lymphocytic) leukemia (ALL)
3. Chronic myeloid (myelocytic) 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

These are cancers of the hematopoietic progenitor cells. They are rapidly growing tumors. They have a sudden onset with signs related to depressed bone function. Progress rapidly.

Pathophysiology of acute leukemia

Although acute leukemia is rapidly growing tumors, normal bone marrow progenitors grow at an even more rapid rate. *The principal pathogenesis problem in acute leukemia is*

a block in differentiation. This leads to the accumulation of immature leukemic blasts in the bone marrow, which suppress the function of normal hematopoietic stem cells by physical displacement and other poorly understood mechanisms, eventually bone marrow failure results, which accounts for the major clinical manifestations of acute leukemia. Thus, the therapeutic goal is to reduce the leukemic clone sufficiently to allow normal hematopoiesis to resume.

Clinical Features of Acute Leukaemias
The acute leukaemias have the following characteristics:

1. *Abrupt stormy onset:* Most patients present within 3 months of the onset of symptoms.
2. *Symptoms related to depression of normal marrow function:* These include fatigue, pallor, dyspnoea, weakness (mainly due to anaemia), fever (reflecting infections resulting from the absence of mature leukocytes), Bleeding disorders (petechiae, ecchymoses, epistaxis, gum bleeding, purpura, bruises, prolonged bleeding) secondary to thrombocytopenia (low platelets).
3. *Bone pain and tenderness:* These result from marrow expansion and infiltration of the sub periosteum.
4. *Generalized lymphadenopathy, splenomegaly, and hepatomegaly:* These reflect dissemination of the leukemic cells, and are more pronounced in ALL than in AML due to infiltration.
5. *Central nervous system manifestations:* These include headache, vomiting, irritability and nerve palsies resulting from meningeal spread of leukemic cells; (Leukemic meningitis. these features are more common in children than in adults and are more common in ALL than AML.
6. *Infection and fever resulting from too few* normal white blood cells.
7. *Gum hypertrophy due to infiltration.*
8. Chloromas : soft tissue masses in the skin or orbit due to infiltration by tumors.

The main 4ps are: **Pallor, Pyrexia, Purpura and Pain**

Sub classification : This is based on immunologic markers.

1. Acute lymphoblastic leukemia
-common type (pre-B ALL
-T cell ALL
-B cell ALL
-Undifferentiated (Null or Unclassified) which lack B or T markers and may be the committed stem cells.

2. Acute myeloid (Acute Granulocytic Leukemia) (French American British (FAB)
-M0-undifferented leukemia
-M1-minimal differentiation: more than or equal to 90%blasts and less than 10% promyelocytes, Common in older adults.

-M2-differentiated leukemia: 30-89% blasts and 10% promyelocytes, common in older adults.
-M3- Acute promyelocytic Leukemia: more than 30% blasts. Common in mediu age 39yrs. There is increased WBCs.
-M4- Acute myelomonocytic Leukemia: both myeloblasts and monoblasts are seen in the BM and peripheral blood.
-M5- Acute monocytic Leukemia: the cells in the BM are monocytic
-M6- Acute Erythrocytic Leukemia: the BM has abnormal erythroblasts
-M7- Acute megakaryocytic

NB the M5 is devided in to 2
M5A poorly differentiated > 80% monoblasts
M5B well differentiated <80% monoblasts

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

<u>Investigation</u>

(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. the total number of WBCs may be increased, decreased or normal.
(ii) PBF may show blast cells or other primitive cells. (Immature WBCs)
(iii) Thrombocytopenia.

(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.
- Cytogenetic
- 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/A + 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 leukemic 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 hematopoietic tissues will occur and to give supportive care. There are four general types of therapy;

1. Chemotherapy where a combination of drug are used.
2. Bone marrow transplant.
3. Radiotherapy
4. Immunotherapy which stimulates the patient's own immune system to mount a response against the malignant cells.
5. Monoclonal antibodies ie Ritoxin

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. The drugs used include Vincristine and Glucocorticoids (Predinsolone, Dexamethasone) with addition of one or two agents

2. Remission consolidation/Intensification phase

Since patients in remission induction phase still harbor leukemic cells, further systemic treatment is required to prevent or delay leukemic relapse. This is usually completed within the first 6-12 months after induction. It involves the introduction of new, non-cross-resistant drugs and drug combinations selected for different and often synergistic mechanisms of action to reduce the risk of emergence of drug resistance.

3. Remission maintenance

- If the pt is still in remission after consolidation phase a period of maintenance therapy is given consisting of a repeating cycle of drug administration usually up to 3 years. During maintenance therapy the patient still remain at risk of infection. Fever in children who are receiving chemotherapy must be evaluated and treated aggressively, especially if the patient is either neutropenic or has a central venous access device.

Drugs commonly used in the treatment of Acute Leukemia

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

		6-Mercaptopurine (oral) Methotrexate (oral)	

Central Nervours System Preventive Therapy

This begins during the induction phase and continous through the entire treatment program usually decreasing in frequency with time.

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 treatment of complication arising from BM failure.

1. Anaemia transfusion support with -packed Rbc infusion to maintain Hb>10 gm/dl
2. Bleeding due to thrombocytopenia
   - -platelet concentrate infusion to maintain platelet count above 10 x 10^9/L
   - -coagulation abnormalities
   - -Fresh frozen plasma
3. Infection- Parenteral broad spectrum Antibiotics coz of neutropenia
4. PCP prophylaxis with Septrin may be necessary.
5. Systemic fungal infection or pulmonary aspergilosis may require IV amphotericin B
6. Herpes Simplex infection – Acyclovir 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.
9. Treatment of electrolyte imbalance and dehydration
10. Nutritional support
11. Exchange transfusion
12. monitoring of relapse.

Prognosis

Between 50 and 85% of people who have AML respond to treatment. Between 20 and 40% of people show no signs of the disease 5years after treatment. Bone marrow transplantation has increased the success rate to between 40 and 50%.
Without treatment prognosis poor- 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.
Bone marrow is a semi solid substance within the bones where blood cells such as WBCs, RBCs and platelets are manufactured from the hematopoietic stem cells (HSC). During BMT it's the HSCs which are transplanted to replace the damaged or the diseased cells in the bone marrow with the cells of a normal person. This is called an Allogeneic Hematopoietic Stem Cell Transplant (HSCT). Bone marrow transplant/ stem cell transplant is performed after a high dose of chemotherapy or radiation. The donor must have the same genetic makeup as the patient ie from the family member (brother or sister).

Allogeneic Bone marrow Transplant.

- Healthy 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

Immediate side effects

Nausea and vomiting
Mouth sores
Fatigue
Low levels of platelet
Low levels of RBCs
Diarrhea

Long term side effects

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
viii) Bone pain
ix)Numbness and tingling
x) fatigue

Chronic Leukemias

(i). Chronic Myeloid/myelocytic/myelogenous Leukemia

This is a disease in which a cell in the bone marrow becomes cancerous and produces large number of abnormal granulocytes. The cells range from very immature to mature forms, it's a slowly progressing and uncommon type of blood-cell cancer that begins in the bone marrow but some may be produced in the spleen and liver. These cells range from very immature to mature forms whereas only immature forms are seen in acute myeloid leukemia. It's common in older adults and is caused by a chromosome mutation.

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.(** abnormality of chromosome 22)
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

The phases are based mainly on the number of immature WBCs (blasts) in the bone marrow.

(1) Chronic phase – a period of variable length.

The patients may be generally be asymptomatic but without proper treatment then patient progress to accelerated phase within 4 years. Has slow onset with non- specific symptoms ie weakness and weight loss.

- This is responsive to treatment and is easily controlled.
- It is essentially a benign neoplasm.
- Fewer than 10% of the cells in the blood and bone marrow are blast cells (immature blood cells). Patients have mild symptoms and usually respond well to treatment. Presents with leukocytosis.

(2) Accelerated phase – short phase 6-12 months.

During this phase more and more immature granulocytes enter the blood stream and bone marrow. Its characterized by enlarged spleen, anaemia and progressive abdominal fullness and discomfort. Signs and symptoms include: low grade fever, night sweats, bone pain and weight loss coz of rapid proliferation and hypermetabolism of the leukemic cells. Bleeding and easily Bruising may arise from the dysfunctional platelets.

Blood samples have 15% or more but fewer than 30% blasts, very low counts of Platelets, Basophils make upto 20% or more of the blood.

- Patient not responsive to TREATMENT
- Not easily controlled

(3) Blast crisis phase (acute phase) the terminal phase characterized by increasing no. of myeloid cells.

Symptoms become more pronounced and splenomegally may become more pronounced. There is infiltration in the skin, lymph nodes, bones and central nervous system.

Blood samples have 20% or more blasts (high blast count) Large clusters of blasts are seen in the bone marrow and are spread to tissues and organs

beyond the bone marrow. Patients presents with fever, poor appetite and weight loss.

- 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 and weak
- Loss of appetite
- Weight loss
- Breathlessness
- Abdominal pain and discomfort due to enlarged spleen
- Bleeding tendencies – low platelets
- Gout due to high levels of uric acid from break down of nucleic acid in leukaemic cells
- Visual disturbances
- Neurological manifestation
- Priapism.
- Fever and
- Night sweats
- Pallor due to reduced No. of RBCs
- Swollen lymph nodes

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 immature 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.

<u>Management of CML</u>

No specific therapy is required if the patient is asymptomatic and the leukocyte count is not greatly elevated. The goal of treatment is to eliminate the blood cells that contain the abnormal BCR-ABL gene that causes the over abundance of diseased blood cells

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

This develops from a type of WBC called the B cells. It progresses slowly usually affecting older adults. (B-Lymphocytes) the bone marrow makes too many lymphocytes thus increased mature lymphocytes and enlarged spleen.

- A neoplasm of activated B- cells.
- The CLL cells resemble mature small lymphocytes and accumulate in BM, blood, Lymph Nodes 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
- "B symptoms" (fever, chills, night sweats, weight loss.)
- 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 aspirates /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

There are 2 systems of staging**:** the BINET and RAI

1. **BINET STAGING**:

A-No anemia, no thrombocytopenia

-less than 3 areas of lymphoid enlargement

B-No anemia, no thrombocytopenia

> or = 3 sites of LN enlargement.

C- Anemia HB less than 10g/dl and /or thrombocytopenia less than 100,000/mm3, regardless of the number of areas of lymphoid enlargement.

2. **RAI STAGING**

Stage 0: low risk, there is high lymphocyte count in the blood.

Stage 1: intermediate risk, High lymphocyte count in the blood
Swollen lymph nodes

Stage 2: intermediate risk, High lymphocyte count in the blood
Swollen spleen or liver
With or without swollen lymph nodes

Stage 3: high risk, High lymphocyte count in the blood
Low RBCs count – anemia
With or without swollen lymph nodes, spleen or Liver

Stage 4: high risk, high lymphocyte count in the blood
Low platelets
With or without low RBCs count
Swollen lymph nodes, spleen or liver

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 with antibiotics -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

Cancers or malignancies of the lymphatic system. These are diverse group of solid tumours composed of neoplastic lymphoid cells that vary with respect to molecular features, genetics, clinical presentation and treatment. They start in

lymph nodes but can involve lymphoid tissues and spleen. The lymphatic system carries a specialized type of white blood cells called lymphocytes through a network of tubular channels (lymph vessels) to all parts of the body including the bone marrow. Scattered throughout this network are collections of lymph nodes/ lymph glands.

- Neoplastic transformation of cell reciting in lymphoid tissue.
- . They are often classified according to the degree of cell differentiation and the origin of the predominant malignant cell 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. While high grade divide faster

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. This is a specialized form of lymphoma that features the presence of an abnormal cell called a ***Reed-Sternberg cell***.
- 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.

The WHO classification proposed classifying Hodgkin lymphoma into two major categories: nodular lymphocyte-predominant Hodgkin lymphoma and classic Hodgkin lymphoma. Nodular lymphocyte- predominant Hodgkin lymphoma represents only a small portion of all cases of Hodgkin lymphoma and is a unique form that generally exhibits a nodular growth pattern. Classic

Hodgkin lymphoma is characterized by clonal proliferation of typical mononuclear Hodgkin cells and multinucleated Reed-Sternberg cells.
Pathological classification of Hodgkin's Lymphoma is as follows:-

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

Predisposing factors include

- Immunodeficiency
- Immunodeficiency
- Autoimmune disorder
- Chemotherapy
- Radiotherapy
- Organ transplant
- Viral infection eg Epistein-Barr virus/HIV
- Chemical exposure

Clinical features

(i) Lymphadenopathy

-Painless, discrete, and rubbery as single or group

-Mainly affects the following areas;

- Cervical
- Supraclavicular
- Mediastinal
- axilla

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.)

Chills and pruritis

Investigations

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

2. Renal function Tests - U/E + Creatinine urinalysis
3. 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.
4. LDH
   - Levels are considered to be an adverse prognostic factor.
5. CXR
   - May show mediastinal masses
6. CT scan-chest and abdomen useful in clinical staging of the disease.
7. LN Biopsy-Histological Diagnosis. It may be undertaken surgically or by percuteneous needle biopsy under radiographic guidance.
8. MRI and lymphangiogram

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

The staging is done according to the No. of lymph nodes involved, whether the LN are on one or both sides of the diaphragm and whether there is a disseminated disease involving the bone marrow, liver, lung or skin

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 – unexplained Weight loss of 10 or more within 6months, Drenching night sweats, 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).

The definitive diagnosis is made by the presence of reed-sternberge cell in a biopsy specimen in lymph node tissue

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 chemotherapy

- 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

- Represent a group of cells that are heterogeneous lymphocytic cancers that are multi-centeric in origin and spread to various tissues throughout the body including the bone marrow.
- 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.
- Unlike Hodgkin disease, non-Hodgkin lymphoma can occur even among infants, and the incidence rises steadily with increasing age.

Clinical Features

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

Clinical presentation;

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

HISTORY

- *Past history:* A number of diseases, infectious agents, and drugs or toxins have been associated with the development of NHL.
- A personal or family history of lymphoma or other prior hematopoietic malignancy, use of radiation therapy, immunosuppressive agents, chemotherapy, organ transplantation, and other underlying diseases should be obtained
- Relevant infections include HIV-I, HTLV-I, Epstein-Barr virus (EBV), hepatitis C, Borrelia bergdorferi (B. afzellii species), and perhaps also hepatitis B virus
- Specific disorders associated with the development of NHL include connective tissue diseases (e.g. lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome), immunodeficiency disorders, mixed cryoglobulinemia, Castleman's disease, and inflammatory bowel disease treated with azathioprine/6-mercaptopurine.

- An occupational history should be obtained, as exposure to certain agricultural pesticides and Agent Orange have been implicated in the development of NHL
- Specific illnesses which are risk factors for the development of gastrointestinal lymphoma include: Crohn's disease gastrointestinal nodular lymphoid hyperplasia, Helicobacter pylori-associated chronic gastritis and Celiac disease
- *Systemic complaints (B symptoms)* : About 40 percent of patients with NHL present with systemic complaints of: Fever — temperature >38ºC, Weight loss — unexplained loss of >10 percent of body weight over the past six months, Sweats — the presence of drenching night sweats
- These complaints are of importance in determining prognosis
- Less frequent presenting systemic complaints of fatigue, malaise, and pruritus occur in fewer than 10 percent of patients.
- The presence of bone pain or gastrointestinal symptoms may indicate extranodal involvement in these areas
- *Fever of unknown origin:* Fever of unknown origin (FUO) refers to a prolonged febrile illness without an established etiology despite intensive evaluation and diagnostic testing.
- Historically, the most common causes of FUO have been infection, connective tissue diseases, and malignancy.
- NHL, especially one of the aggressive or highly aggressive variants, is a common cause of FUO due to malignancy.
- *Lymphadenopathy:* More than two-thirds of patients with NHL present with peripheral lymphadenopathy.

<u>Physical examination</u>

- The physical examination needs to be directed to all potentially involved lymphoid sites
- These include:
  - ~ Waldeyer's ring (tonsils, base of the tongue, nasopharynx)
  - ~ Standard lymph node sites (e.g. cervical, supraclavicular, axillary, inguinal, femoral)
  - ~ Liver and spleen
  - ~ Abdominal nodal sites (mesenteric, retroperitoneal)

~ Less commonly involved nodal sites (e.g. occipital, preauricular, epitrochlear, popliteal)

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.

(V) bone marrow biopsy

(vi) chest and abdominal CT scan

(vii) MRI

(viii) positron Emission Tomography

Staging

- Staging system — The Ann Arbor staging system developed in 1971 for Hodgkin's lymphoma (HL) was adapted for staging non-Hodgkin's lymphomas (NHLs)
- This staging system focuses on the number of tumor sites (nodal and extranodal), location, and the presence or absence of systemic ("B") symptoms
  1. *Stage I* refers to NHL involving a single lymph node region (stage I) or a single extralymphatic organ or site (stage IE)
  2. *Stage II* refers to two or more involved lymph node regions on the same side of the diaphragm (stage II) or with localized involvement of an extralymphatic organ or site (stage IIE)
  3. *Stage III* refers to lymph node involvement on both sides of the diaphragm (stage III), or with localized involvement of an extralymphatic organ or site (stage IIIE) or spleen (stage IIIS), or both (stage IIIES)

4. *Stage IV* refers to the presence of diffuse or disseminated involvement of one or more extralymphatic organs (e.g. liver, bone marrow, lung), with or without associated lymph node involvement The presence or absence of systemic symptoms should be noted with each stage designation.

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.

Differences between Hodgkins and non- Hodgkin lymphoma

Hodgkins lymphoma	Non-hodgkins lymphoma
More often localized to a single axial group of nodes (cervical, mediastinal, para-aortic)	More frequent involvement of multiple peripheral nodes
Orderly spread by contiguity	Non-contiguous spread
Mesenteric nodes and waldeyer ring rarely involved	Mesenteric nodes and waldeyer ring commonly involved
Extra-nodal involvement uncommon	Extra-nodal involvement commons