Lecture Notes of Internal Medicine

Haematology

Dr. Osama Mahmoud Mohamed
Assistant Professor of Internal Medicine
Ain Shams University
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1- Haemoglobin: Normal adults values,

**Male:** 13-17 gm/dl  
**Female:** 12-16 gm/dl

- **Anaemia:**  
  **Male:** < 13 gm/dl  
  **Female:** < 12 gm/dl  
  **Pregnant Female:** < 11 gm/dl

2- **RBCs:**

- **Shape:** biconcave disc.
- **Average diameter:** 7.2 micron.
- **Nucleus:** absent.
- **Life span:** is approximately 120 days.
- **Count:**  
  **Male:** (4.5-5.5 million/mm$^3$).  
  **Female:** (3.8-4.8 million/mm$^3$).

**Haematopoiesis:** It is the process relating to the formation of blood cells.

In the embryo this occurs initially in the yolk sac, followed by the liver and spleen, by 5 months in utero haematopoiesis is established in the bone marrow (BM).

**Stages of development of RBCs:**

- Stem cell → Proerythroblast → Erythroblast → Normoblast → Reticulocyte → Mature RBC

- Reticulocytes & mature RBCs are present in peripheral blood, the other stages of RBCs are present in bone marrow.
- As the cell matures, it gets smaller in size.
- Reticulocytes: about 0.2-2%, they are increased in haemorrhage, haemolysis and in response to specific haematinics used in treatment of anaemia (Iron-B$_{12}$). Reticulocytes are decreased in aplastic anaemia.
**Haemoglobin (Hb) Structure**

It is composed of four globin chains, each containing an iron containing protoporphyrin pigment termed haem.

<table>
<thead>
<tr>
<th>Haem</th>
<th>Four globin Polypeptide chains</th>
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<tr>
<td>• Fe ++</td>
<td>The globin chains are a combination of two alpha and two non alpha chains.</td>
</tr>
<tr>
<td>• Protoporphyrin</td>
<td></td>
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**Types of Hb in adults:** (according to the type of globin chains):
1- Hb A: comprises about 97% (2 α & 2 β chains).
2- Hb F : < 1% (2 α & 2 γ chains).
3- Hb A₂: 1.5-3.2% (2 α & 2 δ chains).

**ESR**

It is the rate of sedimentation of RBCs in mm/hr when anticoagulated blood is allowed to stand. This is due to its ability for rouleaux formation. It is a non specific test for inflammation and tissue damage (measure of the acute phase response).

**Factors promoting rouleaux formation**
- Fibrinogen.
- Immunoglobulins.

Fibrinogen and immunoglobulins lead to change of the repellent electrostatic negative surface charge of RBCs → rouleaux formation causing the cells to fall rapidly.

**Methods of determination:**
1- Westergren method: Blood + Na citrate
   Normal values: ♂ < 13 mm/hour
   ♀ < 20 mm/hour

2- Wintrobe method: Blood + dried anticoagulant (EDTA)
   - The anticoagulant is dried with no dilution of blood.
   - So we can also calculate haematocrit value.
ESR is age, sex and pregnancy dependent, slight elevation is relatively insignificant, normal or mild rise of ESR may be seen in pregnancy.

**Causes of moderate rise of ESR:**
- Infections e.g pyogenic, TB.
- Anaemia.
- Myocardial infarction.
- Inflammatory diseases e.g rheumatoid disease, collagen diseases, or rheumatic fever

**Causes of very high ESR (> 100 mm/hr):**
- Malignancy e.g leukaemia, lymphoma.
- Collagen disease e.g SLE.
- Multiple myeloma.
- Active T.B, severe pyogenic infections

**Normal or low ESR:**
- Polycythaemia.
- Hypofibrinogenemia (DIC or partially clotted blood sample).
- Sickle cell anaemia or hereditary spherocytosis.

♀ **Anaemias with low ESR (inability of rouleaux formation)**
- Hereditary spherocytosis
- Sickle cell anaemia

**Haematocrit value**

\[ \text{Packed cell volume (P.C.V)} = \text{Haematocrit value} \]

It is the volume of packed RBCs in 100 ml blood.

**Values:**
- ♂ → 40-50%
- ♀ → 35-45%
- It is decreased with anaemia and increased with polycythaemia.
- It is not affected in acute bleeding except when the plasma volume is restored from extravascular water sources (It falls slowly over 2-3 days).

**Blood indices**

1 - **Mean corpuscular Hb (MCH):** 27-32 pgm (picogm)

\[ \text{MCH} = \frac{\text{Hb in gm/dL}}{\text{RBCs count / mm}^3} \times 10 = 15/5 \times 10 = 30 \text{ pgm} \] (for example).
- It is decreased in hypochromic anaemia (MCH < 27 pg).
- If it is normal = normochromia.
2- **Mean corpuscular volume (MCV)**: (78-98 FL).

\[
\text{MCV} = \frac{\text{PCV} \times 10}{\text{RBCs count} / \text{mm}^3} = 45 \times 10 / 5 = 90 \text{ FL (femtolitre)} \text{ for example.}
\]

- It is increased in macrocytic anaemia (MCV > 100 FL).
- It is decreased in microcytic anaemia (MCV < 78 FL).
- It is normal in normocytic anaemia.

3- **Mean corpuscular Hb concentration (MCHC)**: (32-36 g/dL).

\[
\text{MCHC} = \frac{\text{Hb in gm/dL} \times 100}{\text{PCV}} = \frac{15/45 \times 100}{90} = 33 \text{g/dL for example.}
\]

- It is decreased with hypochromia e.g iron deficiency anaemia, and normal with normochromia.

### A simple method to calculate the blood indices

<table>
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<th>Indices average</th>
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<tr>
<td>RBCs count</td>
<td>5 million/mm³</td>
</tr>
<tr>
<td>Hb content</td>
<td>15 g/dL</td>
</tr>
<tr>
<td>P.C.V</td>
<td>45%</td>
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So:

1. \[
\text{MCH} = \frac{15}{5} \times 10 = 30 \text{Pg} = \frac{\text{Hb content}}{\text{RBCs count}}
\]

2. \[
\text{MCV} = \frac{45}{5} \times 10 = 90 \text{fl} = \frac{\text{PCV}}{\text{RBCs count}}
\]

3. \[
\text{MCHC} = \frac{15}{45} \times 100 = 33 \text{ gm/dL} = \frac{\text{Hb}}{\text{PCV}}
\]

### Abnormal blood film (value of blood film)

- Microcytosis → iron deficiency anaemia
- Macrocytosis → megaloblastic or non-megaloblastic anaemia.
- Hypochromia → diminished Hb concentration e.g in cases of iron deficiency anaemia.
- Anisocytosis (variation in the size of red cells) e.g in megaloblastic or iron deficiency anaemia. It is non specific.
- Poikilocytosis (variation in shape of RBCs). It is also non specific and present in many conditions.
- Punctuate basophilia (basophilic stippling) of RBCs in lead poison.
- Howell Jolly bodies (small round nuclear remnants) e.g in dyshaemopoiesis e.g megaloblastic anaemia and post-splenectomy.
- Pappenheimer bodies in sideroblastic anaemia.
- Polychromasia corresponds to increased reticulocytes e.g in haemolysis.
- Parasites in RBCs e.g malaria.
- Shapes of RBCs (see later).
Shapes of RBCs in different diseases:

- **Burr cell (Echinocyte)**: RBCs with scalloped border → uraemia.
- **Stomatocyte** (mouth cell) → Inherited.
- **Target cell (Codocyte)**: Thalassaemia, iron deficiency, liver disease.
- **Acanthocyte** (spur cell) → Splenectomy, advanced liver disease.
- **Elliptocyte** (oval cell) → Inherited.
- **Sickle cell (Lancet cell)**: Sickle cell anaemia.
- **Elliptocyte** → Inherited.
- **Spherocyte** → inherited, acquired spherocytosis.
- **Schistocytes or schizocytes (Helmet cell)** → Mechanical haemolysis.
- **Tear drop cell (Dacrocyte)** → Myelofibrosis.

- When there are two populations of RBCs in blood film, this is called dimorphic RBCs, this can be seen in cases of double deficiencies (e.g. iron ↓ and folate ↓) or following treatment of anaemic patients with haematinics.
- Red cell distribution width (RDW), it reflects variability of RBCs size, normally it is 11.5-14.5%, its increase expresses anisocytosis e.g in iron, B₁₂ or folic acid deficiency anaemia.

**Iron therapy**

- **Oral iron therapy:**
  - This is by ferrous sulfate 200 mg tab or ferrous gluconate 300 mg tab.
  - **Dose** (About 150 mg elemental iron is usually required)
    - Ferrous sulfate 200 mg tab/8hr gives (120 mg elemental iron/d), or ferrous gluconate 300 mg/12 hour (70 mg elemental iron/d).
    - It is best absorbed if given one hour before meals, it is irritant causing nausea. The dose should be lowered until tolerable or the medication should be discontinued until symptoms resolve and then restarted at a lower dose.
    - Nausea can be avoided by taking iron with food, ascorbic acid can be given to improve absorption.
    - Slow release formulations of iron cause fewer GIT side effects.
Iron intolerance:

- GIT upset → Nausea - vomiting.
- → Abdominal pain.
- → Constipation (stool softeners are needed).

In case of iron intolerance give ferrous sulfate/ 12 hour or shift to ferrous gluconate, if no response consider parenteral iron.

Response to ttt

1- Reticulocyte count starts to increase on the 4th day & lasts for 12 days.
2- Hb level starts to increase after one week & returns to normal within about 4-10 weeks, (Hb should rise by 1 gm/dL every 7-10 days).
3- Clinical improvement.

The patient should be told that the stool will become dark with oral iron therapy.

Duration of therapy:

- For 4-10 weeks till Hb becomes normal.
- Then smaller doses for about 3-6 months to replenish iron stores.

Failure of oral iron (refractory iron deficiency anaemia):

- Wrong diagnosis.
- Failure to take tablets (iron intolerance).
- Malabsorption.
- Chronic haemorrhage.
- Chronic infection.

Parenteral Iron therapy:

**Indications:**
- Oral iron intolerance.
- Chronic blood loss.
- Malabsorption.
- When rapid response is required (severe anaemia).

**Side effects:**
- Anaphylaxis, urticaria.
- Pain.
- Flushing.
- Headache.
- Skin staining due to extravasation into S.C tissue which can be minimized by using the Z track technique in IM injection.

**Preparations:**
- Iron dextran (cosmofer) 100 mg/2 ml (IM, IV).
- Iron sorbitol (ferrlecit) 50 mg/ml (IM only).

Saccharated iron (ferrosac) 100 mg/5ml I.V or ferric gluconate 100 mg/5ml I.V are newer, safer agents and therefore preferable.

**Calculation of the dose:**
1- If the patient is (adult + severe anemia), give about 2 gm = 2000 mg.
2- Calculated required dose = (Normal Hb - Hb of patient) x body weight x 3.
   e.g. Patient with Hb 7, body weight 80 kgm.
   Dose = (15 - 7) x 80 x 3 = 1920 mg.
Methods of intake of parenteral iron

Intermittent I.V infusions
- e.g 50-100mg amp.
  diluted in 100 ml saline infused iv over 1 hour every other day,
or as needed

Total Infusion method, it was used in the past.
- i.e All the required dose can be given by I.V drip very slowly with saline using iron dextran within 24 hours. It leads to arthralgia and myalgia.

Anaemia

Anaemia is present when there is reduction in number of RBCs & Hb content of blood with decreased O2 carrying capacity of blood in relation to age & sex. Other factors including pregnancy and altitudes also affect haemoglobin levels and must be taken into account when considering whether an individual is anaemic.

Classification:

I. Aetiological:
- Deficiency anaemia e.g. Iron ↓ - Vit B<sub>12</sub> ↓ - Folic acid ↓.
- Aplastic anaemia.
- Haemolytic anaemia.
- Haemorrhagic anaemia.

II. Morphological: (according to blood indicies)
- Microcytic hypochromic:
  - Iron deficiency.
  - Thalassaemia.
  - Sideroblastic anaemia.
  - Chronic lead intoxication.
- Normocytic normochromic:
  - Aplastic anaemia.
  - Haemolytic anaemias except thalassemia.
  - Acute blood loss. Anaemia of chronic disease.
- Macrocytic normochromic:
  - Megaloblastic anaemia.
  - Non megaloblastic anaemia (see later) e.g:
    - Chronic liver disease.
    - Haemolytic crises due to increased reticulocytes.
Pathophysiology:
1- Tissue hypoxia leading to the following compensatory mechanisms
2- Compensatory mechanisms (evident in chronic anaemias):
   - Increased erythropoiesis.
   - Increased COP due to peripheral vasodilatation.
   - Increased Plasma volume.
   - Increased Level of 2-3 DPG $\rightarrow$ Hb affinity to O2 $\rightarrow$
     O2 release to the tissues.

General features of anaemias
- Patients with anaemia may be asymptomatic.
- A slowly falling level of Hb allows for compensatory mechanisms to develop (see above).

Symptoms (non specific)
- Fatigue.
- Faintness.
- Angina.
- Headache.
- Breathlessness.
- Palpitations.

Signs
- Pallor.
- Systolic flow murmur (Hemic murmur).
- Tachycardia.
- Heart failure.

Specific signs of different types of anaemias: (see later)

Examples:
- Koilonychia in iron deficiency.
- Jaundice in haemolytic anaemia.
- Leg ulcers e.g in sickle cell anaemia.
- Splenomegaly in haemolytic anaemia.
- Neurological manifestations in vit B12 deficiency.
- Purpuric eruption and throat ulcers in aplastic anaemia.

Iron deficiency anaemia

Iron metabolism:
2- Requirements: 10 mg/d of which 1 mg is absorbed.
3- Absorption: $\uparrow$ with vit C, $\downarrow$ with phosphates, phytates and tannins.
4- Excretion: 1 mg/d through desquamation of cells (from GIT, Skin).
5- Storage: Iron is stored as ferritin. Part of ferritin circulates at a concentration that reflects iron body stores. Normal range of serum ferritin is: 15-400 ng/ml = 15-400 $\mu$g/L in $\delta$.
   10-200 ng/ml = 10-200 $\mu$g/L in $\varphi$. 
Oral iron $\xrightarrow{\text{HCl}}$ ferrous (the form of absorption)
$\downarrow$
Absorption in duodenum & upper jejunum through apoferritin in intestinal mucosa
$\downarrow$
Ferritin
$\downarrow$
To blood as transferrin (it is measured as iron binding capacity)
$\downarrow$
Iron delivered to erythrocytes by binding of transferrin to specific cell receptors
$\downarrow$
Iron then enters mitochondria then incorporated into protoporphyrin to form heme
$\downarrow$
Heme binds to globulin in cytoplasm to produce Hb

- Ferritin is a water soluble complex of iron so, it is available for Hb formation; but haemosidrin is an insoluble iron complex and is difficult for utilization.
- Iron enters and leaves the ferritin molecule so it is available for cell function. With time ferritin is transformed and catabolized to haemosiderin.
- In iron deficiency anaemia, ferritin level $< 10$ ng/ml but with iron overload it may reach thousands.
- Each 1 $\mu$g/L serum ferritin is equivalent to 10 mg stored iron.
- The serum ferritin level also increases with inflammatory conditions (phase reactant).

**Aetiology of iron deficiency anaemia:**

1- Inadequate intake $\rightarrow$ infancy after 6m.
   $\rightarrow$ anorexia.
   $\rightarrow$ old age.

2- $\downarrow\downarrow$ Absorption: phytates (cereals).

3- $\uparrow$ Demand: pregnancy – growing Child.

4- Chronic blood loss
   $\rightarrow$ haemorrhage especially GIT bleeding
   $\rightarrow$ Ankylostoma (Each worm consumes 0.2 ml/d).
   $\rightarrow$ Vaginal bleeding.
   $\rightarrow$ Rarely, chronic haemoptysis or haematuria may cause iron deficiency.

5- Intravascular haemolysis with haemoglobinuria e.g PNH (see later).
C/P:

- General features of anaemia.
- Epithelial changes

  * Nails
  * Angular stomatitis
  * Glazed shiny, tender tongue
  * Brittle nails, loss of Lustre
  * Koilonychia
    = spooning

- C/P of the cause
  - GIT or vaginal bleeding.
  - Malabsorption $\$$(chronic diarrhea), Ankylostoma.
  - Plummer-Vinson $\$$(Iron deficiency anaemia, esophageal web in upper 1/3 of esophagus, dysphagia).

  Menorrhagia, post cricoid web and gastric atrophy may be a sequence as well as a cause of iron deficiency anaemia !?.

Investigations:

1- To prove anaemia (Hb ↓ - RBCs ↓ - PCV ↓).
2- To determine the type of anaemia:
   - Blood indices (MCV ↓, MCH ↓, MCHC ↓).
   - Iron ↓ (Normally it is 50-150 ug/dL)
   - IBC ↑ (Normally it is 250-370 ug/dL)
   - S. ferritin is low.
   - Low Transferrin saturation (\[\frac{S.\text{iron}}{TIBC}\] X 100) (N = 25-50%).
   - Increased Free erythrocyte protoporphyrin.
   - B.M examination → Hyperplasia with normoblasts + decreased B.M iron stores.

3- To determine the cause e.g. to detect the source of bleeding or blood loss.

   Stool for ankylostoma  Occult blood in stool  Upper or lower GI endoscopy
   (it is not reliable)
   i.e search for Hb molecules in stools & not RBCs itself

- Stop meat intake 3 days before the test.
- It is better to be repeated as GIT bleeding is usually intermittent.
**Treatment:**
- Treatment of the cause: e.g. oesophageal varices – peptic ulcer – ankylostoma.
- Iron therapy as before.
- Blood transfusion.
- Multivitamins to correct other associated deficiencies.

**Megaloblastic Anaemia**
- This is a group of anaemias caused by deficiency of vitamin B_{12} or folic acid.
- It is characterized by RBCs with MCV > 100 FL, it may reach > 115 FL.

**Vit B_{12}: (cobalamins):**
- **Requirements:** 1 ug/d.
- **Sources:** Animal sources (strict vegetarians are at risk of developing B_{12} deficiency).
- **Absorption:** Parietal cells of the stomach secrete a glycoprotein called intrinsic factor which combines with vit B_{12}. On reaching the terminal ileum specific receptors on the mucosa bind the B_{12–intrinsic factor complex}. Intrinsic factor is not absorbed. After absorption of vit. B_{12}, it binds to a carrier in plasma (transcobalamin II), then it is transported to the tissues.
- Vit B_{12} stored in the liver, it can give up to 5 years supply.
- The stores in the liver are about 3-5 mg.

**Functions of vit B_{12}:**
1- Methylmalonyl Co A $\xrightarrow{\text{vit B}_{12}}$ succinyl Co A (absence of this reaction $\rightarrow$ neurological complications)
2- Homocysteine $\xrightarrow{\text{vit B}_{12}}$ methionine (absence of this reaction $\rightarrow$ neurologic complications).

**Folic Acid: (peteroyl glutamate)**
- **Requirements:** 50 ug / d.
- **Sources:** Animal foods, vegetables.
- **Absorption:** Duodenum, jejunum.
- **Stores:** 5-15 mg, it gives supply for months.

**(FIGLU test): It is an old test.**
Histidine $\rightarrow$ Formaminoglutamic acid (FIGLU) $\xrightarrow{\text{Folic acid}}$ glutamic acid
So, Folic acid deficiency $\rightarrow$ ↑ FIGLU in urine.
Functions of folic acid:

(1) Amino acid metabolism and DNA synthesis.
(2) Methylation of homocysteine to methionine.

Vit. B<sub>12</sub> and folic acid are essential for generation of methionine from homocysteine, this reactions produces tetrahydrofolate which is converted to thymidine monophosphate for incorporation into DNA, so deficiency of either vit B<sub>12</sub> or folate leading to high plasma levels of homocysteine and impaired DNA synthesis.

Causes of megaloblastic anaemia:

1- Vit B<sub>12</sub> deficiency:
- Decrease intake (rare) e.g. in strict vegetarians.
- Decrease intrinsic factor due to atrophic gastritis.
  Two forms of atrophic gastritis have been described:
  - Type A is true autoimmune gastritis involves the fundus and body of the stomach.
  - Type B is non autoimmune involves the entire stomach and is associated with helicobacter pylori infection.
- Intestinal diseases:
  - Malabsorption $^*$ (terminal ileum disorders) e.g. tropical sprue, Crohn’s disease.
  - Vit B12 utilization by bacteria in stagnant lobe $^*$ or by diphyllobothrium latum.
- Drugs e.g. colchicine, neomycin, PAS.
- Transcobalamin II deficiency.
- Imerslund disease (selective defect in cobalamine absorption) + proteinuria.

2- Folic acid deficiency:
- Decrease Intake: unbalanced diet (common in alcoholics, teenagers, infants).
- Malabsorption $^*$.
- Increase Demand e.g. pregnancy.
- Drugs e.g. • Phenytoin – methotrexate – trimethoprim – pyrimethamine (folate antagonists).
  - Purine and pyrimidine analogues (impair DNA metabolism).

Pernicious anaemia

- This term is limited to megaloblastic anaemia due to failure of secretion of intrinsic factor by the stomach.
- It is an autoimmune disease due to Ab against intrinsic factor or antiparietal cells Ab (type A atrophic gastritis).
- It is rare before 30 years, females > males.
- It may be genetically determined.
- It may be associated with other autoimmune diseases e.g. myxedema, thyroiditis, vitiligo.
Non megaloblastic macrocytosis (i.e. macrocytes in peripheral blood without megaloblastic changes in B.M), RBC size usually > 100FL.

**Causes**
- Chronic liver disease.
- Alcohol excess.
- Hypothyroidism.
- Reticulocytosis (Haemolytic crisis).

Patients with excessive plasma lipids absorb these lipids into RBCs surface leading to enlarged membrane surface area → macrocytosis, e.g. in liver disease there is decrease hepatic synthesis of lecithin-cholesterol acetyl transferase → ↑ plasma free cholesterol which is absorbed into RBC membrane.

**Pathophysiology of megaloblastic Anaemia:**
Vit B₁₂ or folate deficiency leading to impaired DNA synthesis in RBCs

Arrest of nuclear maturation, but the cytoplasmic maturation proceeds (nucleo-cytoplasmic asynchrony)

More cell growth

Larger cells with MCV exceeding 115 FL.

↑↑ size of RBCs in the blood and B.M

Intramedullary haemolysis

Normally between divisions the cells do not have time to regrow to full size So, progressive size reduction occurs, but in megaloblastic anaemia there is a slowing of the rate of cell division → more cell growth.

**Other effects of Vit. B₁₂ ↓↓ & folic acid deficiency.**

- Leucopenia
- Thrombocytopenia
- Atrophy of the rapidly dividing cells of GIT
- Neurological manifestations only in vit B₁₂ deficiency

**C/P of megaloblastic anaemia:**
- Vitamin B₁₂ deficiency
  - Anaemia (see general features of anaemias, as before).
  - GIT manifestations (dyspepsia, atrophic glossitis).
  - Neurological manifestations → peripheral neuropathy and subacute combined degeneration.
- **Folic acid deficiency**
  - Anaemia.
  - GIT manifestations (dyspepsia, glossitis).
  - No neurological manifestations.

The neurological abnormalities of vitamin $B_{12}$ deficiency, if left untreated for a long time, can be irreversible.

**Investigations:**

1. To prove anaemia (Hb ↓, RBCs count ↓).
2. To determine the type of anaemia.
   - Blood indices (MCV ↑, MCHC is normal).
   - B.M showing increase of megaloblasts (megaloblastic erythropoiesis).
3. To determine the cause
   - **Folic acid deficiency:**
     - Serum level $< 4$ ng/ml (Nr. 6-20 ng/ml).
     - Positive FIGLU test.
   - **$B_{12}$ deficiency deficiency:**
     - Serum level $< 100$ ng/ml ($N = 200-900$ ng/ml).
     - Positive schilling test.
     - Gastric function tests, antibodies against parietal cells & intrinsic factor are positive.

**Schilling test**

We give $B_{12}$ I.M to block transcobalamine binding sites, this ensures that any labelled B12 absorbed from the gut will be directly excreted via the kidney, then give $B_{12}$ orally labelled with radioactive material. Normal person secretes $>25\%$ of the radioactive $B_{12}$ in urine over 24 hrs, but patients with pernicious anaemia will secrete $<5\%$, this indicates poor absorption through the small intestine. We can repeat the test after intake of intrinsic factor, if the condition is improved, it is intrinsic factor deficiency, but if there is no response it is a small intestinal disease.

4. **Other findings**
   - Poikilocytosis & anisocytosis. (non specific)
   - Howell jolly bodies (Nuclear remnants), non specific and can be seen in leukaemia and post splenectomy.
   - WBCs ↓ & platelets ↓ → so $B_{12}$ may lead to pancytopenia.
   - Serum bilirubin ↑ due to intramedullary haemolysis.
   - Reticulocytes ↑ with treatment.
   - WBCs showing hypersegmented neutrophils.
   - The ineffective erythropoiesis and intramedullary haemolysis often result in high level of serum lactate dehydrogenase (LDH).

**Treatment:**

1. **Folic acid deficiency**
   
   Give folic acid 5 mg/d till improvement then lower doses for maintenance (1 mg/d).
2. Vitamin $B_{12}$ deficiency
   - Give Hydroxycobalamine with the following dosage:
     1000 ug I.M. twice during, the first week.
     Then $\rightarrow$ 1000 ug/week for 6 weeks
     Then $\rightarrow$ 1000 ug/3months for life.
   - Most patients require life long treatment with parentral $B_{12}$.
   - Reversible causes e.g intestinal bacterial over growth or parasites, treatment may reverse the deficiency.

Folic acid alone should never be given in an undiagnosed case of macrocytic anaemia, folic acid therapy reverses haematologic signs, but neurologic degeneration will continue (in cases of vit B12 deficiency).

Q Three Parasites give different types of anaemia:
   - Ankylostoma $\rightarrow$ Iron deficiency anaemia + eosinophilia.
   - Diphyllobothrium latum $\rightarrow$ vit $B_{12}$ $\downarrow$ $\rightarrow$ megaloblastic anaemia
   - Malaria $\rightarrow$ haemolytic anaemia.

Q D.D. of pancytopenia:
   - Hypersplenism.
   - Aplastic anaemia.
   - Megaloblastic anaemia.
   - BM infiltration e.g myeloma, lymphoma, disseminated TB.
   - SLE – Paroxysmal nocturnal haemoglobinuria – Aleukaemic leukaemia, see later.

Q D.D. of hypochromic microcytic anaemia:
   - Iron deficiency anaemia.
   - Lead poisoning $\rightarrow$ punctate basophilia.
   - Thalassaemia $\rightarrow$ see later.
   - Sideroblastic anaemia:
     This anaemia is caused by disorder of haem synthesis due to defect of iron incorporation with protoporphyrin. There is accumulation of iron in the mitochondria of erythroblasts forming a ring of iron granules around the nucleus giving the morphologic finding of ringed sideroblasts. It is characterized by refractory anaemia.

Causes
   - Hereditary, it may responds to vit $B_6$ therapy because it is due to abnormality in vitamin $B_6$ metabolism. It is x-linked recessive.
Acquired:

- Primary (myelodysplasia, see later)
- Secondary to alcohol, lead and INH therapy which inhibit the enzymes of protoporphyrin synthesis.

- Sideroblasts are normoblasts which contain iron granules within BM and can be detected by prussian blue staining.
- Blood picture showing microcytic hypochromic anaemia due to diminished Hb levels of RBCs.

Diagnosis:
(1) BM examination showing sideroblasts with increase of iron stores.
(2) Peripheral blood showing microcytic hypochromic anaemia, pappenheimer bodies in RBCs.
(3) ↑ Iron level, ↑ transferrin saturation and ↑ serum ferritin.

***: Stop drug – treatment of the cause – Vit B₆ in high doses.

- All patients of sideroblastic anaemia should be given a trial of pyridoxine, however in hereditary cases it may fail (these patients are usually transfusion dependent).
- Acute leukemia develops in about 10% of patients with acquired idiopathic disease, in these patients, the sideroblastic anemia is a preleukemic syndrome, and is classified as a myelodysplastic syndrome (see later).

Q Patient with peptic ulcer + GIT bleeding + History of black stools

Causes
- Melena.
- Iron therapy.
- Bismuth therapy.

- Iron deficiency anaemia → ↓ Iron, ↑ IBC, ↓ ferritin, ↓ iron stores, ferritin saturation is low, ↓ iron in B.M.
- Sideroblastic anaemia → Iron ↑, ferritin ↑, IBC is normal.
- Thalassaemia → Iron is normal or ↑, ferritin is normal or ↑, iron stores are normal or ↑.
- Anaemia of chronic disease → serum iron ↓, ↓ IBC, ferritin is normal or raised.

Q Acute megaloblastic anaemia or disease!? (see later).
Q DD of macrocytosis
- Megaloblastic → vit B12 or folic acid deficiency.
- Non megaloblastic, see later.  
- Myelodysplasia, see later.

We can differentiate by investigations e.g levels of vit. B12 or folic acid and other investigations of the causes of non megaloblastic macrocytosis.
**Haemolytic anaemias**

Group of anaemias due to shortened life span of RBCs (increased rate of RBCs destruction):

- Moderate haemolysis (RBCs life span is about 20-40 days).
- Severe haemolysis (RBCs life span is about 2-20 days).

**Pathophysiology (consequences)**, Haemolysis of RBCs leading to:

1. **Increase of Indirect bilirubin**, since the liver can increase its capacity of conjugation (8-10) folds so jaundice may not occur or may be mild, severe haemolysis → frank jaundice.

2. **Anaemia**, but B.M can increase RBCs production up to 8 folds so some cases present without evident anaemia. (compensated haemolytic state), severe haemolysis → frank anaemia.

3. **Hb becomes free** in blood (intravascular haemolysis) so it is combined with haptoglobin (α-globulin) & haemopexin (β-globulin) forming complex.

   The complex taken up by RES

   Reduced haemopexin & haptoglobin levels in blood

4. **Excessive Haemolysis** with saturated haptoglobin & haemopexin

   Haemoglobinuria

   In most haemolytic conditions RBCs destruction is extravascular, see later.

**General features of haemolytic Anaemia**

1. Features of anaemia (as before).
3. Liver ++ & Spleen ++ due to extramedullary erythropoiesis, especially in thalassemia, spleen ++ also occurs as it is the site of RBCS destruction in extravascular haemolysis.
4. Leg ulcers in the ankle area surrounded by pigmentation due to deposition of haemosidrin under skin. Leg ulcers are also frequent in sickle cell anaemia due to ischaemia.
5. Gall stones (pigment stone) → CBD → Jaundice especially in spherocytosis.

- **Causes of Jaundice in cases of haemolytic anaemia.**
  - Haemolysis - Haemosiderosis - Viral hepatitis - Gall stones.
- Splenomegally does not occur in all types of haemolytic anaemia, see later.
6- **Haemolytic crisis**

- Fever, rigors.
- Pallor, Jaundice, dark urine (haemoglobinuria)
- Bony aches due to active B.M. Abdominal pain.

7- **Hyporegenerative crisis (aplastic crisis)**

Attacks of decreased capacity of B.M to replicate. It may be due to folic acid deficiency or viral infection e.g parvovirus.

Here anaemia is increased without deepening of Jaundice.

8- **Megaloblastic crisis** follows the development of folate deficiency.

9- **Vaso-occlusive crisis** in sickle cell anaemia.

**Investigations for Haemolytic Anaemia**

1- **Blood picture**

- Normocytic normochromic anaemia (the usual picture).
- Microcytic hypochromic e.g in thalassemia.
- Macrocytic anaemia due to folic acid deficiency or during haemolytic crises (reticulocytosis).
- WBCs & platelets are increased (B.M hyperactivity).
- Brisk reticulocytosis.

2- **Hyperactive B.M = erythroid hyperplasia:**

- Normoblasts
- Megaloblastic (in cases of folate deficiency)

**B.M aplasia** in cases of aplastic crisis.

3- **S. bilirubin** → ↑ (indirect).

4- ↓ Haptoglobin, ↓ haemopexin, ↑ LDH.

5- Urine & stools → ↑ urobilinogen, ↑ stercobilin.

6- ↑ LDH.

7- **Special investigations**

- **Blood film e.g** → Spherocytosis
  - Target cell (thalassemia)
- **Hb electrophoresis** → Hb F (thalassemia)
  - Hb S (sickle cell anaemia)
- **Increased osmotic fragility** in spherocytosis.
- **Sickling test** for sickle cell anaemia.
- **Ham’s test** for paroxysmal nocturnal haemoglobinuria.
- **Coomb’s test** for autoimmune haemolytic anemia.

8- Red cell survival can be estimated from $^{51}$Cr – labeled RBCs.

**Evidence of intravascular haemolysis:**

- Haemoglobinemia.
- Haemoglobinuria.
- Haemosiderinuria.
- Marked diminished plasma haptoglobin and haemopexin.
Causes of Haemolytic Anaemia

**Intrinsic (Intracorpuscular) defect**
- Inherited (except PNH).
  - Since childhood.
- 1- Membrane defect
  - Spherocytosis.
  - Paroxysmal nocturnal haemoglobinuria (PNH), it is acquired.
- 2- Haemoglobinopathies (sickle cell anaemia, sickle C disease).
- 3- Defect in globin synthesis (Thalassaemia).
- 4- Enzyme deficiency (G6PD & pyruvate kinase deficiency).

**Extrinsic (Extracorpuscular) defect**
- Acquired.
  - Adults, children.
- 1- Autoimmune haemolytic anaemia.
- 2- Mechanical haemolysis e.g. prosthetic valve, microangiopathic haemolytic anaemia.
- 3- Infection e.g. malaria, clostridia.
- 4- Chemicals e.g. drugs or snake venom.
- 5- Hypersplenism.

- Paroxysmal nocturnal haemoglobinuria is a membrane defect but it is acquired.
- Megaloblastic anaemia is associated with intramedullary (BM) haemolysis.
- Sites of haemolysis: (1) extravascular haemolysis i.e. the RBCs are removed from the circulation by macrophages in reticuloendothelial system, particularly the spleen. (2) intravascular haemolysis i.e. RBC destroyed within the circulation with release of Hb.

**Hereditary Spherocytosis**

It is an autosomal dominant disease, there is ↓ in a lipoprotein of the cell membrane (Spectrin) leading to defect in the membrane sodium – potassium ATPase pump causes RBC swelling. So RBCs become spherocytes (more rigid and less deformable) → destruction in the spleen. So, haemolysis is extravascular (in the spleen). Also there is increased RBCs osmotic fragility.

**C / P**
- General features of anaemia + General features of haemolysis e.g. jaundice, splenomegaly (see before).
- Family history is positive, the onset is usually since early childhood.
- Gall stones of pigment type are common even in childhood due to the increased bile pigment production.

Because the BM capacity to increase erythropoiesis (6 to 8 fold) exceeds the usual rate of haemolysis in this disease, anaemia is usually mild or moderate and may even be absent.
Investigations:
- General investigations of anaemia, MCV is usually normal or slightly decreased (microspherocytes), MCHC is increased in 50% of cases, the anaemia is usually considered as normocytic normochromic!.
- Investigations for haemolysis (↑ bilirubin, ↑ urobinogen, reticulocytosis).
- Osmotic fragility test is +ve.
- Spherocytes in blood film.
- Chest X-ray showing paravertebral masses due to hyperplasia of BM

Red cell survival studies with chromium show short life span of red cells with destruction in the spleen.

Tubes with serial dilution of saline

| Early haemolysis | 0.7 | 0.6 | 0.5 | 0.4 | 0.3 | 0.2 | 0.1 |

Treatment
1- Splenectomy → Striking, permanent improvement. It is better done after the age of 4 years.
2- Blood transfusion.
3- Folic acid 1 mg/d.

- Splenectomy is advised when there is severe anaemia, severe haemolytic crisis or if other members of the family had died from the disease.
- Following splenectomy, penicillin 250 mg/12 hrs is given for at least 5 years. Also pneumococcal, meningococcal and H influenza vaccines should be administrated 2 weeks before splenectomy.
- Rare relapses, due to splenic autotransplants or due to hyperplasia of secondary splenules.

**Hereditary elliptocytosis**
- It is a cell membrane disorder, autosomal dominant. RBCs are elliptical in shape. Clinically, it is similar to hereditary spherocytosis.
- Minority of patients have anaemia and only occasional patients require splenectomy.

**Hereditary stomatocytosis**
- Also it is a cell membrane defect, lack of RBCs membrane stomatin. It is an inherited disease but it may be associated with alcohol intake splenectomy improves the condition.
- Other acquired cell membrane disorders e.g spur cell anaemia with severe hepatocellular disease and paroxysmal nocturnal haemoglobinuria.
- Hereditary cell membrane disorders are spherocytosis, elliptocytosis and stomatocytosis.
In **homozygous B-thalassaemia**, either no normal B chains are produced (B°), or B chain production is very reduced (B⁺), so, there is excess of α chains which precipitate in erythroblasts and red cells leading to ineffective erythropoiesis and haemolysis, there is increased quantities of HbA2 and HbF with small amount of HbA. In **heterozygous B-thalassaemia**, there is usually asymptomatic microcytosis with or without anaemia with mild elevation of HbA2 ± mild elevation of HbF.

**Beta thalassaemia**

Decrease production of beta chains which are replaced by gamma chains

**Types:**

1. **Homozygous (Thalassaemia major):**

   Increased levels of HbF and HbA₂ with low level of HbA → severe symptoms.

2. **Heterozygous (Thalassaemia minor) i.e trait.**

   - Similar to iron deficiency anaemia → Mild anaemia (microcytic hypochromic anaemia) i.e ↓ MCV and ↓ MCH.
   - Splenomegally.
   - Hb F, and Hb A2 are mildly elevated → mild symptoms.
   - It needs no treatment, family counselling is important, iron should not be given except with associated iron deficiency anaemia.

**Thalassaemia intermedia**

It includes patients who are symptomatic with moderate anaemia (Hb7-10 gm/dL) and who do not require regular transfusions. It is more severe than thalassaemia trait but milder than thalassaemia major which is transfusion dependent. It may be due to combination of homozygous mild B⁺ and α thalassaemia, there is ↑ HbF. The patients have splenomegaly; bone deformities, recurrent leg ulcers, galls stones and infections.
**Alpha thalassaemia:**
There is decrease production of alpha chain synthesis. Normally there are two alpha gene loci on chromosome 16 and therefore there are four alpha genes. The disease is often caused by gene deletions as follows:

- One-gene deletion → No clinical effect
- Two-gene deletion → mild hypochromic anaemia.
- Three gene deletion → Hb H disease with moderate anaemia (Hb 7-10 g/dL) with splenomegally.; no specific therapy, avoid iron therapy, folic acid if necessary.
- Four-gene deletion → Bart’s Hb which cannot carry O₂ and is incompatible with life (hydrops fetalis).

**Anaemias with secondary iron loading:**
- Sideroblastic anaemia.
- Transfusional haemosiderosis e.g.
  - 1- Thalassemia major
  - 2- Aplastic anaemia

**Thalassaemia Major**
*Target cell anaemia = Cooley anaemia*

**Aetiology** Abnormal gene is inherited from both parents → defect in the switch of gamma chains to beta chains → increase of Hb F, also Hb A2 is high. Clinical manifestations generally appear after the first 4-6 months of life when the switch from gamma to beta chain production normally occurs.

**C/P**
1- Starts after the age of 6 months.
2- General features of haemolytic anaemia.
3- Mongoloid features due to marked expansion of B.M.
4- Marked hepatosplenomegaly.
5- Patients have peculiar skin colour due to combination of icterus, pallor and increased melanin deposition.
Investigations

1- General investigations for anaemia (microcytic hypochromic) + investigations for haemolysis e.g. ↑ I. bilirubin - ↑ urobilinogen = reticulocytosis.

2- Blood film → target cells.

3- Hb electrophoresis → Hb F↑ - ↑HbA₂.

4- X-ray → Skull hair on end appearance. Long bones showing thin cortex & wide medulla.

5- MCV ↓↓, MCHC normal, ↓ iron binding capacity and high serum ferritin level.

6- Prenatal diagnosis by DNA analysis of chorionic villus biopsy.

Treatment

2. Desferal.
3. Folic acid.
4. B.M transplantation.
5. Splenectomy, indication !? → (increased blood transfusion requirements > 250 ml packed RBCs/kg/year).

Cellular pathogenesis of thalassaemia major

There is excess production of alpha chains. These free alpha chains → membrane permeability abnormalities + destruction of RBCs by the mononuclear phagocytic system. Since these abnormalities start in the RBCs precursors (erythroblasts) → intramedullary destruction of RBCs (ineffective erythropoiesis) and short life span of circulating red blood cells that emerge from B.M So there is extramedullary haematopoiesis in the liver and spleen.
Sickle cell Anaemia

In the homozygous state (sickle cell anaemia) both genes are abnormal (HbSS), whereas in heterozygous state (sickle cell trait) only one chromosome carries the gene (HbAS). The synthesis of HbF is normal, so the disease usually does not manifest itself until the HbF decreases to adult levels at about 6 months of age.

SS (homozygous)  SA (heterozygous)
(Sickle cell anaemia)  (sickle cell trait)
Leading to manifested anaemia  It is asymptomatic, sickling may occur with severe hypoxia e.g. during anaesthesia.

Pathogenesis:
Substitution of valine for glutamic acid at position 6 in beta chain, this change predisposes the Hb to polymerization with hypoxia. The Hb becomes rigid with subsequent membrane and cell shape changes (sickle appearance) so, the affected RBCs become liable to haemolysis. Also Hb S makes the RBCs very liable for adhesion to the endothelium leading to vascular occlusion.

\[
\text{HbS} \xrightarrow{\text{Hypoxia}} \text{RBCs become sickle shaped}
\]

Haemolysis  Vascular obstruction (vaso-occlusive)

Microinfarcts  Macroinfarcts (Painful crises) (Organ damage)

C/P:
1- Features of anaemia and haemolysis, without splenomegally.
2- Vascular occlusion (organ failure or pain crises)
   - Dactylitis.
   - Mesenteric blood vessels → Acute abdomen.
   - Renal infarction, nephrogenic D.I.
   - Splenic infarction → Autosplenectomy.
   - Liver infarcts.
   - Heart → myocardial infarction, iron overload cardiomyopathy.
   - Cerebral lesions e.g Hemiplegia.
   - Retina → Retinal infarcts, retinal detachment.
   - Bone → Pain.
   - Penis → Priapism.
3- Long term sequelae:
- Susceptibility to infections, e.g. pneumococci and salmonella.
- Chronic leg ulcers due to ischaemia, they are usually over the medial or lateral malleoli.
- Gall stones (pigment stones).
- Aseptic necrosis of bone particularly head of femur.
- Chronic renal disease.
- Blindness.

We can summarize the clinical manifestations of sickle cell anaemia into:
(1) Manifestations related to chronic haemolysis e.g normocytic anaemia, Jaundice.
(2) Manifestations related to abnormal adhesions, sickling and vaso occlusion (painful crises and organ failure).
(3) Manifestations related to infections with pneumococci and salmonella.

N.B.: HbS releases its O2 to the tissues more easily than normal Hb, so patients feel well despite being anaemic except during crises or complications.

Investigations:
- General investigations for anaemia: Normocytic normochromic anaemia, evidence of haemolysis.
- Hb electrophoresis → Hb S is high.
- Sickling test (blood + Na bisulphate → hypoxia → sickling)

The test is positive in

<table>
<thead>
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<th>SS</th>
<th>SA</th>
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**Sickle C disease**: 50% HbS + 50% HbC
- Mild to moderate anaemia
- Spleen ++, retinal detachment
- Nearly normal life span.

**Sickle β thalassemia**: 70% HbS + 30% HbF, there is also splenomegaly.

Treatment:
1- Blood transfusion.
2- Sickling crises (pain) → Analgesics.
   → O2 therapy.
   → Na HCO₃, fluids.
   → Fresh blood exchange transfusion to lower Hb S below 50% especially with occurance of stroke, priapism and acute chest syndrome (see later).
3- Drugs that increase Hb F as, this decreases sickling of Hb S. The cytotoxic drug hydroxyurea, can be used but it has unacceptable toxicity !?.
4- Give pneumococcal and H influenza vaccines, penicillin V orally can be used also as a prophylaxis against pneumococcal infection (autosplenectomy).
5- Folic acid, genetic counseling.
6- Bone marrow transplantation, gene transfer therapy.

**Acute chest syndrome**
- It is a specific complication of sickle cell disease which may complicate the sickling process.
- It is presented with fever, hypoxia with unusually brisk leukocytosis, chest X-ray showing lung infiltrate.
- The condition may progress to ARDS like situation.
- The syndrome usually responds very well to exchange transfusion to lower Hb S to below 50%.

**Sickle cell trait:**
These individuals are asymptomatic except with hypoxia e.g anaesthesia, flying in nonpressurized aircraft. Sickle cell trait protects against Plasmodium falciparum !?.

**Glucose 6 phosphate dehydrogenase (G6PD) deficiency**

This enzyme is involved in the hexose monophosphate shunt which is the source of NADPH that protects RBCs against oxidative stress as it is essential to increase the reduced glutathione that resists oxidation. It is an X-linked disease.

**Types:**

1- Manifestations in black Africans (type A), enzyme deficiency is mild, patients are normal but when subjected to oxidative stress (e.g. infections or drugs), they will suffer from haemolysis. Haemolysis is self limiting as the young red cells newly produced by the bone marrow have nearly normal enzyme activity.

2- In caucasians, especially around the mediterranean (Type B), enzyme is markedly deficient in young and old RBCs., so patients suffer from moderate haemolytic anaemia.
3- **Favism**: Two abnormal genes are present leading to:
  - G6PD deficiency.
  - Abnormal metabolism of beans which become an oxidant.

**Clinical presentations or syndromes of G6PD deficiency:**
1. Acute drug induced haemolysis, e.g aspirin, antimalarials, sulfa, dapsone, nitrofurantoin quinolones, vit K, probenecid, quinidine.
2. Chronic haemolytic anaemia.
3. Favism.
5. Infections and acute illnesses will also precipitate haemolysis.

**Investigations**
- General investigations of haemolysis.
- G6PD activity of the red cell is measured, but this may be entirely inaccurate if there is marked reticulocytosis. So it is better to be measured in the steady state, as the reticulocytes are relatively rich in G6PD in comparison to the old extremely deficient RBCs.
- Hienz bodies in blood film (precipitated haemoglobin).
- Evidence of intravascular haemolysis.
- DNA analysis.

**Treatment**
- Avoidance of the cause, treatment of infections, stop any offending drug.
- Blood transfusion during the attack.
- Splenectomy is of no value.

Other enzymopathies leading to anaemia e.g. pyruvate kinase deficiency (Autosomal recessive), RBCs deficient in ATP → haemolysis due to ↑↑ RBCs rigidity, also there is splenomegaly. Pyruvate kinase activity is low. It is treated by blood transfusion, splenectomy may improve the condition.

**Q:** Metabolic disorders of red blood cells? (G6PD↓, pyruvate kinase ↓)
Auto Immune Haemolytic Anaemia (AIHA)

Story: Patient, 45 years old with jaundice

History and examination reveal (Jaundice, pallor)
- Ask for serum bilirubin and Hb
- If there is ↑ l. Bilirubin, ↓ Hb
  - Suspect haemolysis!
  - Blood picture
  - Brisk reticulocytosis
  - Coomb's test
    - If + ve = Autoimmune haemolytic anaemia
  - Ask about type of Ab
    - Cold Ab (lgM)
    - Warm Ab (lgG)
- Search for the cause e.g. SLE, lymphoma, leukaemia.

1. Autoimmune haemolytic anaemia due to warm antibodies

  i.e antibody attaches best to red cells at 37°C. The haemolysis is extravascular.

Causes

1. Idiopathic.
2. Chronic lymphocytic leukaemia.
3. Lymphoma - SLE
4. Alpha methyl dopa.

C/P: (All ages, both sexes, but more in middle aged females).
- Haemolytic anaemia + Manifestations of the cause.
- The spleen is often palpable.

Investigations

- Positive direct coomb's test which detects antibodies on RBCs (lgG).
- Spherocytes in blood film.
- Investigations for haemolysis (as before) and for the cause.
- Autoimmune thrombocytopenia may also present (Evans' syndrome).

When IgG attacks RBCs they become sphérocytes → stimulate splenic phagocytic activity → haemolysis.

**Treatment**
- Treatment of the cause.
- Steroids, prednisolone 1 mg/kg/d, If no response → splenectomy.
- Other immunosuppressive drugs e.g. azathioprine and cyclophosphamide can be used if there is no response to steroids and splenectomy.

II. **Autoimmune haemolytic anaemia due to cold Antibodies**

*i.e antibody attaches best to RBCs at temperature lower than 37°c. The haemolysis is intravascular.*

**Causes**
- Viral infection e.g. infectious mononucleosis.
- Mycoplasma pneumonia.

**C/P**
Haemolytic anaemia + Manifestations of the cause.

**Investigations**
- Positive direct coomb’s test, cold Ab in serum (IgM).
- Other investigations for haemolysis (as before) and for the cause.

**Treatment** (keeping the extremities warm)
- Treatment of the cause, patients should avoid exposure to cold.
- Steroids.
- Splenectomy is of no value.
- Rituximab (see later) therapy is a recent trend.

* Paroxysmal cold haemoglobinuria = Ab that cause haemolysis in cold temperature. e.g. in cases of measles, mumps and chicken pox. It is due to IgG Ab which attacks RBCs (Donath–Landsteiner Ab). It is an intravascular haemolysis.

* **Direct Coomb’s test:** detects Abs coating RBCs. The patient’s RBCs are mixed with antihuman globulin serum, agglutination = positive test.

* **Indirect Coomb’s test:** detects serum Abs, the patient serum mixed with compatible RBCs, agglutination = positive test.
Drugs causing haemolysis

1- Direct interaction with RBC membrane e.g. amphotericin.
2- Immune mediated
   - **Methyldopa type**: Methyldopa and its derivatives e.g. (Levodopa) lead to autoantibody production reacting against Rh antigens of RBCs.
   - **Hapten type**: Drugs acting as hapten e.g. penicillins, cephalosporins, combined with RBC surface, this leads to production of antibody against the penicillin coated RBC membrane.
   - **Quinidine type**: It is commonly called an innocent bystander reaction. It occurs with quinidine, sulfonamides. The drug binds to RBC glycoprotein, the antibody recognizes the complex with activation of complement and deposition on RBC surface.
3- Drugs causing haemolysis in G6PD deficiency e.g. antimalarials, sulfa, nitrofurantoin.

Mechanical haemolysis

1. March haemoglobinuria with prolonged marching or marathon running can cause red cell damage in the capillaries in the feet.
2. Prosthetic valve → haemolysis.
3. Calcific AS may lead to mild haemolysis.
4. Micro-angio-pathic haemolytic anaemia, in which fibrin deposition in capillaries can cause severe red cell disruption.

**Causes of microangiopathic haemolytic anaemia:**
   1- DIC.
   2- Haemolytic uraemic $\$.
   3- Thrombotic thrombocytopenic purpura (TTP).
   4- Malignant hypertension, Scleroderma.

**Diagnosis** Blood film → shistocytes (fragmented RBCs).

**TTT of the Cause.**

Fibrin thrombus

**Toxic causes of haemolysis**

- Malaria.
- Clostridium welchii.
- Pneumococci.
- Copper: overload e.g. Wilson's disease.
- Staph.
- Snake venom.
- Spider venom.

**Advanced liver disease may lead to spur-cell anaemia due to lipid abnormalities leading to haemolysis of these abnormal cells.**
Paroxymal nocturnal haemoglobinuria (PNH)

It is an acquired defect at the level of stem cell (mother cells). So there are defects in (RBCs, Platelets and WBCs), it may lead to aplastic anaemia.

Pathology

**RBCs:** There is absence of specific protein in cell membrane leading to activation of C3 against RBCs e.g during sleep (low PH)! leading to haemolysis. Haemolysis may be also precipitated by infection, surgery or iron therapy. The deficient protein is glycosyl phosphatidyl-inositol (GPI).

**Platelets:** Increased aggregation → thrombosis (complement mediated activation of platelets).

**WBCs:** P.N.L dysfunction → infection.

C/P

1. Haemolytic anaemia (nocturnal), (it is an intravascular haemolytic anaemia)
2. Venous thrombotic episodes e.g. Budd–Chiari $\$, mesenteric or cerebral veins obstruction.
3. Recurrent infections.

Investigations

1- Positive Ham’s test (old test) : Blood + acidic medium (pH of 6.2) → Haemolysis.
2- Recently Flow cytometry of red cells showing the defect.
3- Leukopenia, thrombocytopenia.
4- Bone marrow sometimes hypoplastic or even aplastic despite haemolysis.

Treatment

- Steroids, 25mg prednisone only on alternate day.
- Thrombolytics , anticoagulants for thrombosis.
- Antithymocyte globulin, cyclosporine to treat bone marrow aplasia.
- Bone marrow transplantation in cases with bone marrow failure.
Sickle cell syndromes
- Sickle cell Anaemia.
- Sickle cell beta thalassaemia.
- Sickle C disease (50% Hbs, 50% Hbc)

Thalassaemia syndromes
- Thalassaemia major and minor.
- Thalassaemia Intermedia.
- Sickle cell beta thalassaemia.

- Sickle cell beta thalassaemia: ↑HbS, ↑HF, minimal sickling, splenomegally.
- *Alloimmune haemolytic anaemia is due to: ABO, Rh incompatibility or minor group incompatibility.*

**Q DD of normocytic normochromic anaemia**

The classification is by the degree of bone marrow response to the anaemia:

1. **Anaemia associated with impaired marrow response (↓Reticulocytes):**
   - Aplastic or hypoplastic anaemia with pancytopenia, erythropoietin level is elevated.
   - Bone marrow infiltration (myelophthisic anemias) due to myeloma, lymphoma, granuloma or metastases. Blood examination reveals immature WBCs and nucleated RBCs (leukoerythroblastosis or leukoerythroblastic reaction).
   - Deficiency of erythropoietin e.g chronic renal failure.
   - Other anaemias with hypoproliferation of bone marrow e.g hypothyroidism and chronic liver disease

2. **Anaemia associated with increased RBCs production (↑Reticulocytes):**
   - Post haemorrhagic anaemia.
   - Haemolytic anemias.
1- Primary
(a) Idiopathic, acquired
An autoimmune mechanism may be responsible, activated cytotoxic T cells are responsible for bone marrow failure.
(b) Congenital e.g fanconi anaemia.

C/P:
- Decrease production of :-
  - RBCs ↓→ anaemia.
  - WBCs ↓→ infections.
  - Platelets ↓→ haemorrhage.
- Pallor with other manifestations of anaemia.
- Bleeding within skin and mucous membranes, haematuria and epistaxis are common. Intracranial bleeding is always a risk.
- Necrotic mouth, throat ulcers and monilial infections reflect the neutropenia.

Investigations:
- Secondary Causes of aplastic anaemia must be excluded.
- History of viral illness particularly hepatitis may be important.
- Blood picture showing pancytopenia with normocytic normochromic anaemia. Absence of reticulocytes.
- B.M. examination (trephine) showing pancytopenia.

DD: See before i.e DD of pancytopenia.

2. Secondary aplastic anaemia (Acquired)
- It is important to investigate the reported side effects of all drugs taken over the preceding months.
- In some instances the cytopenia is more selective and affects only one cell line, most often the neutrophils.
- The clinical features and methods of diagnosis are the same as for primary idiopathic aplastic anaemia.
- An underlying cause should be treated or removed.
Causes of Acquired Aplastic Anaemia:

**Drugs:**
- Cytotoxic drugs.
- Antibiotics e.g. chloramphenicol, sulphonamide.
- Antirheumatics e.g. penicillamine, gold, phenylbutazone, indomethacin.
- Antithyroid drugs - Anticonvulsants.

**Chemicals:**
- Benzene - Organophosphates

**Ionizing Radiation.**

**Viral hepatitis B, C, Parvovirus, EBV, HIV.**

**Paroxysmal nocturnal haemoglobinuria**

Q Causes of pure red cell aplasia (with normal WBCs and platelets).
- Immune with thymoma.
- Idiopathic.
- Secondary to renal disease.
- Congenital (Diamond-Blackfan $)

N.B.: Steroids have little effect in severe aplastic anaemia, but are used for serum sickness to ALG, they can be used to treat children with diamond – blackfan $. Adult pure red all aplasia with thymoma can be treated by thymectomy, steroids and cyclosporine can be used.

Q Bone marrow failure syndromes?
- Aplastic anaemia
- Pure red cell aplasia
- PNH
- Agranulocytosis.

Q Anaemia of chronic disease

**Criteria**
- It is due to chronic infection (e.g TB), chronic inflammation (e.g rheumatoid disease, IBD), or neoplasia.
- The anaemia is not related to bleeding, haemolysis or B.M infiltration.
- The anaemia is generally mild with normal MCV (normocytic normochromic), but showing low MVC in 25% of cases.
- The serum iron is low but iron stores are normal or increased (↑ ferritin).

**Pathology:** Failure of iron utilization with decrease release of iron from BM to developing erythroblasts.
- Inadequate response to erythropoietin.
- The mechanism may be mediated by the inhibitory effect of interleukin I and TNF.
**Treatment**
Treatment of the cause, no response to iron therapy.
Erythropoietin therapy for anaemia of renal disease.

**Clinical approach to a case of anaemia:**
1. History of symptoms (e.g. fatigue, palpitation) and causes (e.g. GIT bleeding, drugs), see before.
2. Examination for general signs of anaemia e.g. pallor, and specific signs indicating the etiology of anaemia e.g. splenomegally and jaundice in haemolytic anaemia (see before).
3. Investigations:
   - To prove anaemia (↓ Hb, ↓ RBCs count, ↓ haematocrit).
   - To determine the type of anaemia by blood indicies e.g. MCV, give examples.
   - To determine the cause of anaemia e.g. GIT bleeding causing iron deficiency, B_{12} ↓, haemolysis either inherited or due to acquired causes.

**Acute post haemorrhagic anaemia:**
- It may not be detected due to equal decline of red cell mass and plasma volume.
- PCV does not indicate the extent of blood loss, instead it falls slowly over 2-3 days (see before).
- TLC is increased up to 30.000/mm³ within few hours.
- Platelet count also may reach 1.000.000/mm³.
- Anaemia is normocytic normochromic when detected.

| Chronic bleeding leads to iron deficiency anaemia |
The Leucocytes

Normal total leucocytic count (TLC) count in adults: 4,000–11,000/mm$^3$ (adult).

Leucocytes are classified into:

- Myeloid line:
  - Neutrophils
  - Eosinophils
  - Basophils
  - Monocytes

- Lymphoid line:
  - Lymphocytes

Development of WBCs:

- Pluripotent stem cell

<table>
<thead>
<tr>
<th>Myeloid stem cell</th>
<th>Lymphoid stem cell</th>
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<tbody>
<tr>
<td>Myeloblast</td>
<td>Lymphoblast</td>
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<tr>
<td>Eosinophil blast</td>
<td>Pre-lymphocyte</td>
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<tr>
<td>Eosinophil</td>
<td>Monocyte</td>
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<tr>
<td>Basophil blast</td>
<td>Lymphocyte</td>
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<tr>
<td>Basophil</td>
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<tr>
<td>Monoblast</td>
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</tr>
</tbody>
</table>

- Neutrophils
- Eosinophil
- Basophil
- Monocyte
- Lymphocytes and Blood Platelets
Normally, there is immature WBCs in peripheral blood < 3%.
- Shift to the left = immature WBCs > 3% + leucocytosis. This occurs in
  Infections
  Bleeding
  Haemolysis
- Leucopenia means reduction of TLC below 4000/mm³.
- Leucocytosis means rise of TLC above 11000/mm³.

The cytokines G-CSF (granulocyte colony stimulating factor), GM-CSF (granulocyte – macrophage CSF), M-CSF (monocyte – CSF) are involved in the production of myeloid cells and can be used clinically e.g. to hasten recovery of neutrophil count after chemotherapy.

**Neutrophils**

They constitute about 40-75% of TLC. The absolute count = 2000 -7000/mm³. Functions
- Phagocytosis.
- Chemotaxis (chemical attraction to the site of invasion)

| **Neutrophilia**
| **Neutropenia**
| (> 7000/mm³) | (< 2000/mm³) |
| **Physiological:** (e.g exercise, pregnancy).
**Pathological:**
- Pyogenic infections.
- Tissue damage (burns, myocardial infarction).
- Myeloproliferative disorders e.g: Polycythaemia vera.
Leukaemia (Chronic myeloid), Myelofibrosis.
- Rheumatoid disease.
- Drugs as corticosteroids and leucocyte adhesion disorders.
- Acute haemorrhage or haemolysis.

| **Infections:** Brucella, Typhoid fever.
| **Drugs:** Phenothiazines
| **B.M depression:** Aplastic anaemia.
| **Immunological:** SLE
| **Drugs:** Antithyroid, NSAID.
| **Familial:** cyclic neutropenia.

Viral infections.
Agranulocytosis

Hypersplenism.
Familial benign chronic neutropenia and cyclic neutropenia have good prognosis, although they are associated with increased liability of infections e.g. boils when the neutrophil count is less than 500/mm$^3$. They respond well to G-CSF.

Functional disorders of neutrophils involves a compromised ability to fight infections e.g. in cases of Chediak – Higashi syndrome and chronic granulomatous disease of childhood.

Normally, it is 1-6% of TLC (20 – 500/mm$^3$).

Function: phagocytosis – antibody production – release neurotoxin to kill the parasites.

**Causes of eosinophilia:**

- Allergic and atopic diseases
- Parasitic infestation. e.g. hydatid disease, fasciola and ankylostomiasis.
- Addison’s disease.
- Primary hodgekin’s disease.
- Some types of vasculitis e.g. Strug Strauss vasculitis.
- Primary hypereosinophilic $.$
- Eosinophilic leukaemia.
- Myeloproliferative disorders

Primary hypereosinophilic syndrome characterized by very high level of eosinophils with invasive toxic effects to the heart and lung.

Normally, it is < 2% (0 – 100/mm$^3$).

Function: They combine with IgE causing release of histamine and other contents involved in acute hypersensitivity.

**Causes of basophilia: (> 100/mm3)**

- Myeloproliferative disorders:
  - Chronic myeloid leukemia.
  - Myelosclerosis.
  - Polycythemia rubra vera.
- Acute hypersensitivity.
- Hypothyroidism.

- Inflammatory bowel disease.
- Tuberculosis
Lymphocytes

Normally, it is 20-40% (1500-3500/mm³). Lymphocytes are originally supplied by B.M (stem cells) but proliferate in lymph nodes.

**Types**
- B- lymphocytes 20% (humoral immunity)
- T- lymphocytes 80% (cellular immunity)

<table>
<thead>
<tr>
<th><strong>Lymphocytosis</strong> (&gt; 3500/cmm)</th>
<th><strong>Atypical lymphocytosis</strong></th>
<th><strong>Lymphopenia</strong> (&lt; 1500/cmm)</th>
</tr>
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<tbody>
<tr>
<td>- Viral infection (IMN – CMV)</td>
<td>- Infectious mononucleosis.</td>
<td>- Corticosteroids therapy.</td>
</tr>
<tr>
<td>- Bacterial infections (T.B, brucellosis, typhoid).</td>
<td>- Lymphoma, leukaemia.</td>
<td>- Congenital Immunodeficiency</td>
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<tr>
<td>- Protozoal: toxoplasmosis.</td>
<td>- Viral hepatitis.</td>
<td>- Chemotherapy.</td>
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<td>- Lymphoma, chronic lymphocytic leukaemia.</td>
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<td>- HIV.</td>
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<td></td>
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<td>- Illnesses that cause elevated serum cortisol levels e.g acute infections and inflammatory states.</td>
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Monocytes

Normally, 2-9% or 200-800/mm³. Monocytes are phagocytic cells. They originate in the B.M → circulate in the blood → then they leave the circulation to the tissues → Converted into tissue macrophages.

**Functions:** Phagocytosis of bacteria, virus and immune complex.
- Secretion of TNF, interferon, granulocyte – macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF).

**Causes of Monocytosis:** (> 1000/mm³)
2. Viral: CMV, IMN.
3. Protozoa: (malaria).
4. Rheumatoid disease, sarcoidosis.
5. Monocytic leukaemia (acute myeloid leukaemia).
6. Haematologic and lymphatic malignancies.
7. Inflammatory bowel disease.
**Monocytopenia:** Occurs in combination with decrease in other cell lines in cases of aplastic anaemia, hairy cell leukaemia and steroid use.

---

**Value of B.M. examination**

**Diagnostic:**
- Multiple myelofibrosis
- Aplastic anaemia
- Sideroblastic anaemia
- Myeloma
- Leukaemia

**Confirmatory:**
- Leukaemia
- Iron deficiency anaemia
- Megaloblastic anaemia
- I. T.P

**Site of B.M puncture:**
1. Sternum (aspiration).
2. ASIS trephine (biopsy), used in myelofibrosis and hairy cell leukaemia as they give dry tap with B.M aspiration.

**Q Leukemoid reaction**

It is blood picture with marked increase of TLC > 25,000 - 30,000/mm² (up to > 50,000/mm³) simulating leukaemia, it is a reactive and excessive leucocytosis. It is caused by infections, and after acute haemolysis or haemorrhage. BM metastases also may be a cause.

**Criteria:**
- Usually there is a cause e.g. infection.
- TLC may exceed 50,000/mm³.
- Immature cells never > 5% e.g myeloblasts or myelocytes.
- Platelets are normal.
- RBCs are normal or there is mild decrease.
- B.M proliferation (normal) with no increase of blasts.
- Leukocytic alkaline phosphatase is high.

Leukemoid reaction may be myeloid reaction e.g in haemorrhage, haemolysis, BM metastases or suppurative infections. It may be lymphocytic reaction e.g in CMV, IMN, and TB.
Q **Value of blood picture in case of fever (see different chapters)**
- Infection: T.B – Viral – Brucella, Pyogenic infection.
- Malignancy → Leukaemia – lymphoma (confirmatory tests are required).
- Collagen diseases and inflammatory conditions: SLE, rheumatoid disease.

Q **How can you differentiate between Leucocytosis due to infection or steroid therapy.**
Infection → neutrophils showing toxic grannulation i.e. granule staining becomes more intense.

Q **Leukoerythroblastic reaction?**
i.e presence of immature WBCs or RBCs in peripheral blood due to B.M infiltration e.g myeloma, leukaemia, myelofibrosis, lymphoma, TB.
Leukaemias are disorders in the maturation of haematopoietic tissue (abnormal proliferation of immature WBCs series) that are characterized by the presence of immature leukocytes in the bone marrow (BM) and peripheral blood.

Proliferation occurs initially within B.M before dissemination to the peripheral blood, and infiltrating tissues e.g. spleen, lymph nodes and others (see later), so there are 3 disorders:

1. **Infiltration of B.M**: this interferes with haemopoiesis (BM failure):
   - RBCs↓↓
   - Platelets ↓↓
   - Neutropenia

2. **Immunological disorders**
   - Neutropenia + immature WBCs
   - WBCs with abnormal function
   - Auto antibodies
   - Infections

3. **Tissue infiltration**
   - Liver
   - Spleen
   - CNS
   - Others (see later)

So causes of death are:
- Infections – Bleeding.
- Infiltration of vital organs.

**Aetiology**

1. Genetic theory
   - Increased incidence in the identical twin of patients with leukaemia.
   - Abnormal chromosome in chronic myeloid leukaemia (see later).

2. Chemicals
   - benzene industry

3. Ionizing radiation
   - CML, AML and ALL (see later). High incidence in survivors of Hiroshima and Nagasaki and in patients treated with ionizing radiation.

4. Alkylating agents e.g. chlorambucil

5. Immune deficiency states are associated with an increase in haematological malignancy.

6. Viruses (retrovirus) e.g.
   - HTLVI (human T-cell lymphotropic virus), it is a retrovirus → T-cell leukaemia
Classification of leukaemia (According to cell origin and rapidity of the course)

- **Acute leukaemia**
  - Lymphoblastic
  - Myeloid
- **Chronic leukaemia**
  - Myeloid
  - Lymphocytic.

- **Acute leukaemia** → rapid clinical course resulting in death within months without effective treatment, this is due to early B.M failure.
- **Chronic leukaemia** → a more prolonged natural history, this is because B.M failure is delayed. Accelerated forms may occur (see later).

**Acute Leukaemia**

Malignant proliferation of BM blast cells. Clinical symptoms occur due to BM failure (anaemia, neutropenia and thrombocytopenia) as a result of BM infiltration with blast cells. Tissue infiltration by blasts cells may also occur.

It may occur at any age but:

- **Acute Lymphoblastic (ALL)**
  - Common in children
- **Acute Myeloid (AML)**
  - Common in young adults

(1) **ALL**
- 85% of cases of ALL occur in children and 90% of leukemia that occur in children is ALL.
- ALL is not a common leukemia in adults.
- The ALL cell origin is in the lymphoid line, 75% of cases from B-cell line.
- T-cell variety of ALL are more resistant to therapy and have far worse prognosis than B-cell variety.

(2) **AML**
The AML cell of origin probably arises at different levels of haematopoiesis in different patients, which accounts for the clinically subtypes of AML. In most cases the AML clone arises from multipotential precursors capable of differentiating into granulocyte, erythrocyte, macrophage or megakaryocyte colony forming units.

**C/P of acute leukemia**
(The manifestations are mainly due to BM failure), i.e BM infiltration by non maturing functionless blast cells → anaemia, bleeding, infections.

**I. Manifestations of BM failure:**

- Fever due to infection (neutropenia), common sites are throat, mouth, lung, anorectal and urinary tract.
- Anaemia: due to encroachment on RBCs precursors.
- Bleeding: (thrombocytopenia) e.g epistaxis.
II. Manifestations of tissue and organ infiltration:

- Bone: painful tender sternum, pathological fractures.
- Liver ++, spleen ++, lymphadenopathy.
- Skin → itching (leukaemia cutis).
- Nervous system → infiltration of meninges with headache and cranial nerve paralysis.
- Retina → diminished vision.
- Porta hepatis → obstructive jaundice.
- Serous membranes → effusions.
- Lung → haemoptysis.
- Heart → cardiomyopathy.
- Kidney tubular disorder with hyponatremia, hypokalemia.
- Leukostasis with occlusion of the microcirculation e.g in brain, lung, penis (priapism)

Liver, spleen & L.N++ common with lymphoblastic leukaemia, hepatosplenomegally occurs in about 30% of AML. Lymphoblastic leukaemia have better prognosis than myeloid (bad prognosis).

Investigations:

1- TLC is variable: approximately, 25% of patients having WBCs counts > 50,000/mm$^3$, 50% having WBCs counts between 5000-50,000 and 25% having low count (< 5000/mm$^3$). In most cases excessive blasts are present in the peripheral blood. In some patients blasts may be low or absent, see below.

2- RBCs: normochromic normocytic anaemia.

3- Platelets: Thromobocytopenia.

4- Very high ESR.

5- B.M examination (confirmatory): > 20-30% blast cells in B.M. BM examination will provide material for cytology, cytochemistry and immunological phenotyping (see later).

The presence of Auer rods in the cytoplasm of blast cells indicates a myeloid type.

6- Other investigations e.g serum uric acid, LDH, renal and hepatic profiles, CT brain, pelvi abdominal sonar.

The TLC and presence of blasts cells in peripheral blood is variable so there are:

Subleukaemic leukaemia → Normal or subnormal WBCs count with predominant blasts in peripheral blood.

Aleukaemic leukaemia → Normal or subnormal WBCs count with no blasts in peripheral blood, B.M examination is diagnostic.
D.D. - Fever with sore throat e.g. infectious mononucleosis.
- Other causes of anaemia.
- Other causes of thrombocytopenia.
- Causes of leukemoid picture.
- Causes of lymphadenopathy.

**Poor prognosis of acute lymphoblastic leukaemia.**

- Age < 2 years or > 10 years
- Platelets < 25,000

**Treatment:**

**General supportive measures**

- **Anaemia:** blood transfusion (the haemoglobin level should be maintained above 8-10 gm/dl).
- **Bleeding:** platelet transfusion (the platelet count should be above 10,000-20,000/mm³).
- **Infections:** neutropenic patients (PNL < 500/mm³) are susceptible to most of organisms especially gm –ve bacteria and fungi, so isolation is important plus antibiotics, gamma globulin or granulocyte transfusion, antifungal, sutrim for pneumocystis carniil, acyclovir for herpes simplex, gancyclovir for CMV.
- **Hyperuricemia:** Allopurinol, alkaline urine, hydration.
- **Phosphate binders** e.g calcium carbonate or acetate for hyperphosphatemia.
- **Leukostasis:** is treated by leukopheresis.

- Stimulation of marrow recovery using growth factors. e.g myeloid colony stimulating factors result in more rapid recovery of PNL count in AML.
- Cytotoxic therapy of bulky disease may cause ↑ uric acid, ↑K, ↑P (tumour lysis $)$.

**Treatment of acute lymphoblastic leukaemia (ALL)**

**I – Remission induction** (for 4 weeks).

In this phase the bulk of the tumour is destroyed by combination chemotherapy (marrow ablation) i.e ablation of leukemic cell line in BM with some sparing of normal marrow (ALL blasts are more selectively sensitive to chemotherapy than AML blasts). the drugs are:

- **Vincristine** (oncovin)
  - 1.4 mg/m² up to 2 mg/m² (day 1,8,15,22) I.V

- **Adriamycin**
  - 40mg/m² I.V on running vein (i.e with fluids) to avoid thrombophlebitis (day 1,8,15,22).
  - Adriamycin is one of anthracyclines.

- **Prednisolone**
  - 40 mg/m² oral daily (day 1-28)

- **L-asparaginase**
  - 5000 IU IV (day 15-28)
Manifestations of remission

Improvement of C/P B.M blasts below 5% No blasts in blood

II- Remission consolidation (4 weeks)

If remission has been achieved by induction therapy, residual disease is attacked by therapy during the consolidation phase by:

- Cyclophosphamide (Endoxan) 650 mg/m² (day 1,15,28 I.V), plenty fluid to avoid haemorrhagic cystitis.
- Cytosine arabinoside (Ara-c) 100 mg/m² infusion over 24 hrs. (day 3,4,5,6) every week for 4 weeks.
- 6-Mercaptopurine 50 mg/m² oral (day 1-28).

In acute lymphoblastic leukaemia, CNS prophylaxis must be done by intrathecal methotrexate + hydrocortisone + cytosine arabinoside, this therapy is done as soon as blasts cleared from the blood (during consolidation therapy).

III- Maintenance therapy:

For about 2 years

6- Mercaptopurine oral,daily 50mg/m²

Methotrexate IM or IV 10 mg/m² weekly

Reinforcement therapy can be given during the maintenance therapy in the form of cycles of vincristine, prednisolone, doxorubicin and Ara-C alternating with cyclophosphamide for 5 days every 3 months plus intrathecal therapy twice/3months.

Treatment of acute myeloid leukaemia (AML)

Remission induction: This requires ablation of all marrow elements, both blasts and normal tissue, recovery of normal marrow tissue is possible.

- Cytosine arabinoside (ara-c). I.V, 100 mg/m²/12 hr (day 3-9).
- 6-Thioguanine (lanvis) Oral, 100 mg/m² (day 1-7).
- Adriamycin (Doxorubicin) I.V, 25 mg/m² (day 1,2,3).

This cycle can be repeated according to marrow response.

Consolidation therapy:

- As above for 2-4 cycles ± CNS prophylaxis (used for M₄, M₅)

Maintenance therapy is not thought to be of benefit in most patients with AML!? BM transplantation is an excellent choice. Methotrexate and 6-thioguanine can be used for maintenance if BM transplantation is not feasible.
Cases of M₃ treated by retinoic acid as it can correct the coagulation disorders of M₃ followed by Ara-C and an anthracyclin drug.

- **Bone marrow transplantation** (BMT) is definitive, curative therapy for acute leukaemia, it is used after the first remission has been obtained. The goal of BMT is permanent eradication of the residual leukaemia and prevention of relapse. Ultra-high dose chemotherapy alone or with radiotherapy prior to BMT may be given in doses that are not limited by concerns of toxicity to the marrow. When no matched donors are available, **autologous BMT** using marrow infusion of harvested and stored remission marrow.

**FAB Classification of acute lymphoblastic leukaemia**

L1: cells are small and homogenous (child variant).

L2: cells are large and heterogenous (adult variant).

L3: Burkitt like large cells, vaculated cytoplasm (aggressive type).

**FAB Classification of Acute myeloid leukaemia**

- M0: Undifferentiated
- M1: Myeloblastic without maturation
- M2: Myeloblastic with maturation
- M3: Promyelocytic
- M4: Myelomonocytic
- M5: Monocytic or monoblastic
- M6: Erythroleukemia
- M7: Megakaryoblastic

- The above classifications depend on the shape of cells in BM (cytology).
- In M₃ DIC is common.
- M₄, M₅ characterized by tissue infiltration.
- Gingival hypertrophy common with M₅.
- M₆ characterized by formation of multinucleated RBC blasts in BM.
- M₇ characterized by acute myelofibrosis.

**Cytochemistry:**
- AML blasts are myeloperoxidase positive (contain the enzyme).
- ALL blasts are myeloperoxidase negative.

**Immunolgoical classification of acute leukaemia:**
Antibodies are used to detect specific antigens on blast cells:
- Myeloid markers (CD₁₃, CD₃₃) are positive in AML.
- B cell markers (CD₁₉, CD₂₀) are positive in B- ALL.
- T cell markers (CD₂, CD₃, CD₅) are positive in T-ALL.
Chronic myeloid leukemia (CML)

Abnormal proliferation of granulocytes precursors (immature myeloid cells) in the B.M, blood, & other tissues. Also mature neutrophils are proliferating, CML accounts for about 14% of all leukaemias. It is a disease of adults with peak at 40-60 years. Unlike acute leukaemia CML has a more slowly progressive course.

C/P: (30% of patients are asymptomatic at the time of diagnosis).

Symptoms:
- Dragging pain in the left hypochondrium (huge spleen).
- Stitching pain due to splenic infarction.
- Bony aches, manifestations of anaemia.
- Fever, sweating, not due to infection.
- Bleeding tendency (uncommon)
- Symptoms of leukostasis present with TLC ≥ 300,000/mm³ e.g headache, focal neurologic deficits and priapism.

Function of neutrophils and platelet count are nearly normal so, infection and bleeding are not a feature of the chronic phase of the disease.

Signs: - Huge spleen, friction rub with splenic infarction. - Fever, pallor
- Lymphadenopathy with blast crises– sternal tenderness.

An accelerated phase of the disease is defined by the development of increasing the degree of anaemia or platelet count < 100,000, or marrow or blood blasts between 10-20%.

Blast crisis phase in which the disease transforms into a pattern indistinguishable from acute leukaemia either myeloid (80%) or lymphoblastic (20%). The marrow or blood blasts ≥ 20-30%. Blast crises are the cause of death in the majority of cases.

Investigations:
1- Blood Picture: TLC is increased usually above 25,000/mm³ and often above 100,000, it may reach 1000000/mm³
It is mainly of myeloid series, in the form of myelocytes, promyelocytes and mature neutrophils. Myeloblasts are less than 10%, marked increase of myeloblasts occurs with blast crises. Basophilia and eosinophilia are usually present, platelet may be normal, low or raised. Basophilia tends to increase as the disease progresses. Normocytic normochronic anaemia.
2- Sternal puncture showing increased myeloid precursors (myelocytes promyelocytes).

3- ↑↑ Uric acid, ↑LDH. High levels of vit B12 due to ↑ granulocyte production of transcobalamin I.

4- BM examination for chromosomal study showing Philadelphia (ph) chromosome. It is translocation of long arm of chromosome number 22 to long arm of chromosome number 9. It is present in the marrow precursor cells, and present in 90-95% of cases.

| Fusion of chromosomes 9 with 22 produces fusion oncogene that encodes elongated protein tyrosine phosphokinase, this makes stem cells to turn off the apoptosis pathway of programmed cell death. Thus, these abnormal cells are immortalized with accumulation in bone marrow and peripheral blood. |

5- CML is now diagnosed using PCR to reveal the abnormal fusion protein, this is used when the marrow appears normal using morphology and routine cytogenetics.

6- Leucocytic alkaline phoshatase is low.

**Treatment:**
(No specific therapy is required, if the patients is asymptomatic and the leucocyte count not greatly elevated, but in the majority of patients, treatment is necessary).

1- G. measures → Blood transfusion - Antibiotics for infection.

2- Specific treatment.

- **Hydroxyurea** for hyperleukocytosis, 1-6 gm / day orally then tailored to maintain TLC within normal range. It is considered to be a palliative agent to reduce the leukaemia cell burden in the chronic phase of CML. The dose is decreased as the count decreases and is usually 1-2 gm/d when TLC reaches 20,000/mm³. Maintenance doses can be used if needed to keep TLC at about 5-10,000/mm³.

- **Alpha interferon** administrated three times weekly, it can control the disease in 70% of patients. It can induce reduction in the percentage of ph-positive cells in about 20% of patients and apparent elimination of the ph chromosome in about 5%, this will give prolonged survival.

- **Radiotherapy** for the spleen or splenectomy to decrease symptoms.

- **Leucopharesis**.
Imatinib, a tyrosine kinase inhibitor that reverses the enzymatic actions of the fusion protein, it is recently used in cases of CML.

- Treatment of accelerated phase and blast crisis of the disease is more difficult:
  - In accelerated phase we can give hydroxyurea ± cytosine arabinoside.
  - When blast crisis occurs, the type of blast cell should be determined, if lymphoblastic give the treatment of acute lymphoblastic leukemia, if myeloid give the treatment of acute myeloid leukemia. Response to treatment for the later is very poor.

Recently imatinib also can be used in treatment of accelerated phase and blast crisis.

- Bone marrow transplantation can be done. It is the therapy of choice for younger patients, autologous stem cell transplantation also can be done.

**Chronic lymphocytic leukaemia**

This is the most common variety of leukaemia in adults, and accounting for about 25% of all leukaemias. The male to female ratio is 2 : 1. There is accumulation of mature appearing lymphocytes in blood, BM and lymphoid tissue.

It is a leukaemia characterized by:

- Mostly, the cell of origin is B lymphocyte
- Infiltration of lymphoid organs e.g. spleen, lymph nodes, liver and also BM.
- Reduced immunoglobulins → infection.
- Abnormal immune reaction → auto antibodies

**C/P:**

1- Age (usually the disease occurs at age >45 years with peak at 65).
2- Some cases are asymptomatic.
3- Generalized lymphadenopathy.
4- Liver & spleen enlargement.
5- Anaemia in advanced cases, autoimmune haemolytic anaemia.
6- Bleeding tendency.
7- Recurrent infections (reduced immunoglobulins).
Staging of chronic lymphocytic leukaemia:

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<tr>
<td></td>
<td>• Blood and marrow Lymphocytosis.</td>
<td>• Blood and marrow Lymphocytosis three or more areas of lymphoid tissue enlargement.</td>
<td>• Blood and marrow Lymphocytosis</td>
</tr>
<tr>
<td></td>
<td>• Less than 3 areas of lymphoid tissue enlargement.</td>
<td>• No anaemia or thrombocytopenia.</td>
<td>• Anaemia and/or thrombocytopenia regardless the number of areas of lymphoid tissue enlargement.</td>
</tr>
<tr>
<td></td>
<td>• No anaemia or thrombocytopenia.</td>
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Investigations:

1- Diagnosis of CLL requires sustained absolute lymphocytosis with minimal level > 5000/mm³, it may reach 40,000-150,000/mm³. TLC in the majority of patients is between 50-200,000/mm³, although it may increased up to 1,000,000/mm³, about 95% of these cells are mature looking lymphocytes.

2- Normocytic normochromic anaemia with stage C.

3- Low platelets with marrow failure or immune destruction.

4- Coomb’s test is + ve i.e autoimmune haemolytic anaemia may occur (warm Ab).

5- Sternal puncture, BM heavily infiltrated with lymphocytes (> 30%).

6- Immunoglobulins are low or normal.

Treatment

Indications of therapy in CLL:

• Anaemia  
• Markedly enlarged spleen.
• Symptomatic lymphadenopathy.
• Autoimmune complications e.g autoimmune haemolytic anaemia.
• Richter transformation, see later.

♦ Stage A: - No specific treatment is required
  - Life expectancy is normal in older patients. The patient should be reassured with follow up.

♦ Stage B: Chemotherapy with chlorambucil may be initiated in symptomatic patients (see below). Local radiotherapy to L.N may be given if causing discomfort (see below).

♦ Stage C: - Transfusion of packed RBCs for anaemia and platelet concentrate for thrombocytopenia.
  - If there is BM failure, we give prednisolone 40 mg/d for 2-4 weeks, a degree of BM recovery is usually achieved.
  - More aggressive combination chemotherapy may be beneficial.
* Cytotoxic therapy:
Chlorambucil 2-4 mg / d orally, up to 6-8 mg/d with dose adjustment according to blood counts. It will reduce the blood count, and decrease lymphadenopathy and splenomegally (it palliates the disease). The BM rarely return to normal.
Cyclophosphamide also can be used 50-100 mg/d.
* The treatment is usually limited to a few months and then withheld until progression, maintenance therapy has no definite value.

* Corticosteroid are indicated with:

- Autoimmune haemolytic anaemia
- Pancytopenia (BM failure)

* Radiotherapy:
- local radiotherapy may be used to reduce spleen size or for local symptoms caused by lymphodenopathy.

* Infections: must be treated vigorously, recurrent infections respond to immunoglobulin replacement.

* Splenectomy: to treat autoimmune haemolytic anaemia, huge spleen or hypersplenism.

Rituximab is a monoclonal antibody directed against tumour cell surface antigens (anti-CD20 surface antigen), it can be used in combination therapy in CLL with good response. Tumour cell lysis occurs by both complement and antibody dependent cellular cytotoxicity.

**Prognosis of chronic leukaemia:**
- Chronic myeloid leukaemia, patients who have significant reduction in the ph chromosome with treatment do best.
- Chronic lymphocytic leukaemia rarely transforms to an aggressive high grade lymphoma, so called Richter’s transformation.

**Hairy cell leukemia**
- It is a lymphoid neoplasm, the term hairy is descriptive of cytoplasmic projections of the leukemic cells (hairs).
- There is accumulation of abnormal B lymphocytes in the marrow, peripheral blood and spleen. BM fibrosis and cytopenia are frequent.

**Diagnosis** (age around 50 years, $\frac{\mathcal{G}}{\mathcal{F}}$ ratio 4 : 1)
- Splenomegally occurs in 80%, of cases, lymphadenopathy is uncommon.
- There is vasculitis, erythema nodosum.
- Neutropenia, anaemia, thrombocytopenia due to marrow fibrosis or hypersplenism.
- Hairy cells (lymphocytes with cytoplasmic projections) in the blood and B.M.
BM aspiration is usually inadequate (dry tap) due to marrow fibrosis so, BM biopsy is necessary.

**Treatment**
- Splenectomy in the past was the corner stone of therapy, now it is indicated in severe cytopenia (hypersplenism).
- Interferon therapy - Antibiotic for infection - Steroids for vasculitis.

Recently purine analogues 2-chloroadenosine acetate and pentostatin can be used with good response. Also, rituximab is used if there is no response.

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**Neutropenia and agranulocytosis**

- Neutropenia is defined as a circulatory neutrophil count below 1500/mm$^3$.
- Neutrophil count of less than 500/mm$^3$ is regarded as severe neutropenia.
- A virtual absence of neutrophils is called agranulocytosis.

**Causes of neutropenia:**

**Acquired**
- Viral infection (the commonest cause).
- Severe bacterial infection e.g typhoid.
- Immune neutropenia.
- Pancytopenia:
  - BM aplasia (see before).
  - Hypersplenism.
- Pure white cell aplasia.

**Inherited:**
- Cyclic neutropenia.
- Chediak – Highashi $\$
- Kostmann’s $\$ (infantile agranulocytosis).

**Aetiology:**

**C/P:**
- Recurrent infections.
- Sore throat with throat ulcers, with scanty pus and minimal signs of inflammation.
- Life threatening infections e.g pneumonia and septicaemia with severe neutropenia.

**Investigations:**
- Blood Picture $\rightarrow$ ↓ P.N.L. (leucopenia with relative lymphocytosis).
- RBCs, platelets are normal.
- BM examination will indicate whether neutropenia is due to depressed production or increased destruction of neutrophils.

**ttt:**
- Antibiotics are necessary.
- Treatment of the cause e.g stopping the offending drug.
- G-CSF is used to decrease the period of neutropenia after chemotherapy and haemopoietic transplantation.
The myeloproliferative disorders are clonal stem cell disorders characterized by leukocytosis, thrombocytosis, erythrocytosis, splenomegally and bone marrow hypercellularity. They are dividing into the following types according to the predominant hyperproliferative cell type:

- Polycythemia vera → dominant increase of RBCs precursors.
- Essential thrombocythemia → dominant increase of megakaryocytes.
- Chronic myeloid leukemia → dominant increase of myeloid cells.
- Myelofibrosis → dominant increase of dysplastic megakaryocytes that produce fibroblast growth factors stimulating fibroblasts.

It is a neoplasm of BM stem cells affects mainly erythroid line, also there are increase of WBCs and platelets. If may progress to myelofibrosis.

**C/P:**

- Insidious onset, age > 60 years:
- Plethora.
- Hyperviscosity $\rightarrow$ C.H.F, thrombosis, sluggished cerebral blood flow with vertigo, tinnitus and visual disturbances. Also there is hypertension together with intermittent claudication.
- Splenomegaly.
- Engorged retinal veins by fundus examination.
- Platelet dysfunction $\rightarrow$ Thrombosis, bleeding.
- Itching due to ↑ histamine production due to basophilia, the itching occurs usually after a hot bath or when the patient is warm.

**Criteria for diagnosis of polycythemia. Vera :-**

| A1 | E elevated red cell mass | B1 | Platelet > 400,000/mm$^3$ |
|    | > 36 ml/kg ($\delta$), > 32 ($\varphi$) | B2 | TLC > 12,000/mm$^3$ |
| A2 | Normal arterial O2 saturation, >92% (to exclude hypoxia as a secondary cause of polycythemia) | B3 | High leucocytic alkaline phosphatase |
| A3 | Splenomegaly | B4 | High serum B12 |

**Diagnosis = A1 + A2 + A3 or A1 + A2 + only two from B**
**Investigations:**
1- Blood Picture → Elevated count in all series mainly RBCs, ↑ Red cell mass.
2- B.M examination showing erythroid hyperplasia, ↑ megakaryocytes.
3- Low erythropoietin level.
4- Elevated serum B12, leucocytic alkaline phosphatase and uric acid.
5- Artrial PO2 is often slightly low, with low normal O2 saturation at the time of diagnosis, increasing to normal following therapeutic reduction in the red cell mass with decreased blood viscosity.

**Treatment:**
1- General treatment: allopurinol to decrease uric acid production, low dose aspirin (100 mg/d) to prevent thrombotic events. Antihitaminics (H1 blockes) and avoidance of very hot baths to treat itching.
2- Venesection to keep the PCV to 45% range.
3- Radioactive p (I.V) or chlorambucil but they may lead to acute leukaemia.
4- Hydroxyurea is better than chlorambucil and radioactive P.
5- Interferon is effective to control myeloproliferation and splenomegally.
6- Treatment of complications.

**Causes of polycythemia** (Absolute erythrocytosis)
1- Polycythemia rubra vera (myeloproliferative disorder).
2- Secondary polycythemia:
   → Hypoxia e.g. COPD, interstitial lung diseases, cyanotic heart disease and high altitude.
   → Cushing $ (↑ cortisol).
   → Polycystic kidney disease (↑ erythropoietin).
   → Hypernephroma, hepatoma (↑ erythropoietin).
   → Drugs e.g erythropoietin, androgens.

- Stress polycythemia (Gaisbock’s polycythaemia), affects obese hypertensive men. No required treatment.
- Relative erythrocytosis due to known causes of contracted plasma volume e.g excessive diuresis and severe gastroenteritis.

In secondary polycythemia there are plethora, hyperviscosity but no splenomegaly, no itching and the erythropoietin level is high. It is treated by venesection with treatment of the cause.
Myelofibrosis

- Expansion of all B.M elements with stimulation of bone marrow fibroblasts by fibroblast growth factors produced by dysplastic megakaryocytes leading to deposition of excessive collagen with marrow fibrosis (the fibrosis is a secondary late event).
- Extramedullary haematopoiesis → liver ++ & spleen ++.

C/P:
- Anaemia, and massive splenomegaly are the hallmarks of the disease.
- Severe Pain related to respiration may indicate perisplenitis due to splenic infarction
- Bleeding tendency due to thrombocytopenia
- Portal hypertension may occur due to increased portal blood flow.

Investigations:
1- Normocytic normochromic anaemia - Tear drop cells (RBCs)?!.
   Leucoerythroblastic features may present e.g nucleated RBCs and WBCs precursors, later leucopenia may developed.
2- Leucocytosis with shift to the left (immature granulocytes).
3- B.M aspiration showing dry tap.
4- B.M biopsy (trephine from iliac crest) is essential.

Treatment:
- Supportive • Folic acid, allopurinol. • Blood transfusion.
  • Danazol → ↑ Hb.
- Hydroxyurea decreases WBCs and platelet count, increases haematocrit and decreases splenic size. Steroids for autoimmune haemolytic anemia.
- Splenectomy: may be required for huge spleen and also to reduce blood transfusion requirement (hypersplenism) and to control thrombocytopenia and refractory haemolysis.
- B.M transplantation.

Essential thrombocytosis

- It is a myeloproliferative disorders.
- Increased platelet count is usually ≥ 600,000 /mm$^3$ (sustained) with → bleeding or thrombosis.
- Occasionally splenomegally is present.
- BM showing megakaryocytic proliferation.
**Treatment:**

- Urgent platelet count reduction can be achieved by plateletpheresis.
- Hydroxyurea can reduce platelet count.
- Anagrelide inhibits marrow megakaryocyte maturation.
- Interferon also can suppress the abnormal megakaryocyte clone.
- Aspirin therapy is controversial because of the associated increased risk of bleeding.

<table>
<thead>
<tr>
<th>Causes of Benign or reactive thrombocytosis</th>
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<tr>
<td><strong>Platelet count is usually ≥600,000 (non sustained).</strong></td>
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<tr>
<td>- Stress and exercise.</td>
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<tr>
<td>- Splenectomy, or hyposplenism (loss of a major site of platelet destruction).</td>
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<td>- Bleeding.</td>
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<tr>
<td>- Haemolytic anaemia.</td>
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<tr>
<td>- Chronic inflammatory diseases e.g. rheumatoid arthritis, inflammatory bowel disease or infections. (thrombocytosis is a part of acute phase response).</td>
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</tbody>
</table>

**N.B.:** Thrombocytosis occurs in other myeloproliferative disorders.
HAEMOSTASIS AND BLEEDING DISORDERS

Definition:
• It means stopping of bleeding and prevention of blood loss when a blood vessel is injured with the formation of haemostatic plug.
• It occurs by the following sequences:
  1. Vasoconstriction.
  2. Platelet plug.
  3. Formation of blood clot.
  4. Repair of the damaged blood vessel.

This needs:
• Coagulation factors.
• Platelets.
• Vascular endothelium and blood vessel wall.
  So haemostasis is similar to a building which needs the following:

  Base Stones Cement substance
  Blood vessel wall Platelets Fibrin (coagulation)

Platelets tests

1- Platelet count: Normally, it is 150.000 – 400.000/mm³.

Thrombocytopenia
  i.e. platelet count < 150.000

Clinical petechiae
  with platelet count < 50.000-20.000

Serious spontaneous
  Bleeding e.g GIT or CNS
  platelet count < 10.000 – 20.000

• The rate of drop of platelet count is very important so, sudden drop
  of the count → bleeding (regardless the exact count)!?
• Platelet count 80.000-100.000 is adequate for haemostasis.

II- Bleeding time:

It is the time (in minutes) that is taken for bleeding to cease from a small superficial wound. It is mainly affected by platelet count, function and integrity of vessel wall.

- Reference range:
  Ivy’s method → 2-7 m.
  Duke’s method → up to 5 m.

- If bleeding time is prolonged, this means
  Thrombocytopenia
  Thrombasthenia
  e.g uraemia, von willebrand’s disease
  Vascular abnormality e.g Henoch scholein purpura.
III- Platelet function tests:
- Platelet adhesion tests
- Platelet aggregation tests, to measure the platelet response to ADP, ristocetin and adrenaline.

**Hess capillary fragility test (old test) !?:**
It may detects vascular purpura, it may be positive in other types of purpura, Put syphgomanometer cuff on the arm & inflate between systolic and diastolic pressure then draw an area below the cubital fossa 5 cm diameter. Normally, 0–5 petichae are seen in this area, after 5 minutes.

In vasculitis e.g Henoch schonlein Purpura, hereditary hemorrhagic telangiecstasia, bleeding time may be normal.

---

**Role of platelets in haemostasis**

**Vascular injury**

- Exposure of collagen
- Release of (VWF) from endothelium
- Platelet adhesion
- Platelet release
- P.G. + ADP
- Platelet aggregation

**Vasoconstriction**

By:
- Nervous reflex
- Myogenic contraction
- Release of

**Thromboxyane A$_2$ (TA$_2$)**

Enhances platelet aggregation.

**Platelet factor 3**

Enhances coagulation

**Fibrin**

**Platelet plug**
Other Functions of platelets:
Release of growth factors that cause multiplication and growth of fibroblasts as well as the vascular endothelium and smooth muscle cells (which repair the damaged vascular walls).

Process of coagulation

1- Extrinsic pathway: (It is a rapid process) i.e. occurs within about 15 seconds
   It is triggered by trauma
   Release of tissue thromboplastic
   Activation of factor VII
   To common pathway to activate factor X in presence of calcium (Ca)

2- Intrinsic pathway: (It requires few minutes)
   It is triggered by contact of blood with foreign surface e.g. any surface other than endothelium. eg. collagen.

Common pathway:
Intrinsic pathway Or Extrinsic pathway

X → Xa
Ca
Va
Prothrombin → Thrombin

IXCa → IXa+VIIIa+Ca
Activation of factor X
(Common pathway)

Both systems are involved in clotting following tissue injury, where the extrinsic system occurs first followed by the intrinsic system.
**Factors of coagulation:**

(All are present in the plasma except factor III)

I  : Fibrinogen.  
II : Prothrombin.  
III : Thromboplastin (in tissue only).  
IV : Calcium  
V  : Proaccelerin.  
VII: Proconvertin.  
VIII: Anti-haemophilic globulin.  
IX : Christmas factor.  
X  : Stuart prowar factor.  
XI : Plasma thromboplastin.  
XII: Hegman factor.  
XIII: Fibrin stabilizing factor.

**Factor VIII has three components:**
- VIIIc, it is necessary for coagulation.
- VIIIvw, It is necessary for platelets adhesion.
- VIIIAg, is the antigenic portion.

---

**Tests for intrinsic pathway of coagulation**

Clotting time and partial thromboplastin time are indicators of the intrinsic pathway.

1. **Whole blood clotting time**
   It is about 5-10m. this test is insensitive as activation of Hegman factor takes several minutes.

2. **Partial thromboplastin time PTT (activated)**
   It is performed by adding a surface activator (e.g Kaolin), phospholipids and calcium to the patient’s plasma (intrinsic system).
   It is very sensitive.
   It is normally 30-40 seconds. It is prolonged in deficiency of factors: I, II, V, VIII, IX, X, XI or XII. Also it is prolonged in DIC, heparin therapy and liver disease.

- Heparin therapy affects clotting time & PTT.
- In patients under heparin therapy, we can adjust the dose according to PTT (it must be 1.5-2 times the patient's preheparin PTT).
- Thrombin time (TT): 12-20 seconds. It is performed by adding thrombin to the patient's plasma. It is prolonged in
  - Hypofibrinogenemia, dysfibrinogenemia.
  - Increased fibrin degradation products (FDPs).
  - Heparin therapy.
Tests for extrinsic pathway of coagulation

- **Prothrombin time (PT):**
  It is measured by adding tissue thromboplastin and calcium to the patient's plasma (extrinsic system).
  It is normally 10-14 seconds, it indicates the efficiency of the extrinsic pathway.
  It is prolonged in:
  - liver disease, vit K ↓.
  - deficiency of factors I, II, V, VII or X.
  - oral anticoagulant therapy, DIC.

- In patient under oral anticoagulant, we can adjust the dose by PT, it must be 1.5-2 times the control value.
- Prolonged PT with normal PTT means extrinsic pathway defect. e.g. deficiencies or inhibitors of factors 2, 5, 7, 10 and with oral anticoagulant therapy.
- Prolonged PTT with normal PT means intrinsic pathway defect. e.g. deficiencies or inhibitors of factors 8, 9, 11, 12, and with heparin therapy.
- Prolonged PT & PTT means common pathway defect or combined defects.

- **INR (international normalized ratio),** it is equal to \((PT \text{ ratio})^{\text{factor}}\).
  PT ratio = patient PT / control PT.
  The INR is an accurate method for monitoring oral anticoagulant therapy. It is normally 0.8-1.2, the recommended therapeutic target is an INR with range of 2-3 INR for all indications except prosthetic heart valves, INR 2.5-3.5 is suggested.

### Fibrinolytic system

| Plasminogen (tissue plasminogen activator) → plasmin → Fibrin → Fibrin degradation product (FDP) |

### Inhibitors of coagulation

1. Tissue factor pathway inhibitor (TFPI) which rapidly removes the tissue factor – factor Vila complex that initiates coagulation.
2. Antithrombin III, it is enhanced by heparin.
3. Protein C: This protein is activated by thrombin-thrombomodulin complex. Activated protein C inactivates factor V and factor VIlia, this inactivation is enhanced by protein S.

- Fibrinogen assay (160-450 mg/dl), it is used to detect hypofibrinogenaemia.
- Hypofibrinogenaemia or dysfibrinogenemia leading to prolonged PT and PTT.
- FDP assay (it is normally <10 ug/ml), it is elevated in DIC.
**Definition:** Multiple spontaneous capillary bleeding in the skin & mucous membranes due to defects in platelets or in the capillary wall.

**Causes:**

I. **Platelet disorders:**

A. **Thrombocytopoenia**

- **Platelet Survival**
  - ITP
  - Hypersplenism and splenic platelet sequestration.
  - Auto Ab e.g SLE,
  - Drugs (see below)

- **Platelet Production**
  - Vit. B 12↓, folic ↓
  - B.M depression or infiltration
  - Uraemia
  - Congenital deficiency of megakaryocyte CFUs.
  - Drugs (see below)

- **Consumption**
  - DIC
  - TTP
  - HU $ (see later)

- Alchohol, thiazides, estrogens, cyclophosphamide $\rightarrow$ Inhibition of megakaryocytic series production.
- Penicillin, cephalosporines, sulfa & methyl dopa $\rightarrow$ destroy platelet through immune mechanism.
- Heparin may lead to thrombocytopoenia due to drug Ab binding to platelets or by direct aggregation of platelets by heparin. The Ab mediated thrombocytopoenia is paradoxically associated with thrombosis.

B. **Thrombathenia**

- Hereditary
- Acquired
  - Drugs
  - Uraemia

C. **Thrombocytosis leading to**

- Purpura with Platelet dysfunction
- Hypercoagulable state

II. **Vascular purpura**

- **Senile**
  - Allergic purpura (Henoch schonlein purpura)
  - Other vasculitides

- **Infections**
  - (Meningitis with septicemia) leading to purpura fulminans

It occurs as a result of degeneration and loss of dermal collagen, elastin and subcutaneous fat.

**Purpura simplex** denotes easy bruisability, observed especially in females in lower extremities. No excessive bleeding with surgery, normal bleeding time, it is a benign condition.
**C/P of purpura:**

I- Bleeding:
   i. Skin: Multiple petichae, without raised edge in platelet disorders, or with raised edge with vascular disorders. Small ecchymosis can also occur.
   ii. Bleeding per orifices and mucous membranes: e.g. epistaxis, uterine bleeding or gingival bleeding.
   iii. Internal organ haemorrhage: e.g. cerebral haemorrhage

II- Features of the cause.

Vascular disorders are characterized by bleeding into skin, but bleeding from mucous membranes sometimes occurs, the bleeding is rarely severe.

---

(A) **Disorders of Platelets**

(1) **Idiopathic thrombocytopenic purpura (ITP)**

It is an autoimmune disease → auto Ab → attack platelets. The antibody – coated platelets are removed following binding to Fc receptors on macrophages in the reticuloendothelial system.

**Types:**

**ITP in children:**
- The condition is usually acute but self-limiting and may follow a viral infection or immunization.
- There is sudden onset of purpura and sometimes oral and nasal bleeding.

**ITP in adults:**
- The presentation is usually less acute than in children. It is usually seen in women and may be associated with other autoimmune disorders e.g. autoimmune haemolytic anaemia (Evan’s syndrome).

**C/P of ITP:**
- Major haemorrhage is rare except in cases of severe thrombocytopenia.
- Purpuric eruption, epistaxis and menorrhagia are common.
- Splenomegaly is rare.

**Investigations:**
- Low Platelet count.
- B.M examination → hyperplasia of megakaryocytes.
- Antibodies against platelets.

The detection of platelet autoantibody is not essential to confirm the diagnosis, we can depend on exclusion of other causes of thrombocytopenia.
**Treatment:**

**Children:**
- Asymptomatic patients with platelet counts > 40,000/mm³, no specific therapy will be given. (majority of cases are self limiting within few weeks).
- Presence of moderate to severe purpura, bruising or epistaxis and platelet count less than 20,000-30,000/mm³, give prednisolone 2mg/kg/d (short course), the platelet count usually rises within 1-3 days.
- Persistent bleeding should be treated by platelet transfusion, I.V immunoglobulin.

**Adults:** Prednisone for 2-3 months (1 mg/kg/d), it is less rewarding than in children.
- If no response → splenectomy.
- If no improvement after splenectomy give:
  - I.V immunoglobulin.
  - Immunosuppressive agents e.g azathioprine, cyclosporine.
  - Danazol.
- Blocking Ab (IgG), the infused IgG works by blocking FC receptors on macrophages (binding sites), making fewer of them available for platelet binding and destruction
- Generally patients with platelet counts greater than 40,000/mm³ require no treatment except when they are exposed to surgery.

Q Immune thrombocytopenia:
- ITP
- SLE
- Evan’s syndrome
- Post transfusion purpura
- Drugs (see before).
- Heparin induced thrombocytopenia.

**Platelet consumption**

**Causes:**
1- DIC.
2- Thrombotic thrombocytopenic purpura (TTP).
3- Haemolytic uraemic $\$

**TTP:**
- Middle aged female.
- Thrombocytopenia.
- Microangiopathic haemolytic anaemia.
- Neurological & renal abnormalities.

**Haemolytic uraemic $\$
- Microangiopathic haemolytic anaemia.
- Thrombocytopenia..
- Hyaline thrombi in kidneys with renal failure.

- Dilutional thrombocytopenia can follow massive transfusion.
- Huge spleen can sequester up to 90% of platelets.
(3) Qualitative platelet Disorders

I- Inherited

Adhesion defect  Aggregation defect
e.g Bernard soulier $,  e.g Glanzmann's disease
and Von Willebrand’s disease (VWD)

Von willebrand’s disease (VWD)
- It is the most common inherited bleeding disorder.
- Autosomal dominant (types 1, 2), type 3 is recessively inherited.
- Bleeding time is prolonged (normal platelet count, normal platelet
  aggregation, abnormal adhesion) PTT may be prolonged.
- VWF is decreased, also factor VIII is low.

VWF is a carrier to the antithaemophilic factor so patients manifest both
coagulopathy and abnormal platelet function.

- Type 1: Bleeding time and PTT are normal or ↑. VWF is normal or ↓.
- Type 2: Bleeding time is ↑, PTT is ↑ or normal, VWF is normal or ↓.
- Type 3: Bleeding time and PTT are very high, VWF is absent.

Treatment
i. Factor 8 concentrate.
ii. Fresh frozen plasma, cryoprecipitate.
iii. DDAVP (synthetic ADH) release VWF.

- Acquired VWD may be caused by antibodies that inhibit VWF e.g
  in autoimmune and lymphoproliferative disorders.
- Wiskott-Aldrich $ and TAR $ (thrombocytopenia with absent radii)
  leading to thrombocytopenia with qualitative defect.
- Chediak-Higashi $ leading to qualitative defect only.

II- Acquired disorder of platelets

Platelet arachidonic acid $\xrightarrow{\text{Cyclo-oxygenase}}$ Thromboxan $A_2$ (TA$_2$) $\rightarrow$ Aggregation

Causes:
- Aspirin & NSAID suppress the cyclooxygenase enzyme.  • Uraemia.
- Penicillins, cephalosporins and heparin suppress platelet function.

(B) Disorders of blood vessels and vascular tissue

(1) Henoch–schonlein purpura
It is a type of small vessel vasculitis which occurs in children and young adults.

Aetiology:
- It is a hypersensitivity vasculitis.
- It may be preceded by streptococcal, viral infection or drug administration.
C/P:

- Child or young adult.
- Arthritis, abdominal pain, GIT bleeding may occur.
- Purpuric eruption, petechiae (mainly on the buttocks and legs) with raised edge.
- Glomerulonephritis with haematuria, small percent may develop acute renal failure. The renal lesion is a focal segmental proliferative GN with mesangial hypercellularity with deposition of IgA in the mesangium.

Investigations: Laboratory finding are nonspecific although serum IgA is frequently high, serum complement levels usually are normal.

Treatment

Treatment is usually supportive. Corticosteroids alone are effective for gastrointestinal and joint involvement but glomerulonephritis may requires treatment with both steroids and immunosuppression.

(2) Other disorders of blood vessels and vascular tissues.

(A) Scurvy: It is caused by vitamin C deficiency leading to impaired collagen synthesis. It is associated with perifollicular petechiae and gingival bleeding. Therapy with 1 gm/day of vitamin C rapidly corrects all bleeding.

(B) Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease): It is an autosomal dominant, associated with abnormally thin vessel walls and impaired vascular contractility with friable blood vessels.

C/P: • Abnormally prominent capillaries, venules, arterioles in skin or mucous membranes. e.g on the lips, face, ears, tongue and GIT mucosa.

- GIT bleeding and epistaxis with resultant iron deficiency anaemia.

Treatment: • Nasal emollients (soothing or softening).

- Epsilon Amino Caproic Acid (EACA), it is an antifibrinolytic.
- Iron therapy.

(C) Steroid therapy: Leading to diminished collagen synthesis results in vascular fragility and skin bleeding.
(C) Disorder of Coagulation

Haemophilia is an inherited coagulation defect. It is transmitted as X-linked recessive with deficiency of factor VIII.

C/P:
- Severe cases diagnosed after birth, by cephalohaematoma or bleeding at circumcision.
- Excessive prolonged haemorrhage after trauma.
- Ecchymosis, haematoma.
- GIT bleeding, CNS bleeding.
- Haemarthrosis → fibrosis & deformity.
- Femoral neuropathy due to pressure from retroperitoneal haematoma.
- Calcified haematoma (pseudotumour syndrome).

Investigations:
- Clotting time ↑ - PTT ↑.
- Normal platelet count.
- Normal PT.
- Low factor VIII

Complications:
- Arthropathy.
- Hepatitis (C&B) and HIV.

Severity of Hemophilia (according to the level of factor 8 (u/dl))
- Severe (0-2 u/dl) haemarthrosis, spontaneous bleeding, very prolonged PTT.
- Moderate (2-5 u/dl) haemarthrosis, infrequent spontaneous bleeding, prolonged PTT.
- Mild (5-25 u/dl) haemarthrosis and spontaneous bleeding very unusual, variable PTT.
- Subclinical (25-49 u/dl) bleeding after major trauma or injury, normal PTT.

Treatment:
- Avoid antiplatelet drugs.
- Fresh frozen Plasma, cryoprecipitate.
- Factor VIII concentrate.
- Antifibrinolytic e.g. tranxamic acid (cyklokapron) or epsilon aminocaproic acid (EACA).
- DDAVP (desmopressin) → ↑ level of factor VIII.
- Liver transplantation can result in cure of haemophilia, but this has been done rarely.
• Factor IX deficiency (Haemophilia B), it is X-linked recessive. It is similar to haemophilia A.
• Hegman factor deficiency, there is prolonged PTT but with no bleeding tendency.

Q. Clinical approach to a case with bleeding tendency

<table>
<thead>
<tr>
<th>Coagulation Defect</th>
<th>Platelet defect</th>
<th>Vascular defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematoma, Haemarthrosis, large ecchymosis</td>
<td>Mucosal bleeding (epistaxis), gum bleeding, Petichae without raised edge or small ecchymosis</td>
<td>Petichae with raised edge (palpable purpura)</td>
</tr>
<tr>
<td>Poor effect of compression</td>
<td>Good effect of compression</td>
<td>Good effect of compression</td>
</tr>
<tr>
<td>Bleeding is post-traumatic</td>
<td>The bleeding is usually spontaneous</td>
<td>The bleeding is usually post-Traumatic</td>
</tr>
<tr>
<td>• Prolonged PT or PTT or both, normal bleeding time. • Assay of factors of coagulation is important.</td>
<td>Prolonged bleeding time. Normal PT and PTT. PTT is prolonged in VWD.</td>
<td>Normal PT, PTT bleeding time is usually normal in most cases. Specific tests for vasculitides.</td>
</tr>
</tbody>
</table>

Classification of coagulation disorders:

(1) Hereditary coagulopathies:
• Hemophilia A, B.
• Von willebrand’s disease.
• Factor 11, 12 deficiency.

(2) Acquired coagulopathies:
(A) Vitamin K-dependent factor deficiency (e.g. hypoprothrombinemia)
• Liver failure, biliary obstruction.
• Malabsorption and nutritional disorders with vitamin K deficiency.
(B) Disseminated intravascular coagulopathy.
Disseminated intravascular coagulation

It represents a widespread coagulopathy (microvascular thrombi) with consumption of coagulation factors due to activation of coagulation process either by intrinsic or extrinsic pathways with resultant fibrinolysis. It may lead to haemorrhage or thrombosis or both.

Etiology and pathogenesis:

- DIC is a common acquired coagulopathy that occurs secondary to other disease processes e.g:
  
  (a) Activation of the intrinsic coagulation pathway by endothelial damage e.g gram negative sepsis, meningococcemia and viremia.
  
  (b) Activation of the extrinsic pathway by abnormal entry of tissue thromboplastins into the circulation e.g in obstetric complications, carcinomatosis and massive trauma.

DIC is initiated by stimuli in the systemic circulation that activate the intrinsic or the extrinsic pathways → excessive formation of thrombin → activation of coagulation in microcirculation (organ damage)

Consumption of coagulation factors and platelets with activation of the fibrinolytic system with subsequent bleeding tendency.

Causes of acute DIC:
- Spesis, burns, trauma.
- Amniotic fluid embolism.
- Abruptio placentae.

Causes of chronic DIC:
- Malignancy.
- Retained dead fetus (IUFD).

C/P (Notice the clinical features of the cause)

It varies depending on the balance between intravascular-coagulation / fibrinolysis and factors depletion. Usually there is bleeding together with organ failure due to microvascular thrombi.

(a) In acute cases, depletion is dominant and the major symptoms are bleeding and shock, organ failure also occur.

(b) In chronic cases, thrombosis may predominate with organ failure, bleeding is usually minor.

Many cases of DIC involve abnormal coagulation parameters but with no bleeding or clotting (subclinical disorders), whereas other cases have a mixture of both bleeding and clotting complications.
Investigations:

<table>
<thead>
<tr>
<th>Acute DIC</th>
<th>Chronic DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Platelet markedly ↓.</td>
<td>• Platelet mild ↓.</td>
</tr>
<tr>
<td>• ↑↑ PT, PTT.</td>
<td>• PT &amp; PTT may be normal,</td>
</tr>
<tr>
<td>• ↑↑ FDPs.</td>
<td>• ↑ FDPs.</td>
</tr>
<tr>
<td>• Fibrinogen ↓.</td>
<td>• Fibrinogen may be normal.</td>
</tr>
<tr>
<td>• TT ↑.</td>
<td>• TT may be normal</td>
</tr>
<tr>
<td>• ↓ V, VIII.</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment of DIC:** (It is controversial)

- Treatment of the triggering causes.
- In **acute DIC** blood products should not be administered unless clinically significant bleeding is present or if the risk of bleeding is felt to be high e.g. markedly lowered levels. In this situation there is no convincing evidence that transfusion support (fueling the fire) so, give RBCs concentrate plus:
  - Platelet transfusion for a target platelet count 20,000-30,000 or > 50,000/mm³ in life threatening haemorrhage.
  - Cryoprecipitate can be given with fibrinogen levels < 80-100 mg/dL.
  - Fresh frozen plasma should be given for significant bleeding and prolonged PT and PTT.

In most cases of acute DIC heparin does not decrease the mortality, its use may aggravate bleeding (it can be used with caution in cases of ongoing bleeding despite appropriate treatment !?)

- In case of **chronic DIC** we can give heparin 500-750 units/h without loading bolus.
- Antithrombin and/or activated protein C have been used in selected cases.
- EACA or tranexamic acid (antifibrinolytics) are contraindicated but may be used in patients with profuse bleeding with no response to other treatment (in whom FDPs are felt to be inhibiting platelets) !?.

**Important notes:**

- Protein C, S and antithrombin III are vit K dependent factors, they are natural anticoagulants.
- Thrombin - Thrombomodulin complex activates protein C in the presence of protein S.
• The activated protein C inactivate factor V and factor VIII.
• Recently a specific mutation in factor V that render it resistant to inactivation by protein C (factor V Leiden).
• Coagulation disorders include bleeding tendency (coagulation defect) and hypercoagulability !?.

**Hypercoagulable states (thrombophilia)**

**Acquired medical disorders**
1- Malignancy (Trousseau's syndrome) i.e chronic DIC.
2- Behcet's syndrome
3- Nephrotic $ (wasting of antithrombin III in urine).
4- Pregnancy and oral contraceptive agents cause elevation in most procoagulants and diminution of most fibrinolytic and inhibitor proteins.
5- Polycythaemia rubra vera
6- Essential thrombocytosis.
7- Myelofibrosis
8- Paroxysmal nocturnal haemoglobinuria.
9- Hyperlipidemia.

**Deficiency of anticoagulants**
1- Antithrombin III deficiency (often causes recurrent venous thrombosis in young patients with resistance to heparin therapy).
2- Protein C deficiency (venous thrombosis and predisposition to skin necrosis usually occur with warfarin therapy without concomitant heparin).
3- Protein S deficiency.

Warfarin inhibits production of vit K dependant protein C synthesis, and because of its short half-life, protein C levels rapidly fall before a decline in the levels of procoagulant factors II, VII, IX and X, this leading to microvascular thrombosis.

**Factor V Leiden** i.e. resistance of factor V to protein C. It is now known to be the most common inherited hypercoagulable state.

**Antiphospholipid antibody (see later)**
Inherited causes of thrombophilia are (antithrombin III, protein C, S, deficiency and factor V leiden.)
Presentations of hypercoagulable states (thrombophilia):

- Recurrent venous thrombosis.
- An unusual venous thrombosis e.g mesenteric, cerebral vein thrombosis and Budd chiari $.
- Venous thrombosis under age 40 years.
- Arterial thrombosis in the absence of arterial disease.
- Recurrent abortions.
- Recurrent superficial thrombophlebitis.

Investigations:

- Prolonged PTT, Lupus anticoagulants and anticardiolipid (antiphospholipid $).
- Detection of levels of protein C, S and antithrombin III in serum.
- Detection of factor V leiden.
- Blood picture e.g for polycythaemia, thrombocytosis.
- Urine analysis for nephrotic $.
- Screening tests for malignancies e.g by tumour markers, CT-scan.
- Duplex study to detect the site of venous or arterial thrombosis.

Treatment:

The treatment is directed to DVT, cerebral thrombosis for example and also directed to the cause of thrombophilia. Most congenital protein deficiency states are managed with life long warfarin therapy. Hypercoagulability associated with cancer usually requires long term subcutaneous heparin therapy because warfarine in not effective.

Antiphospholipid antibody syndrome

- Antiphospholipid antibody syndrome is an acquired prothrombotic disorder. It may present as a primary disorder, or it may be secondarily associated with other autoimmune diseases e.g SLE.
- It is manifested by recurrent venous or arterial thrombosis, thrombocytopenia and recurrent fetal loss resulting from placental vascular insufficiency.
- In the antiphospholipid antibody syndrome, an antibody in the patient’s plasma has activity against enzymatic reactions in the coagulation cascade.
- The antibody, in vitro prolongs the PTT as it interacts with the phospholipid in the reaction tube and inhibits the enzymatic interactions of coagulation components. In contrast the antibody in vivo induces a hypercoagulable state.
When the Ab inhibits coagulation in these ways it is known as the lupus anticoagulant (this Ab was first detected in SLE, but is not limited to patients with lupus).

In some individuals the antibody binds to cardiolipin (anticardiolipin antibody).

The term antiphospholipid antibody $ includes both lupus anticoagulant and anticardiolipin antibody.

Serologic markers for this syndrome are anticardiolipin antibody and/or lupus anticoagulant. PTT is prolonged despite thrombosis.

Warfarin is the usual drug of choice, the rate of pregnancy loss is markedly reduced with aspirin in combination with either heparin or steroids.

**Hypersplenism**

It is an exaggeration of normal function of the spleen in which the spleen removes (phagocytosis) excessive quantities of RBCs, granulocytes or platelets from the circulation.

**Aet.**

- Portal hypertension – chronic haemolytic anaemia e.g thalassaemia and spherocytosis
- Rheumatoid disease (felty’s $).
- Lymphoma, chronic leukaemia, amyloidosis, myelofibrosis.

**C/P**

- Mono or pancytopenia $\rightarrow$ manifestations of anaemia, thrombocytopenia and recurrent infections.

**Investig**

- Empty blood + full (proliferating) B.M.
- RBCs with chromium phagocytosed inside the spleen.

**ttt**

Transfusion of RBCs, platelet concentrates - antibiotics for infections – treatment of the cause – splenectomy is sometimes required for severe cytopenia.

**Criteria of diagnosis of hypersplenism**

- Cytopenia of one or more cell lines.
- Compensatory reactive BM hyperplasia.
- Splenomegally.
- Correction of the abnormality by splenectomy.
**Hyposplenism:** (hyposplenia or asplenia are used to indicate diminished or absent splenic function respectively)

**Causes:**
- Splenectomy.
- Congenital absence.
- Sickle cell disease (autosplenectomy).
- Splenic irradiation.

**LAB:**
- Howell jolly bodies within RBCs, Acanthocytes.

**Complications:**
- Liability to infections with encapsulated organisms e.g pneumococcal, Neisseria meningitidis and H influenza.

**Treatment:**
- Vaccine for the above organisms.
- Prophylactic penicillin.
- All febrile infections should be considered serious so, give antibiotics. Broad spectrum antibiotic before tooth extraction.

---

**Complications of blood transfusion**

**Immunological:** (Alloimmunization and incompatibility):
- **Red cells:**
  Immediate or delayed haemolytic transfusion reactions.
- **Leucocytes and platelets:**
  - Non-haemolytic (febrile) transfusion reactions.
  - Post-transfusion purpura.
  - Poor survival of transfused platelets and granulocytes.
  - Transfusion associated lung injury.
- **Plasma proteins:**
  - Urticaria and anaphylactic reactions.

**Non Immunological:**
- **Transmission of infection:**
  - Viruses: HBV, HCV, HIV, CMV, EBV.
  - Parasites: Malaria – Trypanosomiasis – Toxoplasma.
- **Circulatory volume overload.**
- **Iron overload** due to multiple transfusions.
- **Massive transfusion** of stored blood may cause bleeding reactions e.g (dilutional coagulation defect) and electrolyte disturbances.
- **Thrombophlebitis.**
- **Air embolism.**
Acute haemolysis

Due to incompatible red cells, usually in the ABO system, this occurs within minutes. There is complement activation by Ag-Ab (IgM antibody).

C/P  - Rigors and fever.  - Lumbar pain.  - Haemoglobinuria

Management:

- Stop the transfusion.
- Re-group and repeat cross matching.
- Check blood count, bilirubin.
  * Monitor pulse, blood pressure.
  * Fluid intake.
  * Alkalinization of urine.

Febrile non haemolytic transfusion reactions

These reactions are common in patients who have previously been transfused or pregnant, due to presence of leucocyte antibodies against donor leucocytes, leading to release of pyrogens or cytokines from donor leucocytes.

C/P  Fever – chills and rigors.

ttt  - Stop transfusion       - Exclude haemolytic reaction.
     - Antipyretics.         - Use of leucodepleted blood.

Potent leucocyte antibodies in the plasma of donors, against recipient leucocytes, may cause severe pulmonary reactions called transfusion – related acute lung injury (TRALI) characterized by dyspnea, fever, cough, lung shadow in the perihilar and lower lung fields on the x-ray chest, hypoxia. Mechanical ventilation may be required.

Delayed haemolytic transfusion reactions

This occurs 5-7 days after transfusion. The transfusion has stimulated the production of antibodies (IgG) which was not detected at the initial cross match. Haemolysis is usually extravascular (IgG mediated).

C/P  Anaemia + jaundice

Diagnosis & TTT  - Antibody detection, spherocytes in blood film.
                  - Compatible blood use.
**Blood components and products**

- **Whole Blood**
  The average of blood is 470 ml + 63 ml anticoagulant, stored at 4°C for about 5 weeks (shelf-life). It is used for acute blood loss.

- **Packed red cells**
  The mean volume is about 330 ml. Used in treatment of blood loss without causing volume load e.g. in heart diseases.

- **Washed red cell concentrates**
  Used in patients with history of severe recurrent urticarial or anaphylactic reactions.

---

**Autologous transfusion:**
An alternative to using blood from volunteer donor is to use the patient’s own blood, types:

1. **Predeposit**: The patients donates 2-5 units of blood at approximately weekly intervals before elective surgery.
2. **Preoperative haemodilution**: one or two units of blood are removed from the patient immediately before surgery and retransfused to replace operative losses.
3. **Blood Salvage**: Blood lost during or after surgery may be collected and retransfused.

- **Platelet concentrates**
  They may be stored for up to 5 days at 22°C, used in cases of thrombocytopenia with bleeding.

- **Granulocyte concentrate**
  For patients with severe neutropenia.

- **Fresh frozen plasma**
  It is prepared by freezing the plasma from one unit of blood at -30°C within 6 hours of donation. The volume is about 200ml, used for replacement of coagulation factors. Shelf-life is about 1 year.

- **Cryoprecipitate**
  It is obtained by allowing the frozen plasma to thaw at 4-8°C and removing the supernatant.
  Volume about 20ml, it is stored at -30°C. It contains factor VIIIc, VWF and fibrinogen.
  It is useful in DIC. It is no longer used for the treatment of haemophilia A and VWD because of the greater risk of virus
transmission compared with virus inactivated coagulation factor concentrates.

- **Factor VIII and IX concentrates:**
  These are freeze dried preparations of specific coagulation factors prepared from plasma, they are used for haemophilia and VWD. Recombinat coagulation factor concentrates are of choice when available.

- **Immunoglobulins**
  Prepared from plasma, used to prevent infections e.g anti-hepatitis B.

- **Human albumin**
  Human albumin solution 20% (salt poor albumin), contains 200 g/L albumin and 130 mmol/L sodium and is available in 50 and 100 ml bottles.

Myelodysplasia

Group of acquired bone marrow disorders due to stem cells defect characterised by macrocytosis, variable cytopenia, hypogranular neutrophils with nuclear hypo or hypersegmentation, there is a hypercellular marrow with dysplastic changes in all three cell lines. Myelodysplasia comprises the following conditions:

1. **Refractory anaemia.**
2. **Refractory anaemia with ring sideroblasts (sideroblastic anaemia).**
3. **Chronic myelomonocytic leukaemia.**
4. **Refractory anaemia with excess of blasts (RAEB).**
5. **Refractory anaemia with excess of blasts in transformation (RAEB-t).**

Myelodysplasia represent steps in the progression of acute myeloid leukaemia especially the above types (3,4,5).

**Diagnosis**

- Anaemia, infection or bleeding due to pancytopenia.
- BM is hypercellular with dysplasia.
- Increased myeloblasts in BM. Myeloblasts, pancytopenia, and macrocytosis in peripheral blood.
- Chromosome analysis reveals abnormalities in chromosomes 5 or 7.

**Management (treatment is unsatisfactory)**

- Blood transfusion, platelets transfusion and antimicrobials.
- Erythropoietin and G-CSF, GM-CSF.
- Aggressive antileukaemic therapy in patients with excess blasts in the marrow, azacytidine can improve blood count and survival.
- Bone marrow transplantation offers the hope of cure in patients under age of 50 with refractory anaemia without excess blasts.
Plasma cell disorders (Gammopathies)

Plasma cell disorders include a group of B cell neoplasms that arise from a clone of immunoglobulin secreting cells with production of monoclonal immunoglobulins.

If the monoclonal Ig is of the IgM Class, the disease is Waldenstrom's macroglobulinemia

If the monoclonal Ig is of the IgG, IgA, IgD or rarely IgE class, the disease is Multiple myeloma

Multiple Myeloma (MM)

It is a malignant disease of the plasma cells of BM, there is abnormal proliferating plasma cells producing a monoclonal paraprotein, mainly IgG or IgA and rarely IgD.

**C/P (♂ > ♀)** The median age of presentation 60 years, it is rare below age of 40).

- **Bone involvement (bone pain):** malignant plasma cells may secrete cytokines that activate osteoclasts leading to osteoporosis with fractures of long bones or vertebral collapse with spinal cord compression and hypercalcemia.
- **Anemia:** due to marrow invasion by plasma cell.
- **Renal impairment:** hypercalcaemic and hyperuricaemic nephropathy, amyloid deposition and toxic effects of light chains on tubules.
- **Infections:** e.g. pneumonia.
- **Bleeding Tendency:** (platelet function and count are decreased, antibodies to clotting factors).
- **Hyperviscosity $^\$:** due to high concentration of the M protein which tends to aggregate (M for monoclonal).

**Investigations**

- **ESR** is almost always high and is usually above 100 mm/hr (the paraprotein cause rouleaux of RBCs).
- Plasma proteins electrophoresis showing monoclonal Ig (abnormal M protein level).
- B.M examination is diagnostic, normally BM contains about 5% of plasma cells. In multiple myeloma, plasma cells may reach greater than 10-20%.
- Alkaline phosphatase enzyme is usually normal (multiple myeloma stimulates osteoclasts and not osteoblasts). ↑ uric acid, ↑ Ca.
• Urine may be positive for **Bence Jones proteins** (free light chains), either kappa or lambda.

• Immuno

show

ing the type of immunoglobulins e.g IgG (55%), rare.

**Myeloma staging system**

<table>
<thead>
<tr>
<th>I</th>
<th>All the following</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hb &gt; 10 gm/dl</td>
</tr>
<tr>
<td></td>
<td>Normal bone radiograph or solitary lesion.</td>
</tr>
<tr>
<td></td>
<td>Low M component production (M for monoclonal)</td>
</tr>
</tbody>
</table>

| II | Fitting neither I nor III |
|    |                           |

| III | One or more of the following |
|     | Hb < 8.5 gm/dl |
|     | S Ca > 12 mg/dl |
|     | Advanced lytic bone lesions |
|     | High M component production. |

**Subclassification**

<table>
<thead>
<tr>
<th>A</th>
<th>Serum creatinine ≤ 2 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Serum creatinine &gt; 2 mg/dl</td>
</tr>
</tbody>
</table>

**Treatment:**

**(A) Supportive therapy**

- Pneumococcal vaccine, antibiotics for infection.
- Treatment of hypercalcemia by bisphosphonates.
- Allopurinol to prevent urate nephropathy.
- I.V gamma globulin, plasmapheresis for hyperviscosity $.
- Anaemia should be corrected, blood transfusion may be required, erythropoietin is often helpful.
- Bone pain can be treated by radiotherapy.

**(B) Specific therapy**

- The standard treatment has consisted of pulses of melphalan with prednisone (response rate, 50%).
- VAD therapy (vincristine, adriamycin and dexamethasone) which is less toxic to bone marrow stem cells can be used.
- Recently, **Thalidomide** is an anti-angiogenesis agent to reduce the paraprotein. Bortezomab also can be used recently !?
**Waldenstrom's macroglobulinemia**

- This is a clonal disease of IgM secreting plasmacytoid lymphocytes, usually it affects older people.
- IgM is a large molecule and remains in the intravascular compartment, so if increased it will lead to hyperviscosity $\$$.  

**C/P & diagnosis.**
- Blue cyanotic fingers, toes, nose and earlobes on exposure to cold.
- Nosebleeds, retinal haemorrhage.
- Congestive heart failure, mental confusion, visual disturbance (hyperviscosity $\$)$.
- In contrast to MM there is hepatosplenomegally together with lymphadenopathy.
- Foot, leg ulcers and vascular occlusion with gangrene.
- Raynaud's phenomenon.
- Peripheral neuropathy.
- Renal disease is not common, no bone lesions or hypercalcaemia.
- Electrophoresis reveals high levels of IgM.

**ttt**
- Severe hyperviscosity and anaemia may necessitate plasmapheresis to remove IgM and make blood transfusion possible.
- Cytotoxic drugs e.g. chlorambucil or cyclophosphamide to minimize the lymphadenopathy and splenomegaly, but they don't alter the nature of the disease.

**The Lymphomas**

- Lymphomas are commoner than leukaemias. They arise as the result of abnormal proliferation of the lymphoid system, and hence occur at any site where lymphoid tissue is found. They are mostly manifested with lymphadenopathy, but primary extranodal presentations occur in about 20% of non-Hodgkin's lymphoma.
- These neoplasms are divided clinically and histologically into Hodgkin's and non-Hodgkin's lymphoma. The majority are of B-cell origin. Non-Hodgkin's lymphoma are divided into low-grade, intermediate grade and high-grade tumours on the basis of their proliferation rate.
The histological hallmark of Hodgkin's disease is the presence of Reed-Sternberg cells.

**Pathological classification of Hodgkin's lymphoma**
- Lymphocyte-predominant
- Mixed cellularity
- Nodular sclerosing
- Lymphocyte-depleted

**Epidemiology and aetiology of Hodgkin's disease**

**Incidence:**
- 4/100000.

**Sex ratio:**
- Slight male excess (1.5:1).

**Age:**
- First peak in 20-35 and second peak in 50-70 age group.

**Aetiology:**
- Unknown, no causal link to Epstein-Barr virus.

**Pathogenesis:**
- B cells: there is lack of expression of surface immunoglobulin in the Hodgkin and reed-strenberg cell.
- Resistance to apoptosis of lymphoma cell.
- Developmental of non regulatory growth signals.
- Environmental e.g infection !?
- Genetic factors.

**Clinical features**
There is painless rubbery lymphadenopathy, usually in the neck or supraclavicular fossae; the lymph nodes may fluctuate in size. Mediastinal masses may cause dry cough and some breathlessness. Hepatosplenomegaly may be present. Extranodal disease, such as bone, brain or skin involvement, is rare. Fever with night sweats (25%).

**Clinical stages of Hodgkin's Lymphoma (ANN ARBOR classification)**

**Stage I:** Involvement of a single lymph node region.

**Stage II:** Involvement of two or more lymph node regions on one side of the diaphragm.

**Stage III:** Involvement of lymph node regions on both sides of the diaphragm.

**Stage IV:** Diffuse involvement of one or more extralymphatic tissue.
- e.g. liver or bone marrow.
Each stage can be divided into

<table>
<thead>
<tr>
<th>A: no systemic symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B: positive systemic symptoms.</td>
</tr>
</tbody>
</table>

**Investigations**

- Full blood count, it may be completely normal. A normochromic normocytic anaemia may be present together with lymphopenia. Eosinophilia or neutrophilia may be present.
- ESR, it is usually raised with disease activity.
- Renal function and liver function tests. Uric acid and serum Ca may be elevated.
- LDH, Raised levels are an adverse prognostic factor.
- Chest X-ray, CT. scan chest, **lymph node biopsy (definitive diagnosis)**.
- BM examination is seldom done, but show involvement in patients with advanced disease.

**Management**

1. **Radiotherapy.**

   **Indications:**
   - Stage I disease.
   - Stage IIA disease.
   - For lesions causing serious pressure symptoms.
   - After chemotherapy to sites where there was originally bulk disease (see below)

2. **Chemotherapy** (It is used for stage III or IV) with or without irradiation).

   - Previously the regimen was developed from the original **MOPP** regimen nitrogen mustard (mustin), vincristine (oncovin), prednisolone and procarbazine, with drugs substituted to reduce vomiting, alopecia and long-term toxicity. It was consist of chlorambucil, vinblastine procarbazine and prednisolone.

   - **Recently ABVD** chemotherapy is used (Adriamycin, Bleomycin, Vinblastine, Dacarbazine). This regimen is currently the first line of treatment (more effective and less toxic).

   - Also **BEACOPP** therapy is recently used (Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone).
Non-Hodgkin's lymphoma (NHL) represents a monoclonal proliferation of lymphoid cells and may be of B-cell origin (70%) or T-cell origin (30%).

**Epidemiology and Aetiology**

**Incidence:**
- 12/100 000

**Sex ratio:**
- Slight male excess.

**Age:**
- Median age 65-70 years.

**Aetiology:**
- EBV (linked to Burkitt's lymphoma). Gastric lymphoma can be associated with Helicobacter pylori infection (MALT lymphoma). MALT means mucosal associated lymphoid tissue. HIV also may be a cause.
- Immunodeficiency states and in immunosuppressed patients e.g post-organ transplantation.
- Chromosomal lesions.

**Pathogenesis:**
There is a malignant clonal expansion of lymphocytes, this malignant transformation may be due to cytogenetic abnormalities e.g chromosome translocation.

**Classification of NHL:**
- Low grade e.g follicular small cleaved cell.
- Intermediate grade e.g diffuse mixed small cleaved and large cell.
- High grade e.g Burkitt and non Burkitt lymphoma.

**Clinical features**
Compared to Hodgkin's disease, NHL is often widely disseminated at presentation. Patients present with lymph node enlargement which may be associated with systemic onset; weight loss, sweats, fever and itching. Hepatosplenomegaly may be present. Extranodal disease is more common in NHL, with involvement of the bone marrow, gut, thyroid, lung, skin, testis, brain and more rarely bone. Extranodal disease is more common in T-cell disease.
Staging: ANN ARBOR staging system is also used to stage NHL.

Investigations
- Lymph node biopsy, BM examination is always performed.
- Immunophenotyping to distinguish T- and B-cell tumors.
- Immunoglobulin determination. Some lymphomas are associated with IgG or IgM paraproteins.
- Serum uric acid and calcium, HIV testing.

Management
Low-grade NHL
Asymptomatic patients may not require therapy. Indications for treatment include marked systemic symptoms, lymphadenopathy causing discomfort or disfigurement, bone marrow failure or compression syndromes, the following methods of treatment can be used:
- Radiotherapy. For localized stage I.
- Chemotherapy, with chlorambucil or cyclophosphamide with or without prednisone.
- Monoclonal antibody therapy (Rituximab).
- Autologous stem cell transplantation.

High-grade NHL
- Chemotherapy for the majority of patients, CHOP regimen (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone). Recently R-CHOP (R, means Rituximab).
- Radiotherapy for stage I disease. Also, it can be used for residual bulky disease after chemotherapy.
- Autologous stem cell transplantation.

Intermediate grade lymphoma often respond to combination chemotherapy and rituximab with or without radiotherapy.

B.M Transplantation (BMT)

Indications:
1- Thalassaemia major
2- Aplastic anaemia
3- Leukemia.
4- Sickle cell anaemia
5- Myelodysplasia.
6- Lymphoma
Method
Multiple marrow aspirations are performed on the iliac crests. The aspirated BM is given by IV infusion to the recipient.

Complications
- Infections (herpes, CMV, fungal, pneumocystis carinii).
- Recurrence – effects of cytotoxic drugs.
- Graft versus host disease (see later).

When no matched donors are available, autologous BMT using marrow infusion of harvested and stored remission marrow in cases of leukaemia (see before).

Graft versus host disease (GVHD):
It is due to the cytotoxic activity of donor T lymphocytes which become sensitized to their new host.

Acute GVHD: It appears 14-21 days after the grafting, it can affect the skin, liver, and gut. It is treated by cyclosporine, methotrexate and steroids.

Chronic GVHD: This may follow acute GVHD, It is similar to connective tissue disease, with rash, it can be treated by steroids and cyclosporine.

Effects of blood diseases on different systems
(organ involvement in blood diseases)

(1) CVS:
- Hyperdynamic circulation with anaemia.
- Hypertension with hyperviscosity $.
- Myocardial infarction in sickle cell anaemia.

(2) Chest:
- Chest infections with leukaemia, lymphoma.
- Acute chest $ in sickle cell anaemia.
- Pulmonary infiltration in leukaemia and lymphoma.
- Thrombophilia leading to pulmonary embolism.

(3) Nervous system:
- Cerebral infarction in sickle cell anaemia.
- Hyperviscosity $ (sluggished cerebral circulation)
- Infiltration of meninges by leukaemia and lymphoma.
- Thrombophilia $\rightarrow$ cerebral infarction.
- Cerebral haemorrhage with severe bleeding tendency.
(4) GIT:
- GIT lymphoma e.g (MALT).
- Liver ++, spleen ++ in leukaemia and lymphoma.
- Mescentric occlusion in sickle cell anaemia.
- Budd chiari $ in PNH.

(5) Skin:
- Itching in polycythaemia, lymphoma leukaemia, haemolytic anaemia.
- Leg ulcers in sickle cell anaemia.
- Raynaud’s phenomenon in waldenstrom’s disease.
- Eruption of purpura, haemophilia.

(6) Kidney:
(See MM, leukaemia, Lymphoma, Sickle cell anaemia).

**Haematological manifestations of different organ diseases**

- Liver, renal diseases, see nephrology and hepatology.
- Endocrinal diseases, see endocrinology.
- GIT diseases e.g peptic ulcer → Iron deficiency anemia.
  Atrophic gastritis → Megaloblastic anaemia.
- Lung disease: Hypoxia → secondary polycythaemia.
  Chronic infection → anaemia of chronic disease.

**Immune mediated blood diseases:**
(1) Autoimmune haemolytic anaemia. (2) Pernicious anaemia.
(3) PNH and ITP (4) GVHD (5) Primary aplastic anaemia

**Causes of bone marrow failure:**
(1) Aplastic anaemia and pure red cell aplasia (see before).
(2) Marrow infiltration:
  - Lymphoma
  - Myelofibrosis
  - Metastatic carcinoma
  - Leukaemia
  - Myelomatosis
  - Miliary TB.
(3) Nutritional defect:
  - $B_{12}$, folate or pyridoxine deficiency.
  - Iron deficieney
(4) Hormonal erythropoietin deficiency (renal) and hypothryroidism.
Haematologic paramalignant syndromes:
- Erythrocytosis with renal cell and hepatic carcinoma.
- Pure red cell aplasia with thymoma.
- Autoimmune haemolytic anaemia with lymphoma or chronic lymphocytic leukaemia.
- DIC with malignancy of pancreas and stomach.
- Thrombocytosis with some malignancies e.g Hodgkin’s lymphoma, lund cancer, ovarian tumours.

Chemotherapy of malignancy leading to mono or pancytopenia.

Haematological manifestations of systemic disease
(1) SLE → autoimmune haemolytic anaemia, thrombocytopenia, lymphopenia.
(2) Rheumatoid disease → anaemia of chronic disease, hypersplenism (felty’s $).
(3) Cushing’s $ → Erythrocytosis.
(4) Addisone’s disease → Eosinophilia.
(5) Hypothyroidism → Anaemia of chronic disease, Macrocytosis.
(6) DM → it leads to ↓ RBCs deformability, disordered fibrinolysis, increase of platelet aggregation as there is high level of TA₂.
(7) Chronic renal failure → anaemia.
(8) Liver cell failure (see hepatology).
(9) Malignant hypertension → microangiopathic haemolytic anaemia.
(10) HIV, IMN, CMV (see infections).

You can enumerate the haematological paramalignant syndromes!?

Haematologic malignancies:
- Leukaemias.
- Lymphomas.
- Plasma cell disorders.
- Myeloproliferative disorders.

Acute megaloblastic anaemia or disease:
- It is a rapidly developing thrombocytopenia and/or leucopenia with very little change in Hb level. The marrow is floridly megaloblastic within 12 to 24 hours.
- The commonest cause is nitrous oxide anesthesia, also this occurs with a weak antifolate e.g trimethoprim to a patients with marginal tissue folate stores. ICU patients under prolonged TPN are also liable.
- The condition responds rapidly to folate plus cobalamin therapy.
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Author's available books

2. Gastroenterology.
4. Rheumatology.
5. Cardiology.
7. Hematology.
8. Neurology and psychiatry.
9. Infectious diseases, tropical diseases, immunology, nutrition, genetics, geriatric, toxicology and therapeutics.
10. Respiratory diseases.
11. Clinical medicine (symptoms and examination).
   - Cardiology.
   - Chest.
   - Abdomen.
   - Neurology.
   - General.