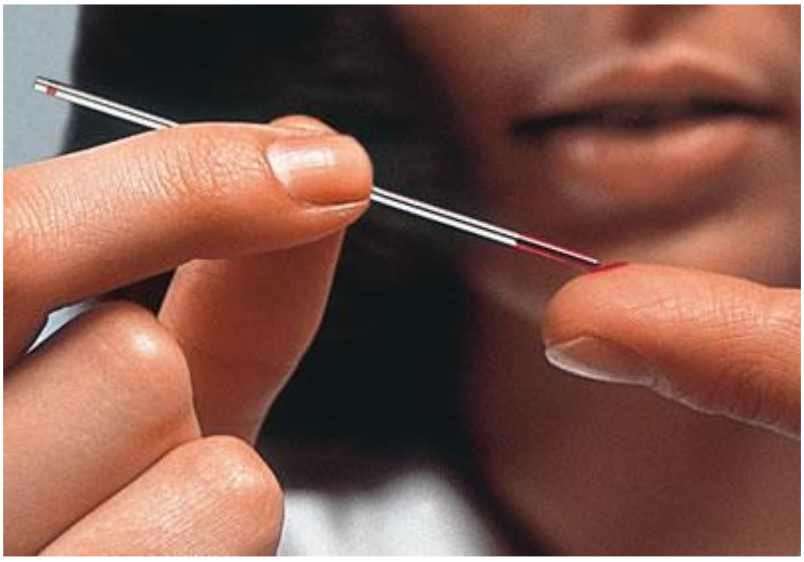
Hematology

Is a study of blood, blood-forming tissues, and disorders

Blood is specialized liquid connective tissue consisting of cellular elements suspended in plasma.



➢ **Description:**

- Average Volume 5-6 liters men & 5 liters women (7-8% TBW)
- pH 7.35-7.45 slightly alkaline
- Connective Tissue
- Makes up 25% of ECF
- Color ranges from scarlet (oxygen-rich) to dark red (oxygen poor).
- Viscosity is 5x that of water, due primarily to the presence of formed elements.

➢ **Functions**

A. Transportation

1- Transport of nutrients from digestive tract to tissues.

2- Transport of metabolites and excretory products from tissues to excretory organs.

3- Transport of gases (O_2&CO_2) between respiratory organs & tissues.

B. Regulation/Maintenance

1- Hormonal, carries hormones from endocrine organs to target tissues.

2- Temperature, when temp is high, diverts blood from deep vessels to superficial vessels/when temp low, diverts blood from superficial to deeper vessels to help keep body warm

3- Maintains normal pH

4- Maintains adequate fluid volume

C. Protection/Prevention

1- Coagulation, prevents blood loss

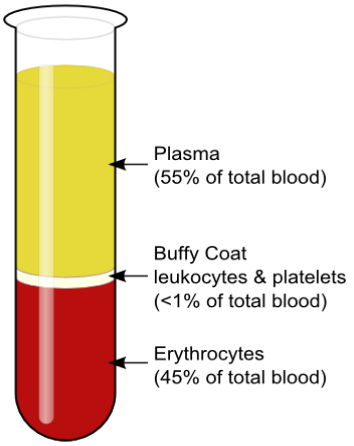
2- Prevents infection via WBCs and plasma immune proteins.

Normal blood is composed of three types of cell (red blood cells, white blood cells & platelets) suspended in a pale yellow fluid called plasma.

Major Components of Blood

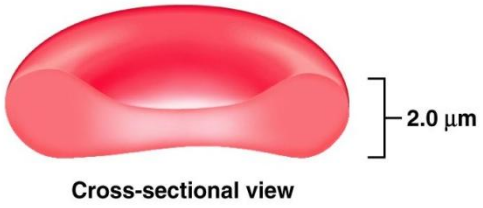
1. Formed elements, the actual cellular components of blood:
- Erythrocytes - red blood cells
- Leukocytes - white blood cells
- Platelets - cell fragments for clotting

2. Blood plasma, complex non-cellular fluid surrounding formed elements.



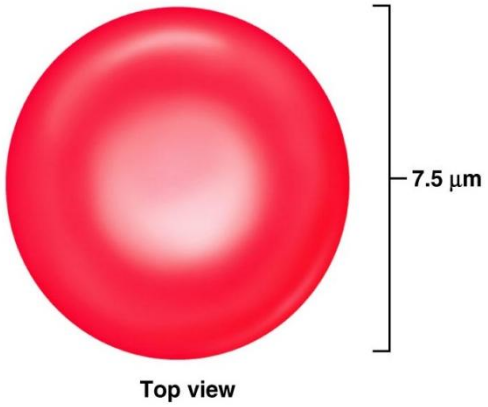
❖ **Red blood cells (Erythrocytes)**

-Mature RBCs, or erythrocytes, are the most numerous of the blood cells, about 5 million red blood cells are present per one microliter of blood.



-RBCs are biconcave discs approximately 7.5 micron in diameter & 2 micron thick, this shape maximizes the surface area of the cell and facilitates the diffusion of oxygen across the cell membrane.

-Red blood cells survive in the circulation for about 120 days before being sequestered in the spleen. As such, red blood cells must be replaced at a rate of 2 to 3 million cells per second. Erythrocyte production is regulated by the hormone *erythropoietin*



-The major function of red cells is to transport hemoglobin, which in turn carries oxygen from the lungs to the tissues & transport CO_2 from tissues back to the lungs. In addition, hemoglobin is an excellent acid – base buffer.

-The percentage of the total blood volume comprised of red blood cells is called the hematocrit, & this is normally about 40% in women & about 45% in men (blood viscosity is determined primarily by these elements).

❖ **White blood cells (leucocytes)**

-The leucocytes are the mobile units of the body's protective system. They act primarily within the tissues; those found in the blood are actually in transit. Leukocytes are also found in lymphoid tissues such as the thymus, spleen, and lymph nodes.

-They are formed partially in the bone marrow (the granulocytes & monocytes, & a few lymphocytes) & partially in the lymph tissue (lymphocytes & plasma cells), but after formation they are transported in the blood to the different parts of the body where they are to be used.

-The number of white blood cells in the blood is normally about 4000 to 11,000 leukocytes per microliter of human blood (only 1/600 the number of red blood cells).

-Leucocytes are of two main types:

(1) Granular leucocytes. (2) A granular leucocytes.

- **Granular leucocytes:**

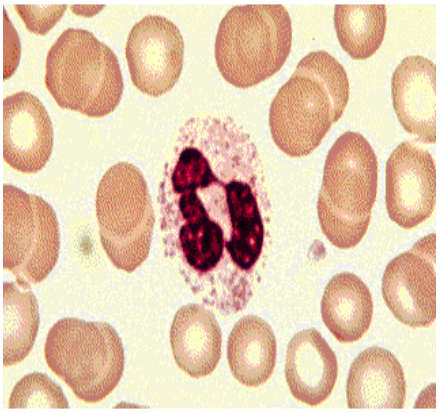
- Are the most numerous, phagocytic cells, contain specific granules & they are characterized by the presence of many lobed nucleus for this reasons they are referred to as polymorphonuclear leucocytes. There are three types of granular leucocytes:

(a) Neutrophils

(b) Eosinophils

(c) Basophils.

Neutrophils



-They are the most numerous of the leukocytes in human blood, which constitute 50-70% of the total white blood cells.

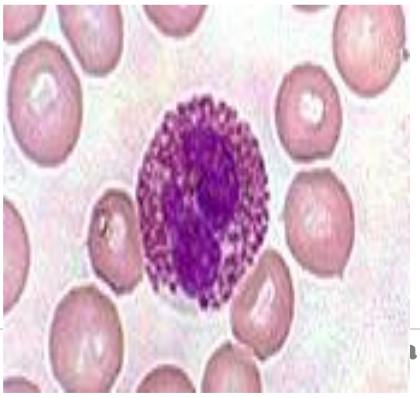
-The neutrophil nucleus is highly polymorphous which usually consist of from 3 to 5 irregular ovoid lobes connected by a thin chromatin strand.

-Neutrophil cytoplasm contains numerous fine neutrophil granules, which are special types of lysosomes that contain principally hydrolytic enzymes.

-Neutrophils constitute the first line of defense against invading organism so the main function of neutrophils is bacterial killing by phagocytosis, so these cells are usually the first to arrive at a site of injury or inflammation.

-Neutrophils are highly mobile, highly phagocytic, & are attracted out of the blood into tissue areas where tissue destruction is occurring by a process called chemotaxis, which means attraction by the destruction products from the damaged tissues.

Eosinophil



-They normally constitute about 1 to 4 percent of the total white blood cells.

-The nucleus is usually bilobed.

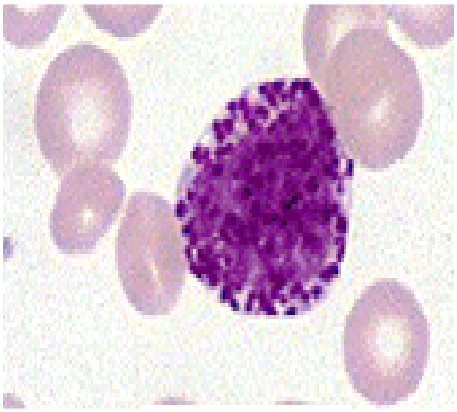
-This name is derived from the staining characteristic of the large cytoplasmic granules of uniform sized which stain

strongly with the acidic dye eosin.

-They are only weak phagocytes. These leukocytes are produced in large numbers in individuals with internal parasitic infections. The parasites are usually too large to be phagocytized, but the eosinophils attach themselves to the surface & release lethal substances that can kill many of the parasites.

- Large numbers of eosinophils also appear in the blood in allergic conditions & may help detoxify toxins that are released by allergic reactions.

Basophils



-These cells are difficult to find in human blood, since they constitute only about 0.5 to 1 percent of the total number of leucocytes.

-The nucleus often is irregular in outline & partially constricted into two lobes (S shape like). The cytoplasmic granules are round & variable in size, which stain with basic dyes.

- They are similar structurally and functionally to the mast cells found in connective tissues, especially in the lungs, skin, and gastrointestinal tract. Basophils and mast cells play an important role in allergic reactions.

- The granules of these cells liberate heparin into the blood, a substance that can prevent blood coagulation. As well as histamine & small quantities of bradykinin

-Basophils differ from neutrophils in that they are not phagocytic.

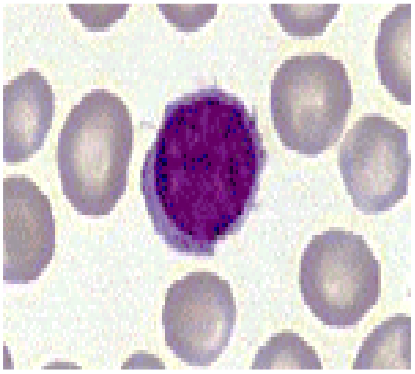
- **A granular leucocytes**

These cells have cytoplasm that appears homogenous & a single, large nonsegmented nucleus. There are two types of a granular leucocytes:

Lymphocytes

-Lymphocytes are the second most common white cell in the blood, with arrange of 20 to 40 percent of circulating white blood cells.

-Typically, lymphocytes are much smaller than monocytes (10 – 12 micron in diameter).



-Most of lymphocytes are formed in lymph nodes, thymus & spleen.

-Lymphocytes are of two types:

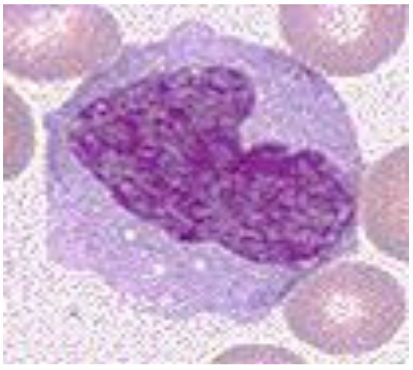
- B-lymphocytes (70 – 80%)
- T-lymphocytes (20 – 30%)

The primary function of the B lymphocytes is to produce antibodies, which are molecules that identify and lead to the destruction of foreign substances such as bacteria. The B-lymphocytes and the antibodies they produce are responsible for humoral immunity

T-lymphocytes provide immunity against viruses and cancer cells. These lymphocytes directly attack and destroy their targets by forming holes in the target cell membrane, causing cell lysis. The T-lymphocytes are responsible for cell-mediated immunity.

Monocytes

- Account for about 5% of the total number of white blood cells.



- Immature in the blood, these leukocytes leave the vascular compartment and enter the tissues, within which they enlarge, mature, and develop into tissue macrophages. The macrophage system has generally been called the reticuloendothelial system.

- Macrophages are large phagocytic cells that can ingest bacteria, necrotic tissue, and even dead neutrophils.

- The life span of the macrophage may range from months to years until it is ultimately destroyed as a result of phagocytic activity.

❖ **Platelets (thrombocytes)**

- Are small protoplasmic disks, which are non – nucleated, granulated bodies, constitute about 300,000 per mm^3 of circulating blood. They are replaced about once every 10 days.

-The primary role of the blood platelet is in the arrest of blood loss. Adequate number of functionally normal platelets are essential for optimal hemostasis.

Plasma

The fluid portion of the blood, the plasma, accounts for 55 to 60% of total blood volume and is about 90% water. The remaining 10% contains proteins (8%) and other substances (2%) including hormones, enzymes, nutrient molecules, gases, electrolytes, and excretory products. The three major plasma proteins include:

- Albumin
- Globulins
- Fibrinogen

Albumins

Albumin synthesized in the liver, is the most abundant (about 55%) of the plasma proteins. An important functions of albumin:

1- Act as carrier protein, transporting substances throughout the circulation.
2- Albumin also serves as an osmotic regulator. Because capillary walls are impermeable to plasma proteins, these molecules exert a powerful osmotic force on water in the blood.
When the concentration of albumin is severely reduced (as in liver disease because of protein synthesis is depressed; or in nephritis because large amounts of albumin are lost in the urine), this lead to decrease in the plasma oncotic pressure, so excess extracellular fluid may accumulate, the fluid accumulation is described as edema.

Globulins

The globulins account for about 38% of plasma proteins. The three types of globulins are alpha (a), beta (b), and gamma (g). The alpha and beta globulins are involved with several activities. They transport substances in the blood (hormones, cholesterol, iron), function as clotting factors, and serve as precursor molecules (angiotensinogen). The gamma globulins function as antibodies, which play an important role in the immune response. Alpha and beta globulins are synthesized in the liver; the gamma globulins are made by the lymphocytes (a type of white blood cell).

Fibrinogen

Accounts for about 4% and plays a role in the blood clotting process. It serves as a precursor for fibrin, which forms the meshwork of a blood clot. Fibrinogen is synthesized in the liver.

Serum has no fibrinogen so total plasma protein minus serum proteins give a measure of fibrinogen.

-Function of plasma proteins:

1. They act as protein reserve to the body, & can be used to supply body protein in states of starvation.
2. The plasma proteins increase the viscosity of the blood.
3. Plasma proteins exert on osmotic pressure of about 25 mm Hg, (oncotic pressure) which plays an important role in the reabsorption of tissue fluid.
4. They are important in transporting certain hormones, drugs & other substances in the blood.
5. They also have the ability on neutralize both acids & alkalis that is they act as a buffer.
6. Globulins act as defense mechanism through formation of antibodies.

Hematopoiesis

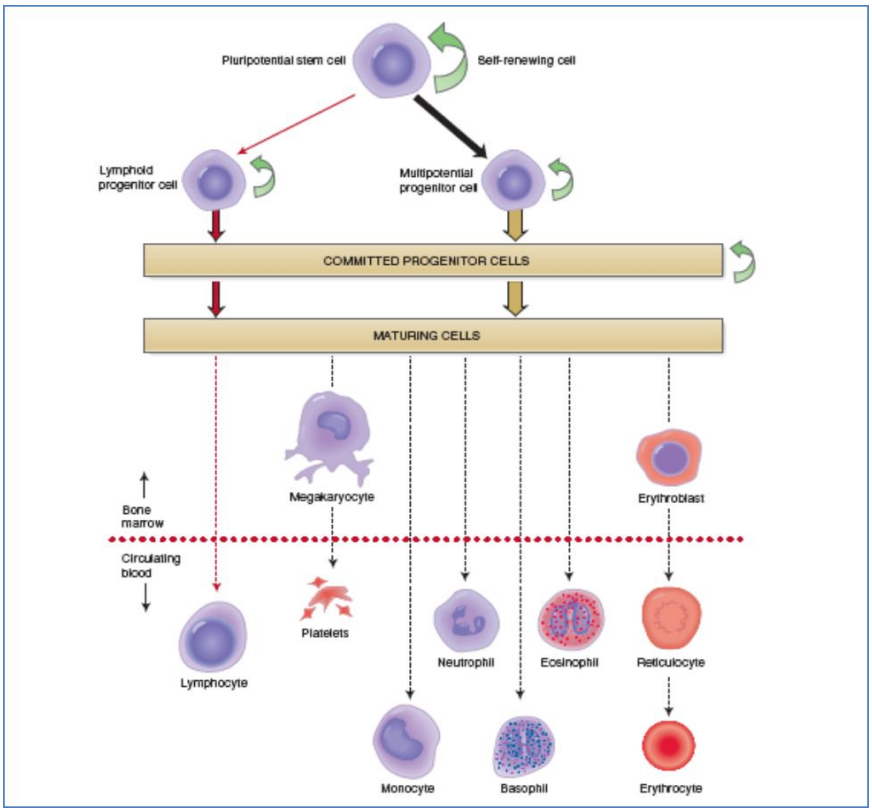
-Hematopoiesis refers to the formation & development of the various types of blood cells.

-During the first weeks of embryonic life, hematopoiesis begins in the yolk sac.

-During the third month of fetal life, yolk sac stem cells migrate first to the liver & then to the spleen, thus making the liver & spleen early sites of blood cell formation.

-About the end of 12th week of embryogenesis erythropoiesis begins in the marrow.

-At the time of birth, the liver & spleen have ceased cell development & the active sites hematopoiesis is in bone marrow.



There are two types of bone marrow have been described according to their appearance on gross examination:

(A): Red bone marrow:

-Whose color is due to the presence of numerous erythrocytes & their precursors in several phases of maturation.

(B): Yellow bone marrow:

-Rich in adipose cells which does not produce blood cells, except upon conversion into red bone marrow that is induced by sever bleeding or hypoxia.

-In new born, all bone marrow is red & is therefore active in the production of blood cells. As the child grows, most of the bone marrow changes into the yellow.

Erythropoiesis:

-The erythropoiesis involved number of stages:

1-Proerythroblast

2-Basophilic erythroblast

3-Poly chromatophilic erythroblasts

4-Normoblast

5-Reticulocytes

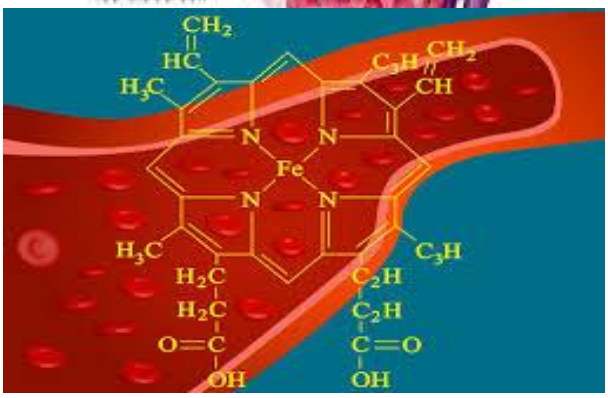
6-Erythrocytes (mature RBCs)

The hemoglobin

-Hemoglobin is the iron containing pigment of the red blood cells that functions to carry oxygen from the lungs to the tissues.

-Hb is the main constituent of RBCs, which comprises 95% of the RBC's dry weight.

-Normal blood has about 16 gm/dI (deciliter) of Hb in adult men & about 14 gm/dI in adult women.



Hemoglobin structure

-Hb is a globular molecule made up of four subunits each subunit contains a heme conjugated to a poly peptide.

-Heme is an iron containing porphyrin. Porphyrins can combine with Fe to form the heme, the Fe^{++} (as ferrous) is bound equally to all four nitrogen atoms of the pyrrole rings.

-Globin is consist of two pairs of polypeptides, one pair containing one type of polypeptide & the second pair contain another type.

-Since in normal adult human Hb (HbA), the two types of polypeptide are called the chains, α chains each of which contains 141 a.a. residues, & B chains each of which contains 146 a.a. residues. Thus HbA is designated α2B2.

-Not all the Hb in the blood of normal adults is Hb A. About 2.5% of the Hb is HbA_2, in which B chains are replaced by Delta chains (α2 δ2).

-The Delta chains also contain 146 a.a residues, but 10 individual residues differ from those in the B chains.

-While the blood of the fetus normally contains fetal Hb (HbF). Fetal Hb is normally replaced by adult Hb soon after birth, its structure is similar to that of HbA except that the B chains are replaced by gamma chains.

-The gamma chains also contain 146 a.a. residues but have 37 a.a. that differ from those in the B chain. So HbF is designated (α2 γ2).

-In the body, O2 content of HbF at a given PO2 is greater than that of adult Hb. This facilitates the movement of O_2 from the maternal to the fetal circulation.

Normal adult RBC contains the following types of hemoglobin:

-92-95% of Hb is HbA, which consist of α2 B2 chains.

-2-3% of the Hb is HbA_2, which consist of α2 δ2 chains.

-1-2% of the Hb is HbF (fetal Hb) which consist of α2 γ2 chains.

Normal hemoglobin production is dependent on three processes

1- Adequate iron delivery & supply.

2- Adequate synthesis of protoporphyrins (the precursor of heme).

3- Adequate globin synthesis.

Iron metabolism

-Normal Plasma iron level is about 130 µg /dI in men and 110 µg /dI in women.

-Iron is released from food complexes by digestive enzymes & is partially reduced to the ferrous form (Fe^{+2}).

-In general, an acidic condition, or lower pH, favors the ferrous state & iron absorption, whereas neutral & alkaline pH favor the ferric state & decreased iron absorption.

-The best sources of dietary iron are liver, red meat, egg yolk, dried fruits.

-Iron is stored in the tissues in two forms: as a soluble form, called ferritin & as insoluble iron or hemosiderin. Ferritin is found in all tissues & in high concentration in liver, spleen & bone marrow.

-About 70% of the storage iron is present as ferritin & the remainder as hemosiderin.

Erythrocyte disorders

a) Polycythemia

Dangerous excess of RBCs that caused by factors that stimulate states of chronic hypoxemia which stimulates erythropoietin secretion like cancer, emphysema, smoking, air pollution, etc.

Excess number of RBCs make the blood stream packed full of RBCs; hard to get all of them through capillaries lead to poor circulation, clogged capillaries, which result in heart failure, stroke and embolism.

b) Anemia

Anemia is a functional inability of the blood to supply the tissue with adequate oxygen for proper metabolic function, caused by reduction in number of RBCs, quantity of Hb & volume (PCV) per 100 ml of blood.

Various causes:

1) *Nutrional anemia*—dietary deficiency of factor needed for erythropoeisis, (iron).
2) *Pernicious anemia*—inability to absorb enough ingested Vitamin B_{12}—need for normal RBCs development and maturation
3) *Hemorrhagic anemia*—due to excessive bleeding
4) *Renal anemia* from kidney disease
5) *Aplastic anemia*—failure of bone marrow to produce enough RBCs—may be due to toxic chemicals, exposure to radiation, cancer, chemotherapy
6) *Hemolytic anemia*—caused by rupture of too many RBCs.

Example: **Sickle Cell Anemia** due to hereditary hemoglobin defects, occur mostly among people of African, Mediterranean descent. RBCs are sickle-shaped due to problem in one of the hemoglobin chains. RBCs tend to clump together and shape of cell causes it to block small blood vessels. It can lead to heart failure and kidney failure.

Thalassemia is another hereditary type of anemia in which the RBCs are unable to synthesize adequate amounts of either the alpha or beta polypeptide chains required to form the Hb.

There are two major types of thalassemia:

Alpha thalassemia which is caused by a defect in the rate of synthesis of α chains.

-In α thalassaemia Hb A, A_2 & F are equally depressed & there is microcytic, hypochromic anemia.

Beta thalassemia caused by a defect in the rate of synthesis of beta chains.

-In β thalassaemia is reduced B chain production therefore HbA produced is less & the anaemia produced is microcytic, hypochromic anemia.

-Total Hb is maintained by increase in gamma & delta chains so, HbA_2 &HbF increase.

Morphological classification of anemia:

-Based on morphology of RBCs, which depend on the RBC indices.

-The RBC indices are the mean cell volume (MCV), mean cell hemoglobin (MCH), & mean cell hemoglobin concentration (MCHC).

(1) Macrocytic anemia

There is increase in the volume of RBCs (MCV), with MCHC remaining normal, this type of anemia usually occur in association with folate or vitamin B_{12} deficiency.

(2) Normocytic normochromic anemia

The number of RBCs is reduced, while the MCV, MCH, & MCHC remain practically unchanged.

(3) Microcytic hypochromic anemia

This anemia usually related to iron deficiency anemia and thalassemia

In which the MCV & MCHC are reduced.

Hemostasis & blood coagulation

The term hemostasis means prevention of blood loss.

Whenever a vessel is ruptured, hemostasis is achieved by several different mechanisms including:

(1) Vascular spasm.

(2) Formation of platelet plug.

(3) Blood coagulation.

(4) Growth of fibrous tissue into the blood clot
to close the hole in the vessel permanently.

Fibrinolysis (Fibrin lysing)

Fibrinolysis, is the physiologic process of removing un wanted fibrin deposits, in which the liquefaction of a fibrin clot is achieved by splitting a small number of peptide bonds, of fibrin to form soluble fragments.

These fragments are then removed from the circulation by the macrophages of the reticuloendothelial system.

-This action of the fibrinolytic system re establishes blood flow in vessels occluded by a thrombus.

-The fibrinolytic system is mediated mainly by the enzyme plasmin, which acts on fibrin to produce lysis of the clot.

-Plasmin is generated from the circulating inactive enzyme called plasminogen.

Abnormalities of Hemostasis

-Hemophilia A

Is of interest because it is relatively common, is a congenital defect due to abnormalities of the gene on X chromosome that codes for factor VIII.

-Hemophilia B

Also congenital bleeding disorder caused by a deficiency of factor IX.

-Hemophilia C

A hereditary bleeding disorder caused by a deficiency of factor XI.

Another cause of depressed formation of clotting factors by the liver is vitamin K deficiency.

-Vit. K is necessary to promote the formation of four of the most important clotting factors, prothrombin, factor VΠ, Factor IX,& factor X. In the absence of vit. K, insufficiency of these coagulation factors can also lead to a serious bleeding tendency.

-Vitamin. K is continually synthesized in intestinal tract by bacteria so that vit. K deficiency rarely, except in newborn children before they establish their intestinal bacterial flora. However, vitamin k deficiency does often occur as a result of poor absorption of fats from the GIT, because vit. K is fat-soluble.

Immunity

-Immunity is the resistance of the body to invasion by bacteria, viruses, or other infectious agents or toxins.

-A person is born with innate immunity.

-Each person is born with a certain amount of innate immunity that results from several special mechanisms:

1-The reticuloendothelial system & white blood cells.

2-Resistance of the intact skin to invasion by microorganisms.

3-Destruction of bacterial organisms by the digestive enzymes in the stomach.

4-Substances circulating in the blood.

-Acquired immunity occurs following exposure to invading agent or foreign substances.

Two types of immunity

1: Humoral immunity.

2: Cell mediated immunity.

-**In humoral immunity**, the body develops circulating antibodies.

-The foreign antigens first enter the lymphoid tissue, especially the lymph nodes.

-Is mediated by B-lymphocytes.

-Plasma cells, which are derived from lymphocytes, to produce large quantities of antibodies.

-Once these antibodies have been formed & released into the body fluids, which usually requires I week to several weeks, they then destroy the specific invader that had caused their formation & can destroy any future invader of this same typed.

-Antibodies are destroy the invading agent or make it more susceptible to phagocytosis by the tissue macrophages or by white blood cells, or, in the case of toxins; the antibodies can simply neutralize these agents by combining chemically with them.

Cell mediated immunity (cellular immunity)

-Is mediated by T lymphocyte.

-Cell mediated immunity involves activation of lymphocytes processed in the thymus gland.

-The lymphocytes that are processed in the thymus gland also end up in the lymph nodes & other lymphoid tissues of the body.

-However, instead of forming antibodies when the lymph node is exposed to antigens, these cells form so called sensitized lymphocytes, also called T cells because of their earlier processing in the thymus.

-Large numbers of T cells are then released into the circulating blood & they spread throughout the body.

-There are three major types of sensitized T cells:

(1): Cytotoxic T cells

-This type of T cells combin directly with antigens on the surfaces of invading organisms & can therefore destroy the organisms.

(2) Helper T cells

-That function mainly in association with the plasma cells in the lymph nodes.

-They multiply many folds the capability of the plasma cells to produce humoral antibodies in response to antigens.

(3) Suppressor T cells

-That suppress some of the immune reactions, in this way preventing the immune system from running wild & becoming destructive to normal tissues.

Anaemia

is not one disease, but a condition that results from a number of different pathologies. It can be defined as a reduction from normal of the quantity of haemoglobin in the blood. t

WHO defines anaemia as Hg level less than 13 g/dl for adult males and less than 12 g/dl for females.

Types:

Iron deficiency is the commonest form of microcytic anaemia worldwide.

Folate and B12 deficiency are the main cause of Macrocytic (Megaloblastic) anaemia.

Haemolytic anaemias include the generic disorders of sickle cell anaemia, thalassaemia and glucose-6-phosphate dehydrogenase deficiency.

Sideroblastic anaemia is a rare anaemia caused by impaired haem synthesis.

Aetiology :

- **The low haemoglobin level that defines anaemia results from two different mechanisms:**

A-Increased haemoglobin loss due to:

-haemorrhage (red cell loss).

-haemolysis (red cell destruction).

B-Reduced haemoglobin synthesis due to:

-lack of nutrient.

-bone marrow failure.

Table 49.1 Examples of conditions that cause reduced haemoglobin synthesis

Reduced proliferation of precursors	Defective maturation of precursors
Iron deficiency	Vitamin B_{12} deficiency
Anaemia of chronic disease	Folate deficiency
Anaemia of renal failure	Iron deficiency
Aplastic anaemia (primary)	Disorders of
Aplastic anaemia (secondary to drugs, etc.)	– globin synthesis (thalassaemias)
Infiltration of the bone marrow:	– iron metabolism (e.g. sideroblastic)
– leukaemia or lymphoma	Myelodysplastic syndrome
– myelofibrosis	
– metastases	

Box 49.1 Non-specific signs and symptoms associated with anaemia

Tiredness
Pallor
Fainting
Exertional dyspnoea
Tachycardia
Palpitations
Worsening angina
Worsening cardiac failure
Exacerbation of intermittent claudication

Investigation

1.In most patients, the anaemia is a consequence of a reduced concentration of haemoglobin. Blood volumes may be increased in pregnancy and heart failure and haemoglobin concentration appear falsely low.

2.The most important parameter to assess anaemia is the haemoglobin concentration of the blood. It is also usual to count the number of red cells. In addition the size, shape and colour all contribute to the investigation.

1.Iron deficiency anaemia : is the commonest form of anaemia worldwide and may be present in up to 20% of the world's population. Blood loss, dietary iron deficiency, pregnancy and Parasitic infections like hook worm are the main causes of Iron Deficiency Anaemia.

Anaemia may result from a mismatch between the body's iron requirements and iron absorption. The demand for iron varies with age as in the following table:

Table 49.2 Typical daily requirements of iron	
Infant (0–4 months)	0.5 mg
Adolescent male	1.8 mg
Adolescent female	2.4 mg
Adult male	0.9 mg
Menstruating female	2.0 mg
In pregnancy	3–5 mg
Postmenopausal female	0.9 mg

Clinical manifestation:

Box 49.4 Features of iron deficiency anaemia

Pale skin and mucous membranes
Painless glossitis
Angular stomatitis
Koilonychia (spoon shaped nails)
Dysphagia (due to pharyngeal web)
Pica (unusual cravings)
Atrophic gastritis

- **After Hb, the main parameter used to help establish the iron status of the patient is the serum ferritin.**
- **The serum ferritin level is low in iron deficiency anaemia and markedly raised in iron overload.**
- **Care needs to be used in interpreting raised ferritin levels as these are sometimes found in cancer, inflammatory conditions and liver disease. Treatment:**
- **The standard treatment should supply 100- 200 mg elemental iron for adults. For children, the daily iron should not exceed 10- 11mg. It typically takes between 1-2 weeks for the haemoglobin level to rise 1 g/dL.**
- **Nausea or abdominal pain trouble some patients& this tends to be related to the dose of elemental iron.**
- **Giving the iron with food makes it better tolerated.**

- **There is a limited place for parenteral iron in iron deficiency anaemia; it should be reserved for patients who fail on oral therapy, usually because of poor adherence or intolerable gastro-intestinal side effects.**
- **Parenteral iron: Iron dextran (CosmoFer®), iron sucrose (Venofer®), iron III isomaltoside (Monofer®) and ferric carboxymaltose (Ferinject®)**
- **2.Anaemia of chronic disease:**
- **This is the second most common form of anaemia (after iron deficiency).**
- **It is associated with a wide variety of inflammatory diseases including arthritis, malignancies, inflammatory bowel disease, HIV and other infections.**
- **In malignancies, in addition to the anaemia of inflammation, the cytotoxic treatments themselves decrease erythrocyte production through their anti-proliferative effects on the bone marrow. Certain cytotoxic agents, such as platinum-based therapies, are more likely to cause anaemia. In chronic kidney disease and chronic heart failure, the reduced renal blood flow leads to a decreased production of erythropoietin.**

Table 49.4 Differentiation between iron deficiency anaemia and anaemia of chronic disease

Test	Iron deficiency anaemia	Anaemia of chronic disease
Serum iron	Low	Low
Serum ferritin	Low	Normal or high
Serum transferrin	High	Normal or low
Total iron binding capacity	High	Low

Treatment:

Treating the underlying chronic condition is the most important cornerstone in this kind of anaemia.

Blood transfusions are rarely needed in anaemia of inflammation. Oral iron therapy is not usually indicated despite the apparent reduced iron availability since these patients have a functional iron deficiency rather than an actual iron deficiency; also, the raised hepcidin levels reduce the oral absorption of iron .

Patients with chronic renal failure appear to have a functional iron deficiency that responds to intravenous iron with Epoietins with main outcome of improvement in the quality of life.

Patients with anaemia-associated IBD or with RA respond to intravenous iron; however, the use of intravenous iron in chronic inflammatory conditions is not generally recommended because of an increased risk of infections and also possible increased risk of acute cardiovascular events.

*Patients with cancer are not always recommended to use erythropoietin analogues with parenteral iron compounds as some studies suggested that they may increase disease progression.

3.Sideroblastic anaemias :

are a group of conditions that are diagnosed by finding ring sideroblasts in the bone marrow. There are both hereditary and acquired forms.

Aetiology: In the majority of hereditary forms, there is an X chromosome-linked pattern of inheritance. The main defect is a reduced activity of the enzyme 5-aminolevulinate synthase (ALAS) which is involved in haem synthesis.

The acquired forms include idiopathic forms, forms associated with myeloproliferative disorders and forms secondary to the ingestion of drugs and toxins.

Investigation: An examination of the bone marrow typically shows a number of erythroblasts that have iron granules surrounding the cell nucleus. These cells are known as ring sideroblasts.

Drugs and toxins: Alcohol can lead to the formation of ring sideroblasts. Ethanol is metabolized to acetaldehyde. It is the acetaldehyde that lowers the levels of ALAS and pyridoxal.

Clinical manifestations: The hereditary forms typically develop in infancy or childhood. The anaemia can range from mild to severe (haemoglobin typically 4–10 g/dL). The idiopathic acquired forms tend to develop insidiously usually in middle age or later. Many patients may be asymptomatic for long periods.

Treatment: In patients with the hereditary forms, large doses of pyridoxine (typically 100–200 mg daily or even up to 400 mg) may reduce the severity of the anaemia. Long-term high-dose pyridoxine has been associated with peripheral neuropathy and so lower maintenance doses are sometimes tried.

Haem arginate (licensed for use in porphyria) has been shown to increase the red cell count and decrease the number of ring sideroblasts in some patients with acquired sideroblastic anaemia.

4.Megaloblastic anaemias:

The megaloblastic anaemias are macrocytic anaemias (raised MCV). There is an abnormality in the maturation of haematopoietic cells in the bone marrow. In addition to abnormal red cells, the white cells and platelets may be affected.

The two major causes are folate deficiency and vitamin B12 deficiency.

Aetiology: 1- Folate deficiency anaemia:

Dietary deficiency is common.

2- Vitamin B12 deficiency anaemia:

Deficiency occurs from inadequate intake or malabsorption. The only dietary source of vitamin B12 (cyanocobalamin) is from food of animal origin.

Treatment: 1- Folate deficiency: managed by replacement therapy. The normal daily requirement of folic acid is approximately 100 μcg a day; despite this, the usual treatment doses given are 5–15 mg a day and the duration depend on the cause of the condition*.

2- Vitamin B12 deficiency anaemia: The standard treatment is hydroxocobalamin 1 mg intramuscularly three times a week for 2 weeks then 1 mg every 3 months.

5.Haemolytic anaemias:

In the haemolytic anaemias, there is a reduced life span of the erythrocytes.

Anaemia occurs when the rate of destruction of the erythrocytes exceeds their rate of production. There are a wide range of haemolytic anaemias with both genetic and acquired disorders.

Haemolytic anaemias account for approximately 5% of all anaemias

Table 49.6 Some examples of haemolytic anaemias

Genetic disorders of	Examples
Haemoglobin	Sickle cell anaemias Thalassaemias
Energy pathways	Glucose-6-phosphate deficiency
Membrane	Hereditary spherocytosis Hereditary ovalcytosis
Acquired disorders	
Immune	Autoimmune Rh or ABO incompatibility
Non-immune	Infections (parasitic, bacterial) Drugs and chemicals Hypersplenism

Clinical manifestations:

Patients with acute haemolytic anaemia commonly complain of malaise, fever, abdominal pain, dark urine and jaundice.

They have haemoglobulinaemia, hyperbilirubinaemia, reticulocytosis and increased urobilinogen levels in the urine. Patients with chronic haemolytic anaemia also usually have splenomegaly. Their anaemia is usually normochromic and normocytic.

Treatment:

Many patients with chronic haemolytic anaemia will have an over active bone marrow to compensate for the chronic haemolysis.

This increases the demand for folate and therefore folic acid supplements are often required, particularly for patients with a poor diet.

Patients who require frequent transfusions are at risk of iron overload and require chelation therapy with desferioxamine, desferiprone or deferasirox.

Hypothalamus, Pituitary, Thyroid, Parathyroid, Adrenal, and Gonads

I. Hypothalamus

Def: is a small but critical region of the diencephalon that serves as the primary link between the nervous and endocrine systems.

Function

- Integrates nervous and endocrine systems
- Secretes releasing and inhibiting hormones into the hypophyseal portal system to control the anterior pituitary
- Produces oxytocin and vasopressin (ADH), stored/released from the posterior pituitary

Key Hypothalamic Hormones

Hypothalamic Hormone	Target Pituitary Cell	Pituitary Hormone Affected
TRH (Thyrotropin-Releasing Hormone)	Thyrotrophs	↑ TSH
CRH (Corticotropin-Releasing Hormone)	Corticotrophs	↑ ACTH
GnRH (Gonadotropin-Releasing Hormone)	Gonadotrophs	↑ FSH/LH
GHRH (Growth Hormone–Releasing Hormone)	Somatotrophs	↑ GH
Somatostatin (GHIH)	Somatotrophs	↓ GH
Dopamine (PIF – Prolactin-Inhibiting Factor)	Lactotrophs	↓ Prolactin

Diseases of the Hypothalamus

Hypothalamic dysfunction typically causes secondary (central) endocrine disorders due to impaired releasing/inhibiting hormone production.

Common Causes:

- Tumors (craniopharyngioma—most common in children; gliomas)
- Infiltrative diseases (sarcoidosis, histiocytosis)
- Trauma or surgery (e.g., post-resection)
- Inflammation (autoimmune hypophysitis)
- Genetic disorders (e.g., Prader-Willi, Kallmann syndrome—GnRH deficiency)

Clinical Syndromes:

Deficiency	Consequence
CRH	Secondary adrenal insufficiency (↓ ACTH, ↓ cortisol)
TRH	Secondary hypothyroidism (↓ TSH, ↓ T4)
GnRH	Hypogonadotropic hypogonadism (↓ FSH/LH, amenorrhea/infertility)
GHRH	Growth failure in children; reduced IGF-1 in adults
ADH (if neuronal loss)	Central diabetes insipidus (polyuria, polydipsia, hypernatremia)
Dopamine loss	Hyperprolactinemia (even without pituitary tumor)

Diagnostic Approach

1. Assess for multiple hormone deficiencies
2. Differentiate hypothalamic vs. pituitary origin:
    - Hypothalamic: Pulsatile or low-normal pituitary hormones; may respond to synthetic releasing hormones (e.g., CRH, GnRH)

- Pituitary: Low pituitary hormones with no response to hypothalamic hormones

3. MRI brain with pituitary protocol → evaluate hypothalamus, stalk, and pituitary
4. Water deprivation test if Diabetes Insipidus suspected

II. Pituitary Gland ("Master Gland")

Divided into anterior (adenohypophysis) and posterior (neurohypophysis).

A. Anterior Pituitary Hormones

Hormone	Target	Main Actions
TSH	Thyroid	Stimulates thyroid hormone synthesis
ACTH	Adrenal cortex	Stimulates cortisol production
FSH	Gonads	Follicle development (♀), spermatogenesis (♂)
LH	Gonads	Ovulation (♀), testosterone production (♂)
GH	Liver, bone, muscle	Promotes growth, lipolysis, insulin resistance
Prolactin	Breast	Milk production

B. Posterior Pituitary (Storage, Not Synthesis)

Hormones released (produced in hypothalamus):

1. ADH (Antidiuretic Hormone / Vasopressin)
   - Acts on renal collecting ducts → ↑ water reabsorption → ↓ urine output
   - Also, a vasoconstrictor (important in shock)

- Regulated by plasma osmolarity and blood volume

2. Oxytocin
   - Uterine contraction (labor), milk ejection (suckling reflex)
   - Role in social bonding (less clinically relevant in disease)

Common Pituitary Disorders (General Principles)

A. Hypopituitarism (Pituitary Underactivity)

Causes:

- Pituitary adenomas (most common)
- Apoplexy (hemorrhage/infarction)
- Surgery/radiation
- Infiltrative diseases (sarcoid, hemochromatosis)

Pattern of Deficiency:

Hormone loss typically follows this order:

GH → FSH/LH → TSH → ACTH → Prolactin (variable)

Clinical Features:

1. ACTH deficiency: fatigue, hypotension, hyponatremia, hypoglycemia (life-threatening!)
2. TSH deficiency: secondary hypothyroidism (milder than primary)
3. FSH/LH deficiency: amenorrhea, infertility, low libido, loss of secondary sex characteristics
4. GH deficiency: in adults → decreased muscle mass, fatigue, dyslipidemia

B. Hyperpituitarism (Hormone Excess) – Usually Due to Adenomas

Adenoma Type	Key Features
Prolactinoma	Galactorrhea, amenorrhea, infertility, ↓ libido; treat with dopamine agonists (cabergoline)
GH-secreting	Adults: acromegaly (enlarged hands/feet, jaw, organomegaly); Children: gigantism
ACTH-secreting	Cushing's disease (not syndrome!) – central obesity, moon facies, hypertension, hyperglycemia
TSH-secreting	Rare cause of hyperthyroidism with elevated TSH

Diagnostic Approach

Step 1: Screen for Hormone Excess or Deficiency Excess:

- Prolactin → serum prolactin
- GH → IGF-1 (screen), then oral glucose tolerance test (GH should suppress)
- ACTH → overnight dexamethasone suppression test, late-night salivary cortisol

Deficiency:

- Morning cortisol + ACTH
- TSH + free T4
- LH, FSH, estradiol/testosterone
- FSH/LH + sex steroids for hypogonadism

Step 2: Imaging

- MRI pituitary with contrast – gold standard for structural evaluation

- CT if MRI contraindicated (less sensitive)

Management Principles

Condition	First-Line Treatment
Prolactinoma	Dopamine agonist
Acromegaly	Surgery (transsphenoidal), then somatostatin analogs
Cushing's disease	Transsphenoidal resection
Non-functioning adenoma	Observation (if small) or surgery (if mass effect)
Hypopituitarism	Hormone replacement:

III. Thyroid Gland

Hormones

- Primary hormones: T4 (thyroxine, prohormone), T3 (triiodothyronine , active form)
  - ✓ regulate metabolism, heart rate, thermogenesis, CNS development
- Calcitonin (from parafollicular C cells): lowers serum calcium (minor role in humans)

Regulation

- Hypothalamus → TRH → Pituitary → TSH → Thyroid → T3/T4
- Negative feedback: high T3/T4 → ↓ TSH

Common Disorders

1. **Hypothyroidism:**

- Hashimoto's thyroiditis

A. Causes

- Primary (95%): Hashimoto's thyroiditis (autoimmune) = most common cause, post-ablative (surgery/RAI), iodine deficiency/excess

B. Clinical Features: fatigue, weight gain, cold intolerance, bradycardia, myxedema

C. Treatment: Levothyroxine (LT4)

2. Hyperthyroidism:

A. Cause

- Graves' disease (TSH-receptor antibodies) = most common cause
- **Mechanisms**: Autoantibodies (TRAb) stimulate TSH receptor → ↑ hormone synthesis.

Clinical Features

Common Symptoms (due to ↑ metabolic rate):

- ✓ Weight loss despite ↑ appetite
- ✓ Heat intolerance, sweating
- ✓ Tremor, anxiety, insomnia
- ✓ Palpitations, tachycardia, atrial fibrillation
- ✓ Fatigue, muscle weakness (proximal myopathy)
- ✓ Menstrual irregularities

Management Approach:

A. Antithyroid drug.
B. Block hormone release – Iodine (to avoid substrate for hormone synthesis)
C. Block T4→T3 conversion – PTU, glucocorticoids (dexamethasone)
D. Decrease symptoms – Beta-blockers.

3. Goiter:

- **Def**: Enlargement of the thyroid gland visible or palpable on neck exam.
- Nodular vs. Diffuse:
  - ✓ Diffuse: smooth, symmetric enlargement (e.g., Graves', early Hashimoto's)
  - ✓ Nodular: single (solitary) or multiple nodules (multinodular goiter)
- Toxic vs. Nontoxic:
  - ✓ Toxic: associated with hyperthyroidism (e.g., Graves', toxic MNG)
  - ✓ Nontoxic: euthyroid or hypothyroid (most common)

Management Principles

Management depends on function, size, symptoms, and malignancy risk.

A. Nontoxic Diffuse Goiter (Euthyroid)

- If small & asymptomatic: observe (annual TSH + clinical exam)
- If due to iodine deficiency: iodine supplementation (e.g., iodized salt)
- If large or growing in iodine-sufficient area:
  - ✓ Levothyroxine suppression therapy (controversial):

B. Nontoxic Multinodular Goiter (MNG)

- Monitor if asymptomatic
- Surgery indicated if:
  - ✓ Compressive symptoms (dysphagia, dyspnea)
  - ✓ Cosmetic concern

C. Toxic Goiter

- Graves': see Hyperthyroidism lecture (Antithyroid drugs , Radioactive Iodine, surgery)

- Toxic MNG or toxic adenoma:
  - ✓ Radioactive Iodine (first-line)
  - ✓ Surgery if large, compressive, or Radioactive Iodine contraindicated

D. Hashimoto's with Goiter

- Usually, no specific goiter treatment
- Treat hypothyroidism with levothyroxine → goiter may shrink over months
- Large goiters may persist despite treatment

IV. Parathyroid Glands

The parathyroid glands maintain serum ionized calcium within a narrow range (8.5– 10.5 mg/dL) via parathyroid hormone (PTH).

Hormone

- Parathyroid hormone (PTH): primary regulator of calcium and phosphate

Key Actions of PTH:

Target Organ	Effect
Bone	Stimulates osteoclasts → ↑ bone resorption → releases Ca^{2+} and PO_4^{3-}
Kidney	- ↑ Calcium reabsorption (distal tubule) - ↓ Phosphate reabsorption (proximal tubule) → phosphaturia - ↑ 1α-hydroxylase activity → converts vitamin D to active calcitriol ($1,25\text{-}(OH)_2D$)
Intestine	Indirect: via ↑ calcitriol → ↑ dietary Ca^{2+} and PO_4^{3-} absorption

Disorders

- **Hyperparathyroidism:**

1. Primary (adenoma): ↑ PTH, ↑ Ca^{2+} → "stones, bones, groans, moans"
2. Secondary (e.g., CKD): ↑ PTH due to hypocalcemia/vitamin D deficiency

1. Primary Hyperparathyroidism

Causes:

- Sporadic solitary adenoma (~85%)
- Hyperplasia (~15%)
- Carcinoma (<1%)

Clinical Features:

- "Stones, bones, groans, moans, and psychiatric overtones":
- Renal: nephrolithiasis, nephrocalcinosis
- Skeletal: osteoporosis, brown tumors, fractures
- GI: nausea, constipation, pancreatitis
- Neuromuscular: fatigue, weakness
- Psych: depression, cognitive fog

Diagnosis:

- Persistent ↑ serum calcium + ↑ or non-suppressed PTH
- ↓ Phosphate, ↑ urine calcium (but can be normal)
- 25-OH Vitamin D level: check for deficiency (common; worsens hyperparathyroidism)

Management:

- Surgery (parathyroidectomy) = only curative treatment

2. Secondary & Tertiary Hyperparathyroidism

Secondary (e.g., CKD):

Cause: ↓ renal phosphate excretion → ↓ vitamin D activation → ↓ Ca^{2+} → compensatory ↑ PTH

Management:

- Phosphate binders
- Vitamin D analogs (calcitriol, paricalcitol)
- Cinacalcet (for severe cases)

Tertiary:

- Occurs after kidney transplant—parathyroid glands become autonomous
- May require parathyroidectomy

Special Considerations

- Magnesium is essential for PTH secretion:
- Severe hypomagnesemia → functional hypoparathyroidism
- Always check Mg^{2+} in hypocalcemia!

Hypoparathyroidism

Causes:

- Post-surgical (most common—after thyroid/parathyroid surgery)
- Autoimmune
- Genetic: DiGeorge syndrome (22q11 deletion), familial hypoparathyroidism
- Infiltrative: iron/copper overload (hemochromatosis, Wilson's)

Clinical Features (due to hypocalcemia):

Neuromuscular irritability:

- Chvostek's sign: facial twitch with tapping on facial nerve
- Trousseau's sign: carpopedal spasm with BP cuff inflation
- Paresthesias (fingers, lips)
- Seizures, laryngospasm (severe)
- Long-term: basal ganglia calcification, cataracts, dental abnormalities

Diagnosis:

- ↓ Calcium + ↓ or inappropriately normal PTH
- ↑ Phosphate
- Low magnesium → can cause functional hypoparathyroidism (correct Mg first!)

Management:

Acute hypocalcemia (symptomatic):

- IV calcium gluconate.
- Correct magnesium if low.

V. Adrenal Glands

Two distinct parts: cortex and medulla

A. Adrenal Cortex (3 zones)

Zone	Hormone	Function
Zona glomerulosa	Aldosterone	↑ Na^+ reabsorption, ↑ K^+/H^+ excretion (RAAS)
Zona fasciculata	Cortisol	Gluconeogenesis, anti-inflammatory, stress response
Zona reticularis	Androgens (DHEA, androstenedione)	Pubic/axillary hair (adrenarche)

B. Adrenal Medulla

- **Hormones:** Secretes Epinephrine (80%) and Norepinephrine (20%)
- **Function:** "Fight-or-flight" response → ↑ HR, BP, blood glucose, bronchodilation

Clinical Correlations

A. Adrenal Insufficiency

- **Primary (Addison's disease):**
  - ✓ Autoimmune destruction (most common), TB, metastasis
  - ✓ Features: Fatigue, hyperpigmentation (↑ ACTH/MSH), hyponatremia, hyperkalemia, hypotension
  - ✓ Diagnosis: ↓ Cortisol, ↑ ACTH, positive ACTH stimulation test
- **Secondary:**
  - ✓ Pituitary failure → ↓ ACTH
  - ✓ Features: Similar but no hyperpigmentation or hyperkalemia (aldosterone preserved)

B. Cushing's Syndrome

Causes:

- ✓ Exogenous glucocorticoids (most common)
- ✓ Pituitary adenoma (Cushing's disease)
- ✓ Adrenal tumor
- ✓ Ectopic ACTH (e.g., small cell lung cancer)

Features: Central obesity, moon face, buffalo hump, purple striae, hypertension, glucose intolerance, osteoporosis

C. Hyperaldosteronism

- **Primary (Conn's syndrome):**

✓ Adrenal adenoma → ↑ aldosterone → hypertension + hypokalemia + metabolic alkalosis

✓ Low renin (key diagnostic clue)

- **Secondary:** Due to volume depletion (e.g., heart failure, cirrhosis) → high renin

D. Pheochromocytoma

- Tumor of adrenal medulla → excess catecholamines
- **Classic triad:** Episodic headache, palpitations, sweating
- **Diagnosis:** ↑ Urinary or plasma metanephrines
- **Rule of 10s:** 10% bilateral, 10% malignant, 10% extra-adrenal, 10% familial.

VI. Gonads

Def: Primary reproductive organs that produce gametes and sex hormones.

A. Testes (♂)

Cell Types & Functions

Cell Type	Function
Sertoli cells	Support spermatogenesis (stimulated by FSH)
Leydig cells	Produce testosterone in response to LH

B. Ovaries (♀)

Cell Types & Structures

Cell Type	Function
Granulosa cells:	produce estradiol (FSH-dependent)
Theca cells:	produce androgens → converted to estrogen
Corpus luteum	produces progesterone post-ovulation

Regulation

- ✓ Hypothalamus → GnRH → FSH/LH → Gonads → Sex steroids
- ✓ Negative (and positive in mid-cycle) feedback on pituitary

Clinical Correlations

Condition	Key Features
Klinefelter syndrome (47,XXY)	Small testes, infertility, gynecomastia, tall stature
Turner syndrome (45,X)	Streak ovaries, primary amenorrhea, short stature, webbed neck
Androgen insensitivity syndrome	46,XY; testes present (often intra-abdominal); external female phenotype; no uterus
Polycystic ovary syndrome (PCOS)	Anovulation, ↑ androgens, insulin resistance, multiple ovarian cysts

Cryptorchidism	Undescended testes → ↑ risk of infertility & testicular cancer
Ovarian torsion	Acute pelvic pain; surgical emergency

Diseases of Connective Tissue and Rheumatology Introduction, Major Manifestations, and Key Investigations

I. Introduction

Connective tissue diseases (CTDs)

- **Def:** are a heterogeneous group of autoimmune and inflammatory disorders that primarily affect the connective tissues structures rich in collagen and elastin (e.g., skin, joints, blood vessels, muscles, and internal organs).
- Umbrella term for > 200 disorders that target collagen, elastin and ground substance
  - **Pathogenesis:** Loss of immune tolerance → autoantibody production, immune complex deposition, chronic inflammation → tissue damage.
  - **Common features:** Multisystem involvement, female predominance, chronic course, flares and remissions.
  - **Key concept:** Many CTDs are systemic autoimmune diseases, often associated with specific autoantibodies that aid diagnosis and prognosis.
- **Rheumatology** is the branch of medicine focused on disorders of the musculoskeletal system and autoimmune/connective tissue diseases (CTDs). These conditions are often chronic, systemic, and immune-mediated, affecting not only joints but also skin, kidneys, lungs, heart, and blood vessels.
- **Rheumatic diseases** often present with non-specific systemic symptoms and organ-specific signs. A careful history and physical exam are crucial.

II. Major Connective Tissue Diseases & Core Manifestations

1. Systemic Lupus Erythematosus (SLE)

- **Def:** SLE is a chronic, systemic autoimmune disease characterized by loss of immune tolerance, production of autoantibodies (especially anti-nuclear antibodies), and immune complex–mediated inflammation affecting multiple

organs.

- **Hallmark Features**: Malar rash, photosensitivity, oral ulcers, arthritis, serositis, renal disease (lupus nephritis), neuropsychiatric symptoms, cytopenias.
- **Key Organ Systems Involved**: Skin, joints, kidneys, CNS, serosal membranes, blood

2. Rheumatoid Arthritis (RA)

- **Def:** RA is a chronic, systemic autoimmune disease primarily targeting synovial joints, leading to symmetrical inflammatory polyarthritis, joint destruction, and extra-articular manifestations.
- **Hallmark Features**: Symmetric inflammatory small joint arthritis (Metacarpophalangeal joints, Proximal Interphalangeal joints, wrists), morning stiffness >1-hour, rheumatoid nodules
- **Key Organ Systems Involved**: Joints (erosive), lungs (ILD, nodules), eyes, vasculature

3. Systemic Sclerosis (Scleroderma)

- **Def:** Systemic sclerosis is a chronic, multisystem autoimmune disease characterized by vasculopathy, immune dysregulation, and excessive fibrosis of the skin and internal organs (e.g., lungs, heart, kidneys, GI tract).
- **Hallmark Features**: Skin thickening, Raynaud's phenomenon, esophageal dysmotility, pulmonary fibrosis, renal crisis
- **Key Organ Systems Involved**: Skin, GI tract, lungs, kidneys, heart

4. Sjögren's Syndrome

- **Def:** Sjögren's syndrome is a chronic systemic autoimmune disorder primarily targeting exocrine glands (especially salivary and lacrimal glands), leading to dry eyes and dry mouth. It can occur alone (primary) or alongside another connective tissue disease like RA or SLE (secondary).
- **Hallmark Features**: Dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia), parotid enlargement, fatigue
- **Key Organ Systems Involved**: Exocrine glands, joints, lungs, kidneys, lymphoma risk ↑

5. Dermatomyositis/Polymyositis

- **Def:** Both are autoimmune disorders causing chronic muscle inflammation and progressive proximal muscle weakness.
- Dermatomyositis = Skin + muscle involvement, Polymyositis = Muscle only (no skin findings)

- **Hallmark Features**: Proximal muscle weakness, heliotrope rash, Gottron's papules (DM only), dysphagia.
- **Key Organ Systems Involved**: Muscles, skin, lungs (ILD), heart

6. Mixed Connective Tissue Disease (MCTD)

- **Def:** MCTD is a systemic autoimmune disorder characterized by overlapping clinical features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), and rheumatoid arthritis (RA)—along with high-titer anti–U1 ribonucleoprotein (anti-U1 RNP) antibodies.
- **Hallmark Features**: Overlap of SLE, SSc, and PM features; severe Raynaud's, puffy hands, anti-U1-RNP antibody.
- **Key Organ Systems Involved**: Joints, skin, lungs (pulmonary hypertension), muscles

Note:

- Raynaud's phenomenon is a common early sign in many CTDs (especially SSc and MCTD).
- Interstitial lung disease (ILD) and pulmonary hypertension are major causes of morbidity/mortality.

III. Common Clinical Manifestations Across CTDs

Symptom/Sign	Possible Underlying CTDs
Arthralgia/Arthritis	SLE, RA, Sjögren's, MCTD
Raynaud's phenomenon	SSc, MCTD, SLE
Photosensitivity	SLE, dermatomyositis
Myalgia/Weakness	Myositis, SLE, MCTD
Dry eyes/mouth	Sjögren's (primary or secondary)
Skin tightening	Systemic sclerosis
Unexplained fevers, fatigue, weight loss	Nearly all systemic CTDs

IV. Key Laboratory and Diagnostic Investigations

1. Screening Tests

- ANA (Antinuclear Antibody):
- High sensitivity for SLE (>95%), also positive in Sjögren's, SSc, MCTD, myositis.
- Low specificity—can be positive in healthy individuals (especially elderly).
- Pattern matters: Homogeneous (SLE), speckled (Sjögren's, MCTD), nucleolar (SSc).

2. Disease-Specific Autoantibodies

Antibody	Associated Disease(s)	Clinical Significance
Anti-dsDNA, Anti-Smith (anti-Sm)	SLE	High specificity for SLE; anti-dsDNA correlates with renal activity
Rheumatoid Factor (RF), Anti-CCP	RA	Anti-CCP >95% specific for RA; predicts erosive disease
Anti-SSA (Ro), Anti-SSB (La)	Sjögren's, SLE	Linked to neonatal lupus, congenital heart block, photosensitivity
Anti-Jo-1	Polymyositis/dermatomyositis	Part of "antisynthetase syndrome" (myositis + ILD + Raynaud's + fever)

3. Inflammatory Markers

- ESR ↑: Often elevated in active disease (e.g., RA, polymyalgia rheumatica)
- CRP ↑: More acute-phase; may be normal in SLE (unless serositis/infection)

4. Organ-Specific Investigations

- Urinalysis + renal function: For lupus nephritis (proteinuria, casts)
- PFTs (Pulmonary Function Tests) and HRCT (High-Resolution Computed Tomography) chest: For ILD (common in SSc, myositis, RA)
- Echocardiogram: Screen for pulmonary hypertension (in SSc, MCTD)
- Schirmer's test / salivary gland biopsy: For Sjögren's
- EMG (Electromyography) / muscle enzymes (CK, aldolase): For myositis
- Joint X-rays / Ultra sound/ MRI: For RA (look for erosions, synovitis)

V. Approach to Suspected CTD

1. Detailed history: Pattern of symptoms (joint vs. systemic), duration, family history.
2. Thorough physical exam: Skin, joints, oral cavity, lymph nodes, lung/heart auscultation.
3. Start with Antinuclear Antibody (ANA) + Extractable Nuclear Antigen (ENA) Panel, Rheumatoid Factor (RF), Anti-Cyclic Citrullinated Peptide (anti-CCP), CBC, creatinine, LFTs, urinalysis.
4. Refine with disease-specific antibodies based on clinical picture.
5. Assess organ involvement early—especially kidneys, lungs, heart.

PRINCIPLES OF CRITICAL CARE MEDICINE , MAJOR MANIFESTATIONS OF SHOCK \ SEPSIS

- Acute medicine is part of general medicine that is concerned with the immediate & early management of

medical patients who require urgent care

- There are many systems developed to deal with critically ill patients & its aim is to rapid determination of physiological deterioration in the patient & rapid response
- One example of rapid response system is medical emergency team (MET) . The team operates on the basis that when the patient meets certain criteria, the team is alerted. & expected to make a rapid assessment & institute immediate management .
- They either escalate to critical care , or following contact with patient initial clinical team , ongoing ward –based care.

The trigger for MET may be single parameter such as shock (low Bl. Pressure or tachycardia , or a score based composite warning . Such as abnormalities in respiratory rate , SpO2, temperature

1-PRINCIPLES OF CRITICAL CARE MEDICINE

- For immediate assessment of deteriorating patient the following approach is used&

can be summarized by the mnemonic)C-A-B-C-D-E.(

- C : control of obvious problem e.g .VT , significant blood loss.
- A & B : airway & breathing . e.g .if the patient can talk a full sentence , then the airway is clear & breathing is adequate .A rapid Hx .Is obtained while the initial assessment is carried out . Breathing should be assessed with focus on respiratory examination .SpO2 , ABGs , should be checked early.
- C : circulation , cardiovascular exam .Should include the H.R , .RHYTHM , JVP . Any evidence of recent bleeding , signs of shock& , abnormal heart sounds .Carotid pulse should be palpated in shocked collapsed unconscious patient . The peripheral pulses) radial , brachial ,femoral (pulses may disappear as condition progress.

2-PRINCIPLES OF CRITICAL CARE MEDICINE

- D : disability , conscious level should be assessed using GCS) Glasgow coma scale, ( )Eye opening , Best motor response , Verbal response ,(EMC) electronic medical compendium .(A brief neurological examination looking for focal sign should be performed . Capillary blood glucose should always be measured to exclude hypoglycemia or sever hyperglycemia.
- E : exposure &evidence , exposure indicates the need for targeted clinical examination of the remaining body system , particularly the abdomen & lower limbs .

Evidence may be collected from collateral history from other health– care professional or family members , recent investigations , prescriptions or monitoring charts.

MAJOR MANIFESTATIONS

a. Chest pain : it is common symptom in patients presenting to hospital . It has wide list of differential diagnosis , so the detailed Hx. & through clinical examination is of paramount importance to guide the direction of investigations. The major causes of chest pain are:
    i. Central chest pain:

2) Cardiac , (IHD , Myocarditis , pericarditis, MV.prolapse.(
3) Aortic , dissection & aneurysm.
4) :3Oesophageal , (esophagitis, spasm, Mallory-Weiss syndrome , perforation.(
5) -4Pulmonary embolism.
6) -5Mediastinal , malignancy,
7) -6Anxiety \ emotion.

i. Peripheral chest pain :
ii. 1- lung & pleura .(pulmonary infarction , pleurisy , pneumothorax.(
iii. 2-musculoskeletal (trauma, osteochondritis).
iv. 3- neurological. (herpes zoster, intervertebral disc herniation).

Acute breathlessness : a history with rapid & careful examination will usually suggest the diagnosis , which is then confirmed by routine investigations such as CXR , 12-lead ECG, ABG sampling . The rapidity with which acute breathlessness occur may give important clue for the underlying etiology. The most important causes of acute breathlessness are:

1) Acute pulmonary oedema.
2) Massive pulmonary embolism.
3) Acute sever asthma.
4) Acute exacerbation of COPD.
5) Pneumonia.
6) Metabolic acidosis.
7) Psychogenic.
8) Foreign body inhalation , is important cause in children

Syncope \ presyncope : the term syncope refers to sudden loss of consciousness due to reduce cerebral perfusion. Presyncope , refers to lightheadedness in which the individual thinks he\she may black out . Dizziness & presyncope is particularly common in old age. The main 3 principal mechanism s for syncope\presyncope are:

1- Cardiac syncope. (mechanical dysfunction or arrhythmias.(
2- Neurocardiogenic syncope , also known as vasovagal or reflex syncope.
3- Postural hypotension , in which peripheral vasoconstriction on standing is impaired leading to hypotension. It is important to differentiate the cardiac from non-cardiac causes of syncope, by premonitory symptoms, unconscious period & recovery process.

SHOCK & SEPSIS

- Septic shock : is a condition in which bacterial infection causes hypotension) systolic Bl .Pressure equal or below 90 mmHg\ & ,or diastolic Bl .Pressure drops below 60 mmHg ,(vasodilation & organ failure. MAP is sometimes used for assessment of patient status & follow up. These manifestations occur due to sever systemic inflammatory response to bacterial & other organism infection .The infection can start any where in the body) bl .Stream ,bone , lung , kidney , brain , skin ,liver ,gall bladder & bowel.(
- The major symptoms & signs of sepsis & septic shock are:
- -1Hypotension. -2Tachycardia -3 . Tachypnoea. -4Hypoxemia-5 .lightheadedness

,disturbed consciousness & coma -5 .Fever or hypothermia -6 . Chills -7 . skin changes) warm

or cold skin , skin rash , petechiae.(

- The mean arterial Bl.pressure) MAP (utilize both systolic & diastolic Bl .Pressure in single reference value . A MAP of more than 65 mmHg will maintain renal perfusion in majority of patients ,.although a MAP of up to 80 mmHg may be required in patients with chronic hypertension.
- MAP = Diastolic blood pressure) + systolic – diastolic
-

INVESTIGATIONS IN SEPTIC SHOCK.

After full medical Hx. & though physical examination , the infection is often confirmed by blood culture. Although it may be negative in people receiving prior antibiotics , & some infection can not be diagnosed by blood culture.

Other test that may be done include:

Blood gases.

Renal function tests.

Complete blood film for platelet count , fibrin degradation products (D-dimer) , coagulation tests (PT , APTT) to check for DIC & bleeding risk. WBC count & differential also carried out.

Other tests according to site if suspected focus of infection such as CSF , in cases of meningitis , bone imaging studies , ultrasound for liver & gall bladder diseases.

Specific Forms of Organ Failure in Critical Illness

I. Introduction

Organ failure is a hallmark of severe illness, especially in the intensive care unit (ICU). It can affect one organ (e.g., acute kidney injury) or multiple systems simultaneously, a condition known as multiple organ dysfunction syndrome (MODS) the leading cause of death in non-coronary ICUs.

Five critical syndromes:

1. Multiple Organ Dysfunction Syndrome (MODS)
2. Acute Respiratory Distress Syndrome (ARDS)
3. Disseminated Intravascular Coagulation (DIC)
4. Acute Renal Failure (Acute Kidney Injury, AKI)
5. Acute Hepatic Failure

Each represents a final common pathway of severe physiological stress—often triggered by sepsis, trauma, or massive inflammation.

II. Multiple Organ Dysfunction Syndrome (MODS)

Definition:

- Progressive dysfunction of two or more organ systems in an acutely ill patient, requiring intervention to maintain homeostasis.
- Not due to direct injury to the organs (e.g., not from bilateral pneumonia causing only lung failure).

Pathophysiology:

- Driven by a systemic inflammatory response (e.g., from sepsis, pancreatitis, burns).

- Cytokine storm → endothelial damage → capillary leak → microcirculatory failure → cellular hypoxia.

Common Sequence of Organ Involvement

1. Lungs (within 24–72 hrs) → ARDS
2. Liver → elevated bilirubin, coagulopathy
3. Kidneys → oliguria, rising creatinine
4. Heart/CNS → hypotension, encephalopathy

Prognosis

- Mortality increases with number of failing organs:

- ✓ 2 organs: ~30% mortality
- ✓ ≥3 organs: >70% mortality

III. Acute Respiratory Distress Syndrome (ARDS)

Definition (Berlin Criteria):

ARDS is acute, diffuse inflammatory lung injury leading to:

- Onset within 1 week of known insult
- Bilateral opacities on CXR/CT (not fully explained by effusion, collapse, or nodule)
- Respiratory failure NOT fully explained by cardiac failure
- Impaired oxygenation, classified by PaO_2/FiO_2 ratio:
  - Mild: 200–300 mmHg
  - Moderate: 100–200 mmHg
  - Severe: <100 mmHg

Common Causes

- Sepsis (most common)
- Pneumonia
- Aspiration
- Trauma (fat embolism, lung contusion)
- Pancreatitis

Pathophysiology:

Alveolar-capillary membrane damage → protein-rich fluid leaks into alveoli → non-cardiogenic pulmonary edema → stiff lungs, poor gas exchange.

Clinical Features:

- Rapid onset dyspnea
- Tachypnea
- Hypoxemia refractory to oxygen
- "White-out" lungs on CXR

Management Principles:

- Treat underlying cause (e.g., antibiotics for sepsis)
- Lung-protective ventilation:
  - Low tidal volume (6 mL/kg predicted body weight)
  - Limit plateau pressure <30 cm H_2O
- Prone positioning (in severe ARDS)
- Conservative fluid strategy
- Avoid routine steroids (controversial)

IV. Disseminated Intravascular Coagulation (DIC)

Definition

- Systemic activation of coagulation leading to:

- Widespread microthrombi → organ ischemia
- Consumption of platelets/clotting factors → bleeding

Common Triggers

- Sepsis (most common)
- Trauma (especially with tissue injury)
- Obstetric emergencies (amniotic fluid embolism, placental abruption)
- Malignancy (e.g., acute promyelocytic leukemia)

Clinical Features

- Bleeding: petechiae, ecchymoses, oozing from IV sites
- Thrombosis: acral ischemia, purpura fulminans
- Organ failure: renal, respiratory (from microthrombi)

Lab Findings (Typical Pattern)

Test	Result
Platelets	↓↓
Fibrinogen	↓ (late)
PT/aPTT	↑↑
D-dimer	↑↑↑ (markedly elevated)
Fibrin split products	↑

Note: D-dimer is always elevated in DIC—this helps distinguish it from liver disease or warfarin effect.

Management

- Treat the underlying cause (e.g., antibiotics, delivery in obstetric DIC)
- Supportive care:
  - Platelets if <50,000 or actively bleeding
  - Cryoprecipitate (if fibrinogen <1.5 g/L)
  - Fresh Frozen Plasma (FFP) if severe bleeding + prolonged PT/aPTT
- Avoid anticoagulants in bleeding-predominant DIC

V. Acute Renal Failure (Acute Kidney Injury – AKI)

Definition (KDIGO Criteria):

AKI = any of the following within 48 hours:

- ↑ Serum creatinine by ≥0.3 mg/dL
- ↑ Creatinine to ≥1.5× baseline
- Urine output <0.5 mL/kg/h for 6+ hours

Classification by Cause

Type	Mechanism	Examples
Prerenal	↓ Renal perfusion	Hypovolemia, sepsis, heart failure
Intrinsic	Direct kidney damage	Acute tubular necrosis (ATN), glomerulonephritis, vasculitis
Postrenal	Urinary tract obstruction	Prostate enlargement, stones, tumors

Key Clues on Urinalysis

- Prerenal: bland sediment, high urine osmolality (>500), low FeNa (<1%)
- ATN (intrinsic): muddy brown casts, granular casts, FeNa >2%
- Glomerulonephritis: hematuria, RBC casts, proteinuria

Management

- Prerenal: fluid resuscitation (if hypovolemic)
- Intrinsic: treat cause (e.g., immunosuppression for vasculitis); avoid nephrotoxins
- Postrenal: relieve obstruction (e.g., Foley catheter, nephrostomy)

- Renal replacement therapy (dialysis) if:

- ✓ Refractory hyperkalemia
- ✓ Pulmonary edema
- ✓ Uremic complications (pericarditis, encephalopathy)

VI. Acute Hepatic Failure (AHF)

Definition

Rapid loss of liver function (within 26 weeks) in a patient without pre-existing liver disease, leading to:

- Coagulopathy (INR ≥1.5)
- Hepatic encephalopathy (any grade)

If no encephalopathy, it's acute liver injury, not failure.

Common Causes

- Drugs: Paracetamol (acetaminophen) overdose (most common in West)
- Viral: Hepatitis A, B, E

- Autoimmune hepatitis
- Ischemic hepatitis ("shock liver")
- Toxins: Amanita phalloides (mushroom)

Clinical Features

- Jaundice
- Coagulopathy (bruising, bleeding)
- Encephalopathy: confusion → asterixis → coma
- Cerebral edema (in grade III–IV) → herniation risk
- Hypoglycemia, lactic acidosis

Key Labs

- ↑↑ Bilirubin
- ↑ INR (out of proportion to transaminases in late stages)
- AST/ALT: very high early (e.g., >1000 in toxic hepatitis)
- ↓ Glucose, ↓ pH

Management

- Admit to ICU (risk of rapid deterioration)
- N-acetylcysteine (NAC): for paracetamol overdose—and also beneficial in non-paracetamol AHF
- Correct coagulopathy only if bleeding (prophylactic FFP not recommended)
- Monitor for cerebral edema: elevate head, consider mannitol/hypertonic saline
- Liver transplant evaluation if poor prognosis.

VII. Integration: How These Syndromes Interact

- Sepsis is the most common trigger for MODS, leading to ARDS, AKI, DIC, and liver dysfunction together.

- DIC can cause renal cortical necrosis → AKI
- ARDS often requires sedation/paralysis → prolonged ICU stay → multi- organ stress
- Hepatic failure → coagulopathy → bleeding → hypovolemic shock → AKI

Critical care is about connections: failure in one organ stresses others.

VIII. Summary

Syndrome	Key Diagnostic Feature	Immediate Action
MODS	≥2 failing organs	Treat trigger (e.g., sepsis), suppo organs
ARDS	PaO_2/FiO_2 <300 + bilateral infiltrates	Lung-protective ventilation
DIC	Bleeding + ↑ D-dimer + low platelets	Treat cause, replace clotting factors bleeding
AKI	↑ Creatinine or ↓ urine output	Determine prerenal/intrinsic/postrenal
Acute Liver Failure	INR ≥1.5 + encephalopathy	NAC, ICU, transplant eval