Ministry of Higher Education and Scientific Research

College of Health and Medical Technology

Anesthesia Techniques Department

Subject: Basic of Medicine-2,

2nd stage.

2025-2026

Introduction to Hematology – Major Manifestations and Key Investigations

I. Introduction to Hematology

Hematology is the branch of medicine concerned with the study, diagnosis, treatment, and prevention of diseases related to blood and blood-forming organs. Blood is a dynamic tissue composed of:

- Plasma (liquid component)
- Cellular elements:
- Red blood cells (RBCs) – carry oxygen via hemoglobin
- White blood cells (WBCs) – part of the immune system
- Platelets (thrombocytes) – critical for hemostasis

Hematopoiesis

Def. The physiologic process of formation of blood cells is called as hematopoiesis.

Hematopoiesis formation sites:

- First quarter of gestation: It takes place in the yolk sac, outside the embryo.
- In the second quarter of gestation: The liver mainly takes part and to a lesser extent the spleen, start of the bone marrow and lymphoid organs to take part in hematopoiesis in mammals.
- At the time of birth nearly all blood cells are produced in the bone marrow (medullary hematopoiesis) and hematopoiesis immediately or gradually stops in the liver and spleen.
- In certain disease conditions, when there is great need for blood cells these two organs retain their ability for manufacturing blood cells (extra medullary hematopoiesis).

Hematologic disorders can arise from:

- Defects in production (e.g., aplastic anemia)
- Abnormal function (e.g., hemophilia)

- Excessive destruction (e.g., hemolytic anemias)
- Malignant transformation (e.g., leukemias, lymphomas)

Bone marrow: is soft, gelatinous tissue that fills the medullary cavities, the centers of bones.

There are two types of bone marrow:

- Red marrow composed of hematopoietic tissue (active marrow).
- Yellow marrow composed of fat cells (inactive marrow).

Both types of bone marrow are enriched with blood vessels and capillaries. Bone marrow makes more than 200 billion new blood cells every day.

Active sites of hematopoiesis are: pelvis, vertebra, skull, ribs, sternum, and proximal

ends of long bones.

Note: All the blood cells circulating in the peripheral blood are derived from the primitive mesenchymal cells called as pluripotent hematopoietic stem cells (PHSCs); the term pluripotent refers to the ability to produce many cell types.

Regulate and control of hemopoiesis:

1. POIETINS:

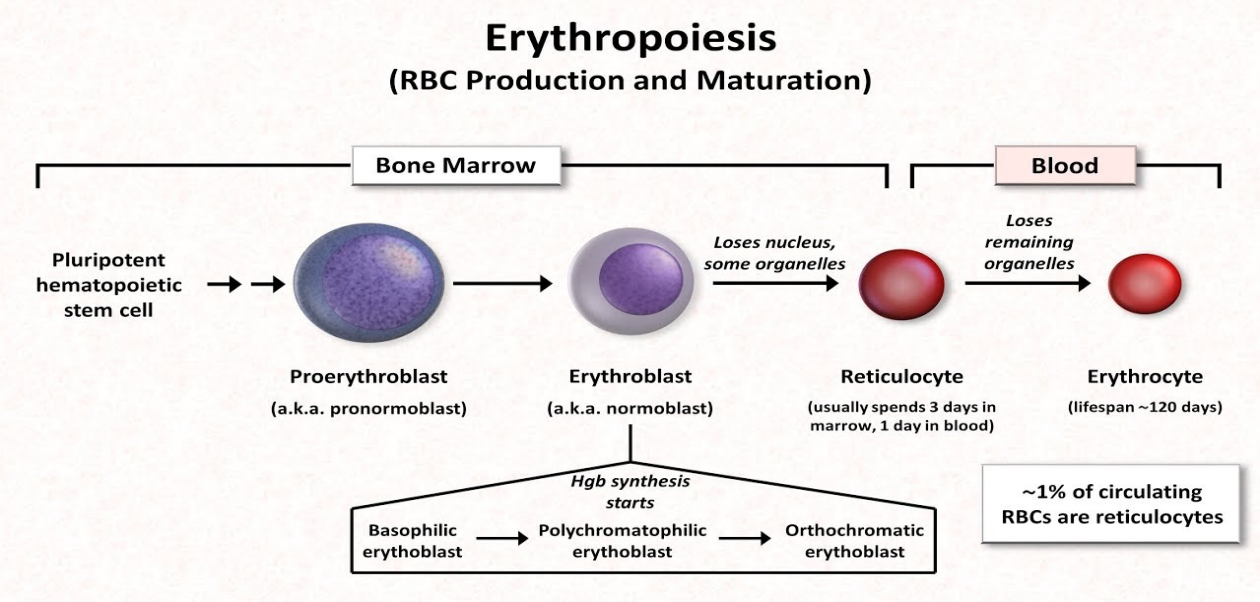
a) **Erythropoietin (EPO);** It is a hormone-like circulatory glycoprotein produced mainly in the kidney; lesser amount is produced in Kupffer cells in the liver. EPO stimulate erythropoiesis in response to hypoxia.

b) **Thrombopoietin (TPO):** It is synthesized in the kidney and in the liver; it stimulates platelets production on different levels in the bone marrow (BM).

2. Colony Stimulating Factors (CSFs): They are glycoproteins act directly on haemopoietic sub –populations in the BM, produced from adventitial cells, T lymphocytes, macrophages and stromal cells, e.g., stem cell factor (SCF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF) etc.

3. Interleukins: It is a family of proteins produced by different cells (cytokines) like fibroblasts, macrophages, activated T lymphocytes, endothelial cells... etc. they control some aspects of hematopoiesis & immune response.

Erythropoiesis: the process of red blood cell (RBC) production is a tightly regulated, dynamic system essential for oxygen delivery. It occurs primarily in the bone marrow and is influenced by a variety of hormonal, nutritional, environmental, and pathological factors. Disruptions in any of these can lead to anemia or polycythemia.



Key Regulator: Erythropoietin (EPO)

- **Source:** Primarily peritubular interstitial cells in the kidney (some from liver, especially in fetal life).
- **Stimulus:** Tissue hypoxia (detected via oxygen-sensing prolyl hydroxylase–HIF pathway).
- **Action:**
  - ✓ Binds EPO receptors on erythroid progenitors (CFU-E, proerythroblasts).

- ✓ Promotes survival, proliferation, and differentiation → increases RBC production in 2–5 days.

Clinical note: In chronic kidney disease (CKD), EPO deficiency is a major cause of anemia of chronic disease.

Hormonal & Cytokine Influences

1. Thyroid hormones: Enhance EPO sensitivity and basal metabolic rate → mild anemia in hypothyroidism.
2. Androgens: Stimulate EPO production → higher hematocrit in males; used therapeutically (e.g., danazol in aplastic anemia).
3. Glucocorticoids: May increase RBC survival (mild erythrocytosis).
4. Inflammatory cytokines (e.g., IL-6, TNF-α):
   - ✓ Suppress erythropoiesis in anemia of chronic inflammation.
   - ✓ Increase hepcidin → iron sequestration in macrophages.

Nutritional Factors

Adequate substrates are essential for hemoglobin synthesis and RBC maturation:

Nutrient	Role in Erythropoiesis	Deficiency Manifestation
Iron	Core component of heme	Microcytic hypochromic anemia
Vitamin B12	DNA synthesis (via folate metabolism)	Macrocytic anemia, neurologic symptoms
Folate (B9)	DNA/RNA synthesis in rapidly dividing erythroblasts	Macrocytic anemia (no neurologic signs)
Copper	Cofactor for ceruloplasmin (iron oxidation/transport)	Anemia (often with neutropenia)
Vitamin B6	Cofactor in heme synthesis	Sideroblastic anemia

(Pyridoxine)		
Vitamin E	Protects RBC membrane from oxidative damage	Hemolysis (especially in premature infants)

Oxygen Availability & Environmental Factors

1. High altitude: Chronic hypoxia → ↑ EPO → secondary polycythemia.
2. Smoking: Carbon monoxide binds hemoglobin → functional hypoxia → mild polycythemia.
3. Chronic lung/heart disease: Tissue hypoxia → compensatory erythrocytosis.

Erythrocyte lifespan

- The average erythrocyte lifespan: ~120 days in healthy adults.
- In certain disease situations the survival time of the erythrocytes is shortened, particularly some nutritional deficiencies (iron, vitamin B_{12}, folic acid.

Why Do Erythrocytes Die After ~120 Days?

As RBCs age, they undergo progressive changes:

1. Membrane changes: Loss of membrane phospholipid asymmetry and surface area → decreased deformability.
2. Oxidative damage: Accumulation of reactive oxygen species damages hemoglobin and cytoskeletal proteins.
3. Metabolic exhaustion: Depletion of ATP and NADPH impairs ion pumps and antioxidant defenses.
4. Recognition by macrophages: Aged RBCs display "eat-me" signals like exposed phosphatidylserine and altered surface proteins.

These changes make older RBCs less flexible—critical because they must navigate narrow splenic sinusoids (3 μm) despite being ~7–8 μm in diameter.

Site of Erythrocyte Clearance

Primary site: Spleen (also liver and bone marrow to a lesser extent).

Mechanism:

1. Macrophages in the red pulp of the spleen phagocytose senescent or damaged RBCs.
2. Hemoglobin is broken down into:
   - ✓ Heme → converted to biliverdin → bilirubin (unconjugated).
   - ✓ Globin → recycled into amino acids.
   - 🌍 Iron → bound to transferrin and reused for erythropoiesis or stored as ferritin.

Factors That Shorten or Prolong RBC Lifespan

Shortened Lifespan	Prolonged Lifespan
Hemolytic anemias (sickle cell, G6PD deficiency, hereditary spherocytosis)	Hypersplenism absent (e.g., post-splenectomy – RBCs may live longer)
Mechanical trauma (e.g., prosthetic heart valves)	Certain storage conditions (not physiologic)
Infections (e.g., malaria)	—
Autoimmune hemolytic anemia	—

Clinical Application

1. Anemia evaluation: Differentiating between decreased production vs. increased destruction hinges on understanding RBC turnover.
2. Neonatal jaundice: Fetal RBCs have a shorter lifespan (~70–90 days) → increased bilirubin load.

3. Chronic kidney disease: Reduced EPO → fewer new RBCs → relative excess of older cells.
4. HbA1c interpretation: Reflects average glycemia over ~2–3 months—the typical RBC lifespan. In conditions with shortened RBC survival (e.g., hemolysis), HbA1c may be falsely low.

II. Major Clinical Manifestations in Hematology

Hematologic diseases often present through systemic or specific signs related to dysfunction in one or more blood components.

A. Manifestations of Anemia (RBC Disorders)

- ✓ Fatigue, pallor, dyspnea on exertion
- ✓ Tachycardia, palpitations
- ✓ Pica (in iron deficiency)
- ✓ Jaundice and dark urine (in hemolysis)
- ✓ Neurologic symptoms (e.g., paresthesia in B12 deficiency)

B. Manifestations of Leukocyte Disorders

- ✓ Leukopenia/neutropenia: recurrent or severe infections (bacterial/fungal)
- ✓ Leukocytosis: may be reactive (infection, stress) or malignant (leukemia)
- ✓ Lymphadenopathy, splenomegaly, night sweats, weight loss (B symptoms – suggestive of lymphoma)

C. Manifestations of Platelet/Coagulation Disorders

- Bleeding tendency:

- ✓ Petechiae, purpura, ecchymoses (platelet disorders)
- ✓ Hemarthrosis, deep tissue hematomas (coagulation factor deficiencies like hemophilia)

- ✓ Thrombosis: unexplained DVT/PE, stroke in young patients (e.g., antiphospholipid syndrome, Factor V Leiden)

D. Systemic Symptoms

- ✓ Fever, weight loss, fatigue (common in malignancies)
- ✓ Bone pain (e.g., in leukemia or marrow infiltration)

III. Key Investigations in Hematology

A systematic approach to diagnosis combines clinical suspicion with targeted lab testing.

1. Complete Blood Count (CBC) with Differential

- Hemoglobin (Hb), hematocrit (Hct) → assess anemia/polycythemia
- MCV → classify anemia (microcytic, normocytic, macrocytic)
- WBC count and differential → detect infection, leukemia, or marrow failure
- Platelet count → evaluate thrombocytopenia/thrombocytosis

2. Peripheral Blood Smear

- Essential for morphology:

- Schistocytes → microangiopathic hemolytic anemia (e.g., Thrombotic Thrombocytopenic Purpura)
- Target cells → thalassemia, liver disease
- Blast cells → acute leukemia
- Howell-Jolly bodies → asplenia or hyposplenism

3. Reticulocyte Count

- **Reticulocyte:** Immature, anucleate RBCs recently released from the bone marrow.
- **The reticulocyte count** is a simple but powerful test that reflects the bone marrow's ability to produce and release red blood cells (RBCs) in response to anemia or blood loss.

- Measures bone marrow response:

- ↑ in hemolysis or blood loss
- ↓ in marrow failure or nutritional deficiency

4. Iron Studies, B12, Folate Levels

- For anemia workup:

- Low ferritin → iron deficiency
- High MCV + low B12 → pernicious anemia

5. Coagulation Tests

Coagulation tests assess the integrity of the hemostatic system, which involves platelets, coagulation factors, blood vessels, and natural anticoagulants/fibrinolytics. These tests help diagnose bleeding disorders, monitor anticoagulant therapy, and evaluate thrombotic risk.

- PT/INR → extrinsic pathway (e.g., warfarin effect, liver disease)
- aPTT → intrinsic pathway (e.g., hemophilia A/B)
- Fibrinogen, D-dimer → DIC, thrombosis

6. Bone Marrow Aspiration & Biopsy

Bone marrow examination: comprising aspiration and core biopsy is a cornerstone diagnostic procedure in hematology, oncology, and infectious disease. It provides critical information about cellularity, architecture, and cellular morphology of the hematopoietic system. Indicated for unexplained cytopenia's, suspected leukemia, lymphoma infiltration, or myelodysplastic syndromes

7. Hemoglobin Electrophoresis

Hemoglobin electrophoresis is a key laboratory test used to identify and quantify different types of hemoglobin (Hb) in the blood. It plays a central role in diagnosing hemoglobinopathies inherited disorders (e.g., sickle cell

disease, thalassemia) caused by structural or quantitative abnormalities in globin chains.

8. Flow Cytometry & Cytogenetics

Flow cytometry and cytogenetics are indispensable tools for diagnosing, classifying, and risk-stratifying hematologic malignancies especially leukemias, lymphomas, and myelodysplastic syndromes.

Why both?

- ✓ Flow cytometry tells us what the cells are (immunophenotype).
- ✓ Cytogenetics tells us what's wrong with their DNA (chromosomal abnormalities).

9. Direct Antiglobulin Test (Coombs Test)

The Direct Antiglobulin Test (DAT), commonly known as the Direct Coombs Test, is a pivotal laboratory assay used to detect antibodies or complement proteins attached to the surface of red blood cells (RBCs) in vivo. It is a cornerstone in diagnosing immune-mediated hemolytic anemias.

Anemia – Introduction, Manifestations, Classification, and Investigation

I. Introduction

Hemoglobin

- Hemoglobin is the iron-containing oxygen-transporting protein in the red blood cells of vertebrates. The deficiency of hemoglobin in the red blood cells decreases blood oxygen-carrying capacity leading to symptoms of anemia.
- Hemoglobin consists of heme and globin; each complete hemoglobin unit is a tetramer or globular unit made up of four subunits; each subunit contains hem conjugated to a polypeptide chain of the globin. The globin chains are identical pairs (dimers), designated as α-chains or β-chains.
  - **Hem:** is an iron containing porphyrin derivatives (ferrous iron Fe^{+2}), there are four hem units in each (Hb) molecule.
  - **Globin:** Are polypeptides, two pairs of polypeptides in each hemoglobin molecule, they are of special amino acid sequences.

Major Hemoglobin Types by Developmental Stage

1. Embryonic hemoglobin (Weeks 3–8 of gestation): These are transient and not detectable after birth.

2. Fetal Hemoglobin (HbF)

- Structure: $\alpha_2\gamma_2$
- Onset: ~6 weeks gestation
- Dominant: From 10 weeks gestation to birth (~70–90% at birth)
- Function:
  - ✓ Higher oxygen affinity than HbA → facilitates oxygen transfer from maternal to fetal circulation.

- ✓ Resists sickling → therapeutic target in sickle cell disease.
- ✓ Decline: Rapidly decreases after birth; <1% by 6–12 months.

3. Adult Hemoglobins

- HbA ($\alpha_2\beta_2$):
  - ✓ >95% of adult hemoglobin
  - ✓ Begins production at ~6 weeks gestation, becomes dominant by 6 months of age.
- **HbA_2 ($\alpha_2\delta_2$):**
  - ✓ 2–3% in healthy adults
  - ✓ Elevated in β-thalassemia trait (diagnostic clue).
- **HbF ($\alpha_2\gamma_2$):**
  - ✓ Normally <1%, but may persist or reactivate in certain conditions.

Abnormal hemoglobin's (hemoglobin variants) are structurally altered forms of hemoglobin caused by mutations in globin genes, most commonly point mutations in the β-globin gene (HBB) on chromosome 11. These variants can lead to:

- Hemoglobinopathies (e.g., sickle cell disease)
- Thalassemia syndromes (reduced globin chain production)
- Unstable hemoglobin
- High- or low-oxygen-affinity variants

Packed Cell Volume (PCV), also known as hematocrit (Hct), is a simple, widely used laboratory test that measures the proportion of blood volume occupied by red blood cells (RBCs). It provides critical insight into a patient's oxygen-carrying capacity and is essential in evaluating anemia, polycythemia, hydration status, and response to therapy. Adult males 40–50% and Adult females 36–48%.

Clinical Interpretation

A. Low PCV (Anemia)

Indicates reduced RBC mass. Causes include:

- Blood loss (acute or chronic)
- Hemolysis (e.g., sickle cell, G6PD deficiency)
- Decreased production (e.g., iron/B12 deficiency, aplastic anemia, CKD)
- Hemodilution (e.g., pregnancy, overhydration)

Caution: In acute hemorrhage, PCV may be normal initially (equal loss of RBCs and plasma)—drops over 24–72 hours as interstitial fluid shifts in.

B. High PCV (Polycythemia)

- Relative polycythemia:
  - ✓ Due to dehydration or plasma loss (e.g., burns, diarrhea) → hemoconcentration
  - ✓ RBC mass is normal; corrects with rehydration
- **Absolute polycythemia:**
  - ✓ Primary: Polycythemia vera (JAK2 mutation)
  - ✓ Secondary: Chronic hypoxia (COPD, cyanotic heart disease), EPO-secreting tumors, high altitude

Red blood cell (RBC) indices are quantitative parameters derived from the complete blood count (CBC) that describe the size, hemoglobin content, and concentration of red blood cells. They are essential for classifying anemia and guiding further diagnostic workup.

Index	Full Name	Formula	Normal Range	What it tells You
MCV	Mean Corpuscular Volume	Hematocrit (L/L) ÷ RBC count (x10^{12}/L)	80–100 fL	Average RBC size
MCH	Mean Corpuscular Hemoglobin	Hemoglobin (g/L) ÷ RBC count (x10^{12}/L)	27–31 pg	Average hemoglobin mass per RBC
MCHC	Mean Corpuscular Hemoglobin Concentration	Hemoglobin (g/dL) ÷ Hematocrit (dL/dL)	32–36 g/dL	Hemoglobin concentration within the RBC

Note: fL = femtoliters (10^{-15} L), pg = picograms (10^{-12} g), MCHC is the only concentration (not total amount)

Anemia is defined as a reduction in the total circulating red blood cell (RBC) mass or hemoglobin (Hb) concentration below normal for age and sex. The World Health Organization (WHO) defines anemia as:

- Hb <13 g/dL in men
- Hb <12 g/dL in non-pregnant women
- Hb <11 g/dL in pregnant women and elderly

Anemia is not a diagnosis but a clinical sign of an underlying disorder. It results from:

1. Decreased RBC production (e.g., iron deficiency, bone marrow failure)

2. Increased RBC destruction (hemolysis)

3. Blood loss (acute or chronic)

Because oxygen delivery to tissues is impaired, anemia can significantly affect quality of life and, if severe or acute, lead to cardiovascular compromise.

II. Major Clinical Manifestations

Symptoms of anemia depend on severity, onset (acute vs. chronic), and patient comorbidities (e.g., cardiac disease).

General Symptoms (due to tissue hypoxia):

- ✓ Fatigue, weakness
- ✓ Pallor (conjunctiva, nail beds)
- ✓ Dyspnea on exertion
- ✓ Tachycardia, palpitations
- ✓ Dizziness, headache

Symptoms Specific to Etiology:

- ✓ Iron deficiency: Pica (craving for ice, clay), koilonychia (spoon nails), glossitis
- ✓ Vitamin B12/folate deficiency: Neurological symptoms (numbness, paresthesia, ataxia – B12 only), smooth red tongue
- ✓ Hemolytic anemias: Jaundice, dark urine (hemoglobinuria), splenomegaly
- ✓ Chronic disease: Often asymptomatic beyond underlying illness

Note: Patients with chronic anemia may tolerate very low Hb levels due to compensatory mechanisms (e.g., increased cardiac output, 2,3-DPG shift).

III. Classification of Anemia

Anemia can be classified morphologically (by RBC size) or etiologically (by mechanism). Both approaches are complementary.

A. Morphological Classification (Based on MCV – Mean Corpuscular Volume)

Type	MCV (fL)	Common Causes
Microcytic	<80	Iron deficiency, thalassemia, anemia of chronic disease (sometimes), sideroblastic anemia
Normocytic	80–100	Acute blood loss, hemolysis, anemia of chronic disease, bone marrow failure (e.g., aplastic anemia), early iron/B12/folate deficiency
Macrocytic	>100	Megaloblastic: B12/folate deficiency, drugs (methotrexate) Non-megaloblastic: alcohol, liver disease, hypothyroidism, myelodysplastic syndromes

B. Etiological Classification (Pathophysiologic)

1. Impaired RBC Production

- Nutritional deficiencies (iron, B12, folate)
- Bone marrow disorders (aplasia, infiltration, myelodysplasia)
- Anemia of inflammation/chronic disease (AI/ACD)

2. Increased RBC Loss

- Acute hemorrhage (trauma, surgery)
- Chronic blood loss (GI bleed, menorrhagia → often leads to iron deficiency)

3. Increased RBC Destruction (Hemolytic Anemias)

- Intrinsic RBC defects:

- ✓ Membrane (hereditary spherocytosis)
- ✓ Enzyme (G6PD deficiency)
- ✓ Hemoglobinopathies (sickle cell, thalassemia)

- Extrinsic causes:

- ✓ Immune (AIHA), mechanical (prosthetic valves), infections (malaria), toxins

IV. Diagnostic Approach & Key Investigations

A stepwise evaluation guides accurate diagnosis.

Step 1: Confirm Anemia & Assess Severity

- CBC: Hb, Hct, MCV, RDW, reticulocyte count
- Peripheral blood smear: RBC morphology (e.g., spherocytes, schistocytes, target cells)

Step 2: Determine RBC Production Status

- Reticulocyte count (corrected or index):

- High → hemolysis or blood loss
- Low/normal → underproduction

- ✓ Corrected reticulocyte count = % reticulocytes × (patient Hct / 45)
- ✓ Reticulocyte production index (RPI) <2 = inadequate response

Step 3: Classify by MCV and Target Testing

A. Microcytic Anemia (MCV <80 fL)

- Serum ferritin (best initial test for iron deficiency; low = deficient)
- Iron, TIBC, transferrin saturation
- Hb electrophoresis if thalassemia suspected (↑ RBC count, normal/high ferritin, elevated HbA2 in β-thalassemia trait)

- CRP or ESR: to assess inflammation in anemia of chronic disease

B. Macrocytic Anemia (MCV >100 fL)

- Check for megaloblastic features on smear (hypersegmented neutrophils)
- Serum B12 and folate levels

- Methylmalonic acid (MMA) & homocysteine:

✓ ↑ MMA + ↑ homocysteine → B12 deficiency
✓ Normal MMA + ↑ homocysteine → folate deficiency
✓ Consider liver function tests, TSH, alcohol history if non-megaloblastic

C. Normocytic Anemia (MCV 80–100 fL)

- Reticulocyte count is key:

High: Think hemolysis or bleeding → check LDH, haptoglobin, indirect bilirubin, Coombs test

Low: Think underproduction →

✓ Anemia of chronic disease: normal/high ferritin, low serum iron, low TIBC
✓ Bone marrow failure: pancytopenia, consider marrow biopsy
✓ Endocrine causes: hypothyroidism, hypogonadism

Additional Tests (as indicated):

✓ Haptoglobin, LDH, indirect bilirubin → hemolysis
✓ Direct Antiglobulin Test (DAT/Coombs) → autoimmune hemolytic anemia
✓ G6PD assay (during hemolytic episode or after recovery)
✓ Stool for occult blood → chronic GI blood loss
✓ Bone marrow biopsy → unexplained cytopenias, suspected malignancy

Diseases of the Endocrine Glands – Introduction

The Endocrine System

Definition: The endocrine system consists of glands and organs that synthesize and secrete hormones directly into the bloodstream to regulate target tissues, including:

- Metabolism
- Growth and development
- Reproduction
- Mood and stress response
- Fluid, electrolyte, and glucose balance

Unlike the nervous system (which uses electrical signals for rapid communication), the endocrine system acts slowly but persistently to maintain homeostasis.

Major Endocrine Glands

The key endocrine glands include:

Gland	Main Hormones	Primary Functions
Hypothalamus	TRH, CRH, GnRH, ADH, oxytocin	Controls pituitary; links brain to endocrine system
Pituitary	TSH, ACTH, FSH, LH, GH, prolactin, ADH	"Master gland"—regulates other endocrine organs
Thyroid	T3, T4, calcitonin	Controls metabolism, heart rate, temperature
Parathyroids	Parathyroid hormone (PTH)	Regulates calcium and phosphate

Adrenals	Cortisol, aldosterone, adrenaline	Stress response, blood pressure, salt balance
Pancreas (islets)	Insulin, glucagon	Blood sugar regulation
Gonads	Testosterone (testes), estrogen/progesterone (ovaries)	Sexual development, reproduction

Note: ADH and oxytocin are made in the hypothalamus but stored/released from the posterior pituitary.

Key Hormone Types:

- Peptide/protein hormones (e.g., insulin, ACTH): act via cell surface receptors → activate second messengers
- Steroid hormones (e.g., cortisol, estrogen): lipid-soluble → cross membranes → bind intracellular receptors → affect gene transcription
- Amine hormones (e.g., T3/T4, epinephrine): derived from tyrosine; T3/T4 act like steroids, catecholamines act like peptides

Principles of Endocrine Regulation

1. Negative Feedback Loops

- Most common (e.g., HPA axis: CRH → ACTH → cortisol → inhibits CRH/ACTH)
- Maintains hormonal homeostasis

2. Positive Feedback (rare)

- Example: LH surge during ovulation

3. Pulsatile Secretion

- Hormones often released in pulses (e.g., GnRH); disruption → pathology (e.g., hypothalamic amenorrhea)

4. Circadian Rhythms

- Cortisol peaks in the morning; melatonin at night

Core Principles of Endocrine Physiology

Understanding disease starts with understanding normal control:

1. Hormone Regulation via Feedback Loops

- Most endocrine axes use negative feedback: Example: High thyroid hormone (T4) → tells pituitary to reduce TSH.
- Disruption leads to disease (e.g., low T4 + high TSH = primary hypothyroidism).

2. General Mechanisms of Endocrine Disease

Category	Examples
Hypofunction	Autoimmune destruction (e.g., Hashimoto's, T1DM), surgical removal, infarction (Sheehan syndrome), enzyme defects
Hyperfunction	Adenomas (e.g., pituitary prolactinoma), autoimmune stimulation (Graves'), ectopic hormone production (e.g., ACTH from lung cancer)
Hormone Resistance	Type 2 DM (insulin resistance), androgen insensitivity syndrome
Receptor/Post-receptor Defects	Pseudohypoparathyroidism (end-organ resistance to PTH)
Iatrogenic Causes	Exogenous steroid use → adrenal suppression

3. Common Causes of Endocrine Disorders

- Autoimmune (most common—e.g., type 1 diabetes, Graves', Addison's)
- Tumors (benign or malignant—e.g., pituitary adenoma, pheochromocytoma)
- Genetic/congenital (e.g., congenital adrenal hyperplasia)
- Iatrogenic (e.g., steroid-induced Cushing's syndrome)
- Infiltrative diseases (e.g., hemochromatosis damaging the pancreas)

Clinical Approach to Endocrine Disorders

A. Common Presentations

- Metabolic: weight change, fatigue, glucose abnormalities
- Reproductive: amenorrhea, infertility, libido changes
- Growth: short stature, gigantism, acromegaly
- Electrolyte disturbances: hyponatremia (SIADH), hypercalcemia (hyperparathyroidism)
- Pigmentation changes: hyperpigmentation (Addison's), vitiligo (autoimmune polyglandular syndromes)

B. Diagnostic Strategy

1. Clinical suspicion based on signs/symptoms

2. Initial hormone testing:

- ✓ Measure peripheral hormone and upstream regulator (e.g., TSH + free T4; cortisol + ACTH)

3. Dynamic testing if basal levels inconclusive:

- ✓ Stimulation (e.g., ACTH stimulation test for adrenal insufficiency)
- ✓ Suppression (e.g., dexamethasone suppression test for Cushing's)

4. Imaging:

- ✓ Ultrasound (thyroid), CT/MRI (adrenals, pituitary)

5. Autoantibodies:

- ✓ TPO antibodies (Hashimoto's), TSH receptor antibodies (Graves')

C. Localization of Lesion

- Primary: problem in the gland itself → abnormal hormone ± compensatory change in upstream hormone
  - ✓ Example: Primary hypothyroidism → ↑ TSH, ↓ T4
- Secondary: problem in pituitary → ↓ stimulating hormone → ↓ target hormone
  - ✓ Example: Secondary adrenal insufficiency → ↓ ACTH, ↓ cortisol
  - ✓ Tertiary: hypothalamic dysfunction → ↓ releasing hormone → ↓ pituitary hormone → ↓ target hormone

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.

Diseases of the Nervous System – Introduction

I. Introduction

The nervous system is the body's command and communication center, responsible for:

- Controlling voluntary and involuntary actions
- Processing sensory information
- Enabling thought, memory, and emotion

It is divided into two main parts:

1. **Central Nervous System (CNS):** Brain and Spinal Cord.
2. **Peripheral Nervous System (PNS):** Everything else.
   - ✓ Peripheral Nerves: Motor, sensory, autonomic.
   - ✓ Neuromuscular Junction (NMJ): The synapse between nerve and muscle.
   - ✓ Muscle: The final effector organ.

II. Why Study Neurological Disease?

- ➢ Neurological disorders are common: stroke, epilepsy, migraine, dementia, and peripheral neuropathy affect millions worldwide.
- ➢ Many are treatable or preventable (e.g., stroke with anticoagulation, myasthenia gravis with immunotherapy).
- ➢ Early recognition can be life-saving (e.g., subarachnoid hemorrhage, bacterial meningitis, spinal cord compression).
- ➢ Neurological symptoms often reflect systemic disease (e.g., vitamin B12 deficiency, lupus, cancer).

III. Major Categories of Nervous System Disease

Neurological disorders can be classified by mechanism and anatomic location:

A. By Mechanism

Category	Examples
Vascular	Stroke (ischemic/hemorrhagic), vasculitis
Infectious	Meningitis, encephalitis, brain abscess, neurosyphilis
Autoimmune/Inflammatory	Multiple sclerosis (MS), Guillain-Barré syndrome (GBS), myasthenia gravis
Degenerative	Alzheimer's disease, Parkinson's disease, Huntington's
Neoplastic	Primary brain tumors (glioma, meningioma), metastases
Traumatic	Concussion, spinal cord injury, peripheral nerve injury
Metabolic/Toxic	Wernicke's encephalopathy, hepatic encephalopathy, lead poisoning
Congenital/Genetic	Cerebral palsy
Seizure Disorders	Epilepsy, febrile seizures
Functional/Neuropsychiatric	Conversion disorder, psychogenic non-epileptic seizures

B. By Anatomic Localization

1. Cerebral (cortical): Aphasia, hemiparesis, seizures

2. Brainstem: Diplopia, vertigo, dysphagia, crossed signs

3. Cerebellar: Ataxia, dysmetria, intention tremor

4. Spinal cord: Paraplegia, sensory level, bowel/bladder dysfunction

5. Peripheral nerve: Weakness, numbness, reduced reflexes (e.g., GBS)

6. Neuromuscular junction: Fatigable weakness (e.g., myasthenia gravis)

7. Muscle: Proximal weakness, elevated CK (e.g., muscular dystrophy)

IV. Common Presenting Symptoms in Neurology

Neurological disease rarely presents with a single classic sign. Clusters of symptoms help narrow the diagnosis:

Symptom	Possible Causes
Headache	Migraine, tension-type, meningitis, brain tumor
Dizziness/Vertigo	Benign paroxysmal positional vertigo (BPPV), stroke (brainstem/cerebellum)
Weakness	Stroke, GBS, myasthenia gravis, spinal cord compression
Sensory loss	Peripheral neuropathy, spinal cord lesion, MS
Seizures	Epilepsy, brain tumor, metabolic derangements, trauma
Tremor/Gait disturbance	Parkinson's, essential tremor, cerebellar ataxia
Altered mental status	Encephalitis, stroke, drug overdose, sepsis, metabolic encephalopathy

V. Approach to the Neurological Patient

1. Take a focused history:

- ✓ Onset (sudden vs. gradual)
- ✓ Progression (stable, relapsing, progressive)
- ✓ Associated symptoms (fever, trauma, recent infection)
- ✓ Medications, toxins, family history

2. Perform a thorough neurological exam:

- ✓ Mental status: (Orientation, 3-word recall, clock drawing).
- ✓ Cranial nerves (I–XII): Pupils, eye movements, facial symmetry, gag reflex.
- ✓ Motor system: Drift, pronator sign, heel/shin slide.
- ✓ Sensory system (light touch, pain, vibration, proprioception).
- ✓ Reflexes (deep tendon, plantar response).
- ✓ Coordination: Finger-nose-finger, rapid alternating movements.
- ✓ Gait: Observe walking, tandem gait.

3. Localize the lesion (CNS vs. PNS? Cortical vs. spinal?)

4. Generate a differential diagnosis based on mechanism

5. Order targeted investigations

VI. Basic Investigations in Neurology

Test	Purpose
CT head	Rapid assessment of hemorrhage, mass, fracture (first-line in acute settings)

MRI brain/spine	Superior for soft tissue—detects stroke (after first few hours), MS plaques, tumors
Lumbar puncture (CSF analysis)	Infection (↑ WBC), SAH (xanthochromia), MS (oligoclonal bands), GBS (albuminocytologic dissociation)
EEG	Seizure diagnosis, encephalopathy
Nerve conduction studies (NCS) & EMG	Differentiate axonal vs. demyelinating neuropathies (e.g., GBS vs. diabetic neuropathy)
Blood tests	Glucose, electrolytes, B12, thyroid, autoimmune panels, infectious serologies

Diseases of the Nervous System – Major Manifestations and Key Investigations

I. Introduction

Neurological diseases affect the central nervous system (CNS: brain and spinal cord) and peripheral nervous system (PNS: nerves, neuromuscular junctions, muscles). Because the nervous system controls nearly every bodily function, its disorders can present with a wide variety of symptoms from subtle sensory changes to life-threatening coma.

Diagnosis in neurology relies on three pillars:

1. Accurate localization (Where is the lesion?)

2. Pattern recognition (What is the clinical syndrome?)

3. Targeted investigation (What test confirms the cause?)

II. Major Clinical Manifestations of Nervous System Disease

Neurological symptoms often reflect dysfunction in a specific anatomic region. Recognizing patterns helps narrow the diagnosis.

1. Altered Mental Status (AMS)

- **Spectrum:** Confusion → lethargy → stupor → coma

- **Causes:**

  - Metabolic (hypoglycemia, hepatic/uremic encephalopathy)
  - Infectious (meningitis, encephalitis)
  - Structural (stroke, tumor, hemorrhage)
  - Toxic (alcohol, drugs, sedatives)

- Seizure-related (post-ictal state)

Key clue: Evaluate level of consciousness, pupillary response, and motor symmetry to assess brainstem function and lateralization.

2. Headache

- Primary headaches (not due to disease):

- ✓ Migraine: pulsating, unilateral, nausea/photophobia
- ✓ Tension-type: bilateral, band-like, no nausea

- Secondary (red flag) headaches:

- ✓ Thunderclap onset → subarachnoid hemorrhage
- ✓ Worsening with Valsalva or lying down → brain tumor
- ✓ Fever + neck stiffness → meningitis
- ✓ New headache in elderly + jaw claudication → giant cell arteritis

3. Focal Neurological Deficits

Indicate localized CNS damage, often from stroke or mass lesion:

- Hemiparesis/hemisensory loss: contralateral cortex or internal capsule
- Aphasia: dominant (usually left) frontal/temporal lobe
- Visual field defects: optic pathways (e.g., homonymous hemianopia = post-chiasmal lesion)
- Cranial nerve palsies: e.g., facial droop (CN VII), diplopia (CN III/IV/VI)

4. Seizures

- Generalized tonic-clonic: loss of consciousness, stiffening, jerking
- Focal (partial) seizures: may involve motor, sensory, or psychic aura

- Causes: epilepsy, brain tumor, trauma, infection, metabolic (Na^+, Ca^{2+}, glucose)

5. Movement Disorders

- Tremor:

- ✓ Resting tremor → Parkinson's disease
- ✓ Action/intention tremor → cerebellar disease
- ✓ Postural tremor → essential tremor

- Bradykinesia, rigidity, postural instability → Parkinsonism

- Chorea, dystonia, tics → Huntington's, Wilson's disease.

6. Sensory Symptoms

- Numbness, tingling, burning:

- ✓ Glove-and-stocking → peripheral neuropathy (e.g., diabetes, B12 deficiency)
- ✓ Sensory level (e.g., below T6) → spinal cord lesion
- ✓ Unilateral face + body numbness → brainstem stroke

7. Weakness

Classify by pattern:

- Upper motor neuron (UMN):

- Spasticity, hyperreflexia.
- Seen in stroke, MS, spinal cord injury

- Lower motor neuron (LMN):

- Flaccidity, hyporeflexia, muscle atrophy

- Seen in ALS, polio, peripheral neuropathy

- Proximal symmetric weakness:

- Myopathies (e.g., muscular dystrophy, polymyositis)

- Fatigable weakness (worse with use):

- Myasthenia gravis (neuromuscular junction disorder)

8. Ataxia and Gait Disturbance

- Cerebellar ataxia: wide-based gait, dysmetria, intention tremor
- Sensory ataxia: stomping gait, worse with eyes closed (positive Romberg) → dorsal column disease (e.g., B12 deficiency)
- Parkinsonian gait: shuffling, reduced arm swing, freezing

9. Visual and Ocular Symptoms

- Diplopia (double vision): cranial nerve palsy (III, IV, VI) or myasthenia
- Optic neuritis: painful vision loss, color desaturation → often first sign of MS
- Nystagmus: vestibular or cerebellar dysfunction

III. Key Investigations in Neurological Disease

No single test diagnoses all neurological conditions. Investigations are guided by clinical suspicion.

1. Neuroimaging

Test	When to Use	Key Findings
Non-contrast CT head	Acute stroke, trauma, suspected hemorrhage	Hemorrhage (bright), mass effect, fracture

MRI brain/spine	Subacute/chronic symptoms, demyelination, tumor	MS plaques, infarcts (>6h), tumors, cord compression
MRA/CTA	Suspected vascular cause (e.g., aneurysm, dissection)	Vessel stenosis, occlusion, aneurysm

2. Lumbar Puncture (LP) & CSF Analysis

Indications: suspected meningitis, encephalitis, SAH (if CT negative), MS, GBS

CSF Parameter	Bacterial Meningitis	Viral Meningitis	GBS	MS
Opening pressure	↑↑	Normal/↑	↑	Normal
WBC	↑↑ (neutrophils)	↑ (lymphocytes)	Normal	↑ (lymphocytes)
Protein	↑	Mild ↑	↑↑ (>100 mg/dL)	Mild ↑
Glucose	↓↓	Normal	Normal	Normal
Special	+ Gram stain/culture	PCR for viruses	—	Oligoclonal bands (IgG)

3. Electrodiagnostic Studies

- EEG (Electroencephalogram):

- ✓ Diagnose seizures, classify epilepsy, assess encephalopathy

- NCS/EMG (Nerve Conduction Studies / Electromyography):

- ✓ Differentiate axonal vs. demyelinating neuropathies
- ✓ Confirm radiculopathy, myopathy, or neuromuscular junction disorders

4. Blood Tests (Targeted)

Test	Purpose
Glucose, Na^+, Ca^{2+}, Mg^{2+}	Metabolic causes of AMS/seizures
CBC, CRP, blood cultures	Infection/inflammation
TSH, B12, folate, HbA1c	Reversible causes of neuropathy/cognitive decline
CK	Muscle damage (e.g., rhabdomyolysis, myositis)
Autoantibodies	e.g., AChR Ab (myasthenia), ANA (SLE with neuropsychiatric features)
Infectious serology	HIV, syphilis, Lyme.

5. Other Specialized Tests

- ✓ Evoked potentials: assess optic, auditory, or sensory pathways (used in MS)
- ✓ Genetic testing: Huntington's, Charcot-Marie-Tooth, mitochondrial disorders
- ✓ Brain biopsy: rare—reserved for undiagnosed encephalitis or tumor

Principles of Critical Care Medicine – Major Manifestations of Critical Illness, Shock, and Sepsis

I. Introduction to Critical Care Medicine

Critical care medicine (intensive care) is the specialty focused on the diagnosis and management of life-threatening conditions that require close monitoring, organ support, and rapid interventions.

Patients in the ICU typically have one or more of the following:

- Respiratory failure
- Circulatory instability (shock)
- Altered mental status or coma
- Acute kidney injury
- Severe infection (e.g., sepsis)
- Post-operative instability or trauma

The goal of critical care is not only to support failing organs but also to treat the underlying cause and prevent complications.

II. Core Principles of Critical Care

1. Early recognition of physiological deterioration (e.g., rising lactate, falling urine output)
2. ABCs first: Airway, Breathing, Circulation – stabilize before diagnosis
3. Hemodynamic monitoring: assess perfusion (BP, heart rate, capillary refill, lactate, urine output)
4. Organ support: mechanical ventilation, vasopressors, renal replacement therapy

5. Multidisciplinary approach: intensivists, nurses, respiratory therapists, pharmacists
6. Goals of care: balance life support with patient values and prognosis

III. Major Manifestations of Critical Illness

Critically ill patients often present with non-specific signs of physiological stress. Recognizing these early can prevent cardiac arrest.

System	Manifestation	Possible Cause
Cardiovascular	Hypotension, tachycardia, weak pulses	Shock (septic, cardiogenic, hypovolemic)
Respiratory	Tachypnea, hypoxia, use of accessory muscles	Pneumonia, ARDS, pulmonary edema, PE
Renal	Oliguria (<0.5 mL/kg/h), rising creatinine	Acute kidney injury (AKI) from hypoperfusion or toxins
Neurological	Agitation, confusion, coma	Hypoxia, sepsis, metabolic derangement, stroke
Metabolic	Lactic acidosis, hyperglycemia, electrolyte imbalances	Tissue hypoperfusion, stress response
Hematologic	Bleeding, thrombocytopenia, coagulopathy	DIC (disseminated intravascular coagulation)

Red flags:

- Lactate >4 mmol/L → severe tissue hypoperfusion
- Urine output <0.5 mL/kg/h for >2 hours → acute kidney injury
- Altered mental status in infection → possible sepsis

IV. Shock: Definition and Types

Shock

Definition: It is a clinical condition characterized by decreased blood flow to vital organs due to imbalance between size of vascular bed and effective circulating blood volume, resulting in **circulatory failure**, anoxia and inability of the body tissues to metabolize nutrients normally.

Def: Shock = A state of systemic hypoperfusion → inadequate oxygen delivery (O_2) to meet tissue metabolic demands → cellular hypoxia → anaerobic metabolism → lactic acidosis → organ dysfunction → death if untreated.

Classification of Shock

There are 4 main types:

1. Cardiogenic
2. Hypovolemic
3. Obstructive
4. Distributive (includes Septic, Anaphylactic, Neurogenic)

1. Cardiogenic Shock

Def: Failure of the heart to pump effectively → ↓ cardiac output (CO) despite adequate intravascular volume.

Causes:

- Acute myocardial infarction (MI) (most common).
- Severe cardiomyopathy.
- Myocarditis.

- Arrhythmias (e.g., ventricular tachycardia (VT) / ventricular fibrillation (VF), severe bradycardia).
- Valvular emergencies (acute Mitral Regurgitation (MR) and Acute Aortic Stenosis (AS).

Clinical Features:

- Cold, clammy skin.
- ↑ Jugular Venous Pressure (JVP).
- Pulmonary edema (rales, hypoxia).
- Hypotension + tachycardia (usually).
- Low urine output

2. Hypovolemic Shock

Def: Loss of intravascular volume → ↓ preload → ↓ Stroke Volume (SV) → ↓ cardiac output (CO).

Causes:

- Hemorrhage (trauma, GI bleed, ruptured Abdominal Aortic Aneurysm, postpartum)
- Plasma loss (burns, peritonitis)
- Dehydration (vomiting, diarrhea, DKA, diuretics)

Clinical Features:

- Tachycardia (early sign!)
- Hypotension (late sign)
- Cool extremities, delayed capillary refill
- ↓ JVP, flat neck veins
- ↓ Urine output

- Mental status changes (late)

3. Obstructive Shock

Def: Mechanical obstruction to blood flow → ↓ CO despite normal myocardial function and intravascular volume.

Causes:

- Tension pneumothorax
- Massive pulmonary embolism (PE).
- Cardiac tamponade
- Severe pulmonary hypertension.

Clinical Features:

- ✓ Hypotension + ↑ JVP (except tension pneumo — may have tracheal deviation, absent breath sounds)
- ✓ Pulsus paradoxus (tamponade)
- ✓ Muffled heart sounds (tamponade)

4. Distributive Shock

Def: Systemic vasodilation → ↓ Systemic Vascular Resistance → maldistribution of blood flow → relative hypovolemia.

Subtypes:

A. Septic Shock

- ✓ Infection + vasodilation + endothelial injury + cytokine storm.
- ✓ Warm shock early (vasodilated), cold shock late (exhausted).
- ✓ Lactate >2 mmol/L + need for vasopressors after fluid resuscitation = Septic Shock.

B. Anaphylactic Shock

- IgE-mediated massive histamine release → vasodilation + bronchospasm + angioedema
- Urticaria, wheezing, stridor, gastrointestinal (GI) symptoms.
- Rapid onset after allergen exposure.

C. Neurogenic Shock

- ✓ Spinal cord injury (usually above T6) → loss of sympathetic tone → unopposed vagal tone
- ✓ Hypotension + **bradycardia** (key differentiator!)
- ✓ Warm, dry skin
- ✓ Poikilothermia (body temp matches environment).

Clinical Recognition — Early Signs

- ✓ Tone (↓ muscle tone in infants/children).
- ✓ Interactiveness (lethargy, confusion).
- ✓ Consolability (irritable or inconsolable).
- ✓ Look/gaze (fixed stare, "not right" appearance)
- ✓ Speech/cry (weak cry, muffled speech)

In adults:

- ✓ Tachycardia (often first sign).
- ✓ Tachypnea (compensatory for acidosis).
- ✓ Altered mental status.
- ✓ Oliguria.
- ✓ Cool extremities (except early septic/anaphylactic).

Diagnostic Approach

1. Airway, Breathing, Circulation — stabilize first!

2. Vital signs: HR, BP, RR, Temp, SpO_2

3. Physical exam: Skin temp, JVP, lung sounds, heart sounds, capillary refill, mental status

4. Bedside tests:

- ✓ Lactate (critical!)
- ✓ ABG (pH, base deficit)
- ✓ ECG (ischemia, arrhythmia)
- ✓ CXR (pulmonary edema, pneumothorax)

5. Labs: CBC, coagulation, cultures (if septic), troponin (if cardiogenic).

Prognosis

Mortality varies:

- ✓ Septic shock:20–50%
- ✓ Cardiogenic shock (MI-related): ~40%
- ✓ Hypovolemic (treated early): better prognosis

Early recognition, timely antibiotics (in sepsis), and reperfusion (inMI) dramatically improve outcomes.

Management — general principles

GOAL: Restore perfusion → reverse hypoxia → prevent MODS

1. Resuscitate Airway, Breathing, Circulation: airway, oxygen, IV access
2. Fluid resuscitation: crystalloids (except cardiogenic shock)
3. Treat underlying cause
4. Vasopressors: norepinephrine (1st line), epinephrine, vasopressin
5. Monitor: arterial line, urine output, lactate trends.

V. Sepsis: Definition, Recognition, and Management

What is Sepsis?

- Sepsis = Life-threatening organ dysfunction caused by a dysregulated host response to infection
- Septic shock = Sepsis + circulatory/metabolic abnormalities (e.g., need for vasopressors, lactate ≥2 mmol/L)

Clinical Recognition: Use the qSOFA Score (Quick Sequential Organ Failure Assessment)

≥2 of the following suggests high risk of poor outcomes:

- Respiratory rate ≥22/min
- Altered mentation (GCS <15)
- Systolic BP ≤100 mmHg

Key Signs of Sepsis

- Fever or hypothermia
- Tachycardia, tachypnea
- Hypotension (late sign!)
- Elevated lactate (>2 mmol/L = tissue hypoperfusion)

- Signs of organ dysfunction:

- Oliguria
- Confusion
- Thrombocytopenia
- Coagulopathy

Sepsis Management: The "Sepsis Six" (to be done within 1 hour)

1. Give oxygen (target SpO_2 94–98%)
2. Take blood cultures (before antibiotics if possible)
3. Administer broad-spectrum IV antibiotics
4. Give IV fluids (30 mL/kg crystalloid for hypotension or lactate ≥4)
5. Measure serum lactate (repeat if initially elevated)
6. Monitor urine output (catheterize if needed)

Golden hour: Mortality increases by ~8% for every hour antibiotics are delayed in septic shock.

Advanced Management (ICU)

- Vasopressors (e.g., norepinephrine) if fluid-refractory hypotension
- Source control (e.g., drain abscess, remove infected line)
- Support failing organs (ventilation, dialysis)
- Corticosteroids (only in refractory shock)

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), support organs
ARDS	PaO_2/FiO_2 <300 + bilateral infiltrates	Lung-protective ventilation
DIC	Bleeding + ↑ D-dimer + low platelets	Treat cause, replace clotting factors if bleeding
AKI	↑ Creatinine or ↓ urine output	Determine prerenal/intrinsic/postrenal
Acute Liver Failure	INR ≥1.5 + encephalopathy	NAC, ICU, transplant eval