🩸 "Hematology & Oncology for USMLE" 🩸

Anemias

Comprehensive Classification of Anemia

Anemias are first classified by Mean Corpuscular Volume (MCV), which reflects the average size of red blood cells. This initial step narrows the differential diagnosis and guides further evaluation.

Classification by MCV (Mean Corpuscular Volume) 📏

A. Microcytic Anemias (MCV < 80 fL) 🔬

Microcytic anemias are most commonly due to defective hemoglobin synthesis. The defect may involve globin chains, heme synthesis, or iron availability.

The classic causes can be remembered using TAIL:

- Thalassemias → defective globin chain synthesis
- Anemia of chronic disease (late stage) → impaired iron utilization due to hepcidin
- Iron deficiency anemia (late stage) → inadequate iron for heme synthesis
- Lead poisoning → inhibition of ferrochelatase and ALA dehydratase (defective heme synthesis)

Key concept:
➡️ Hemoglobin synthesis failure leads to smaller, hypochromic RBCs.

B. Normocytic Anemias (MCV 80–100 fL) 🧪

Normocytic anemias have normal-sized RBCs but a reduced number of circulating cells. These anemias are best classified based on the reticulocyte production index (RPI), which indicates whether the bone marrow response is appropriate.

i) Non-hemolytic Normocytic Anemias (Low Reticulocyte Index) ⬇️

These result from decreased RBC production due to impaired bone marrow function or reduced erythropoietin.

Common causes include:

- Early iron deficiency
- Anemia of chronic disease (early stage)
- Chronic kidney disease (↓ erythropoietin)
- Aplastic anemia (bone marrow failure)
- Acute blood loss (before reticulocytosis develops)

Key concept:

➡️ Bone marrow is not responding adequately.

---

ii) Hemolytic Normocytic Anemias (High Reticulocyte Index) ⬆️

These result from premature RBC destruction, prompting a compensatory increase in reticulocytes.

Hemolytic anemias are further divided into intrinsic and extrinsic causes.

---

a) Intrinsic Hemolytic Anemias 🧬

(Defect within the RBC itself)

- Membrane defects
  - Hereditary spherocytosis
  - Paroxysmal nocturnal hemoglobinuria (PNH)
- Enzyme deficiencies
  - G6PD deficiency
  - Pyruvate kinase deficiency
- Hemoglobinopathies
  - Sickle cell anemia
  - Hemoglobin C disease

These conditions are often genetic and cause either extravascular or intravascular hemolysis.

b) Extrinsic Hemolytic Anemias ⚙️

(RBCs are normal initially; destruction is external)

- Autoimmune hemolytic anemia
  - Warm (IgG-mediated)
  - Cold (IgM-mediated)
- Microangiopathic hemolytic anemia
  - DIC, TTP/HUS, HELLP syndrome, malignant hypertension
- Macroangiopathic hemolytic anemia
  - Prosthetic heart valves, aortic stenosis
- Infections
  - Malaria, Babesia

Key concept:

➡️ Bone marrow responds appropriately → high reticulocyte count.

C. Macrocytic Anemias (MCV > 100 fL) 🧫

Macrocytic anemias are caused by defects in DNA synthesis, DNA repair, or nuclear maturation. They are divided into megaloblastic and non-megaloblastic types.

---

i) Megaloblastic Macrocytic Anemias 🧠

These are due to impaired DNA synthesis, leading to nuclear-cytoplasmic asynchrony.

Common causes include:

- Folate deficiency
- Vitamin B12 deficiency
- Orotic aciduria

Key features:

- Macrocytosis
- Hypersegmented neutrophils
- Ineffective erythropoiesis

---

ii) Non-megaloblastic Macrocytic Anemias 🍺🧬

In these anemias, DNA synthesis is normal, but RBCs are large due to membrane or maturation abnormalities.

Causes include:

- Chronic alcohol use
- Liver disease
- Diamond-Blackfan anemia (pure red cell aplasia)
- Fanconi anemia (DNA repair defect causing pancytopenia)

Key distinction:
➡️ No hypersegmented neutrophils.

The Diagnosis Points ✨

1. Check MCV → microcytic, normocytic, or macrocytic
2. If normocytic, check reticulocyte index
3. If hemolytic, decide intrinsic vs extrinsic

4. If macrocytic, decide megaloblastic vs non-megaloblastic

Reticulocyte Production Index (RPI) 🧪

- Definition: Corrected reticulocyte count → reflects bone marrow response
- Interpretation:
  - RPI > 3 → Compensatory RBC production (e.g., hemolysis, acute blood loss)
  - RPI < 2 → Inadequate marrow response (e.g., aplastic anemia, iron/B12/folate deficiency)

Formula:

RPI = % reticulocytes × (Actual Hct / Normal Hct) ÷ Maturation time

---

Mentzer Index 💡

- Used to differentiate thalassemia vs iron deficiency anemia
- Formula: Mentzer index = MCV (fL) ÷ RBC count (millions/μL)
- Interpretation:
  - <13 → Thalassemia (bone marrow compensates by producing MORE RBCs)
  - >13 → Iron deficiency anemia (bone marrow cannot make enough RBCs)
  - = 13 → borderline values usually behave like thalassemia.

Iron Studies: Interpretation Table 🧲

Test	Iron Deficiency	Chronic Disease	Hemochromatosis	Pregnancy / OCP Use
Serum Iron	↓	↓	↑	—

Transferrin / TIBC	↑	↓	↑	↓
Ferritin	↓	↑	↑	—
% Transferrin Saturation	↓ ↓	— / ↓	↑ ↑	↓

Step 1 Pearls:

- Transferrin: Iron transport protein
- TIBC: Indirect measure of transferrin
- Ferritin: Primary iron storage
- ACD evolutionary note: pathogens require circulating iron for growth. To counter this, the body sequesters iron inside cells, limiting its availability in the bloodstream and thereby restricting pathogen proliferation.

Step 1 Mnemonics & Exam Tips ⭐

- TAIL → Microcytic anemia → Thalassemia, Anemia of chronic disease, Iron deficiency, Lead
- High RPI → Think hemolysis or blood loss
- Mentzer <13 → Thalassemia
- Ferritin is the best single test for iron deficiency

Microcytic, Hypochromic Anemias (MCV < 80 fL)

Iron Deficiency Anemia (IDA)

Etiology / Causes

- Chronic blood loss: GI bleeding, heavy menstrual bleeding
- Malnutrition / Poor intake
- Malabsorption / GI surgery: Gastrectomy, celiac disease

- Increased demand: Pregnancy, growth spurts

Pathophysiology

- ↓ iron → ↓ final step of heme synthesis → microcytic, hypochromic RBCs

Laboratory Findings

Parameter	Typical Finding	Reason / Explanation
Serum iron	↓	Decreased total body iron due to chronic blood loss, poor intake, or malabsorption → less iron available in circulation
TIBC (Transferrin)	↑	Liver increases transferrin production to maximize iron-binding capacity when iron stores are low
Ferritin	↓	Ferritin reflects iron stores → depleted in iron deficiency (earliest and most specific marker)

Free erythrocyte protoporphyrin	↑	Lack of iron prevents incorporation into heme → protoporphyrin accumulates inside RBCs
RDW (RBC size variability)	↑	Mixed population of normal and microcytic RBCs during progression of disease
Reticulocyte index	↓	Inadequate iron → ineffective erythropoiesis → poor bone marrow response
Peripheral blood smear	Microcytosis + hypochromasia (↓ central pallor)	Reduced hemoglobin synthesis leads to small, pale RBCs with increased central pallor

Clinical Features

- Fatigue, pallor (especially conjunctival pallor)
- Restless leg syndrome, pica (craving nonfood substances)

- Koilonychia (spoon nails)
- Glossitis, cheilosis
- Plummer-Vinson syndrome: IDA + esophageal webs + dysphagia

Step 1 Pearl ⭐

- Iron deficiency anemia → low RBC count with high RDW, microcytosis, hypochromasia
- Pica and koilonychia are classic exam buzzwords

α-Thalassemia

Genetics

- α-globin gene deletions on chromosome 16 → ↓ α-globin synthesis
- Cis deletion: Both deletions on the same chromosome
- Trans deletion: Deletions on separate chromosomes
- Normal: $\alpha\ \alpha$ / $\alpha\ \alpha$

What does $\alpha\ \alpha$ / $\alpha\ \alpha$ mean?

- Each person has 4 α-globin genes in total
- These genes are located on chromosome 16
- There are 2 α-globin genes on each chromosome

So:

$\alpha\ \alpha$ / $\alpha\ \alpha$

- Left side → one chromosome 16
- Right side → the other chromosome 16
- Each α = one functional α-globin gene

➡️ $\alpha\ \alpha$ / $\alpha\ \alpha$ = all 4 α-globin genes are normal

Population Prevalence

- More common in Asian and African descent

Peripheral Smear Feature

- Target cells (red blood cells with a bull's-eye appearance, central hemoglobinized area, surrounded by a clear zone, outer peripheral rim of hemoglobin)

α-Thalassemia Gene Deletion Table 🧬

# of α-globin genes deleted	Genotype	Disease / Clinical Outcome	Notes
1	$\alpha\ \alpha$ / α-	Silent carrier (α-thalassemia minima)	No anemia
2	Cis: $\alpha\ \alpha$ /-- Trans: α- / α-	α-thalassemia minor	Mild microcytic, hypochromic anemia
3	-- / α-	Hemoglobin H disease (HbH)	Moderate to severe microcytic, hypochromic anemia; excess β-globin $\rightarrow$ β_4

4	-- / --	Hemoglobin Barts disease	Hydrops fetalis; incompatible with life; excess γ-globin → γ_4

Flowchart: α-Thalassemia Severity by Gene Deletion

1 α-gene deleted → Silent carrier → No anemia

2 α-genes deleted → Minor α-thalassemia → Mild anemia

3 α-genes deleted → HbH disease → Moderate-severe anemia → β_4 tetramers

4 α-genes deleted → Hb Barts → Hydrops fetalis → γ_4 tetramers → Incompatible with life

---

Step 1 Pearls ⭐

- α-Thalassemia: RBC count often normal or high, unlike iron deficiency anemia (RBC count ↓)
- Target cells → hallmark peripheral smear finding

- Hydrops fetalis → total absence of α-globin (γ_4 tetramers)

β-Thalassemia 🧬

Genetics & Pathophysiology

- There are two β-globin genes, one on each chromosome 11
- Point mutations in promoter / splice sites / Kozak sequence on chromosome 11
- ↓ β-globin synthesis (β^+) or absent β-globin (β^0)
- Prevalent in Mediterranean populations

Peripheral Smear / Labs:

- Microcytosis, hypochromia, target cells, anisopoikilocytosis
- HbA2 ↑ in β-thalassemia minor

- HbF ↑ compensates temporarily → symptoms after 6 months

β-Thalassemia Clinical Classification Table 🩸

# β-globin genes mutated	Genotype	Disease	Clinical Features
1	β / β	β-thalassemia minor	- Mild microcytic anemia, - Asymptomatic - ↑ HbA2
2	β^+ / β^+ or β^+ / β^0	β-thalassemia intermedia	- Variable severity - Mild → transfusion-dependent
2	β^0 / β^0	β-thalassemia major (Cooley anemia)	- Severe anemia, target cells, marrow expansion → "crew cut" skull, skeletal deformities, - Extramedullary hematopoiesis → HSM

			- Risk of aplastic crisis with Parvovirus B19 - ↑ HbF & HbA2 - Chronic hemolysis → pigmented gallstones
1	β^+ / HbS or β^0 / HbS	Sickle cell β-thalassemia	Mild → moderate sickle cell disease depending on β^+ or β^0 allele

---

Flowchart: β-Thalassemia Severity by Gene Mutation

1 β-gene mutation → β-thalassemia minor → Mild microcytic anemia

2 β-gene mutations → β-thalassemia intermedia → Variable anemia

2 β^0-gene mutations → β-thalassemia major → Severe anemia, transfusion-dependent, marrow expansion, extramedullary hematopoiesis

---

Lead Poisoning (Plumbism) ☠️

Pathophysiology

- Inhibits ferrochelatase & ALA dehydratase → ↓ heme synthesis → ↑ free erythrocyte protoporphyrin
- Inhibits rRNA degradation → basophilic stippling of RBCs

Clinical Features ("LLEEAAD" mnemonic):

- Lead lines on gingivae (Burton lines) & metaphyses of long bones (x-ray)
- Leukocyte changes → basophilic stippling
- Encephalopathy
- Erythrocyte basophilic stippling
- Abdominal colic
- Anemia (sideroblastic)
- Drops → wrist and foot drop

Treatment:

- Chelation therapy: succimer, EDTA, dimercaprol
- Avoid exposure: old houses (pre-1978 paint), occupational risk

---

Sideroblastic Anemia 🧪

Causes

- Genetic: X-linked defect in ALA synthase gene
- Acquired: Myelodysplastic syndromes
- Reversible / Secondary: Alcohol (most common), lead poisoning, vitamin B6 deficiency, copper deficiency, drugs (isoniazid, linezolid)

Pathophysiology

- Impaired heme synthesis → iron accumulates in mitochondria → ringed sideroblasts (Prussian blue stain)

Lab Findings

Parameter	Findings	Reason / Explanation
Iron	↑	Iron accumulates in mitochondria because it cannot be incorporated into heme.
TIBC	Normal / ↓	Total iron-binding capacity is normal or reduced due to functional iron overload.
Ferritin	↑	Reflects increased iron stores in cells (storage iron).
Peripheral smear	Basophilic stippling	RBCs retain aggregates of rRNA due to impaired heme synthesis; seen as small blue dots in RBCs.
Bone marrow	Ringed sideroblasts	Iron-laden mitochondria form a ring around the nucleus of erythroid precursors, visible with Prussian blue stain.

Treatment:

- Pyridoxine (B6) → cofactor for ALA synthase
- Avoid secondary causes

Step 1 Pearls ⭐

- β-Thalassemia minor: ↑ HbA2 → classic lab clue
- β-Thalassemia major: "crew cut skull" → marrow expansion
- Lead poisoning: basophilic stippling + wrist/foot drop + Burton lines
- Sideroblastic anemia: ringed sideroblasts on bone marrow; reversible with B6

Macrocytic Anemias (MCV > 100 fL) 🩸

---

1) Megaloblastic Anemias (Impaired DNA Synthesis)

Pathophysiology:

- DNA synthesis is impaired → nuclear maturation delayed relative to cytoplasm → macrocytosis
- Bone marrow: megaloblastic changes
- Peripheral smear: macro-ovalocytes, hypersegmented neutrophils

Vitamin B12 Deficiency

Causes & Features

Cause / Feature	Reason / Explanation
Pernicious anemia	Autoimmune destruction of gastric parietal cells → ↓ intrinsic factor → impaired B12 absorption.
Malabsorption (Crohn disease, gastrectomy)	Loss of terminal ileum (site of B12 absorption) or reduced intrinsic factor production.
Pancreatic insufficiency	Pancreatic enzymes needed to release B12 from R-protein; deficiency → impaired absorption.

Vegan diet	B12 is only in animal products; dietary deficiency develops over years.
Diphyllobothrium latum (fish tapeworm)	Worm competes for B12 in the intestine → deficiency.

Laboratory Findings

Lab Parameter	Finding	Reason / Explanation
Homocysteine	↑	B12 is a cofactor for methionine synthase; deficiency → impaired homocysteine to methionine conversion → tetrahydrofolate → ↓ DNA synthesis.
Methylmalonic acid	↑	B12 is a cofactor for methylmalonyl-CoA mutase; deficiency → MMA accumulates.
MCV	↑ (macrocytosis)	Impaired DNA synthesis → delayed nuclear maturation → large RBCs.

Neutrophils	Hypersegmented	Nuclear maturation delayed relative to cytoplasm due to defective DNA synthesis.

Clinical Features

Feature	Reason / Explanation
Fatigue	Anemia reduces oxygen delivery to tissues.
Glossitis	Rapidly dividing mucosal cells affected by impaired DNA synthesis.
Neurologic symptoms	Demyelination due to B12 deficiency in CNS: affects dorsal columns (vibration, proprioception), spinocerebellar tracts (ataxia), corticospinal tract (spastic paresis), reversible dementia.
Treatment Note: Folate supplementation	Corrects anemia but does not correct neurologic damage; can worsen neurologic symptoms if B12 deficiency not corrected.

Folate Deficiency 🍃

Causes & Features

Cause / Feature	Reason / Explanation
Malnutrition (chronic alcohol use)	Folate is water-soluble and dietary; alcohol impairs absorption and storage in the liver. ↓ folate → reduced tetrahydrofolate availability → ↓ synthesis of thymidine → ↓ DNA.
Malabsorption	Conditions affecting proximal small intestine (duodenum/jejunum) impair folate uptake.
Drugs (methotrexate, trimethoprim, phenytoin)	Inhibit dihydrofolate reductase → impaired folate metabolism → reduced tetrahydrofolate availability.
↑ Demand (hemolytic anemia, pregnancy)	Increased RBC production or fetal growth consumes folate faster than dietary supply → deficiency.

Laboratory Findings

Lab Parameter	Finding	Reason / Explanation
Homocysteine	↑	Folate is a cofactor for methionine synthase; deficiency → impaired homocysteine to methionine conversion.
Methylmalonic acid	Normal	MMA requires B12 for conversion; folate deficiency does not affect MMA.
MCV	↑ (macrocytosis)	Impaired DNA synthesis → delayed nuclear maturation → large RBCs.
Neutrophils	Hypersegmented	DNA synthesis defect delays nuclear maturation relative to cytoplasm.

Clinical Features

Feature	Reason / Explanation

Fatigue	Anemia reduces oxygen delivery to tissues.
Glossitis	Rapidly dividing mucosal cells affected by impaired DNA synthesis.
Neurologic symptoms	Absent (unlike B12 deficiency) because folate is not involved in myelin synthesis.

💡 Tips:

- Both B12 & folate deficiency → macrocytic, hypersegmented neutrophils + ↑ homocysteine
- Only B12 deficiency → ↑ methylmalonic acid + neurologic symptoms
- Folate deficiency can mask hematologic signs of B12 deficiency if supplemented.

Orotic aciduria🧬

Causes & Features

Cause / Feature	Reason / Explanation
Pathophysiology: Defect in UMP synthase	Autosomal recessive defect → impaired conversion of orotic acid to UMP → blocks de novo pyrimidine synthesis → defective DNA/RNA synthesis
Onset: childhood	Defective DNA/RNA synthesis affects rapidly dividing cells → manifests early in life.
Failure to thrive, developmental delay	Impaired DNA synthesis → poor growth, delayed development.
Refractory to B12/folate	Anemia is due to pyrimidine synthesis defect, not B12/folate deficiency.
No hyperammonemia	Unlike ornithine transcarbamylase deficiency, the urea cycle is normal.

Laboratory Findings

Lab Parameter	Finding	Reason / Explanation
MCV	↑ (macrocytosis)	Impaired DNA synthesis → delayed nuclear maturation → large RBCs.
Bone marrow	Megaloblastic	Impaired DNA synthesis → hypersegmented nuclei in precursors.
Urinary orotic acid	↑	Blocked UMP synthesis → excess orotic acid excreted in urine.

Clinical Features

Feature	Reason / Explanation
Megaloblastic anemia	Defective pyrimidine synthesis → impaired RBC DNA synthesis → macrocytic anemia.
Developmental delay	Impaired DNA/RNA synthesis affects neuronal and tissue growth.

Failure to thrive	Systemic impact of impaired cell division and erythropoiesis.
No hyperammonemia	Urea cycle is intact; ammonia levels normal.
Treatment	Uridine monophosphate or uridine triacetate bypasses the defective enzyme → restores pyrimidine synthesis.

💡 Step 1 tip:

- Orotic aciduria = childhood megaloblastic anemia + ↑ urinary orotic acid + refractory to B12/folate + no hyperammonemia
- Differentiates from OTC deficiency, which also has ↑ orotic acid but with hyperammonemia.

Flowchart: Megaloblastic Anemia Causes

Impaired DNA synthesis → Macrocytic anemia + hypersegmented neutrophils

- Vitamin B12 deficiency → neurologic symptoms, ↑ MMA

- Folate deficiency → no neurologic symptoms, normal MMA

- Orotic aciduria → pediatric onset, ↑ urinary orotic acid, refractory to B12/folate

---

2) Non-Megaloblastic Macrocytic Anemias (Normal DNA Synthesis)

- Causes: chronic alcohol use, liver disease
- Labs: macrocytosis without hypersegmented neutrophils
- Pathophysiology: membrane/lipid abnormalities, ineffective erythropoiesis
- Clinical: often mild anemia; no neurologic symptoms

Congenital Pure Red Cell Aplasia

Diamond-Blackfan Anemia (DBA)

- A congenital form of pure red cell aplasia
- Pathophysiology: intrinsic defect in erythroid progenitor cells → pure red cell aplasia
- Onset: within 1st year of life
- Labs: macrocytic anemia, ↑ % HbF, ↓ total Hb
- Clinical: short stature, craniofacial abnormalities, upper extremity malformations (triphalangeal thumbs in ~50% of cases)

Flowchart:

- Chronic alcohol use, liver disease → macrocytosis without hypersegmented neutrophils

- Congenital pure red cell aplasia → Diamond-Blackfan anemia → ↑ HbF, congenital anomalies

---

Step 1 Pearls

- Hypersegmented neutrophils + macro-ovalocytes → hallmark of megaloblastic anemia
- Neurologic symptoms → only in B12 deficiency
- Folate supplementation can mask B12 deficiency → beware of worsening neuropathy
- Orotic aciduria → treat with uridine, not B12/folate
- DBA → congenital, pure red cell aplasia, ↑ HbF

Normocytic, Normochromic Anemias (MCV 80–100 fL) 🩸

Normocytic, normochromic anemias can be nonhemolytic or hemolytic.

Hemolytic Anemias 💥

Classification:

By RBC defect:

- Intrinsic: defect is inside RBC (membrane, enzyme, hemoglobinopathy)
- Extrinsic: external causes (autoimmune, mechanical, infections)

By location of hemolysis:

- Intravascular: RBC destroyed in blood vessels
- Extravascular: RBC cleared by spleen

Hemolysis Labs:

Laboratory Parameter	Finding	Reason / Explanation
LDH	↑	Lactate dehydrogenase released from lysed RBCs → marker of hemolysis.
Reticulocytes	↑	Bone marrow compensates for RBC destruction → high reticulocyte count indicates active erythropoiesis.
Unconjugated bilirubin	↑	Heme from destroyed RBCs is converted to unconjugated bilirubin → may cause jaundice.

Pigmented gallstones	Present	Chronic hemolysis → excess bilirubin → calcium bilirubinate stones in gallbladder.
Urobilinogen in urine	↑	Breakdown of heme → urobilinogen excreted in urine; reflects increased intravascular or extravascular hemolysis.

Intravascular Hemolysis 🌊

Pathway:

Red blood cell → destroyed in blood vessels → hemoglobin released → binds haptoglobin → if haptoglobin exceeded → hemoglobin dimers → hemoglobinuria → kidneys

RBC destruction also → ↑ unconjugated bilirubin → liver → stercobilinogen in stool and urobilinogen in urine

Key Findings:

- ↓ Haptoglobin -> Free hemoglobin from lysed RBCs binds haptoglobin → depleted levels in plasma.
- Schistocytes on blood smear -> Mechanical fragmentation of RBCs (helmet cells)
- Hemoglobinuria, hemosiderinuria, ↑ urobilinogen in urine

Notable Causes:

- Mechanical hemolysis (prosthetic heart valves)
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Microangiopathic hemolytic anemias (MAHA)

Extravascular Hemolysis 🏞️

Mechanism:

- RBCs cleared by splenic macrophages → no hemoglobinuria
- Hemoglobin degraded → ↑ unconjugated bilirubin → jaundice

- Peripheral smear: spherocytes -> In extravascular hemolysis (mainly spleen), macrophages partially "bite off" portions of RBC membrane to remove antibody/complement-coated areas. This reduces surface area but keeps volume the same, making RBCs spherical instead of biconcave. Seen in hereditary spherocytosis and autoimmune hemolytic anemia.

Notable Causes:

- Hereditary spherocytosis
- Autoimmune hemolytic anemia

Key Findings:

- Splenomegaly -> increased workload and hyperplasia of splenic red pulp → enlarged spleen (splenomegaly).
- Spherocytes on blood smear
- ↑ urobilinogen in urine
- No hemoglobinuria or hemosiderinuria

Non-Hemolytic Normocytic Anemias ⚖️

Anemia of Chronic Disease (ACD) / Inflammation

Pathophysiology:

- Chronic inflammation → ↑ IL-6 → ↑ hepcidin (liver hormone)
- Hepcidin binds ferroportin → ↓ iron transport from enterocytes & macrophages → ↓ iron availability

Associated Conditions: chronic infections, neoplastic disorders, autoimmune diseases (SLE, RA), chronic kidney disease

Labs:

Laboratory Parameter	Finding	Reason / Explanation

Serum iron	↓	Iron is sequestered in macrophages due to ↑ hepcidin from inflammation → less iron available for erythropoiesis.
TIBC (total iron-binding capacity)	↓	Hepcidin also reduces transferrin production; less circulating transferrin → lower TIBC.
Ferritin	↑	Ferritin = iron storage protein; inflammation stimulates ferritin synthesis → reflects iron sequestration, not iron deficiency.
RBC morphology	Normocytic (may become microcytic)	Initially RBCs are normal in size; chronic iron-restricted erythropoiesis may lead to microcytosis over time.

Treatment:

- Treat underlying cause
- Consider blood transfusion judiciously

- Erythropoiesis-stimulating agents (EPO) in CKD

Aplastic Anemia ⚠️

Pathophysiology:

- Failure or destruction of hematopoietic stem cells → pancytopenia

Causes:

- Radiation
- Viral infections: EBV, HIV, hepatitis viruses
- Fanconi anemia (AR DNA repair defect → marrow failure, short stature, café-au-lait spots, thumb/radial defects, malignancy predisposition)
- Idiopathic (immune-mediated stem cell defect, sometimes post-hepatitis)
- Drugs: benzene, chloramphenicol, alkylating agents, antimetabolites

Labs:

Parameter	Finding	Reason / Explanation
Reticulocyte count	↓	Bone marrow failure → reduced RBC production → low reticulocytes.
Erythropoietin (EPO)	↓	In some cases of aplastic anemia, EPO response is inadequate for anemia correction due to stem cell failure.
Pancytopenia	↓ RBCs, ↓ WBCs, ↓ platelets	Failure of hematopoietic stem cells → all three lineages affected.
RBC morphology	Normal	The problem is production, not RBC maturation, so cells appear morphologically normal.
Bone marrow	Hypocellular with fatty infiltration	Stem cell depletion → marrow replaced by fat.

Clinical Features:

Feature	Reason / Explanation
Fatigue, pallor, malaise	↓ RBCs → anemia → reduced oxygen-carrying capacity.
Purpura, petechiae, mucosal bleeding	↓ Platelets → impaired clotting → bleeding tendency.
Infections	↓ WBCs → immunodeficiency → increased susceptibility to infection.

Treatment:

- Remove offending agent
- Immunosuppressive therapy: antithymocyte globulin, cyclosporine
- Bone marrow allograft
- RBC / platelet transfusions
- Bone marrow stimulation: GM-CSF

Flowchart: Normocytic, Normochromic Anemias

Normocytic anemia → MCV 80–100 fL

→ Hemolytic

- Intravascular → schistocytes, hemoglobinuria, ↑ LDH
- Extravascular → spherocytes, splenomegaly, ↑ bilirubin

→ Non-hemolytic

- Anemia of chronic disease → inflammation, ↑ hepcidin, ↓ iron, normocytic
- Aplastic anemia → pancytopenia, hypocellular marrow, fatigue, infection, bleeding

---

Step 1 Pearls ⭐

- Hemolytic anemia: ↑ LDH, ↑ indirect bilirubin, ↑ reticulocytes

- Intravascular vs extravascular: hemoglobinuria = intravascular; spherocytes + splenomegaly = extravascular
- ACD: normocytic → can become microcytic; ↑ ferritin, ↓ iron
- Aplastic anemia: pancytopenia with hypocellular marrow; Fanconi anemia → congenital anomalies + malignancy risk

---

Intrinsic Hemolytic Anemias 🧬

(Defect is within the RBC itself)

These anemias are usually due to membrane defects, enzyme deficiencies, or hemoglobinopathies, leading to premature RBC destruction.

Hereditary Spherocytosis 🔴

Etiology:

- Primarily autosomal dominant
- Defect in RBC membrane skeleton proteins → Ankyrin, spectrin, band 3, protein 4.2
- Leads to loss of membrane surface area → spherical RBCs

Pathophysiology:

Membrane protein defect → ↓ RBC surface area → Spherocyte formation (no central pallor) → ↓ deformability → Splenic macrophage trapping → Extravascular hemolysis

Key Morphology:

- Small, round RBCs
- No central pallor -> Biconcave shape normally creates a pale center. Spherocytes lack the concavity, so central pallor disappears.
- ↑ MCHC ✨ -> Membrane loss concentrates hemoglobin within a smaller volume → higher hemoglobin per unit volume.

Clinical Features:

- Splenomegaly -> Spherocytes are less deformable → get trapped and destroyed by splenic macrophages (extravascular hemolysis) → spleen enlarges due to increased workload.
- Pigmented gallstones (↑ unconjugated bilirubin)
- Aplastic crisis with parvovirus B19

Labs & Tests:

- ↓ Mean fluorescence on eosin-5-maleimide (EMA) binding test
- ↑ Osmotic fragility (RBCs lyse in hypotonic solution)
- Normal to ↓ MCV, but ↑ number of RBCs

Treatment:

- Splenectomy (curative for hemolysis, not membrane defect)

Paroxysmal Nocturnal Hemoglobinuria (PNH) 🌙

Etiology:

- Acquired PIGA gene mutation in hematopoietic stem cells
- ↓ GPI anchor synthesis → loss of protective proteins → CD55 (DAF) and CD59 (MIRL)

Pathophysiology:

- PIGA mutation → ↓ CD55 & CD59 → Unchecked complement activation → Intravascular hemolysis
- Worse at night -> ↓ RR and shallow breathing -> ↑ CO2 -> mild respiratory acidosis -> ↑ complement activity

Classic Triad⭐

- Coombs-negative hemolytic anemia: Hemolysis in PNH is not caused by antibodies. Instead, it is complement-mediated intravascular hemolysis.
- Pancytopenia
- Venous thrombosis (eg, Budd-Chiari syndrome)

Effects:

i) PNH → Complement-mediated intravascular hemolysis → RBC destruction → Anemia → Release of free hemoglobin into plasma → Filtered by kidneys → Hemoglobinuria (dark morning urine 🌅)

ii) Intravascular hemolysis → ↑ Free plasma hemoglobin → Hemoglobin binds nitric oxide (NO) → ↓ NO availability → NO depletion

iii) ↓ Nitric oxide → Loss of smooth muscle relaxation → ↑ Smooth muscle tone → Esophageal spasm → Dysphagia → Intestinal spasm → Abdominal pain → Penile smooth muscle constriction → Erectile dysfunction

iv) ↓ Nitric oxide → Loss of platelet inhibition → ↑ Platelet activation → Venous thrombosis → Budd-Chiari syndrome (hepatic vein thrombosis) → Cerebral / portal vein thrombosis 🚨

v) Free plasma hemoglobin → Filtered through glomeruli → Tubular toxicity → Hemosiderin deposition → Chronic kidney injury / renal failure

Clinical Clues:

- Pink/red urine in the morning 🌅
- Association with aplastic anemia and acute leukemias

Diagnosis:

- Flow cytometry: ↓ CD55 & CD59 on RBCs

Treatment:

- Eculizumab (C5 complement inhibitor)

G6PD Deficiency ⚡

Inheritance:

- X-linked recessive

Pathophysiology:
G6PD deficiency → ↓ NADPH → ↓ reduced glutathione → RBCs vulnerable to oxidative stress → Hemolysis (intravascular + extravascular)

Triggers (remember!):

- Sulfa drugs
- Antimalarials
- Fava beans
- Infections

Mnemonic:

> *"Stress makes me eat bites of fava beans with Heinz ketchup"* 🍅

Clinical Features:

- Back pain
- Hemoglobinuria a few days after oxidative stress

Labs & Smear:

- ↓ G6PD activity *(may be falsely normal during acute hemolysis)*
- Heinz bodies (denatured Hb)
- Bite cells (splenic removal of Heinz bodies)

Pyruvate Kinase Deficiency 🔋

Inheritance:

- Autosomal recessive

Pathophysiology:

Pyruvate kinase defect → ↓ ATP production → loss of energy for maintaining normal RBC shape → Rigid RBCs → Splenic destruction → Extravascular hemolysis

Unique Feature:

- ↑ 2,3-BPG → ↓ hemoglobin affinity for O_2 → Improved oxygen delivery (compensatory)

Presentation:

- Hemolytic anemia in newborns 👶

Blood Smear:

- Burr cells (echinocytes)

Sickle Cell Anemia (HbSS) 🌙

Genetics:

- Point mutation in β-globin gene
- Glutamic acid → Valine substitution
- Creates hydrophobic HbS → polymerization

Pathogenesis:

Low O_2 / acidosis / dehydration → HbS polymerizes → RBC sickling → Hemolysis + vaso-occlusion

Key Points:

- Both intravascular and extravascular hemolysis
- Newborns asymptomatic due to ↑ HbF
- Sickle cell trait → malaria resistance 🦟

Peripheral Smear:

- Crescent-shaped sickled RBCs

X-ray:

- Crew-cut skull (marrow expansion)

Major Complications:

- Aplastic crisis (parvovirus B19)
- Autosplenectomy (Repeated microvascular occlusion in the spleen due to sickled RBCs → ischemia and infarction of splenic tissue → gradual shrinkage and fibrosis of the spleen) → Howell-Jolly bodies (nuclear remnants / DNA in RBCs) → ↑ infection risk with encapsulated organisms (normally removed by a healthy spleen)
- Painful vaso-occlusive crises:
  - Dactylitis
  - Priapism
  - Acute chest syndrome (leading cause of death ⚠️)
  - Stroke, avascular necrosis
- Renal papillary necrosis → hematuria

Hb Electrophoresis:

- ↓ ↓ HbA
- ↑ HbF
- ↑ ↑ HbS

Treatment:

- Hydroxyurea (↑ HbF)
- Hydration, pain control, infection prevention

Hemoglobin C Disease 🔷

Mutation:

- Glutamic acid to Lysine in β-globin

Hemolysis Type:

- Mainly extravascular

Clinical Notes:

- HbSC disease (one HbS + one HbC) → milder than HbSS

Peripheral Smear:

- Target cells
- Hexagonal hemoglobin crystals inside RBCs

Concept ⭐

Intrinsic RBC defect → ↓ deformability / enzyme failure / abnormal Hb → Premature RBC destruction → Hemolytic anemia 🩸

Extrinsic Hemolytic Anemias

(RBCs are normal initially; destruction is due to external factors)

Autoimmune Hemolytic Anemia (AIHA) 🛡️

A normocytic anemia caused by antibodies against RBCs. Typically Coombs positive (⊕).

There are two major types 👇

Warm Autoimmune Hemolytic Anemia ☀️

Mechanism:

- Mainly IgG-mediated
- Causes extravascular hemolysis (spleen)

Associations:

- CLL, Non-Hodgkins Lymphoma, SLE (CNS)
- Drugs: α-methyldopa (increases RBC antibodies by altering Rh antigen on the RBC surface, direct coomb's = +ve), β-lactams (especially penicillin -> acts as a hapten, direct coomb's = +ve)

Mnemonic:

👉 *"Warm weather is Good"* → IgG

Peripheral Smear:

- Spherocytes (partial phagocytosis by splenic macrophages)

- Reason: IgG binds to RBCs -> complete phagocytosis cannot occur by splenic macrophages -> partial phagocytosis

Treatment:

- Steroids (first line)
- Rituximab
- Splenectomy (if refractory)

Cold Autoimmune Hemolytic Anemia ❄️

Mechanism:

- Mainly IgM + complement
- RBC agglutination in cold temperatures
- Leads to extravascular hemolysis

Clinical Features:

- Painful, blue fingers and toes (acrocyanosis) 🧊🖐️
- Symptoms worsen with cold exposure

Associations:

- CLL
- Mycoplasma pneumoniae
- Infectious mononucleosis

Peripheral Smear:

- Agglutinated RBCs
- DAT positive for C3 (as IgM falls off the RBCs on rewarming in central organs)

Treatment:

- Cold avoidance
- Rituximab

Drug-Induced Hemolytic Anemia 💊

Mechanisms:

- Antibody-mediated immune destruction, or

- Oxidative injury via free radicals
  (worse in G6PD deficiency)

Common Offending Drugs:

- Antibiotics (penicillins, cephalosporins)
- NSAIDs
- Immunotherapy
- Chemotherapy

Peripheral Smear Clues:

- Spherocytes → immune hemolysis
- Bite cells → oxidative hemolysis

Hemolysis Type:

- Can be extravascular or intravascular

Microangiopathic Hemolytic Anemia (MAHA) ⚙️

Mechanism:

RBCs are mechanically damaged while passing through narrowed or obstructed vessels

Type of Hemolysis:

- Intravascular

Seen In:

- DIC
- TTP / HUS
- SLE
- HELLP syndrome
- Hypertensive emergency

Peripheral Smear:

- Schistocytes ("helmet cells")
  (schisto = to split) 🔪

Macroangiopathic Hemolytic Anemia ❤️

Cause:

- Mechanical destruction of RBCs by large-scale forces

Examples:

- Prosthetic heart valves
- Aortic stenosis

Peripheral Smear:

- Schistocytes

Hemolytic Anemia Due to Infection 🦠

Mechanism:

- Direct RBC destruction by organisms

Classic Examples:

- Malaria
- Babesia

Characteristic Peripheral Smear Cells in Anemias

Anemia	Characteristic Cells	Reason / Explanation
Iron deficiency anemia	Microcytes, hypochromic RBCs, pencil cells (elliptocytes)	↓ Iron → ↓ heme synthesis → ↓ Hb → smaller RBCs with ↑ central pallor; membrane instability causes pencil cells
Anemia of chronic disease	Usually normal RBCs; late microcytosis	↑ Hepcidin → iron trapped in macrophages → ↓ iron availability → late impaired Hb synthesis
α-thalassemia	Target cells, microcytosis	↓ α-globin → excess β/γ chains → membrane redundancy → target cells
β-thalassemia	Target cells, basophilic stippling	↓ β-globin → excess α chains damage membrane; retained ribosomal RNA → stippling

Sideroblastic anemia	Basophilic stippling (blood), ringed sideroblasts (marrow)	Defective heme synthesis → iron accumulates in mitochondria around nucleus
Lead poisoning	Basophilic stippling	Lead inhibits rRNA degradation → ribosomal aggregates persist
Hereditary spherocytosis	Spherocytes	Defective ankyrin/spectrin → ↓ surface area → spherical RBCs without central pallor
Warm AIHA (IgG)	Spherocytes	Partial phagocytosis of IgG-coated RBC membrane by spleen
Cold AIHA (IgM)	RBC agglutination	IgM binds RBCs in cold → complement-mediated clumping
Microangiopathic hemolytic anemia (DIC, TTP, HUS, HELLP)	Schistocytes (helmet cells)	RBCs mechanically shredded passing through fibrin strands

Macroangiopathic hemolytic anemia	Schistocytes	Mechanical destruction by prosthetic valves or stenotic vessels
G6PD deficiency	Heinz bodies, bite cells	Oxidative stress → denatured Hb (Heinz bodies); splenic macrophages remove them → bite cells
Pyruvate kinase deficiency	Burr cells (echinocytes)	↓ ATP → rigid membrane with spiky projections
Sickle cell disease	Sickle cells, Howell-Jolly bodies	HbS polymerizes when deoxygenated; autosplenectomy → nuclear remnants persist as Howell-Jolly bodies
Post-splenectomy / functional asplenia	Howell-Jolly bodies	Spleen normally removes nuclear remnants
Vitamin B12 deficiency	Macro-ovalocytes, hypersegmented neutrophils	Impaired DNA synthesis → delayed nuclear maturation

Folate deficiency	Macro-ovalocytes, hypersegmented neutrophils	↓ dTMP synthesis → defective DNA replication
Orotic aciduria	Macrocytosis, megaloblastic changes	Defective UMP synthase → impaired pyrimidine synthesis
Aplastic anemia	Normal-appearing RBCs	Bone marrow failure → ↓ production, not abnormal morphology
HbC disease	Target cells, HbC crystals	Mutant HbC crystallizes → altered RBC shape

---

🧠 Rapid Memory Hook

- Sphere → membrane loss (HS, warm AIHA)
- Schisto → mechanical destruction
- Target → excess membrane (thalassemia, HbC)
- Bite + Heinz → oxidative stress (G6PD)
- Howell-Jolly → spleen gone or dead

-> The End <-