hematopoiesis

* 3rd w of gestation

1. erythropoiesis → in yolk sac.
2. Liver * 2 month.
3. B.M * 5-6 month.

Fetus

↓ PO_2 in utero → ↑ fetal EPO in liver → ↑ Hb (normally).

After birth. → kidney

Few months after birth.

- rapid growth
- cessation of erythropoiesis
- shortened RBC survival.

⇓ Nadir (physiological). 8-10 ws.
2-3 months → term
1-2 months → preterm

Hb → Heme (Iron containing porphyrin ring)

4 globin

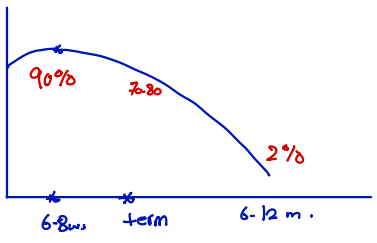
2α (Ch 16) 2β (Ch 11)

RBC

normal life span → In adult → 90-120 day
→ fetal / neonatal → 60-90
∴ more risky.

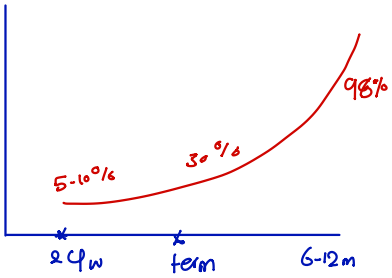
HbF

higher affinity to O_2.



HbA

A : A_2 30 : 1.

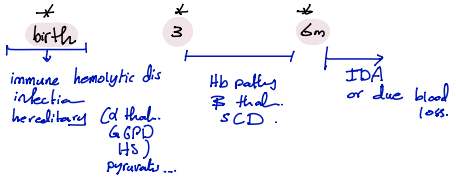


Anemia

↓ RBC # or ↓ [Hb] > 2 SD below the mean.

Terminology

- Hematocrit (HCT): Is the fractional volume of a whole blood sample occupied by RBCs, expressed as a percentage.
- Hemoglobin (HGB): This is a measure of the concentration of the RBC pigment HGB in whole blood, expressed as grams per 100 mL (dL) of whole blood.
- Mean corpuscular volume (MCV): Represents the mean value (in femtoliters [fL]) of the volume of individual RBCs in the blood sample.
- Red cell distribution width (RDW): The RDW is a quantitative measure of the variability of RBC sizes in the sample (anisocytosis).
- Mean corpuscular hemoglobin concentration (MCHC): is a calculated index (MCHC = HGB/HCT) yielding a value of grams of HGB per 100 mL of RBC.



Finding	Possible etiology
Skin	
Hyperpigmentation	Fanconi anemia
Petechiae, purpura	Autoimmune hemolytic anemia with thrombocytopenia, hemolytic-uremic syndrome, bone marrow aplasia, bone marrow infiltration
Jaundice	Hemolytic anemia, hepatitis, and aplastic anemia
Cavernous hemangioma	Microangiopathic hemolytic anemia
Ulcers on lower extremities	Sickle cell disease (S and C hemoglobinopathies), thalassemia
Facies	
Frontal bossing, prominence of the malar and maxillary bones	Congenital hemolytic anemias, thalassemia major, severe iron deficiency
Eyes	
Microcornea	Fanconi anemia
Tortuosity of the conjunctival and retinal vessels	Sickle cell disease (S and C hemoglobinopathies)
Microaneurysms of retinal vessels	Sickle cell disease (S and C hemoglobinopathies)
Vitreous hemorrhages	S hemoglobinopathy
Retinal hemorrhages	Chronic, severe anemia
Edema of the eyelids	Infectious mononucleosis, exudative enteropathy with iron deficiency, renal failure
Mouth	
Glossitis	Vitamin B12 deficiency, iron deficiency
Angular stomatitis	
Hands	
Triphalangeal thumbs	Red cell aplasia DBA
Hypoplasia of the thenar eminence	Fanconi anemia
Spoon nails	Iron deficiency
Spleen and Liver	
Enlargement	Congenital hemolytic anemia, leukemia, lymphoma acute infection, portal hypertension

Clinical Features of Anemia

- **Mild**
- Pallor (noted especially on skin and on mucous membranes)
- **Moderate**
- Weakness and fatigue
- Decreased exercise tolerance
- Irritability
- Tachycardia
- Tachypnea
- Anorexia
- Systolic heart murmur

Clinical Features of Anemia

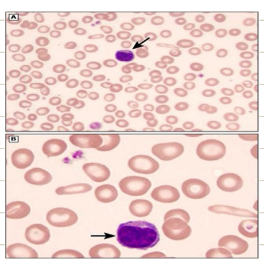
- **Severe**
- Congestive heart failure
- Cardiac dilation
- Shortness of breath
- Hepatosplenomegaly
- Spoon-shaped nails

MCV

< 80 → Microcytic anemia

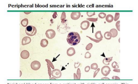
→ serum iron studies. Ferritin

- ↑ TBC + ↓ → **IDA**
  - MC dis during infancy & childhood.
  - MC → inadequate intake.
    - * 9-24 months → ↓ intake, ↓ stores.
  - [The typical toddler's diet consists of large quantities of iron-poor cow's milk.]
  - * adolescent girl ← poor diet, rapid growth, loss in mens blood.
  - * occult blood loss → polyps, Meckel, celiac, IBD; Cow milk → allergy
  - Clinically :-
    - ↓ neurocognitive function in infant.
    - Pica
    - Pagophagia.
  - CBC ⇒ ↑RDW ↓RBC ↔WBC, ↔↑ platelet; ↑ low reticulocyte, ↑ thrombocytopenia
  - ↑ Hb ≥1g/dL after 1 month of iron therapy
  - علاج
  - ✓ mild → moderate ⇒ 4-6 mg/kg/day orally, 3-4 months.
  - Severe ⇒ RBC transfusion → Hb < 4 g/dL.
  - depletion of stores ⇒ 1-3 months.



- ↑/↔ + ↓/↔ TBC
  - ↑ CPR/ESR → **Anemia of Chronic dis.**
    - Malignancy
    - Infections
    - kidney dis.
  - abnormal Hb * electrophoresis → **β-thalassemia minor**
    - mild, asymptomatic
    - ↑ HbA2 > 3.5
    - Mentzer index < 13 (= MCV / RBC); > 13 → IDA
    - normal RDW
    - **α-thalassemia minor**
      - Same features as β
      - Diagnosis by genetic.
  - Basophilic stippling & or ringed sideroblasts in B.M → **Sideroblastic Anemia**
    - * Ringed Sideroblasts ← accumulation of iron in mitochondria of RBC precursor.
    - → inherited; → acquired → drugs (isoniazid, alcohol, lead, chloramphenicol)
    - **Lead poisoning.**
      - * Basophilic stippling on blood film.

Sickle cell anemia



Peripheral blood smear in sickle cell anemia

Peripheral blood smear from a patient with sickle cell anemia. This smear shows multiple sickle cells (arrows). There are also findings consistent with functional asplenia, including a nucleated red blood cell (upper left), a red blood cell containing a Howell-Jolly body (arrowhead), and target cells (dashed arrow).

GENOTYPE	CLINICAL CONDITION	Hb A	Hb S	Hb A2	Hb F	Hb C	OTHER FINDING(S)
		PERCENT HEMOGLOBIN					
SA	Sickle cell trait	55–60	40–45	2–3	–	–	Usually asymptomatic
SS (MC & most severe)	Sickle cell anemia	0	85–95	2–3	5–15	–	Clinically severe anemia; Hb F heterogeneous in distribution

- **Anemia**
  - Chronic, onset 3–4 month of age; may require folate therapy for chronic hemolysis; hemoglobin usually 6-10 g/dL
- **Aplastic crisis**
  - Parvovirus infection, reticulocytopenia; acute and reversible; may need transfusion
- **Sequestration crisis**
  - Massive splenomegaly (may involve liver), shock; treat with transfusion
- **Hemolytic crisis**
  - May be associated with G6PD deficiency
- **Dactylitis**
  - Hand-foot swelling in early infancy
- **Painful crisis**
  - Microvascular painful vasoocclusive infarcts of muscle, bone, bone marrow, lung, intestines
- **Cerebrovascular accidents**
  - Large and small vessel occlusion → thrombosis/bleeding (stroke); requires chronic transfusion
- **Acute chest syndrome**
  - Infection, asthma, atelectasis, infarction, fat emboli, severe hypoxemia, infiltrate, dyspnea, absent breath sounds
- **Chronic lung disease**
  - Pulmonary fibrosis, restrictive lung disease, cor pulmonale, pulmonary hypertension
- **Priapism**
  - Causes eventual impotence; treated with transfusion, oxygen, or corpora cavernosa-to- spongiosa shunt
- **Ocular** :Retinopathy
- **Gallbladder disease**
  - Bilirubin stones; cholecystitis
- **Renal**
  - Hematuria, papillary necrosis, renal concentrating defect; nephropathy
- **Cardiomyopathy**
  - Heart failure
- **Skeletal**
  - Osteonecrosis (avascular) of femoral or humeral head
- **Leg ulceration**
  - Seen in older patients

Infections ← هذا مهم

Functional asplenia, defects in properdin system; pneumococcal bacteremia, meningitis, and arthritis; deafness from meningitis; *Salmonella* and *Staphylococcus aureus* osteomyelitis; severe *Mycoplasma* pneumonia

Growth failure, delayed puberty

Psychological problems

Narcotic addiction (rare), dependence unusual; chronic illness, chronic pain syndrome

- RBC life span → 10-50 days.
- ↓ Hb → 6-9
- ↑ reticulocyte 5-15%
- ↑ indirect bilirubin.
- blood smear
- B.M → erythroid hyperplasia.

✓ Hydroxyurea ↓ vasoocclusive crises.
- penicillin daily oral
- Folic acid
- Immunization ← Influenza/yearly, pneumococcal 2ys, Meningococcal.
- B.M transplant → curative → severe cases

SS Hemoglobinopathies.

- 1 in 800 black newborns in US.
- # Single aa substitution (Valine for Glutamic acid)
- ↓ on number 6 position of β chain
- polymerization ⇒ -low O_2 -acidosis.
- distorted RBC shape (sickled)
  - ↓ life span
  - occlusion of small vessels
- ⇒ distal ischemia / infarction / organ dysfunction.
- Clinically present 6 months of age
- sudden episodes → Crisis

80-100 → Normocytic anemia

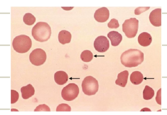
← reticulocyte → (immature RBC in circulation)

- ↓ (< 2%) (B.M suppression) → EPO
  - ↓ → **Chronic kidney dis.**
  - ↑/↔ → **Aplastic anemia** — pancytopenia.
- ↑/↔ (> 2%) signs of hemolysis? (↓ haptoglobin, ↑ LDH, ↑ indirect bilirubin)
  - No → **Blood loss.**
  - Yes → **Hemolytic anemia**

Intrinsic RBC defect

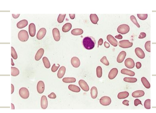
RBC membrane dis. (MC)

Spherocytosis



- **Hereditary spherocytosis**
  - asymptomatic → transfusion dependent!
  - ↓ or abnormality in spectrin
  - AD
  - Infant → jaundice, → anemia; 2-3 ys of age → pallor, weakness, splenomegaly
  - ✓ splenectomy ✓ Folic acid
  - Comp: * aplastic crisis (ass. with parvovirus B19); * pigmentary gall stones.
  - indirect hyperbilirubinemia; Osmotic fragility test → abnormal; flow cytometry EMA binding test.

Elliptocytosis



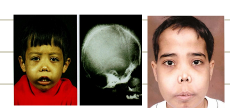
- **Hereditary elliptocytosis**
  - AD
  - spectrin structure defect
  - majority → asymptomatic.
  - Jaundice → splenomegaly & gallstones; 50% at birth; Later
  - ✓ splenectomy.

RBC enzyme dis.

- G6PD ↓ (MC) → acute, → chronic.
  - X-linked
  - Triggers ← infection, Fava beans, Naphthalene balls; Drugs (sulpha, antimalarial)
  - ✓ Cardiovascular, Comprehensive, ✓ Transfusion
- PK ↓
  - AR
  - pallor, jaundice, splenomegaly, kernicterus (neonate)
  - Blood smear → polychromatic RBCs.
  - ✓ Transfusion & splenectomy.

Hemoglobinopathy → Thalassemia

- α
  - silent carrier (α-/αα) ← no anemia, asymptomatic
  - α-thalassemia minor → mild microcytic anemia (αα/-- or α-/α-)
  - Hemoglobin H (α-/--) → microcytic anemia, mild hemolysis, not transfusion dependent.
  - Hydrops Fetalis (--/--) → severe anemia, intrauterine anasarca, CHF, death in utero.
- β
  - β-thalassemia major (Cooley anemia) → Mediterranean background, severe hemolysis, transfusion dependent, hepatosplenomegaly, iron overload.
  - ✓ Life long transfusion, Chelation therapy, Splenectomy, B.M transplant, Gene therapy (curative)
  - Comp: Hemochromatosis
  - Thalassemia intermedia → not transfusion dependent.
  - Thalassemia minor → microcytosis, mild anemia.
- marrow activity ↑, marrow spaces enlarge, ↑ size of bones, & face, skull



"hair on end" · Chipmunk face

Extrinsic

- # Autoimmune hemolytic anemia (AIHA)
  - ab. misdirected against RBC
- # Alloimmune hemolytic anemia.
  - Rh (strong +ve coomb) → severe jaundice, anemia, hepatosplenomegaly, hydrops fetalis
  - ABO (weakly +ve coomb) can occur in 1st preg.
  - ✓ phototherapy, mild, mod; exchange transfusion, severe
- # Cold agglutinin dis
- # paroxysmal cold Hburia
- # Hypersplenism.
- # Sys. dis → Infection, Liver dis, Renal dis
- # Microangiopathies MHA → mechanical damage to RBC → passage through an injured vascular endothelium
  - Causes: Giant hemangioma, DIC, artificial heart valves.
  - S&S of anemia, thrombocytopenia. "burr" cells & schistocytes.
- # Hemolytic uremic syndrome HUS
- # Thrombotic thrombocytopenic purpura TTP
- # Disseminated Intravascular Coagulation DIC
- # Mechanical damage
  - artificial heart valve
  - kasabach - Merritt phenomena
- # Wilson dis.

Bone Marrow Failure syndromes

- Single line: early presentation 1-2 months of age
- Erythroid precursors: **DBA**
- Megakaryocyte precursors : congenital megakaryocytic thrombocytopenia **(CAMPT)**
- All lines: late presentation 5-7 year of age
- **Fanconi Anemia**

Peripheral destruction

3 main mechanisms:

(1) Autoimmune disorders:

Single line:

Hemoglobin: AIHA

Platelets : ITP

Multiple lines:

AIHA and Thrombocytopenia: **Evans syndrome**

Peripheral destruction

(2) Mechanical (MAHA)

HUS, TTP, DIC, hemangiomas

(3)Hypersplenism

> 100 → Macrocytic anemia.

blood smear Megaloblastic changes?

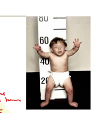
No

- Reticulocytosis
- Liver disease
- Alcohol use
- Myelodysplastic syndrome
- Hypothyroidism
- Multiple myeloma

RBCs aplasia

- **Diamond-Blackfan** (AD)
  - pure red cell aplasia.
  - 1st year of life.
  - 50% → extra-hematopoietic anomalies: triphalangeal thumb, short stature, craniofacial

  - reticulocytopenia, ↑ HbF, ↑ eADA activity, ↓ erythrocyte precursor.
  - ✓ Corticosteroids 80%; Chronic red cell transfusions 20%; HSCT
  - "Cancer predisposition syndrome" ↑ risk → AML / colon carcinoma, myelodysplastic syndrome, osteogenic sarcoma / genital ca.; iron overload.
- **TEC — Transient erythroblastopenia of Childhood**
  - MC aquired red cell aplasia in child.
  - 6 months → 3 years.
  - Follow viral infection
  - MCV & HbF & RBC adenosine deaminase normal
  - reticulocytopenia.
  - ✓ recover within 1-2 mo; RBC transfusion if > 1 → severe
- **Parvovirus B19 associated RBC aplasia**
  - infective & cytotoxic to marrow erythroid progenitor cell.
  - when short life span (RBC) → brief cessation of erythropoiesis → severe anemia "aplastic crisis"
  - IgM & IgG titers / PCR ✓ IVIG high dose
- **Aplastic anemia** → aquired (Drugs / Infection / chemical / radiation), congenital
  - pancytopenia, ↑ HbF, B.M hypocellularity
- **Fanconi anemia** AR
  - DNA repair defect / ↑ Ch breakage
  - 7 years
  - * ecchymosis, petechiae, anemia, recurrent infections
  - * skeletal abnormalities, short stature, absence or hypoplasia of thumb, kidney, skin, cafe au lait, gonads, microcephaly

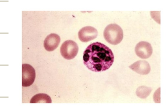


yes → Folic Acid ↓

- ↓ intake (lacked or exclusive feeding with goat's milk)
- ↓ intest. absorption.
  - celiac
  - anti-convulsant
  - OCPs
- S&S of anemia +
  - FTT
  - chronic diarrhea
  - Irritability.

Vit. B12 ↓

- vit B12 + IF ⇒ to be absorbed in terminal ileum.
- ↓ intake (strict vegetarian diet)
- inability to secrete IF → juvenile pernicious anemia.
- inability to absorb vit B12 → chron, short gut syndrome.
- Smooth red tongue
- Neurologic → ataxia, hyporeflexia, +ve Babinski
- ✓ IM vit B12 monthly.
- Hypesegmented neutrophils



- + pancytopenia