Anemia

First: Introduction of Hematopoiesis😉:

نقول بسم رب العلم نبدأ🦋🤍

- Developmental hematopoiesis occurs in three anatomic stages:
  1. **Mesoblastic hematopoiesis** occurs in the yolk sac, begins between the 10th and 14th days of gestation.
  2. **Hepatic hematopoiesis** starts by 6th week of gestation. The liver remains the predominant hematopoietic organ through wk 20-24 of gestation
  3. **(myeloid) hematopoiesis** started by 12 wk. the liver production begins to diminish during the second trimester as bone marrow increases.
- ERYETHROTHROPOIETIN(EPO): is a hormone that regulates RBC production. EPO does not cross the placenta (SO maternal erythropoiesis has no effect of the fetus- stimulation or suppression).
  - ✓ Antenataly produced in the liver.
  - ✓ Postnataly it is produced by the kidney
- Erythropoiesis in utero is controlled by fetal erythroid growth factors.
- Fetal bone marrow space begins to develop around the 8th week post conception. Space start to enlarge by 8-10wks.
- Differentiation of RBC is regulated by:
  - ✓ EPO
  - ✓ IL-1
  - ✓ GM-CSF

NOTE:
The zeta (ζ) chains of Hb Portland and Gower-1 are structurally similar to α chains.Both genes present in chrom. 16.

- HEMOGLOBINL: is a complex protein consists of iron containing heme & globin.
  - ✓ each Hb molecule (tetramer) consists of tow pairs of polypeptide chains. with each chain having a heme group attached
  - ✓ The major hemoglobin of a normal adult (Hb A), is made up of one pair of alpha (α) and one pair of beta (β) polypeptide chains, $\alpha_2\beta_2$
  - ✓ The major hemoglobin in the fetus (Hb F), two alpha and two gamma globin chains, $\alpha_2\gamma_2$
  - ✓ Two pairs of alleles for α & ζ chains are located on human chromosome16.
  - ✓ The β, γ, δ, epsi genes are closely linked on chromosome 11.
  - ✓ (RBC) mass of an embryo, fetus, child, and adult, six different hemoglobins:
    1. EMBRYONIC HEMOGLOBINS Gower-1(ζ_2[epsi]$_2$), Gower-2(α_2[epsi]$_2$), and Portland($\zeta_2\gamma_2$) - embryos of 4-8 wk gestation, the Gower hemoglobins predominate, but by the 3rd month they have disappeared.
    2. FETAL HEMOGLOBIN, Hb F ($\alpha_2\gamma_2$). Resists alkali denaturation (Kleihauer-Betke test). 8th wk ges Hb F is the predominant hemoglobin→ 6th months of ges 90% → birth 70% → 6-12 mo < 2.0%.
    3. ADULT HEMOGLOBINS,
       - Hb A($\alpha_2\beta_2$) 6th months of ges **5-10%** →at term **30%** →6-12 mo of age**>95%**
       - Hb A_2 ($\alpha_2\delta_2$). contains is seen only when significant amounts of Hb A are present. At birth **<1.0%** → 12 mo of age **<3.4%.**
       - Throughout life, the normal ratio of Hb A to A_2 is about 30:1.
    - ✓ Prenatal diagnosis is possible for all types of Hb abnormalities via chorionic villous sampling (diagnosis of major β-chain hemoglobinopathies → 16-20 wk gestation)
    - ✓ ALTERATIONS OF THE HEMOGLOBINS BY DISEASE
      - HB GROWER → trisomy 13 &15
      - HB PORTLAND→ α thalasemia
      - HB F →β thalasemia , sickle cell anemia, hemolytic, leukemia,aplastic anemia)
      - Tetramers of γ chains (γ_4 or Hb Barts) or β chains (β_4, Hb H) in α-thalassemia.
      - HB A2 increase in β thalassemia and megaloplastic anemia (B12 and folic acid), Decrease in α-thalassemia and iron deficiency anemia
  - ✓ The average life span for a neonatal RBC is 60-90 days
  - ✓ When neonatal RBCs are transfused into adults they have short life span but from adult donor to a neonate they have normal life span.
  - ✓ ↑prematurity, remarkably shorter red cell life spans (35-50 days) are found.
  - ✓ THE SHORTENED RED CELL LIFE SPAN OF THE PRETERM AND TERM NEONATE EXPLAINED BY CHARACTERISTICS SPECIFIC TO NEWBORN CELLS:
    1. a rapid decline in ***intracellular enzyme activity and ATP***;
    2. loss of membrane ***surface area*** by internalization of membrane lipids;

Blood indices

i- Hemoglobin content:

- in 1st 2 weeks → 14-20 gm/dl (intrauterine hypoxia →↑ erythropiotin).
- in infancy → 10-14 gm/dl (higher in males due to androgen).

ii- RBCs count:

- in newborn → 6 million / mm^3.
- afterwards → 4-6 million / mm^3.

iii- Hematocrite value (Ht. value) = packed red cell volume.
= percent of RBCs volume in 100 ml blood ≈ 40-50%.

iv- Mean corpuscular volume (MCV)

$$= \frac{\text{Ht.value} \times 10}{\text{RBCs count}} = 72 - 79 \text{ femtolitre.}$$

- if < 70 → RBCs are small (Microcytes).
- if > 85 → RBCs are big (Macrocytes)

(Reference: Manual of Pediatric Hematology and Oncology; page 4, 2005)

v- Mean corpuscular hemoglobin (MCH)

$$= \frac{\text{Hb content} \times 10}{\text{RBCs count}} = 30 \text{ pg.}$$

- if < 25 pg → RBCs are hypochromic.

vi- Mean corpuscular hemoglobin concentration (MCHC)

→ concentration of Hb. In an erythrocyte

$$= \frac{\text{Hb content}}{\text{Ht. value}} \times 100 = 33\%$$

N.B: Mentzer index:

- Equals MCV/ RBCs count in millions
- Usually > 13 in iron deficiency anemia
- Usually < 13 in thalassemia due to higher RBCs count

vii- Platelet count = 150.000 – 400.000 / mm^3

viii- Reticulocytic count = 1 %.

Reticulocytosis occur in:

1- Hemolytic anemias.
2- Hemorrhage
3- Response to hematinics e.g. (iron, folic acid, B_{12})
4- Recovery of bone marrow from suppression.

Seconed:Definiion, CF and of Anemia:

Summary

Anemia is defined as a decrease in the quantity of circulating red blood cells (RBC), represented by a reduction in hemoglobin concentration (Hb), hematocrit (Hct), or RBC count. It is a common condition that can be caused by inadequate RBC production, excessive RBC destruction, or blood loss. The most common cause is iron deficiency. Clinical features, if present, are mostly nonspecific and may include fatigue, dyspnea, conjunctival pallor, and tachycardia. Once anemia has been established, the mean corpuscular volume (MCV) should be checked to distinguish between microcytic, normocytic, and macrocytic anemia and to determine the next diagnostic steps. Reticulocyte count can also be used to evaluate the bone marrow response. Treatment depends on the form of anemia and underlying condition. Acute and/or severe cases of anemia may require transfusion of packed red blood cells.

Definition: It is reduction of hemoglobin **and/or** RBCs count below average value for age and sex **interfering with** O_2 carrying capacity of the blood.

Sequalae of anemia

I- Compensatory mechanisms:

tissue hypoxia due to anemia leads to:

1- ↑ 2, 3 diphosphoglycerate:

↳ ↓ Hemoglobin affinity to O_2 →↑ O_2 delivery to tissues.

2- ↓ peripheral resistance & peripheral vasodilation → hyperdynamic circulation.

3- ↑ Erythropoietin.

4- At Hb < 6g/dl → redistribution of the blood to vital organs → Brain, heart and kidneys.

II- General features of anemia:

- **Symptoms**
  1- Anorexia → weight Loss.
  2- Easy fatiguability
  3- Headache, tinitus, sweating.
  4- Fainting.
- **Signs**
  1- Pallor
  2- Tachycardia (palpitation)
  3- Hemic murmers. (functional, systolic).
  4- Heart Failure in severe anemia (with hemoglobin < 4 gm/dl).

Third: Causes of Anemia:

Causes of anemia

A. Decreased production:

Decreased erythroid cells in bone marrow (Bone marrow failure)	Decreased production despite normal RBCs precursors	Specific factor defeciency (Dyshemopiotic anemia)
* Pure red cell anemia. * Aplastic anemia * Marrow infiltration e.g.: - Leukemia - Myelofibrosis	* Anemia of chronic disease: - Chronic inflammation. - Chronic infection - Chronic renal failure.	* Iron deficiency. * Folic acid & B12 deficiency. * Protein deficiency.

C. Hemorrhagic anemia: - Acute hemorrhage
- chronic hemorrhage.

B. Increased destruction (hemolytic Anemia)

A. Intra corpuscular causes

1- Membrane defects
- Hereditary spherocytosis
- Hereditary elliptocytosis.
- Paroxysmal nocturnal hemoglobinuria.

2- Hemoglobinopathy
- α thalassemia
- β thalassemia.
- Sickle cell disease

3- Enzymatic defects
- G6PD deficiency
- pyruvate kinase deficiency.

B. Extra corpuscular causes

Immunologic (Coombs +ve)

Isoimmune hemolytic anemia (passively acquired antibodies)
1- Hemolytic disease of newborn.
2- Incompatible blood transfusion.

Autoimmune hemolytic anemia (actively formed antibodies)

Non immunologic (Coombs –ve)

1- Microangiopathic hemolytic Anemia (MAHA)
- DIC
- Hemolytic uremic synd (HUS).
- Renal vein thrombosis (RVT).
- Intracardiac prosthesis

2- Septicaemia (Staph strept., clostridia)
3- Malaria.
4- Wilson disease.
5- Drugs & heavy metals.
6- Hypersplenism.

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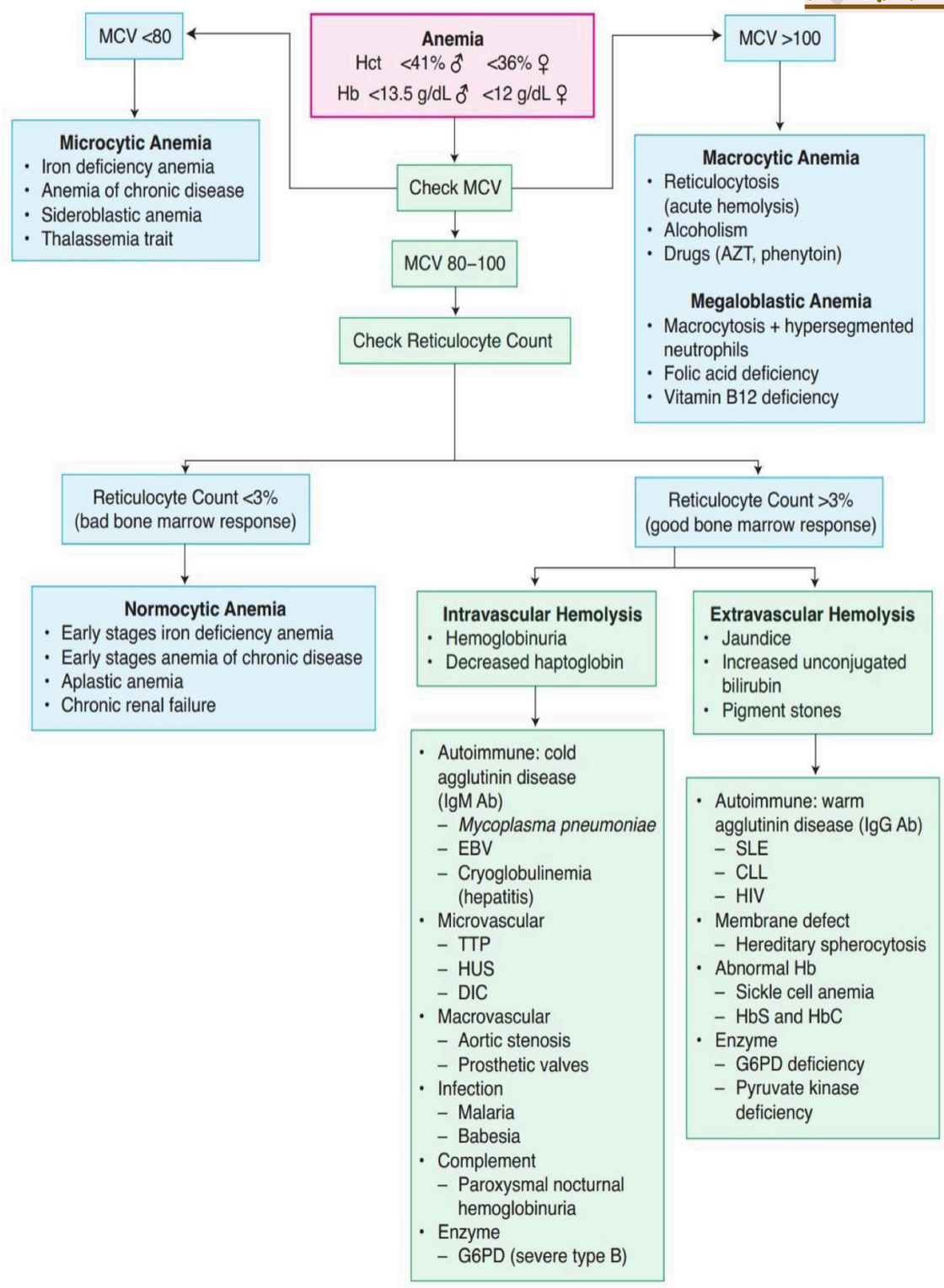
Classification

1. Classification is made on the basis of the **mean corpuscular volume (MCV) and the morphologic appearance of the RBC** (i.e., size, color, and shape). Terms used include the suffix *-cytic,* referring to size, and the suffix *-chromic,* referring to color. Primary classifications include the following:
   a. **Microcytic, hypochromic anemia** (small, pale RBCs; low MCV)
   b. **Macrocytic anemia** (large RBCs; high MCV)
   c. **Normocytic, normochromic anemia** (normal RBCs in size, color, and shape; normal MCV)
2. Classification based on **reticulocyte count** is also helpful. The reticulocyte count reflects the number of immature RBCs in the circulation and, therefore, the activity of the bone marrow in producing RBCs. The usual percentage of RBCs that are reticulocytes is 1% (normal absolute count = 50,000 cells/mm^3). In the steady state, when a patient has a normal Hgb level, the reticulocytes should constitute 1% of all RBCs. In most anemias, reticulocyte counts should rise. A **low reticulocyte count indicates bone marrow failure or diminished hematopoiesis.**

Clinical Features of Anemia

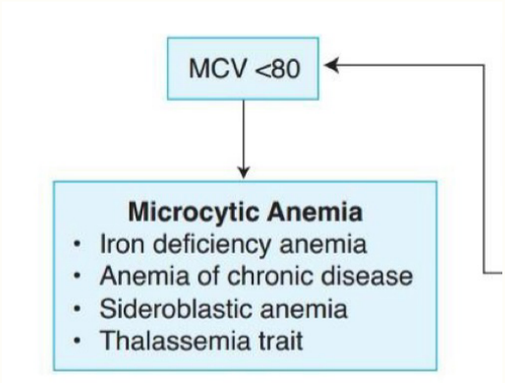
Mild
Pallor (noted especially on skin and on mucous membranes) Diminished attention
Moderate
Weakness and fatigue
Decreased exercise tolerance
Irritability
Tachycardia
Tachypnea
Anorexia
Systolic heart murmur
Severe
Congestive heart failure
Cardiac dilation
Shortness of breath
Hepatosplenomegaly Spoon-shaped nails

المخطط الجميل🤍:



Now, we will discuss all Causes of Anemia one by one😊👍👍

A. Microcytic Anemia:



	Microcytic anemia
MCV (fL)	• < 80
Mechanism	• Insufficient hemoglobin production
Etiology of anemia	• Defective heme synthesis: e.g., IDA, lead poisoning • Defective globin chain (↓ Globin → ↓ hemoglobin → ↓ MCV): e.g., thalassemia

A1.Iron deficiency Anemia:

Summary

Iron deficiency anemia (IDA) is the most common form of anemia worldwide and is caused by inadequate intake, decreased absorption (e.g., atrophic gastritis, inflammatory bowel disease), increased demand (e.g., during pregnancy), or increased loss (e.g., gastrointestinal bleeding, menorrhagia) of iron. Prolonged deficiency depletes iron stores in the body, resulting in decreased erythropoiesis and anemia. Symptoms are nonspecific and include fatigue, pallor, lethargy, hair loss, brittle nails, and pica. Routine screening is only recommended for certain groups. IDA typically manifests as hypochromic, microcytic anemia, but it may also be normocytic. If diagnostic confirmation is needed, a low ferritin level indicates an iron deficiency, but additional iron studies may be necessary. Once IDA is confirmed, the underlying cause must be determined. In adults, this typically involves a gastroscopy and colonoscopy or, in women with abnormal uterine bleeding, a gynecologic workup. In children, a thorough history and review of symptoms, including a comprehensive dietary history, can help direct any further diagnostic evaluation. Patients with anemia severe enough to cause cardiopulmonary instability, or pregnant patients with a Hb < 6 g/dL, require blood transfusions. All other patients can be managed with oral or parenteral iron supplementation.

Incidence: The most common cause of anemia in pediatrics.

Iron metabolism

- Most of dietary iron present in ferric state.
- Iron changes to ferrous by combined action of HCL & vitamin C.
- Only **10%** of dietary iron is absorbed from the jejnum (So daily need = 10 mg/day)
- Absorbed iron is bound to serum **transferrin.**
  - ↳ and stored as **ferrittin** to be used in:
    a. In bone marrow → RBCs
    b. In cell enzymes e.g. Catalase, peroxidase, mono amine oxidase (MAO).

Causes

i- Decrease intake: Common in ages 6-24 months due to:
- Prolonged breast feeding with out supplementation (delayed weaning).
- Cow milk feeders (↓ iron, ↓ lactoferrin, heat labile protein may induce occult blood loss).

ii- Decrease iron absorption:
- Malabsorption syndrome.
- Excess tea, phytate & antiacids.

iii- Decrease iron stores
- Iron deficient pregnant
- Perinatal Blood loss.
- Preterm.

iv- Increase requirements due to:
- Rapid rate of growth in twins, preterm, infants, adolescence.
- Congenital cyanotic heart diseases(due to polycythemia)

v- Increase loss: Common in ages > 2 years.
1- Overt blood loss e.g hematuria, epistaxis,heamodialysis,…..
2- Occult blood loss due to - Ankylostoma
- Peptic ulcer, polyps, gastro esophageal reflux
- Cow milk protein allergy
- Meckle's diverticulum.

DIETARY BASED IRON DEFICIENCY
- total body Fe : 0.5g in newborn to 5g in adult
- 0.8-1.5 mg of elemental Fe is needed daily
- Only 10% of elemental Fe is absorbed in the jejunum → daily elemental Fe required is 8-15 mg/day.
- cows milk Fe content is .75mg/L → at least 10 liters is needed daily → so infants who primarily on cows milk→ iron deficiency anemia
- BREAST FED BABIES ABSORB 50% OF IRON FROM THE BREAST MILK.

Risk factors for pediatric IDA [26][25][11]

- Prematurity [38]
- Small for gestational age (i.e., low birth weight)
- Poor dietary intake of iron-fortified or iron-rich foods, e.g.:
  - Exclusively breastfed infants > 4 months of age not receiving iron prophylaxis
  - Early (i.e., < 12 months of age) and excessive (> 24 ounces/700 mL per day) intake of nonfortified cow's milk
  - Restrictive diets: malnutrition (mainly in resource-limited countries), eating disorders (including pica), picky eating
- GI bleeding (e.g., Meckel diverticulum)
- Heavy menstrual bleeding
- Intellectual disability
- Low socioeconomic status, including living in areas with a high prevalence of IDA

Clinical picture

1- Mild anemia is asymptomatic.
2- Manifestations of anemia (anorexia, pallor,…) vary with severity of iron deficiency.
3- Irritability, decreased alertness, learning & concentration span (due to ↓ iron containing cellular enzymes).
4- Other rare manifestations:
   * Atrophic glossitis (pale & smooth).
   * Pica (Geophagia) desire to ingest unusual substances e.g. dirts
   * Nails ⇒ longitudinal ridges, flattening and spooning (koilonychia)
   * Palpable spleen in about 15% of cases.

Laboratory findings

1. Because iron stores disappear first, an **early finding of iron-deficiency anemia** is **low serum ferritin.** Ferritin can be a useful assessment of iron stores; however, because ferritin is also an acute-phase reactant, it may be increased in infection, disease states, and stress, therefore appearing normal.
2. As **serum iron decreases, iron-binding capacity increases**, manifested as **increased transferrin** and **decreased transferrin saturation.**
3. **Increased free erythrocyte protoporphyrin** may be noted.
4. Other findings include a normal or increased reticulocyte count.

.Hb conc.

- < 6 months of age: varies depending on age [42]
- 6–59 months: < 11 g/dL
- 5–11 years: < 11.5 g/dL
- 12–14 years: < 12.0 g/dL

Hb in infants < 6 months of age changes rapidly, declining from 14.6–22.5 g/dL at birth to a physiological nadir of 10–12 g/dL at ~ 8 weeks of age, after which levels rise again. In premature infants, Hb at birth may be lower and the decline is more severe and rapid. Standardized laboratory reference ranges for the set ages should be used to determine anemia in this age group.

1- For diagnosis:

1 - CBC : Anemia → Hypochromic, Microcytic

- Anemia: ↓ Hb% ; ↓ RBCs count
- Hypochromic: MCH < 27 Pg ; MCHC < 30%
- Microcytic: MCV < 70 fl ; Increased RDW

2- Iron indices:

Index	Iron deficiency	Normal (age dependent)
* Serum Iron.	< 30 µg / dl	60 - 120 µg / dl
* Transferrin saturation.	< 15%	33%
* Soluble serum transferrin receptors.	increased	
* Total iron binding capacity (TIBC).	> 350 µg / dl	250-350 µg / dl
* Serum ferrittin. (index of iron stores)	< 10 ng / ml	25-140 ng/ml

2- For the cause: - Stool analysis for parasites & occult blood tests (Gauiac test)
- GIT barium study, and endoscopy .

Treatment

i- Prophylaxis:

Oral iron given at 4th – 6th months (2mg/kg/d) for breast and cow milk feeders.

ii- Curative:

1- Treat the cause.

2- Diet → Rich in vitamin C, meat, fish
→ Limit amount of cow milk & tea.

3- Iron preparation:

- **Oral Iron:**
  - Ferrous sulphate, gluconate or fumarate.
  - Dose: 6 mg/kg/d. elemental iron inbetween meals.
  - For: 8 weeks after blood values are normalized.
  - Side effects: GIT upset & dark stool.
- **Parentral Iron**
  - Iron Dextran (I.M), or iron hydroxide sucrose complex ;*Venofer* (I.V).
  - For malabsorption or Intolerance to oral iron.
  - Side effect → staining, abscess,anaphylaxis.

4- Packed red cell transfusion:

- in: - Severe anemia (Hb < 4gm/dl).
  - Anemic heart failure.
  - Infection interfering with iron therapy.

Response to iron therapy:

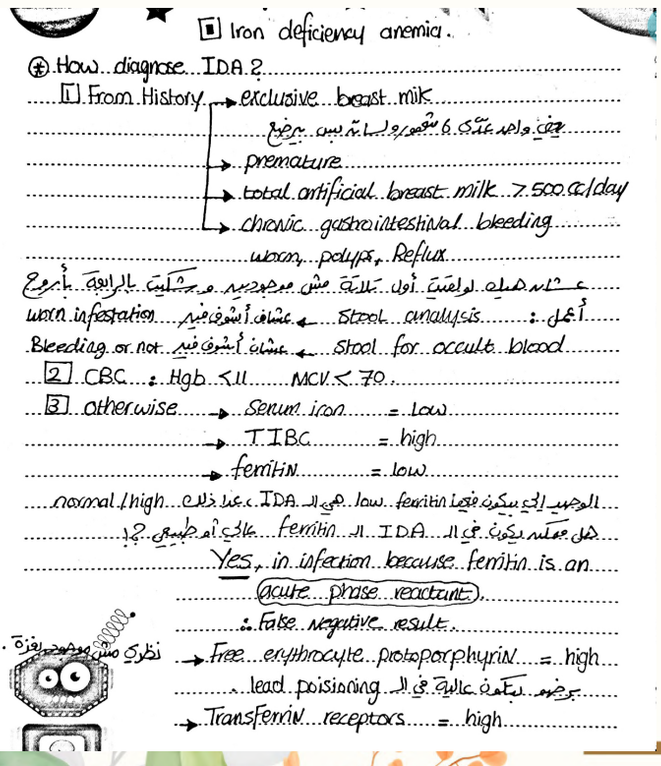
Time after iron administration	Response
By 1st day	Replaced cellular enzymes → ↓ irritability with increased appetite.
By 2nd day	Erythroid hyperplasia in bone marrow.
By 3rd day	Reticulocytosis peaking at 5-7 days (good therapeutic test).
By 1st month	Increase hemoglobin at rate of 0.25 – 0.5 gm/dl/day
1 – 3 months	Repletion of stores.

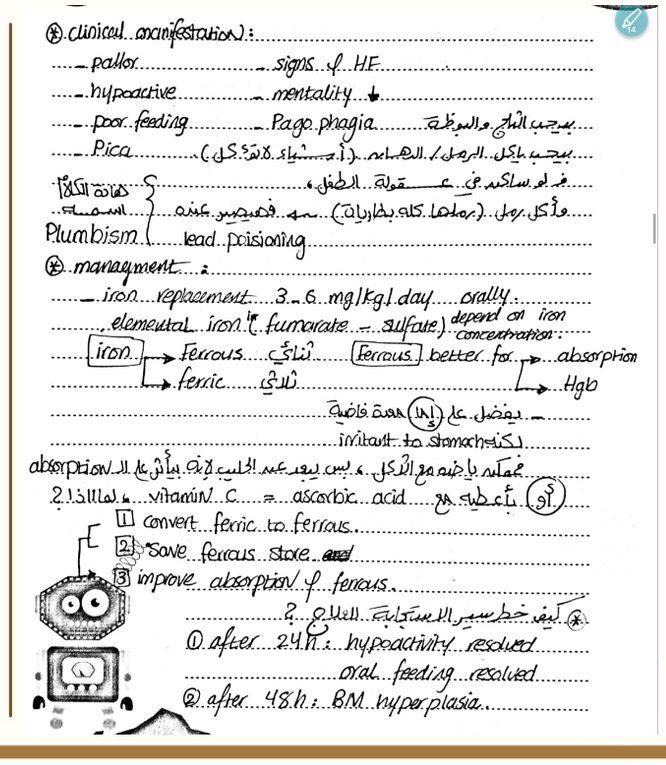
Causes of failure of iron therapy:

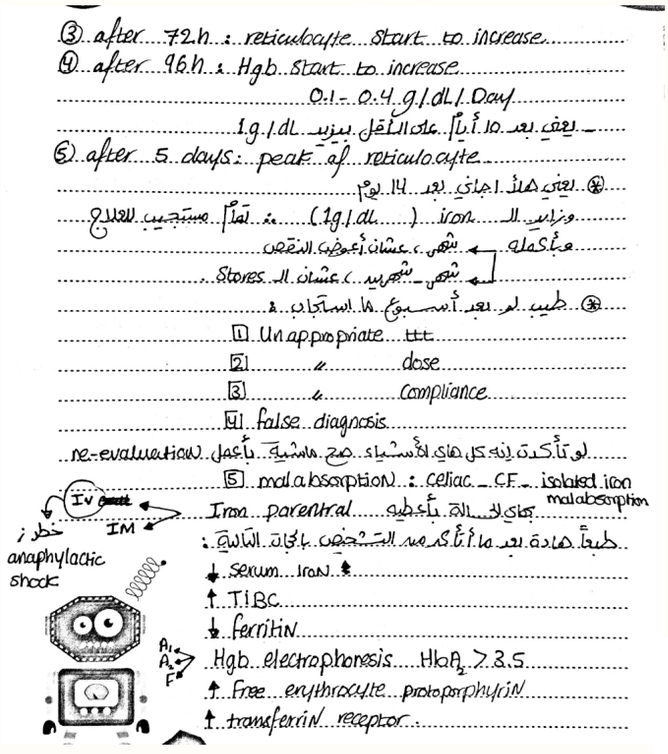
- Non compliance.
- Continuing use of cow milk
- Continuing blood loss
- Coexisting diseases(renal,infection)
- Impaired absorption
- Incorrect diagnosis.

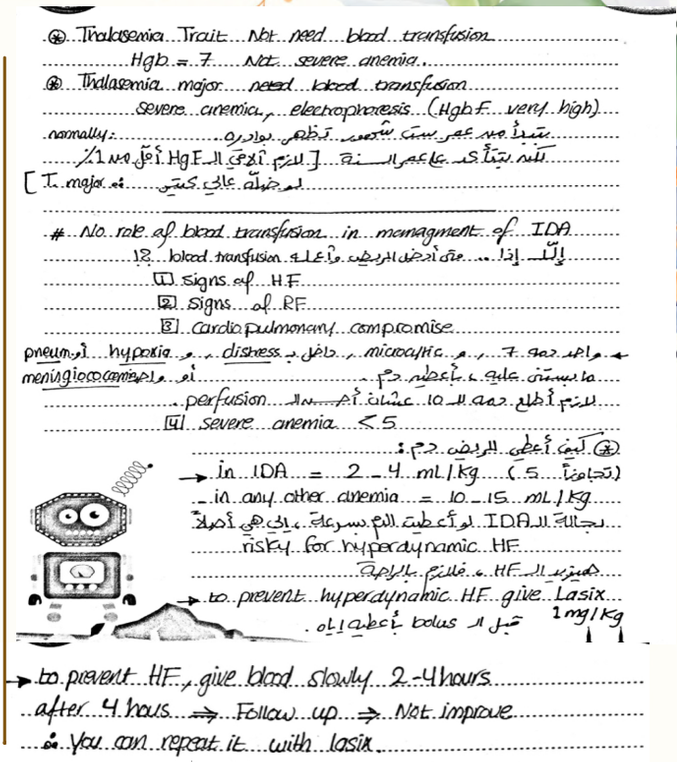
To sum up:

نشوف بقى تلخيص النصر ع السريع









Iron Deficiency Anemia

بلاع الـ sum بتاع اليوورد

Iron deficiency anemia in young children	
Risk factors	• Prematurity • Lead exposure • Age <1 ◦ Delayed introduction of solids (ie, exclusive breastfeeding after 6 months) ◦ Cow's, soy, or goat's milk • Age >1 ◦ >24 oz/day cow's milk ◦ <3 servings/day iron-rich foods
Diagnosis	• Screening hemoglobin at age 1 • Hemoglobin <11 g/dL, ↓ MCV, ↑ RDW
Treatment	• Empiric trial of iron supplementation

1. Microcytic anemia
2. Look for history of prolonged bleeding or poor dietary intake of iron in older children
3. Risk factors for iron deficiency in infants:
   a. Prematurity
   b. Maternal iron deficiency
   c. Early introduction of cow's milk before age 1 year
4. In children, it is often caused by excessive cow's milk intake (>700 ml [24 oz] daily)
   a. <1 year age should NOT be started on cow's milk
   b. >1 year age should not consume excessive amount of cow's milk (i.e, >24 oz)
5. Lab findings
   a. Decreased erythrocyte count
   b. Reactive thrombocytosis (>400,000/mm^3)
      i. This occurs in response to low RBC
      ii. RBC and platelets share a common progenitor cell
   c. Increased RDW
   d. Low reticulocyte count
   e. Mentzer index >13 (due to decline in RBC count)
6. Diagnosis
   a. Universal screening is recommended by age 1 year
   b. Peripheral smear is NOT needed in initial workup
   c. Iron studies
      i. Should not be needed in children with classic presentation
      ii. Correct iron deficiency before evaluating for thalassemia with electrophoresis because iron deficiency can lower hemoglobin A2 and mask the diagnosis
7. Treatment
   a. Empiric oral iron therapy
      i. Recheck in 4 weeks
      ii. If hemoglobin has risen 1 g/dl, the oral therapy should be continued for 2-3 months after the hemoglobin normalizes to replete iron stores

Iron Studies in Sideroblastic Anemia
- Increased serum iron
- Normal TIBC

Corrected Reticulocyte Count Formula:
Corrected reticulocyte count = % reticulocyte x (Hematocrit/45%)

Risk factors for Lead Poisoning:
1. Houses built before 1978
2. Eating dirt/paint chips

Bone marrow evaluation
Consider bone marrow evaluation only when multiple cell lines are depressed

Parameter	Iron deficiency anemia
MCV	↓
RDW	↑
RBCs	↓
Peripheral smear	Microcytosis, hypochromia
Serum iron studies	↓ Iron & ferritin ↑ TIBC
Response to iron supplementation	↑ Hemoglobin
Hemoglobin electrophoresis	Normal

Iron Studies in Microcytic Anemia

Iron studies in microcytic anemia					
Cause	MCV	Iron	TIBC	Ferritin	Transferrin saturation (Iron/TIBC)
Iron deficiency	↓	↓	↑	↓	↓
Thalassemia	↓↓	↑	↓	↑	↑↑
Anemia of chronic disease (inflammation)	Normal/↓	↓	↓	Normal/↑	Normal/↓

Iron Deficiency Anemia Screening

1. It is done at **age 1** and can be considered **once in adolescent girls** due to blood loss from menses

أنا عارفة إنه زودتها بال IDA لكن معلش لمصلحة عمو الـ pt

A2.Thalassemias:

Summary

Thalassemias are a group of hereditary hemoglobin disorders characterized by mutations on the α- or β-globin chains (resulting in alpha or beta thalassemia). Thalassemias can be further classified according to the specific genotype: the α-chain is coded by four alleles, resulting in four possible variants depending on the number of alleles affected, while the β-chain is coded by two alleles, resulting in two possible variants. The number of alleles affected is directly related to the severity of the disease (minor/intermedia/major). Thalassemia mutations are generally more frequent in areas where malaria is endemic; alpha thalassemias occur most commonly in individuals of Asian or African descent, whereas beta thalassemias are predominant in individuals of Mediterranean descent. The key feature in all forms of thalassemia is microcytic hypochromic anemia (which may be very mild in minor forms), but more severe forms may also manifest with hemolysis, splenomegaly, delay in growth and development, and skeletal deformities. The diagnostic workup for suspected thalassemia includes a blood smear, hemoglobin electrophoresis, high-performance liquid chromatography (HPLC), and, possibly, genetic testing. Minor forms of thalassemia usually require no treatment, while patients with thalassemia intermedia/major typically require regular blood transfusions and management of disease and treatment-related complications (e.g., chelating agent for transfusion-mediated iron overload).

b. **Pathophysiology**

1. **Normally,** the major Hgb in RBCs is hemoglobin A_1, a tetramer of two α-chains and two β-chains. HgbA_2 and Hgb F may also be present in small amounts.
2. **α-Thalassemia** results from **defective α-globin chain synthesis,** and **β-thalassemia** results from **defective β-globin chain synthesis.**
3. Both types of thalassemia result in hemolysis that leads to increased bone marrow activity. As marrow activity increases, the marrow spaces enlarge, increasing the size of bones in the face, skull, and other bones if severe and untreated.

- Anemia due to decreased synthesis of the globin chains of hemoglobin.
- ↓ globin → ↓ hemoglobin → microcytic anemia.
- Divided into α- and β-thalassemia based on decreased production of alpha or beta globin chains.
- Beta-thalassemia is the most common thalassemia in patients of Mediterranean descent; alpha-thalassemia is more common in individuals from Southeast Asia.
- Normal types of hemoglobin are HbF ($\alpha_2\gamma_2$), HbA ($\alpha_2\beta_2$), and HbA$_2$ ($\alpha_2\delta_2$).

Definition: Autosomal recessive disorders due to defective globin chain production

1. α thalassemia syndromes:

✧ Impaired α chain production

✧ Due to deletion of one or more of the 4 α globin genes on chromosome 16

A. One gene deletion → **Silent carrier**
- Asymptomatic without any hematologic abnormalities.
- Electrophoresis in neonatal period shows <3 % Bart's hemoglobin (4 γ globin chains) which disappear few months later.

B. Two gene deletion → **α thalassemia trait**
- Familial microcytic anemia ; commonly mistaken as iron deficiency
- Normal iron indices
- Electrophoresis shows:
  * 3-8 % Bart's hemoglobin in neonatal period which disappear by childhood
  * Normal levels of Hb F & Hb A_2 for age.
- Diagnosed by exclusion; to confirm → DNA analysis.

C. Three genes deletion → **Hemoglobin H disease**
- Mild to moderate microcytic hemolytic anemia at birth
- Evidence of chronic hemolysis
- Electrophoresis shows:
  * 15-30 % Bart's hemoglobin in neonatal period
  * Hb H (4β chains).

D. Four genes deletion → **Fetal hydropes**
- Severe intra uterine anemia and anemic heart failure
- Resulting in intrauterine fetal death , still birth or early neonatal death
- Electrophoresis shows: Dominant Bart's hemoglobin with complete absence of normal fetal and adult hemoglobin (i.e require BMT)

2. β-thalassemia syndromes :

- ✧ Impaired β chains production
- ✧ Due to mutation of one or more of the 2 β globin genes on chromosome 11

A. One gene mutation → **β thalassemia trait** (Heterozygous β-thalassemia)

- Most patients have short RBCs survival without evidence of overt hemolysis.
- Microcytic anemia
- Differentiated from iron deficiency anemia by:
  - Normal iron indices.
  - Increased RBCs count in contrast to iron deficiency (Mentzer index >13)
  - Electrophoresis: - ↑ Hb A_2 up to 3-7% in over 90% of cases.(diagnostic)
    - ↑ HbF up to 1-3% in only 50% of cases.

B. Two genes mutation → **β thalassemia major**

β Thalassemia Major

(Cooley's anemia)

The commonest cause of chronic hemolytic anemia in Egypt & Mediterranean areas.

Pathogenesis **1- Impiared β chain production**

↓ production of HbA ($\alpha_2 B_2$)

Deposition of excess unmatched α chain inside the RBCs → hemolysis → Anemia

Compensatory production of other Hb containing non Beta chains especially Hb F ($\alpha_2\gamma_2$) → ↑ Level of HbF (↑O_2 affinity)

→ Tissue hypoxia → Compensatory ↑RBCs production

- Medullary hematopoeisis → Bone marrow expansion **(Skeletal changes)**
- Extramedullary hematopoeisis → **Splenomegaly (± hepatomegaly)** ± hypersplenism

2- Iron overload due to:

- Chronic hemolysis.
- ↑ Iron absorption.
- Repeated blood transfusion.

→ Iron deposition in various organs → hemosiderosis.

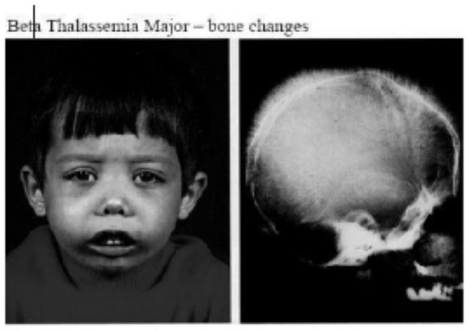
Clinical picture

1- Features of anemia
2- Features of chronic hemolysis

} Starting after the 6th month of age when switch from γ to β chain production normally occur.

3- Hemosiderosis → Iron deposition in:

- ✧ Skin → bronzed color
- ✧ Heart → cardiomyopathy.
- ✧ Pancreas → diabetes mellitus.
- ✧ Liver → cirrhosis.
- ✧ Pituitary → growth retardation & hypogonadism.

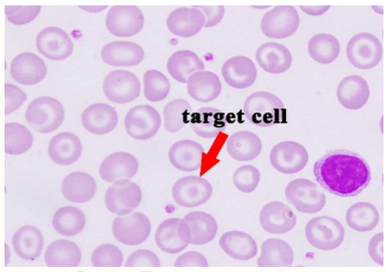


Overview of thalassemia			
Type		**Mutated gene**	**Clinical features**
Alpha thalassemia	**Silent carrier**	• One defective allele (-α/αα)	• Typically no anemia
	Alpha-thalassemia trait	• Two defective alleles (-α/-α or --/αα)	• No or mild anemia
	Hemoglobin H disease	• Three defective alleles (--/-α)	• Jaundice and anemia at birth • Chronic hemolytic anemia (that **may require transfusions**) • Secondary hemochromatosis • Hepatosplenomegaly
	Hemoglobin Bart's disease	• Four defective alleles (--/--) • Consists of four γ-chains (γ-tetramers)	• Intrauterine ascites • Hydrops fetalis
Beta thalassemia	**Beta-thalassemia minor**	• One defective allele (β/β^+ or β/β^0)	• No or mild anemia
	Beta-thalassemia intermedia	• Two defective alleles (β^+/β^+ or β^+/β^0) or coinheritance of other variants	• Variable anemia that may require transfusions during periods of stress (e.g., surgery, infection, pregnancy)
	Beta-thalassemia major	• Two defective alleles (β^0/β^0)	• Severe hemolytic anemia (that requires frequent transfusions) • Secondary hemochromatosis • Hepatosplenomegaly • Growth retardation • Skeletal deformities • Transient aplastic crisis
	Sickle cell beta thalassemia	• Combination of one defective β-globin allele and one defective HbS allele (β^+/HbS or β^0/HbS)	• Features of sickle cell disease

- Diagnostic Tests of microcytic anemia:

- The peripheral smear is not useful as all of the causes of microcytic anemia can be hypochromic or associated with target cells. Target cells are most common with thalassemia.

- Unique findings on iron studies are the best initial test of microcytic anemia.



Complications and cause of death

1- Heart failure may be due to:
- Under transfusion → anemic Heart failure.
- Over transfusion → volume overload.
- Cardiomyopathy due to hemosiderosis.

2- Hemosiderosis:
- Diabetes mellitus → Diabetic ketoacidosis.
- Liver cirrhosis → Liver cell failure.

3- Hazards of frequent blood transfusion:
- Allergic reactions.
- Pyrexial reactions.
- Incompatible blood transfusion.
- Disease transmission (HBV, HCV, AIDS)

4- Hypersplenism → pancytopenia

5- Splenectomy → Sepsis.

Investigations

i- For **anemia** → Low Hb% and Ht. value.

ii- For **chronic hemolysis** →↓ RBCs survival & ↑ erythropioesis.

iii- For **the cause**

1- Blood film → hypochromic, microcytic anemia with target cells.

2- Alkaline denaturation test → Hb F resist denaturation by alkali

3- Hemoglobin electrophoresis :
- β^0 **Homozygous:** ↑↑ Hb F (98%),↑ Hb A_2 (2%), no Hb A (no detectable β chains)
- β^+ **Homozygous:** ↑↑ Hb F, ↑ Hb A_2 , some Hb A (reduced β chains synthesis)

4- Prenatal diagnosis is possible by chorionic villous sampling (CVS)

الشيء ممتع ها، يلا نعترف عشان المتعة لسا ما بدتش😉👌

Treatment

1- Chronic transfusion therapy (Regular packed RBCS transfusion)

- Started when hemoglobin fall below 7gm/dl.
- Aim: To keep Hb between **9.5-12** gm/dl post transfusion (hypertransfusion protocol).
- Dose: 10-15 ml/kg packed RBCs every **3-4** weeks.
- Benefit → allow normal growth
  → ↓ bone marrow activity → ↓ skeletal changes.
  → ↓ extramedullary hematopoeisis → ↓ organomegaly.
- Recently : young red cells transfusions → help reduce iron overload

2- Iron chelation therapy:

- Started when serum ferrittin exceeds **1000** ng/ml.
- Aim: avoid hemosiderosis(keep serum ferrittin close to **1000** ng/ml) .
- Drugs used:

i- Desferroxamine (Desferal):

- Dose: 40-60 mg/kg/day
- Route: IM, IV or by continous SC pump for 10 hours, 5 nights per week.
- Side effect: local reactions ,anaphylaxis, ototoxicity, ocular toxicity & growth retardation (rickets like changes)

ii- Recent drugs:

1- Deferiprone(L1) oral: 75 mg/kg. (better used combined with desferal)
Value: Reduce cardiac iron overload.
Side effects: - Neutropenia & polyarthropathy.
- Possible adverse redistribution of iron .

2- ICL-670 oral : As effective as desferal but with longer half life

- Monitoring? Check serum ferrittin /3-6 months.

3- Supportive treatment:

1- ↓ Iron in diet
2- Folic acid 1mg/day (prevent megaloblastic crisis).
3- Endorcine support as necessary.
4- Hepatitis B vaccine
5- Calcitonin (Miacalcin) and calcium carbonate for osteoporosis.
6- Cardiac support:
- L carnitine.
- Treat heart failure:diuretics,digoxin,desferal infusion 15 mg /kg/hr.

4- Splenectomy:

Indications:

- Hypersplenism suggested by:
  - Increasing need for transfusion by ≥50% than usual for more than 6 monthes.
  - Annual packed RBCs > 250 ml/kg/year in face of uncontrolled iron overload.
  - Severe leucopenia and / or thrombocytopenia.
- Huge spleen with pain or pressure symptoms.

When: Preferably after the **5th** year.

Risk : Overwhelming sepsis (esp. if done < 5 years)

Precautions:

- Two weeks before splenectomy → immunize the patient against:
  - Hemophilus influenzae
  - Pneumococci
  - Meningeococci
- After splenectomy → oral penicillin 250 mg twice daily till adulthood.

5- Recent treatment:

- ⊕ Hydroxyurea → induction of Hb F. → ↓unmatched α chain accumulation → ↓ hemolysis (of limited value due to serious side effects).
- ⊕ Bone marrow transplantation → best for patient less than 3 years.
- ⊕ Gene therapy is under research.

N.B : Tools for measurement of body iron

1. Serum ferritin
2. Hepatic iron concentration by biopsy (The gold standard tool ; but invasive)
3. Superconducting quantum interface device: SQUID (Noninvasive)
4. Magnetic resonance imaging

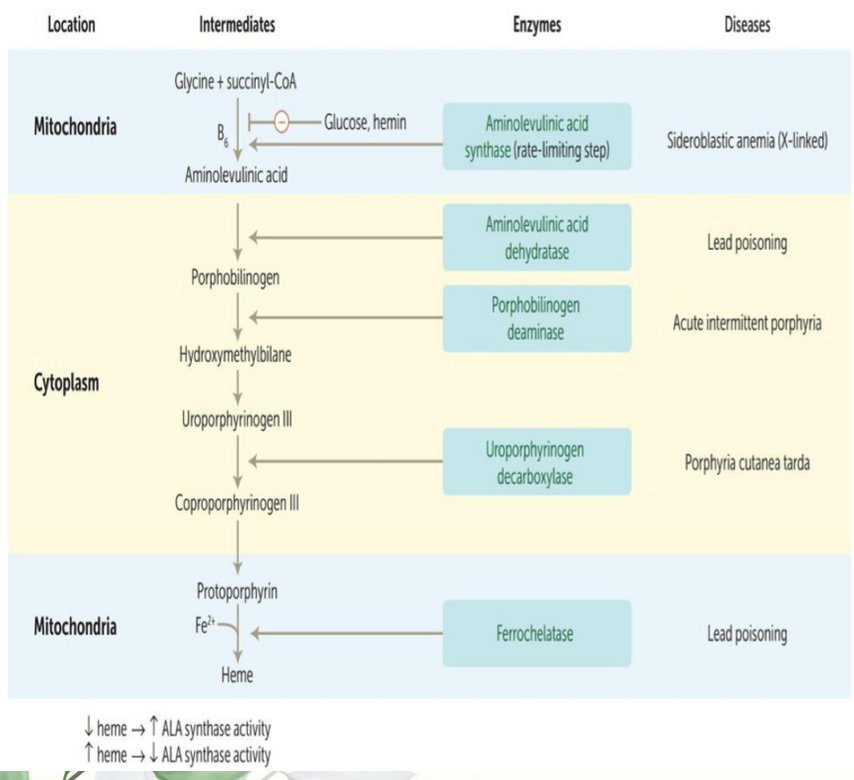
A3.Sideroblastic anemia

- Sideroblastic anemia is a microcytic anemia caused by a disorder in the synthesis of hemoglobin (defective protoporphyrin synthesis), characterized by trapped iron in the mitochondria of nucleated RBCs.
- Iron is transferred to erythroid precursors and enters the mitochondria to form heme. If protoporphyrin is deficient, iron remains trapped in mitochondria. Iron-laden mitochondria form a ring around the nucleus of erythroid precursors; these cells are called ringed sideroblasts (hence, the term sideroblastic anemia).
- Sideroblastic anemia can be congenital or acquired:

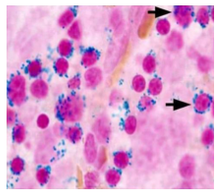
- Congenital defect most commonly involves ALAS (rate-limiting enzyme).
- Acquired causes include:
  - Alcoholism: mitochondrial poison.
  - Lead poisoning: inhibits ALAD and ferrochelatase.
  - Vitamin B6 deficiency: required cofactor for ALAS; most commonly seen as a side effect of isoniazid treatment for tuberculosis.

- Impaired heme synthesis → iron retention in mitochondria → ringed sidroblasts in RBCs precursors in bone marrow.
- High serum iron and ferrittin.
- May respond to vitamin B_6.

- Sideroblastic anemia is the only microcytic anemia in which serum iron is elevated.



- **Etiology**
  - Inherited: X-linked sideroblastic anemia due to a δ-ALA-synthase gene defect
  - Acquired
    - Vitamin B_6 deficiency
    - Lead poisoning
    - **Alcohol use disorder**
    - Drugs (e.g., chloramphenicol, isoniazid, linezolid)
    - Copper deficiency
    - Myelodysplastic syndrome
    - Malignancy
- **Diagnostics**
  - CBC: microcytic anemia
  - Serum iron studies
    - High ferritin
    - **High iron**
    - High transferrin saturation
    - Normal/low TIBC
  - Peripheral blood smear
    - Basophilic stippling of RBCs
    - Normocytes/macrocytes (more common in acquired etiologies)
  - **Prussian blue staining of bone marrow**: ringed sideroblasts



- **Treatment**
  - Cessation of the offending agent
  - Pyridoxine (B_6) supplementation (a cofactor for δ-ALA synthase)

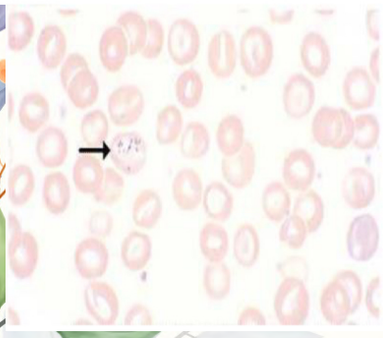
A4.Lead poisining

- Lead inhibits ferrochelatase and ALA dehydratase → ↓ heme synthesis.
- In the United States, lead poisoning (plumbism) is typically thought of as a pediatric condition (usually the result of children ingesting lead-containing paint chips).
- However, lead poisoning can occur in adults as well (especially those who work in battery manufacturing) who inhale particulate lead while working.
- Infants and toddlers are at high risk for foreign body ingestion as much of their normal play involves putting objects in their mouths. They are susceptible to lead poisoning if they live in a home built before 1978, especially if there is peeling paint or dust released during renovation. Other risk factors include lead piping, living near a battery recycling plant, having a parent who works with batteries or pottery, or having a playmate or sibling with a history of lead poisoning.
- Symptoms of LEAD poisoning:

- Lead Lines on gingivae (Burton lines) and on metaphyses of long bones on x-ray.
- Encephalopathy and Erythrocyte basophilic stippling.
- Abdominal colic and sideroblastic Anemia.
- Drops: wrist and foot drop.

- The classic diagnostic finding on peripheral blood smear is coarse basophilic stippling on a background of hypochromic microcytic anemia. Basophilic stippling results from the abnormal aggregation of ribosomes (lead inhibits rRNA degradation).
- Look for a child with recent loss of appetite, intermittent abdominal pain, vomiting, decreased hours of sleep at night, and withdrawal from school activities. Learning disabilities and behavioral problems are also common in children with lead poisoning.
- Targeted screening of high-risk populations is important, as most children with lead toxicity are initially asymptomatic but can have cognitive and behavioral problems that become apparent after school entry.
- The best initial test is a capillary blood finger-stick for lead level. The most accurate test is a serum venous blood level. Lead accumulates throughout the body, but measuring it in hair, teeth, bone, or urine is not recommended.
- The best initial step is to remove the child from the offending exposure.
- Depending upon the degree of lead poisoning, chelation therapy with dimercaprol or succimer may be indicated:

- Severe intoxication (>70 mcg/dL): IV dimercaprol/BAL.
- Moderate intoxication (45-69 mcg/dL): oral succimer as inpatient.
- Mild intoxication (<44 mcg/dL): outpatient follow-up and lifestyle change, which vary based on lead level.

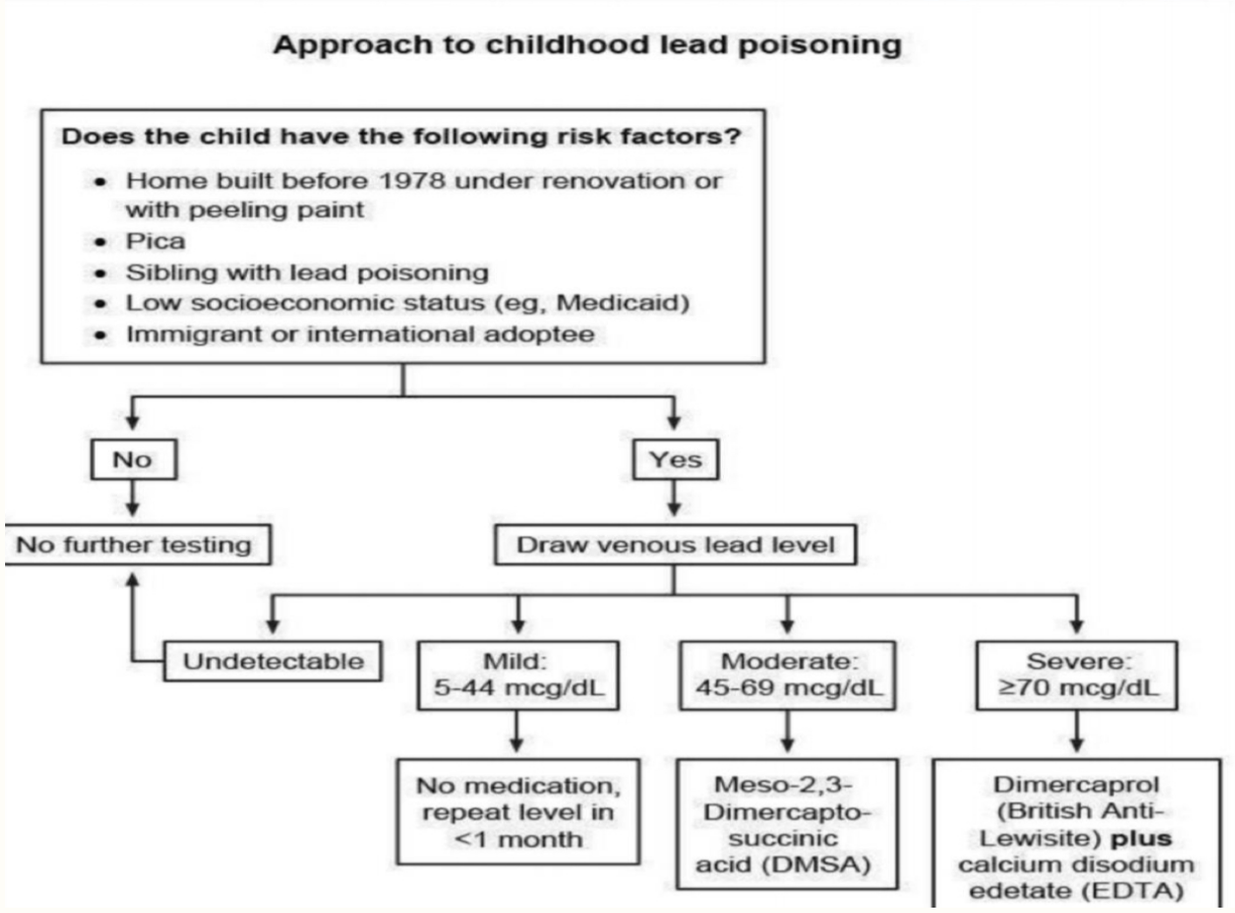




Wrist drop

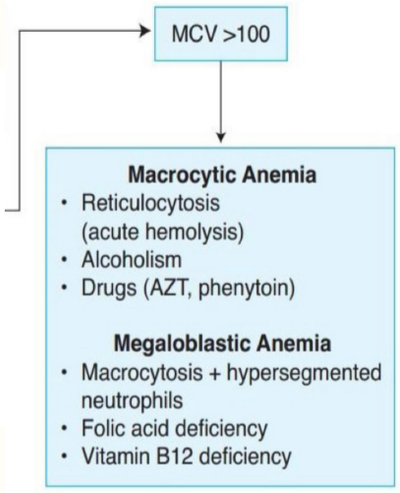


Burton line



B. Macrocytic Anemia

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- Although a macrocytic anemia could be from B12 or folate deficiency, direct alcohol effect on the bone marrow, or liver disease, the first step is a peripheral smear.
- This is to detect hypersegmented neutrophils. Once hypersegmented neutrophils are seen, then you would get B12 and folate levels (with a mean lobe count >4).
- Megaloblastic anemia is the presence of hypersegmented neutrophils. Many factors raise the MCV, but only B12 and folate deficiency and antimetabolite medications cause hypersegmentation.

B1.Vitamine B12 Deficiency

Summary

Vitamin B_{12} (cobalamin) plays an essential role in enzymatic reactions responsible for red blood cell (RBC) formation and proper myelination of the nervous system. Thus, a deficiency of vitamin B_{12} may lead to megaloblastic anemia and a wide range of neurological disturbances. Deficiency may be caused by malabsorption, malnutrition, or increased demand. The most common underlying cause of vitamin B_{12} deficiency is pernicious anemia, an autoimmune disorder characterized by the absence of intrinsic factor (IF). IF is a protein that is crucial for vitamin B_{12} absorption. Patients present with signs of anemia (e.g., fatigue) and/or neurological manifestations such as paresthesia, spasticity, ataxia, and neuropsychiatric disorders. After detecting low serum vitamin B_{12} levels, the diagnostic approach consists of identifying the underlying cause by measuring autoantibodies and possibly conducting a Schilling test. When testing patients with suspected vitamin B_{12} deficiency, it is important to remember that folate deficiency also causes megaloblastic anemia. However, only vitamin B_{12} deficiency can be accompanied by neuropathy and exhibits elevated levels of methylmalonic acid (MMA). Treatment consists of parenteral supplementation; depending on the underlying cause, long-term supplementation may be needed.

- Derived from cobalamin in food (animal sources). Humans cannot synthesize vitamin B_{12}.
- cobalamins → released by the acidity of the stomach → combine with R proteins and intrinsic factor (IF)→ traverse the duodenum→ pancreatic proteases break down the R proteins → IF-cobalamin absorbed in the distal ileum → In the plasma, cobalamin binds to transcobalamin II (TC-II)→carries to the liver, bone marrow, and other sites.
- TC-II enters cells by receptor-mediated endocytosis, and cobalamin is converted to active forms (methylcobalamin and adenosylcobalamin) important DNA synthesis.
- Plasma other two vitamin B_{12}-binding proteins, transcobalamin I and III have no specific transport role but are known to reflect vitamin B_{12} tissue stores.
- Almost all vitamin B_{12} in plasma is bound to TC-I and TC-III, and thus the measurement of serum B_{12} concentration reflects the storage of this vitamin.
- Older children and adults have sufficient vitamin B_{12} stores to last 3-5 yr.
- In young infants born to mothers with low vitamin B_{12} stores, clinical signs of cobalamin deficiency become apparent in the first 6-18 months of life.

ETIOLOGY:

- Inadequate dietary intake of vitamin (rare). is not common in kwashiorkor or infantile marasmus. Breast-fed infants whose mothers are vegans or themselves have pernicious anemia.
- Lack of IF secretion by the stomach. Congenital pernicious anemia is a rare autosomal recessive disorder due to an inability to secrete gastric IF or secretion of functionally abnormal IF.
- Impaired intestinal absorption of IF-cobalamin. inflammatory diseases such as regional enteritis or neonatal necrotizing entero-colitis, terminal ileum has been surgically removed.
- Absence of vitamin B_{12} transport protein. ranscobalamin II (TC-II) deficiency is a rare cause of megaloblastic anemia due to decreased utilization of cobalamin.

CLINICAL MANIFESTATIONS:

- weakness, fatigue, failure to thrive, or irritability.
- **pallor, glossitis, vomiting, diarrhea, and icterus.**
- **Neurologic symptoms include paresthesias, sensory deficits, hypotonia, seizures, developmental delay, developmental regression, and neuropsychiatric changes.**

LABORATORY FINDINGS:

- The hematologic manifestations of folate and cobalamin deficiency are identical.
- The neutrophils may be large and hypersegmented.
- neutropenia and thrombocytopenia can occur, simulating aplastic anemia or leukemia.
- Serum vitamin B_{12} levels are low
- Serum concentrations of METHYLMALONIC ACID AND HOMOCYSTEINE ARE ELEVATED.
- Concentrations of serum iron and serum folic acid are normal or elevated.
- Serum LDH activity is markedly increased a reflection of the ineffective erythropoiesis.
- Moderate elevations (2-3 mg/dL) of serum bilirubin levels also may be found.
- EXCESSIVE EXCRETION OF METHYLMALONIC ACID IN THE URINE (NORMAL AMOUNT <3.5 MG/24 HR) IS A RELIABLE AND SENSITIVE INDEX OF VITAMIN B_{12} DEFICIENCY.

- Diagnostic Tests:

- B12 and folate deficiency are identical hematologically and on blood smear.

- Laboratory abnormalities common to both B12 and folate deficiency are:
  - Megaloblastic anemia.
  - Increased LDH and increased indirect bilirubin levels.
  - Decreased reticulocyte count (Red cells are destroyed as they leave the marrow due to ineffective erythropoiesis).
  - Hypercellular bone marrow.
  - Macroovalocytes.
  - Increased homocysteine levels.

- Only B12 deficiency is associated with an increased methylmalonic acid level.

B12 deficiency: High LDH + High bilirubin + Low reticulocytes = Ineffective erythropoiesis

- USMLE Step 2 CK frequently tests the fact that while both B12 and folate deficiency increase homocysteine levels, only B12 is associated with an increased MMA. The B12 level can be normal in as many as a third of patients with B12 deficiency because the carrier protein, transcobalamin, is an acute phase reactant and can be elevated from many forms of stress such as infection, cancer, or trauma. When the story suggests B12 deficiency and the B12 level is equivocal, use an increased MMA level to confirm the diagnosis of vitamin B12 deficiency.

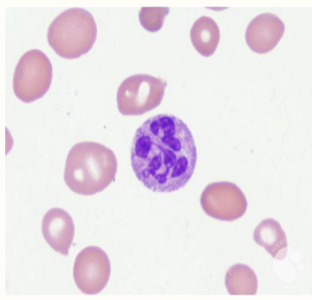
- Tested facts about macrocytic anemia:

- Schilling test is never the right answer. The Schilling test is rarely used to determine the etiology of vitamin B12 deficiency.

- Pernicious anemia is confirmed with anti-intrinsic factor and anti-parietal cell antibodies.

- B12 and folate deficiency can cause pancytopenia as well as macrocytic anemia.

- Neurological abnormalities will improve as long as they are minor (peripheral) and of short duration.



TREATMENT:

- parenteral administration of vitamin B_{12} (1 mg), usually with reticulocytosis in 2-4 days
- If there is evidence of neurologic involvement, 1 mg should be injected intramuscularly daily for at least 2 wk.
- Maintenance therapy is necessary throughout a patient's life; monthly intramuscular administration of 1 mg of vitamin B_{12} is sufficient.
- Oral not used due to uncertain absorption.

B2.Folate Deficiency

Summary

Folate (vitamin B_9) is an essential coenzyme that enables critical biochemical reactions. Dietary sources include naturally folate-rich foods such as leafy green vegetables, fruit and liver, but also supplements and fortified foods. Malnutrition and excessive alcohol use are the most common causes of deficiency. Folate deficiency causes impaired DNA synthesis, which leads to megaloblastic anemia. The clinical picture of anemia is similar to that of vitamin B_{12} deficiency, although folate deficiency is generally not associated with neurological manifestations. Diagnosis is based on laboratory findings such as macrocytosis, hyperhomocysteinemia, and normal levels of methylmalonic acid. Therapy consists of oral supplementation.

- Folates are abundant in many foods, including green vegetables, fruits, and animal organs (e.g., liver, kidney).
- Body stores of folate are limited, and mega-loblastic anemia occurs after 2-3 mo on a folate-free diet.
- megaloblastic anemia due to folate deficiency has its peak incidence at 4-7 mo of age
- affected infants with folate deficiency are irritable, have inadequate weight gain, and have chronic diarrhea.
- Folic acid deficiency accompany kwashiorkor, marasmus, or sprue.

Physiology

- **Folate**: coenzyme in single-carbon transfers and methylation reactions → DNA synthesis and amino acid metabolism [1]
  - Active form: tetrahydrofolate (THF), obtained after reduction of folate by dihydrofolate reductase
  - Sources
    - Leafy green vegetables, fruits, and liver
    - Fortified foods (e.g., bread, flour, and cereal)
  - Absorption: in the jejunum
  - Storage: liver (stores folate for up to three months, after which time signs and symptoms of deficiency begin to appear)

ETIOLOGY:

- decreased folate intake
- increased vitamin requirements (e.g., pregnancy, growth in infancy, chronic hemolysis).
  - ✓ The normal infant daily requirement is 25-35 µg/day.
  - ✓ Human breast milk, pasteurized cow's milk, and infant formulas provide adequate amounts of folic acid.
  - ✓ Goat's milk is deficient of folic acid supplementation
  - ✓ powdered milk also a poor source of folic acid.
  - ✓ Folate supplementation of at least 400 µg/day is recommended from the start of pregnancy to prevent neural tube defects
- Malabsorption due to chronic diarrheal states or diffuse inflammatory disease can lead to folate deficiency
- anticonvulsant drugs (e.g., phenytoin, primidone, phenobarbital)
- Megaloblastic anemia resulting from congenital dihydrofolate reductase deficiency .manifest in early infancy.

LABORATORY FINDINGS

- The anemia is macrocytic (mean corpuscular volume >100 fL).
- Variations in RBC shape and size are common.
- The reticulocyte count is low
- nucleated RBCs demonstrating megaloblastic morphology often are seen in the blood.
- Neutropenia and thrombocytopenia rarely may be present
- The neutrophils are large, some with hyper-segmented nuclei.
- Normal serum folic acid levels are 5-20 ng/mL; with deficiency, levels are <3 ng/mL.
- Levels of RBC folate are a better indicator of chronic deficiency. (n= 150-600 ng/mL of packed cells).
- Levels of iron and vitamin B_{12} in serum usually are normal or elevated.
- Serum activity of lactate dehydrogenase (LDH), a marker of ineffective erythropoiesis, is markedly elevated.
- The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamye-locytes) with cytoplasmic vacuolation also are seen.

- Macrocytic, megaloblastic anemia: ↑ MCV (> 100 μm^3)
- ↑ **Homocysteine**
- Methylmalonic acid **(MMA) is normal** (unlike in vitamin B_{12} deficiency, where MMA is ↑)
- Hypersegmented polymorphonuclear cells (PMNs)
- Folate serum levels are not reliable

If folate deficiency is suspected, always exclude the possibility of vitamin B12 deficiency.

TREATMENT

- Folic acid therapy (0.5-1.0 mg/day) should be continued for 3-4 wk until a definite hematologic response has occurred.
- Maintenance therapy with a multivitamin (containing 0.2 mg of folate) is adequate.
- folate >0.1 mg can correct the anemia of vitamin B_{12} deficiency but may aggravate any associated neurologic abnormalities.

To sum up:

Folate deficiency anemia	
Etiology	• Chronic hemolysis (eg, sickle cell disease) • Poor dietary intake • Malabsorption (eg, gastric bypass) • Medications (eg, methotrexate)
Clinical features	• Dyspnea, fatigue, pallor, weakness
Laboratory findings	• Macrocytic anemia • Poor reticulocyte response (low to normal) • Hypersegmented neutrophils • Low serum folate
Treatment	• Folic acid supplementation

To sum up megaloblastic anemia

Megaloblastic Anemia

Definition: Anemia with megaloblasts in BM and macrocytes in peripheral blood.

Causes: i- Vitamin B_{12} (cobalamin) deficiency ii- Folic Acid deficiency.

Pathogenesis

Folic acid & B_{12} are essential for DNA synthesis in stem cells of RBCs, platelets and WBCs.

so

nucleus can't devide ⇓ ↓ RBCs production

while RNA is normal ⇓ ↑↑ cytoplasm. ⇓ ↑ megalobasts in BM

macrocytes in blood ⇓ trapped in the spleen ⇓ extramedullary lysis

can't leave BM. ⇓ Intramedullary lysis

Metabolism

Vitamin B_{12}	Folic acid
Sources: animal origin only e.g. milk, meat.	- animal & plant (green leaves, fruits)
Requirements: 5-20 mcg./day	20-50 mcg./day
Absorption: gastric parietal cells release intrinsic factor (IF) which binds to B_{12} → B_{12}/IF complex then absorbed from terminal ileum	absorbed from proximal jejunum (need vitamin C)

Causes of B_{12} & folic acid deficiency

	Vitamin B_{12}	Folic acid
↓Intake	very rare except breast feeders of vegetarian mothers	❁ Uncommon; may occur in infants fed on: Goat's milk
↓ Absorption	1-Generalized malabsorption 2- Pernicious anemia: - congenital: no or abnormal IF - Juvenile: antibodies against IF & parietal cells. 3-B_{12} /IF consumption by Diphyllobothrium latum or bacterial overgrowth. 4- Ileal disease. Or resection	❁ same ❁ vit C deficiency ↓ Metabolism ❁cytotoxic drugs→ methotrexate ❁anticonvulsant → phenytoin → valproate
Others	Defective transport: transcobalamin II deficiency.	❁ increase requirements: e.g. - prematures (↓stores) - chronic hemolyis

Clinical picture

a. Anemia (Anorexia, pallor, ……..) with slight jaundice.

b. GIT manifestations esp. in folate deficiency:

- Red glazed tongue & glossitis.
- Abdominal pain and chronic diarrhea.

c. Neurologic manifestations: subacute combined degeneration (**SCD**)

- May occur Only with vitamin B_{12} deficiency:
  1- Posterior column degeneration → sensory ataxia
  2- Pyramidal tract degeneration → delayed motor milestones
  3- Peripheral Nerve degeneration → paraesthesia.

Investigations

1- Is it megaloblastic anemia?

- CBC: - Anemia → ⇓ ↓ Hb% & Ht value; Macrocytic, ⇓ MCV > 100 fl.; Normochromic ⇓ MCHC = normal
  - Hypersegmented neutrophils (contain 4-5 lobes; early finding).
  - WBCs and platelets moderately reduced in advanced cases.
- BM: - Megaloblastic

2- What is the cause?

I- Folic acid deficiency:

1- Low serum folic acid < 3 ng/ml (normal 5-20 ng/ml).
2- FIGLU test: oral load with histadine → ↑ FIGLU secretion in urine.

II- B12 deficiency:

1- Low serum vit B_{12} < 100 pg/ml.
2- Schilling test:
- Small amount of radioactive B_{12} is given orally
- 1 mg non radioactive B_{12} is given IM to saturate B_{12} binding proteins.
- Normally **10-30%** of oral B_{12} excreted in urine.
  - in B_{12} malabsorption → < 2% is excreted.
  - If the test is corrected by oral IF → consider IF deficiency.
  - If the test is not corrected by IF → consider ileal disease.

3- Others: Gastric function tests, IF antibodies, small bowel biopsy.

Treatment

1- Folic acid deficiency:

- Folic acid tablet 0.5 – 1 mg/day for 3-4 weeks.
- If diagnosis of folic acid deficiency is doubtful use smaller dose 0.1 mg/day for a week & look for reticulcytosis (therapeutic test).

(large dose of folic acid worsen neurologic manifestation of vitamin B_{12} deficiency)

2- Vitamin B12 deficiency:

1- Without SCD: B_{12} 1 mg IM monthly for life.
2- With SCD: B_{12} 1mg IM daily for 2 weeks then 1 mg IM monthly for life.

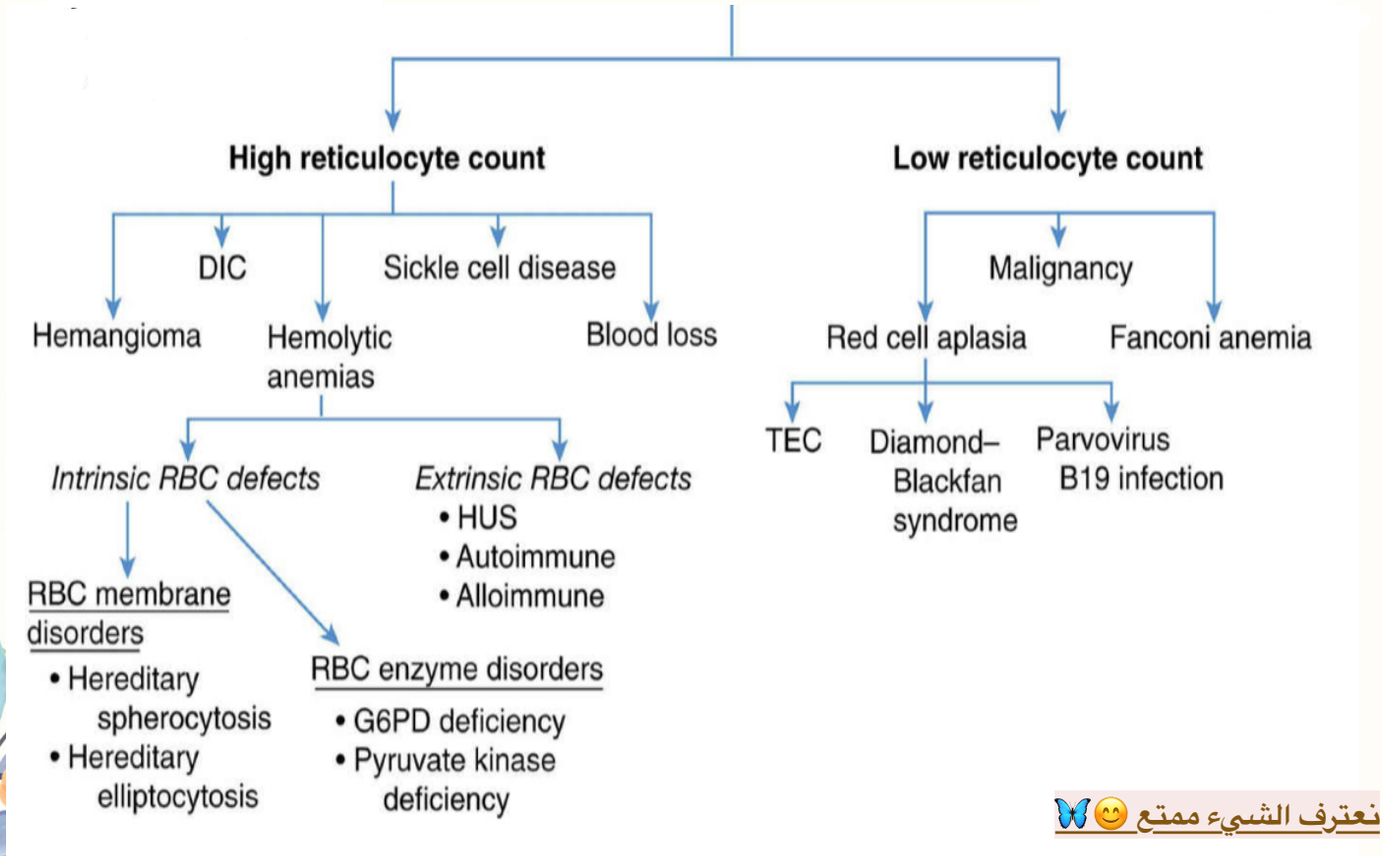
* With successful treatment ; reticulocytosis is seen in 2- 4 days

C. Normocytic anemia

- Anemia with normal-sized RBCs (MCV = 80-100).
- Due to increased peripheral destruction (hemolytic) or underproduction (nonhemolytic).
- Reticulocyte count helps to distinguish between these two etiologies.
- The hemolytic anemias are further classified according to the cause of the hemolysis (intrinsic vs extrinsic to the RBC) and by the location of the hemolysis (intravascular vs extravascular).

❖ Reticulocytosis:

- Normal reticulocyte count (RC) is 1-2%.
- RBC lifespan is 120 days; each day roughly 1-2% of RBCs are removed from circulation and replaced by reticulocytes.
- A properly functioning marrow responds to anemia by increasing the RC to >3%.
- RC, however, is falsely elevated in anemia.
- RC is measured as percentage of total RBCs; decrease in total RBCs falsely elevates percentage of reticulocytes.
- RC is corrected by multiplying reticulocyte count by Hct/45:
  - Corrected count > 3% indicates good marrow response and suggests peripheral destruction.
  - Corrected count < 3% indicates poor marrow response and suggests underproduction.



نعترف الشيء ممتع 😊🦋

In high reticulocyte count:

First/ Intrinsic RBC Defects(hemolytic Anemia)

C1. Hereditary Spherocytosis

Summary

Hereditary spherocytosis (HS) is the most common congenital hemolytic disorder among individuals of northern European descent. In most cases, it is an autosomal dominant disease that is caused by red blood cell (RBC) membrane protein defects, which render the RBCs more vulnerable to osmotic stress and hemolysis. Clinical presentation ranges from mild HS, which is generally asymptomatic, to severe HS, which can already present in utero with hydrops fetalis. Moderate HS, which is the most common form, usually presents in infancy or childhood with the classic triad of anemia, jaundice, and splenomegaly. Diagnosis is established based on family history, typical laboratory findings (e.g., elevated mean corpuscular hemoglobin concentration and RBC distribution width), and tests (e.g., eosin-5-maleimide binding test, osmotic fragility test). Treatment depends on the severity of the disease and involves acute measures (e.g., red blood cell transfusions, phototherapy), medication (e.g., folic acid supplementation), and splenectomy. HS patients are also at risk for complications such as hemolytic and aplastic crises, megaloblastic anemia, and gallstone formation.

1. **Hereditary spherocytosis** is the **most common inherited abnormality of the RBC membrane** and occurs predominantly in persons of Northern European ancestry. There is a large spectrum of phenotypes, with some patients who are largely asymptomatic and others who are transfusion-dependent starting in infancy.

Pathogenesis

* Autosomal dominant disorder
* Due to deficiency of red cell wall skeleton protein "Spectrin or Ankyrin" → ↑ cell wall permeability to Na^+ → ↑ intracellular Na^+ influx.

↑water content inside RBCs → Cells become spherical with rigid cell wall

Over work of Na/k pump to keep Na out the cell (↑ ATP & glucose consumption) → premature RBCs aging

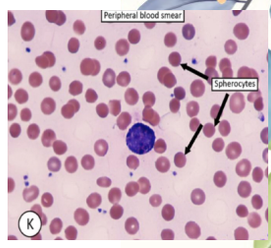
→ RBCs are trapped & destroyed in the spleen.

Clinical picture

* Positive family history usually present (may be absent)
1- Features of anemia
2- Features of chronic hemolysis
} starting early in life; 50% present by neonatal anemia and jaundice.
3- Gall stones occur in 50% of unsplenctomized cases by 4-5 years

Investigations

1. For **anemia** → ↓Hb% and ↓Ht value(usually normocytic , hyperchromic anemia)
   → Most patients have mild anemia with hemoglobin level of 9-12 g/dl
2. For **chronic hemolysis** → ↓ RBCs survival & ↑ erythropioesis.
3. For **the cause:**
   a. Blood film → RBCs are small, rounded without central pallor = spherocytes.
   b. Osmotic fragility test: There's increased osmotic fragility of RBCs
      * Idea of the test:
        - Normally exposure of RBCs to hypotonic solutions cause it to swell and rupture
        - Spherocytes (already swollen cells) lyse more readily than normal biconcave cells in hypotonic solutions
      * Red cell lysis is accentaued by depriving cells of glucose for 24 hours at 37 ^{0}C (Incubated osmotic fragility test) which is more characterstic
   c. Recent; more sensitive tests: Cryohemolysis test &osmotic gradient ektacytometry
   d. Negative Coomb s test (rules out auto immune hemolytic anemia)



COMPLICATIONS:

- Aplastic anemia: viral induced, parvovirus 19 __> severe anemia, low retic, pancytopenia (marrow failure.
- Hyper-hemolysis: by viral illnesses, severe anemia, without marrow failure.
- Megaloblastic anemia: decrease folic acid intake with increase requirement as in all hemolytic diseases. So 1mg/day folic acid is recommended.
- Gallstones: in adolescence & adulthood but can occur as early as 3 years of age.
  ✓ incidence: 5%<10yrs, 40-50% 10-40 yrs, 55-75% >40yrs.
- Others related to anemia: delayed growth and sexual development, frontal bossing & craniofascial features.

Treatment

1- Supportive → folic acid 1mg/day (till splenectomy is done).
2- Slight anemia (Hb > 10 gm/dl and reticulocytic count < 10%) → No treatment.
3- Severe anemia need packed red cells transfusions.
4- Splenectomy:
* **Indication? → Severe anemia with frequent crises, poor growth or cardiomegaly**
* **Value? Clinical cure → prevent hemolysis, crises and gall bladder stones**
* **Timing , precautions and complications ? → See Thalasemia**

🦋.To sum up:

- Before 6 yrs:
  ✓ Only 1 mg/day folic acid with regular follow up: anemia,growth,activity.
  ✓ Partial splenectomy useful in children younger than age 5 yr
- After 6 yrs:
  ✓ according to the severity : splenectomy with response rate 100%
  ✓ Do not recommend splenectomy for patients whose hemoglobin values exceed 10 g/dL and whose reticulocyte percentage is <10%.
  ✓ gallstone is an indication for splenectomy
  ✓ Post-splenectomy: increase Hb, spherocytes & holly jolly bodies, decrease retic, osmotic fragility improves, increase possibility of sepsis.
  ✓ TO REDUCE SEPSIS: pneumococcal, H influenza, meningococcal vaccination at least 2 weeks before splenectomy, prophylactic antibiotic at least 5 years (up to 18 yr of age), splenectomy not before 5 yr old.
  ✓ If no improvement after splenectomy: accessory spleen, so do abdUS before.

Hereditary spherocytosis	
Epidemiology	• Usually autosomal dominant • Northern European descent
Clinical presentation	• Hemolytic anemia • Jaundice • Splenomegaly
Laboratory findings	• ↑ MCHC • Negative Coombs test • Spherocytes on peripheral smear • ↑ Osmotic fragility on acidified glycerol lysis test • Abnormal eosin-5-maleimide binding test
Treatment	• Folic acid supplementation • Blood transfusion • Splenectomy

MCHC = mean corpuscular hemoglobin concentration.

C2.Hereditary elliptocytosis

2. **Hereditary elliptocytosis** is another **autosomal dominant** defect in the structure of **spectrin** that may or may not result in hemolysis. Clinical features are more variable than in hereditary spherocytosis. The **majority of patients are asymptomatic,** although 10% have jaundice at birth, and later may develop splenomegaly and gallstones. **Elliptical RBCs** are found on blood smear in older children. Treatment includes splenectomy for patients with severe chronic hemolysis. No treatment is needed for patients who have well-compensated hemolysis.

Elliptocytes (ovalocytes)	• Oval or elliptical	• **Hereditary elliptocytosis**: caused by mutations in genes encoding RBC membrane proteins (e.g., spectrin, protein 4.1); usually asymptomatic • May also be seen in thalassemia, myelofibrosis, and iron deficiency anemia.

C3.Paroxysmal nocturnal hemoglobinuria

Summary

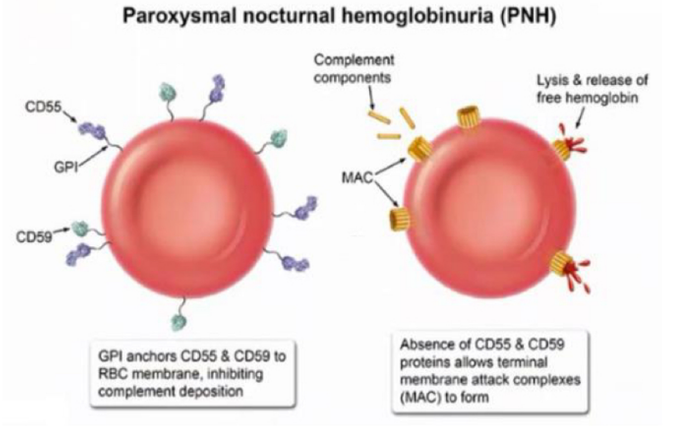
Paroxysmal nocturnal hemoglobinuria (PNH) is a hemolytic anemia caused by an acquired defect of the phosphatidylinositol glycan anchor (PIGA) gene, which leads to dysfunction of a red cell membrane protein (glycosylphosphatidylinositol) that is normally responsible for protecting RBCs from complement-mediated destruction. PNH can present with clinical features of hemolysis (particularly signs of anemia and episodic hemoglobinuria), systemic vasoconstriction, venous thromboemboli, and pancytopenia. It can also occur in patients with aplastic anemia or myelodysplastic syndrome. Diagnostics typically reveal laboratory signs of hemolysis with a negative direct Coombs test (DAT), and PNH can be confirmed using flow cytometry of peripheral blood. Management ranges from watchful waiting and supportive care to targeted anti-C5 antibody therapy (e.g., eculizumab, ravulizumab) for patients with significant clinical manifestations. Notable complications include Budd-Chiari syndrome, infections, and acute leukemia.

- Etiology:

- Acquired defect in myeloid stem cells resulting in absent glycosyl phosphatidyl inositol (GPI); a glycolipid necessary for the attachment of several cell-surface proteins, including CD55 (decay-accelerating factor) and CD59 (MAC inhibitory protein).

- These proteins normally inhibit the activation of complement on red blood cells, but their absence allows the complement membrane attack complex to form and results in hemolysis.

- Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal stem cell defect with increased sensitivity of red cells to complement in acidosis.



- Presentation/"What Is the Most Likely Diagnosis?"

- Intravascular hemolysis occurs episodically, often at night during sleep. Mild respiratory acidosis develops with shallow breathing during sleep and activates complement.

- Pancytopenia (RBCs, WBCs, and platelets are also lysed).

- Clots in unusual places (not just DVT or pulmonary embolism).

- Thrombosis is the most common cause of death (Destroyed platelets release cytoplasmic contents into circulation, inducing thrombosis).

- Large vessel thrombosis of the mesenteric and hepatic veins is the most common site of thrombosis.

- Suspect PNH in patients with hemolytic anemia, a hypercoagulable state, and pancytopenia.

- Complications include iron deficiency anemia (due to chronic loss of hemoglobin in the urine) and acute myeloid leukemia (AML), which develops in 10% of patients.

- Diagnostic Tests:

- CBC often shows pancytopenia in addition to anemia.

- The most accurate test is a decreased level of CD55 and CD59.

- The Ham test and the sucrose hemolysis test are obsolete. Flow cytometry is another way of saying CD55/CD59 testing.

- Treatment:

- Prednisone is the best initial therapy for hemolysis. The mechanism is not clear.

- Allogeneic bone marrow transplant is the only method of cure.

- Eculizumab inactivates C5 in the complement pathway and decreases red cell destruction. Complement overactivation is the mechanism of PNH. Eculizumab is, essentially, a complement inhibitor. Eculizumab is for hemolysis and thrombosis.

- Give meningococcal vaccine prior to eculizumab.

- Give folic acid and iron supplementation.

To Sum Up:

Clinical features of paroxysmal nocturnal hemoglobinuria	
Clinical manifestations	• Hemolysis → fatigue • Cytopenias (impaired hematopoiesis) • Venous thrombosis (intraabdominal, cerebral veins)
Workup	• Complete blood count (**hypoplastic/aplastic anemia,** thrombocytopenia, leukopenia) • Elevated lactate dehydrogenase & low haptoglobin (hemolysis) • Indirect hyperbilirubinemia • Urinalysis (**hemoglobinuria**) • Flow cytometry (**absence of CD55 & CD59**)
Treatment	• Iron & folate supplementation • **Eculizumab** (monoclonal antibody that inhibits complement activation)

C3.Glucose-6-phosphate dehydrogenase deficiency.

Summary

Glucose-6-phosphate dehydrogenase (G6PD) deficiency leads to an impaired regeneration of reduced glutathione, an important antioxidant, which makes RBCs more susceptible to oxidative stress and can result in episodic hemolytic anemia. The condition is inherited in an X-linked recessive pattern and is the most common human enzyme deficiency worldwide. It primarily affects males of African, Asian, and Mediterranean descent. G6PD deficiency is usually asymptomatic, but a sudden surge in oxidative stress (e.g., after infection, consumption of fava beans, or various drugs) may lead to a life-threatening hemolytic crisis. Diagnostic findings include signs of intravascular hemolysis (e.g., normocytic anemia, ↑ LDH, and ↓ haptoglobin), Heinz bodies, and bite cells on blood smear. Management mainly consists of preventing hemolysis by avoiding triggers.

Pathophysiology

- **X-linked recessive** inheritance
- **G6PD** is the **rate-limiting enzyme** of the **pentose phosphate pathway** (also known as the hexose monophosphate shunt). This pathway yields NADPH, which is essential for converting **oxidized glutathione** back to its reduced form. Reduced **glutathione** is capable of neutralizing reactive oxygen species (ROS) and free radicals and therefore protecting RBCs from oxidative damage.
- In the absence of **reduced glutathione** (e.g., due to G6PD deficiency), RBCs become susceptible to oxidative stress that can damage erythrocyte membranes, resulting in **intravascular and extravascular hemolysis**.
- Causes of increased oxidative stress are triggers of hemolytic crisis and include:
  - **Fava beans**
  - Drugs: **antimalarial drugs** (e.g., chloroquine, primaquine), **sulfa drugs** (e.g., trimethoprim-sulfamethoxazole), nitrofurantoin, isoniazid, dapsone, NSAIDs, ciprofloxacin, chloramphenicol
  - Bacterial and viral **infections** (most common cause): Severe enzymatic deficiency can **inhibit respiratory burst** activity due to reduced NADPH production in phagocytes.
  - Inflammation: During an inflammatory reaction free radicals are produced and can diffuse into RBCs.
  - Metabolic acidosis

- Etiology:

- Glucose 6 phosphate dehydrogenase (G6PD) deficiency is an X-linked recessive disorder leading to an inability to generate glutathione reductase and protect the red cells from oxidant stress.

- This renders RBC's susceptible to oxidative stress:
  - RBCs are normally exposed to oxidative stress, in particular H_2O_2.
  - Glutathione (an antioxidant) neutralizes H_2O_2 but becomes oxidized in the process.
  - NADPH, a by-product of G6PD, is needed to regenerate reduced glutathione.
  - ↓ G6PD → ↓ NADPH → ↓ reduced glutathione → oxidative injury by H_2O_2 → intravascular hemolysis.
  - Without G6PD, hemoglobin becomes oxidized and denatures into Heinz bodies.
  - The denatured hemoglobin disrupts red blood cell (RBC) membranes and causes hemolysis.
- The most common oxidant stress is infection. Other causes are dapsone, quinidine, sulfa drugs, primaquine, nitrofurantoin, and fava beans.

- G6PD deficiency has two major variants:
  - African variant: mildly reduced half-life of G6PD leading to mild intravascular hemolysis with oxidative stress.
  - Mediterranean variant: markedly reduced half-life of G6PD leading to marked intravascular hemolysis with oxidative stress.

- "What Is the Most Likely Diagnosis?"

- Because G6PD deficiency is X-linked recessive, it manifests almost exclusively in men.

- Look for African American or Mediterranean men with sudden anemia and jaundice who have a normal-sized spleen with an infection or are using one of the drugs previously listed.

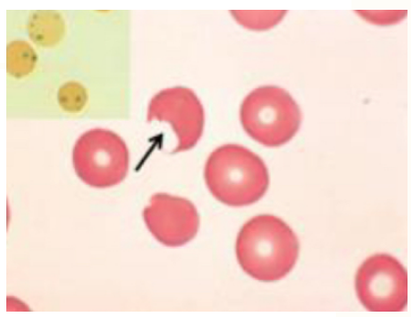
Clinical picture

A. Acute hemolytic anemia:

- Features of acute hemolysis without organomegaly(*see before*).
- Occur 24- 48 hours after exposure to the oxidants.
- Degree of hemolysis varies with triggering agent, amount ingested and severity of enzyme deficiency
- Episodes usually brief as newly produced young RBCs have higher enzyme activity (more abundant and stable)
- May occur in neonatal peroid → neonatal anemia & jaundice.

B. Chronic non spherocytic hemolytic anemia:

- Extremely rare.
- Pallor, tinge of jaundice & mild splenomegaly.



Investigations

1. For **anemia** → Low Hb% and Ht value.
2. For **acute hemolysis** → ↓ RBCs survival & ↑ Erythropiosis.
3. For **the cause:**
   - Blood film → Fragmented RBCs
     → Heinz bodies (intracellular inclusion bodies).
   - Enzyme assay → done **2-3** months after the attack (during the attack, bone marrow produce juvenile RBCs with higher enzymatic activity which may give false normal results).

Treatment

i. Prophylactic:

- Avoid oxidant food & drugs.
- Anti oxidant → vitamin E.
- Anti pyretics in fever → paracetamol or ibubrufen.

ii. During the attack:

- Stop the oxidant agent.
- Packed RBCs transfusion (5-10 ml/kg) → can be repeated in severe attack.

Features of Glucose-6-Phospate Dehydrogenase (G6PD) Deficiency

Epidemiology	Mediterranean, Arabic, Asian, and African ethnic groups
Pathophysiology	G6PD enzyme is critical for protecting the RBC from oxidative stress; deficiency results in RBC damage when the RBC is exposed to oxidants
Triggers of hemolysis	Infection Fava beans Drugs (e.g., sulfa, salicylates, antimalarials)
Clinical features	Symptoms occur 24–48 hours after exposure to oxidant Hemolysis occurs, resulting in abdominal pain, V/D, fever, and hemoglobinuria followed by jaundice; HSM may be present
Laboratory findings	Hemoglobinuria Elevated reticulocyte count Smear shows "bite" cells, "hemighosts" and Heinz bodies
Diagnosis	Low levels of G6PD in RBCs
Treatment	Transfusions as needed; splenectomy is not beneficial

MEDICATIONS THAT TRIGGER HEMOLYSIS IN G6PD DEFICIENCY

Medications that often trigger hemolysis in G6PD deficiency	
Avoid	• Diaminodiphenyl sulfone (dapsone) • Isobutyl nitrite • Nitrofurantoin • Primaquine • Rasburicase
Use with caution	• Acetaminophen • Acetylsalicylic acid (aspirin) • Chloramphenicol • Chloroquine • Colchicine • Diphenhydramine (Benadryl) • Glyburide • Isoniazid • L-dopa • Quinine • Sulfamethoxazole • Trimethoprim • Vitamin K

G6PD = glucose-6-phosphate dehydrogenase.

To Sum up:

Glucose-6-phosphate dehydrogenase deficiency	
Epidemiology	• Hemolytic anemia due to oxidative stress (infection, sulfa drugs, fava beans) • X-linked: Asian, African, or Middle Eastern descent
Manifestations	• Pallor & fatigue • Dark urine, jaundice & icterus • Abdominal/back pain
Laboratory findings	• Hemolysis: ↓ hemoglobin, ↓ haptoglobin, ↑ bilirubin & LDH • Peripheral smear: bite cells & Heinz bodies • Negative Coombs test • ↓ G6PD activity level (may be normal during attack)
Management	• Remove or treat responsible agent/condition • Provide supportive care

LDH = lactate dehydrogenase; **G6PD** = glucose-6-phosphate dehydrogenase.

C4.Pyruvate Kinase deficiency

- **Etiology**: autosomal recessive defect of pyruvate kinase
- **Pathophysiology**
  - Glucose is the only energy source in RBCs
  - Pyruvate kinase catalyzes the last step of glycolysis (i.e., irreversibly converts phosphoenolpyruvate into pyruvate)
  - Absence of pyruvate kinase → **ATP deficiency in RBC**
  - ATP deficiency disrupts the cation gradient along the RBC membrane → rigid RBCs → ↑ hemolysis (extravascular)
  - Accumulation of 2,3-bisphosphoglycerate → ↑ release of O_2 from Hb → masks symptoms of anemia
- **Clinical symptoms**
  - Seldom asymptomatic
  - Typically newborn jaundice due to hemolysis and history of exchange transfusions
  - Splenomegaly
  - Pallor, fatigue, weakness
  - In rare cases: hydrops fetalis
- **Diagnosis**
  - ↓ Pyruvate kinase enzyme activity
  - PKLR gene mutation
  - Blood smear: burr cells
- **Therapy**
  - **Phototherapy** and/or **exchange transfusions**
  - In the case of severe anemia or excessively enlarged spleen: **splenectomy**

Second/Extrinsic RBCs Defect(Hemolytic Anemia)

C5. Autoimmune Hemolytic Anemia

Summary

Autoimmune hemolytic anemias (AIHAs) are a collection of disorders characterized by the destruction of RBCs through antibody-mediated hemolysis (extravascular and/or intravascular). There are two broad types, categorized by the temperature at which the antigen-antibody reactions maximally occur: cold agglutinin hemolytic anemia (cold AIHA) and warm agglutinin hemolytic anemia (warm AIHA). AIHAs can be either idiopathic or secondary to another disease e.g., infectious, lymphoproliferative, or autoimmune diseases. Cold AIHA and warm AIHA share some characteristics, e.g., they can both present with clinical signs of anemia and laboratory signs of hemolysis, and produce symptomatic anemia severe enough to require blood transfusion. However, their pathophysiology, etiology, epidemiology, clinical and diagnostic features, and targeted treatments all have key differences. Careful clinical and diagnostic evaluation (including direct Coombs testing, antibody titers, and peripheral blood smear) can help distinguish between the types, however, occasionally patients may have a mixed-type AIHA or unusual clinical presentations and laboratory findings. Management depends on the clinical presentation, etiology, and subtype, and is typically performed in consultation with a hematologist. Treatments include stabilization with blood transfusion and temporizing measures (e.g., plasmapheresis, plasma exchange), systemic immunomodulators (e.g., glucocorticoids, rituximab), treatment of underlying conditions, supportive care, and in warm AIHA, splenectomy.

1. **Autoimmune hemolytic anemia (AIHA)** occurs when **antibodies are misdirected against the RBCs.**
    a. **Etiology**

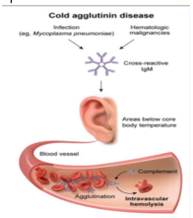
1. **Primary AIHA** is generally **idiopathic** in which no underlying disease is identified. Viral infections and occasionally drugs may be causal in some patients.
2. **Secondary AIHA** is associated with an **underlying disease process,** such as lymphoma, systemic lupus erythematosus (SLE), or immunodeficiency.

Clinical types: According to type of antibodies

	Warm antibodies	Cold antibodies
Causes:		
• Idiopathic	• Idiopathic	• Idiopathic
• Secondary to:		
- Infection	- Cytomegalo virus, Hepatits B virus.	- Mycoplasma, Ebstein Barr virus.
- Vaccination	- DPT, MMR	- MMR
- Disease:	- Lymphoma.	- Lymphoma
	- Systemic lupus erythmatosis	
- Drugs	- Aldomet, penicillin.	
Criteria of Antibodies	- IgG. - active at 37°C	- IgM - active below 37°C

Autoimmune (Warm or IgG mediated) Hemolysis

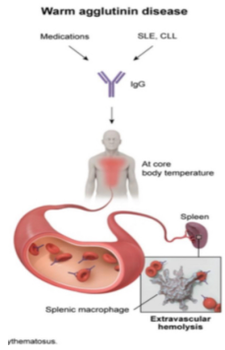
- Etiology:
- Various forms of acquired hemolytic anemias can result from the production of IgG, IgM, or activation of complement C3 against the red cell membrane. They are often sudden and idiopathic.
- Fifty percent of cases have no identified etiology. Clear causes are:
    - Chronic lymphocytic leukemia (CLL).
    - Lymphoma.
    - Systemic lupus erythematosus (SLE).
    - Drugs: penicillin, alpha-methyldopa, rifampin, phenytoin.



- Diagnostic Tests:
- The most accurate diagnostic test is the Coombs test, which detects IgG antibody on the surface of the red cells.
- The direct and indirect Coombs tests tell basically the same thing, but the indirect test is associated with a greater amount of antibody.
- Autoimmune hemolysis is also associated with spherocytes.
- Autoantibodies remove small amounts of red cell membrane and lead to a smaller membrane, forcing the cell to become round. Biconcave discs need a greater surface area than a sphere. Autoimmune hemolysis is associated with microspherocytes.
- Treatment:
- Glucocorticoids such as prednisone are the "best initial therapy" to decrease autoantibody production.
- Recurrent episodes respond to splenectomy.
- Severe, acute hemolysis not responding to prednisone is controlled with intravenous immunoglobulin (IVIg).
- Alternative treatments to diminish the need for steroids in general are: Cyclophosphamide, Cyclosporine, Azathioprine and Mycophenolate mofetil.

Autoimmune (Cold or IgM mediated) Hemolysis

- Definition/Etiology:
- Cold agglutinins are IgM antibodies against the red cell developing in association with Epstein-Barr virus, Mycoplasma pneumoniae, or Waldenstrom macroglobulinemia.
- Cold agglutinin destruction occurs predominantly in the liver. Liver-mediated destruction is not affected by steroids.
- Presentation:
- Symptoms occur in colder parts of the body such as numbness or mottling of the nose, ears, fingers, and toes.
- Symptoms resolve on warming up the body part.
- Diagnostic Tests:
- The direct Coombs test is positive only for complement.
- Cold agglutinin titer is the most accurate test.
- The smear is normal or may show only spherocytes.
- Treatment:
- Keep the patient warm.
- Administer rituximab and sometimes plasmapheresis.



- Steroids and splenectomy don't work well with cold agglutinin disease because the destruction occurs in the liver. You need to control the lymphocytes which control the production of IgM.
- Cyclophosphamide, cyclosporine, or other immunosuppressive agents stop the production of the antibody.
- Cryoglobulins are often mixed up with cold agglutinins. Although both are IgM and do not respond to steroids, cryoglobulins are associated with:
    - Hepatitis C.
    - Joint pain.
    - Glomerulonephritis.

Clinical picture

i- AIHA due to warm antibodies:

1- Acute transient type	2- Chronic type
- in child 2-12 year. - may follow respiratory infection. - acute hemolytic anemia with splenomegaly. - respond to steroids → recover within 3 months.	- in child < 2 or > 12 years - may be underlying systemic disease e.g. lymphoma. - chronic hemolytic anemia. - variable response to steroids.

ii- AIHA due to cold antibodies:

1- Cold agglutinin disease:

⇒ Cold antibodies may present with low titre

↓

infection with mycoplasma or Ebstein Barr virus.

↓

↑↑ antibody titre $\xrightarrow[\text{cold}]{\text{exposure to}}$ acute hemolytic anemia

2- Paroxysmal cold hemoglobinuria:

- Due to Donath landsteiner antibody (IgG which can activate complement)
- Association: 1- infection with mycoplasma , Ebstein Barr virus,Cytomegalo virus
  2- Congenital or acquired syphilis.
- Course: Mild, resolve with infection resolution.

Investigations

i- For **anemia** → Low Hb % & ↓ Ht value.

ii- For **acute hemolysis.**
iii- For **chronic hemolysis** } ↓ RBCs survival & ↑ erythropioesis

iv- For **the cause.**

1- CBC: - Micro spherocytes.
- AIHA plus autoimmune thrombocytopenia → **Evan's Syndrome.**

2- Coombs test.
- Direct: Detects high titre of autoantibodies coating the RBCs
- Indirect: Detects the free autoantibodies in patient serum

Complications

- Anemia may be severe enough to cause cardiovascular collapse
- Severe intra vascular hemolysis may be associated with DIC
- Complications of associated underlying disease e.g. Systemic lupus erythmatosis and immunodeficeincy

Treatment

1- Treat the underlying cause and avoid exposure to cold.

2- Blood transfusion:
- Value: Correct severe anemia.
- Use: Small volume of packed RBCs starting with a test dose.
- Disadvantage:- hard to find totally compatible blood.
  - transient effect.

3- Steroids: - Effective in warm type.
- Dose 2 - 4 mg/kg/d
- Larger dose (6 mg/kg) may be needed to control hemolysis.

4- Plasmapharesis: effective in severe cold type.

5- I.V. immunoglobulin 1 gm/kg for 2 days

6- Splenectomy for resistant warm type cases.

7- Cyclosporin A and Monoclonal antibodies which target B lymphocytes.

To sum up:

Autoimmune hemolytic anemia		
	Warm agglutinin AIHA	**Cold agglutinin AIHA**
Etiology	• Drugs (eg, penicillin) • Viral infections • Autoimmune (eg, SLE) • Immunodeficiency states • Lymphoproliferative (eg, CLL)	• Infections (eg, *Mycoplasma pneumoniae* infection & infectious mononucleosis) • Lymphoproliferative diseases
Clinical presentation	• Asymptomatic to life-threatening anemia • Direct Coombs' positive with anti-**IgG**, anti-C3, or both	• Symptoms of anemia • Livedo reticularis & acral cyanosis with cold exposure that disappear with warming • Direct Coombs' positive with anti-C3 or anti-**IgM**, but usually not IgG
Treatment	• Corticosteroids • Splenectomy for refractory disease	• Avoidance of cold temperatures • Rituximab +/- fludarabine
Complications	• Venous thromboembolism • Lymphoproliferative disorders	• Ischemia & peripheral gangrene • Lymphoproliferative disorders

C6.Alloimmune hemolytic Anemia

2. **Alloimmune hemolytic anemia** occurs when **antibodies from someone else are directed at the patients' RBCs** and is most commonly caused by newborn Rh and ABO hemolytic diseases.
    a. **Rh hemolytic disease** occurs when the mother, who has no Rh antigen (maternal Rh negative), produces antibodies to the Rh antigen on her fetus's RBCs (fetal Rh positive). In **subsequent pregnancies,** antibodies pass from the mother to the fetus causing hemolysis that presents as severe jaundice (which can lead to kernicterus), anemia, hepatosplenomegaly, and **hydrops fetalis.** A direct Coombs test is **strongly positive.**
    b. **ABO hemolytic disease** occurs when the mother is blood group O and her fetus is blood group A, B, or AB. The mother produces antibodies to either the A or B blood group antigen that then pass to the fetus, causing hemolysis with resultant jaundice. A direct Coombs test is **weakly positive.** Of note, **ABO disease can occur in the first pregnancy, unlike Rh hemolytic disease.**
    c. **Management.** Treatment may include phototherapy for mild to moderate jaundice and exchange transfusion for severe jaundice.

C7.Hemolytic Uremic Syn.(HUS)and TTP

Summary

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy in which microthrombi, consisting primarily of platelets, form and occlude the arterioles and capillaries. These occlusions result in the simultaneous occurrence of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI). HUS predominantly affects children and is caused by bacterial toxins, most commonly the Shiga-like toxin of enterohemorrhagic Escherichia coli (E. coli) O157:H7. If there is a strong suspicion of HUS based on clinical presentation and initial laboratory tests, treatment should begin immediately, as the condition may result in renal failure. Patients receive symptomatic treatment for renal symptoms, anemia, and complications affecting other organs, such as the brain and GI tract.

Etiology

- **Bacterial exotoxins** [2]
  - **Shiga-like toxin** (verotoxin)
    - From enterohemorrhagic E. coli (EHEC) strain **O157:H7**
    - Usually transmitted via contaminated foods (e.g., undercooked beef or raw leafy vegetables)
  - **Shiga toxin** produced by **Shigella dysenteriae**
- **Streptococcus pneumoniae infection**
- **Atypical hemolytic uremic syndrome**: Complement dysregulation (hereditary or acquired) accounts for approx. 5% of HUS cases with noninfectious etiologies, referred to as atypical HUS (aHUS). [3]

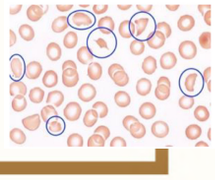
Approx. 15% of children infected with E. coli O157:H7 will go on to develop HUS.

Pathophysiology

HUS is a **thrombotic microangiopathy**, a condition characterized by the formation of microthrombi occluding the microvasculature. The other main thrombotic microangiopathy is thrombotic thrombocytopenic purpura (TTP). The two conditions have some pathophysiology and clinical findings in common, but different etiologies. HUS is caused by bacterial toxins. [4]

1. Infection with **enterohemorrhagic E. coli** (EHEC) or another causative organism
2. Mucosal inflammation facilitates bacterial toxins entering systemic circulation.
3. Toxins cause **endothelial cell damage** (especially in the glomerulus).
4. Damaged endothelial cells secrete cytokines that promote vasoconstriction and platelet microthrombus formation at the site of damage (**intravascular coagulopathy**) → thrombocytopenia (consumption of platelets)
5. RBCs are mechanically destroyed as they pass through the platelet microthrombi occluding small blood vessels (i.e., arterioles, capillaries) → hemolysis (schistocytes), and end-organ ischemia and damage, especially in the kidneys → decreased glomerular filtration rate (GFR)

E. coli O157:H7 infection → Shiga-like toxin in systemic circulation → **toxin-mediated endothelial injury** → microthrombus formation → blockage of small vessels → RBC fragmentation (hemolysis) and end-organ damage



Clinical features

A **diarrheal** illness (usually **bloody**) for the past 5–10 days precedes the onset of HUS symptoms in many children.

The triad of clinical findings occurring in HUS consists of:

- **Thrombocytopenia**
  - Petechiae, purpura
  - Mucosal bleeding
  - Prolonged bleeding after minor cuts
- **Microangiopathic hemolytic anemia**
  - Fatigue, dyspnea, and pallor
  - Jaundice
- **Impaired renal function**
  - Hematuria, proteinuria
  - Oliguria, anuria

Diagnostics

- **Hematology**
  - Hemolytic markers
    - ↓ Hemoglobin
    - ↓ Haptoglobin
    - ↑ Indirect bilirubin
    - ↑ Reticulocytes
    - ↑ LDH
    - ↑ **Schistocytes** on blood smear (up to 10% of RBCs)
  - Coagulation profile
    - ↓ **Platelets**
    - Normal/slightly elevated prothrombin time (PT) and activated partial thromboplastin time (aPTT) in contrast to DIC (see "Differential diagnoses" below)
    - Normal/slightly elevated fibrin degradation products and D-dimer levels
  - ↑ WBC count
  - Negative Coombs test
- **Serum chemistry**: ↑ **BUN** and ↑ **creatinine** (impaired renal function)
- **Urinalysis**: hematuria, proteinuria

The typical HUS patient is a preschooler who has had a diarrheal illness for the past 5–10 days and presents with petechiae, jaundice, and oliguria.

Treatment

- **Supportive care** [2]
  - Avoid antibiotics and antimotility agents (may increase the likelihood of HUS in suspected infection with EHEC).
  - Monitor and correct:
    - Fluid status abnormalities (for more information, see "Clinical assessment of volume status")
    - Electrolyte disturbances (for more information, see "Electrolyte metabolism")
    - Acid-base disorders
    - Blood pressure (due to hypertension or septic shock)
    - RBC transfusions
  - Antiepileptic drugs (e.g., diazepam, phenytoin) in patients with seizures
- **Dialysis** (as indicated for AKI): Up to 50% of HUS patients require dialysis.
- **Plasma exchange therapy**: only in refractory cases
- **Eculizumab**
  - Effective for the treatment of aHUS [5]
  - May be beneficial in HUS with neurological symptoms [6]

.to sum up:

Hemolytic uremic syndrome	
Pathogenesis	• Initial insult from Shiga toxin (*Escherichia coli* serotype O157:H7) • Vascular damage & microthrombi formation
Clinical features	• Preceding bloody diarrhea • Fatigue, pallor • Bruising, petechiae • Oliguria, edema
Laboratory findings	• Hemolytic anemia (schistocytes, ↑ bilirubin) • Thrombocytopenia • Acute kidney injury (↑ BUN, ↑ Cr)
Treatment	• Fluid & electrolyte management • Blood transfusions • Dialysis

BUN = blood urea nitrogen; Cr = creatinine.

Post-diarrheal HUS is a nationally notifiable condition. [7]

Platelet transfusions should be administered with caution unless patients are bleeding or require an invasive procedure. Some studies suggest that they can exacerbate microangiopathy.

C8. Drug induced Hemolytic Anemia

Drug-Induced Hemolytic Anemia

1. Triggers:
    a. NSAIDs
    b. Cephalosporins
    c. Penicillins
2. Mechanisms:
    a. Most drugs cause hemolysis through a variety of mechanisms, for example:
        i. Oxidative injury
        ii. Complement-mediated lysis
    b. Penicillins and cephalosporins trigger hemolysis when the drug binds directly to the surface of erythrocytes and creates a **hapten** for IgG attachment
        i. IgG-coated erythrocytes are then identified by the Fc receptor on **splenic macrophages**, leading to partial or whole erythrocyte phagocytosis (extravascular hemolysis).
        ii. Intravascular hemolysis may also occur due to activation of complement cascade

Drug-induced immune-mediated hemolytic anemia	
Pathogenesis	• Drug coats erythrocytes → IgG binding → splenic destruction of RBCs (extravascular hemolysis) • Drug triggers immune complexes → complement-mediated destruction of RBCs (intravascular hemolysis)
Manifestations	• Sudden onset (within hours of exposure) • Anemia: fatigue, pallor, dyspnea • Hemolysis: jaundice, dark urine, abdomen or back pain ◦ ↑ Reticulocytes, indirect bilirubin & LDH ◦ ↓ Haptoglobin ◦ Spherocytes on peripheral blood smear ◦ + Direct Coombs test (anti-IgG, anti-C3)
Treatment	• Discontinue offending drug • Transfusion (if severe) • ± Glucocorticoids, IVIG
IVIG = intravenous immunoglobulin; **LDH** = lactate dehydrogenase; **RBC** = red blood cell.	

Third/Sickle cell disease

Summary

Sickle cell disease is caused by hereditary hemoglobinopathy, which includes sickle cell anemias (i.e., HbSS and HbSβ^{0}thal) and other compound heterozygous genotypes (e.g., HbSC, Hbβ$^+$thal). Mutations in the hemoglobin β chain lead to the formation of hemoglobin S, which polymerizes when deoxygenated. Deoxygenated HbS results in sickle-shaped erythrocytes that can occlude blood vessels and cause ischemia. Homozygous sickle cell anemia (HbSS) is the most common variant of sickle cell disease and occurs predominantly in individuals of African and Eastern Mediterranean descent, although people of any ethnicity can develop sickle cell disease. Screening for sickle cell disease is routinely recommended for all infants born in the United States. Hemoglobin separation studies (e.g., hemoglobin electrophoresis, high-performance liquid chromatography) and genetic studies are used to confirm the diagnosis. Complications can begin in early infancy and childhood and continue for the rest of the affected individual's lifetime. Acute complications include vascular occlusion events (e.g., vasoocclusive pain crisis, stroke, acute chest syndrome), severe anemia (e.g., sequestration, aplastic anemia), and invasive infections from encapsulated organisms (e.g., bacteremia, pneumonia, meningitis, osteomyelitis). Infants with confirmed sickle cell disease should receive antibiotic prophylaxis against invasive pneumococcal infection and all age-appropriate immunizations, and hydroxyurea therapy. Transfusion therapy (e.g., for vasoocclusive events, secondary prevention of stroke) and hydroxyurea are key aspects of decreasing morbidity and mortality. Screening for complications of sickle cell disease (including annual transcranial Doppler to screen for stroke risk from 2–16 years of age) should occur at regular intervals. Long-term complications include progressive loss of organ function (e.g., functional asplenia, cognitive decline, avascular osteonecrosis) secondary to repeated infarctions. Allogeneic bone marrow transplantation is currently the only curative treatment option.

Sickle cell trait, which occurs in heterozygous carriers (HbSA), is not considered a form of sickle cell disease, but affected individuals can experience acute complications due to sickling under certain conditions, for example during high-intensity exercise or at high altitude.

- **Sickle cell disease**

Sickle cell disease compound heterozygotes where one β-globin gene mutation includes the sickle cell mutation and the 2nd β-globin other, Hb C, Hb β-thalassemia, Hb D, and Hb O Arab. Hb S is >50%.

    - A group of conditions characterized by mutations in the HbS genotype that result in phenotypic manifestations similar to sickle cell anemia
    - Genotypes include HbSS, HbSβ^{0}thal, HbSβ+thal, HbSC, and rarely, HbSD, and HbSE.
    - Symptoms range from mild to severe
- **Sickle cell anemia** [1]

Sickle cell anemia, homozygous Hb S, occurs when both β-globin genes have the sickle cell mutation. , Hb S level = 90%

    - The most severe clinical presentation of sickle cell disease
    - Genotypes include homozygous HbSS and compound heterozygous HbSβ^{0}thal (a form of sickle beta thalassemia).
- **Sickle cell trait** [2]
    - Refers to the sickle cell carrier genotype (HbAS)
    - Not considered a form of sickle cell disease
    - Complications occur rarely (see "Clinical features").

Etiology

✧ Autosomal recessive disorder.

✧ Due to single amino acid substitution in the number 6 position of the β-chains (valine for glutamic) resulting in new Hb → HbS ($\alpha_2\beta_2^{6glut.}$ → $\alpha_2\beta_2^{6val.}$ = HbS).

Pathogenesis

HbS can't withstand hypoxia → if exposed to low O_2 tensions → HbS polymerize→ RBCs distortion → intra vascular sickling with subsequent :

1. Aggregation → vascular occlusion
2. Trapping and hemolysis in reticulo endothelial system in the spleen & liver

Forms: - Sickle cell anemia (homozygous)
- Sickle cell trait (heterozygous)

Clinical picture

✧ Common in negroes

✧ Earliest manifestations:
- Mild hemolysis is evident by 3 months of age with Hb of 7-10 and reticulocytic count of 10-20%
- Hyposplenism can occur as early as 5 months of age and initial splenomegaly can be detected after 6 months of age
- The first crisis detected between 6-12 months of age in about 50% of cases.

✧ Features of anemia
✧ Features of chronic hemolysis
] Starting after the 6th month of age

✧ Renal disorders → proteinuria, nephrotic syndrome, chronic renal failure.

✧ **Crisises**

1. Aplastic 2. Hemolytic 3. Megaloblastic 4. Hyperhemolytic (as before)

5. Vaso occlusive crisis (painful crisis)

Due to : invivo sickling → vascular occlusion → ischaemia ± infarction.

Precipitating factors : fever, acidosis, dehydration, infection & hypoxia.

Clinically:



* Cerebrovascular stroke(esp. middle cerebral artery)
* Pulmonary infarction → hemoptysis
* Acute chest syndrome :
  - Chest pain, fever, leucocytosis and lung infilterates→ fatal in 20%
  - Due to pulmonary emboli of necrotic bone marrow (fat emboli)
* Hand and foot syndrome: Ischemia of metacrapal & metatarsal bones → symmetric bone pain & swelling
* Renal infarction → hematuria
* Priapsim (sustained, painful purposeless erection)
* Leg ulcers

6. Sequestration crisis:

Sudden pooling of the blood in the spleen ± the liver; precipitated by dehydration

Clinically: - Acute pallor with hypovolaemic shock.
- Acute abdominal pain with massive splenomegaly (± hepatomegaly)

7. Infectious crisis: due to hyposplenism (↓Antibodies, ↓opsonins, ↓phagocytosis)

Common organisms: usually encapsulated

Site: - Meningitis (Pneumococci & H.influenzae)
- Pneumonia (Pneumococci)
- Osteomyelitis (Salmonella)

▪ Sickle cell trait (Heterozygous form):

- It is the presence of one mutated and one normal β chain (heterozygous for the sickle gene); resulls in < 50% HbS in RBCs (HbA is slightly more efficiently produced than HbS).

- Generally asymptomatic with no anemia; RBCs with < 50% HbS do not sickle in vivo except in the renal medulla.

- Extreme hypoxia and hypertonicity of the medulla cause sickling, which results in microinfarctions leading to microscopic hematuria and, eventually, decreased ability to concentrate urine.

- The only manifestation of sickle cell trait is a defect in the ability to concentrate the urine or "isosthenuria" and can present as nocturia and polyuria.

Splenic Sequestration Crisis

1. Common finding in patients with Sickle cell who have not yet experienced autosplenectomy
   a. Diagnose by looking for splenomegaly and signs of shock
2. Leads to splenomegaly and splenic sequestration of
   a. RBC
      i. Pallor
      ii. Acute normocytic anemia
      iii. Hypovolemic shock (as majority of blood is trapped in spleen)
      iv. Compensatory reticulocytosis
   b. Platelets
      i. Thrombocytopenia
3. Treatment
   a. Correction of hypovolemia with isotonic fluids
   b. Small-volume transfusions
   c. Eventual splenectomy

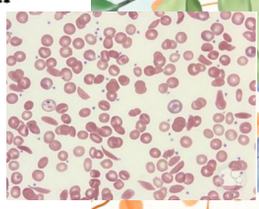
- Individuals with sickle cell trait are generally asymptomatic and have both a normal CBC level and a normal smear result and can lead a healthy life.

- There is no treatment for sickle cell trait.

Clinical Features and Management of Crises Occurring in Sickle Cell Disease

Crisis	Clinical Features	Management
Vaso-occlusive crisis		
Painful bone crisis	Most common crisis Ischemia/infarction of bone or marrow Deep, gnawing, or throbbing pain lasting 3–7 days Subtype: **acute dactylitis**—painful swelling of digits of the hands and feet	Pain control Intravenous fluids at 1–1.5 × maintenance Incentive spirometry to decrease the risk of acute chest syndrome Severe, unremitting pain may respond to partial exchange transfusion. (Simple transfusion of RBCs is not indicated. It increases viscosity of blood and may worsen crisis.)
Acute abdominal crisis	Abdominal pain and distension Often caused by sickling within mesenteric artery	Low threshold for imaging the abdomen Same management as for painful bone crisis
Stroke	Dysarthria and hemiplegia, but may be asymptomatic Occurs in up to 11% of patients (subclinical stroke occurs in up to 20% of patients)	Same management as for painful bone crisis Urgent exchange transfusion Patient should be started on chronic transfusion program to prevent recurrence, which occurs in 60–90%
Priapism	Painful, sustained erection **Always consider SS disease in any patient presenting with priapism**	Same management as for painful bone crisis
Acute chest syndrome (ACS)		
	New pulmonary infiltrate associated with respiratory symptoms (e.g., cough, shortness of breath, chest pain) Hypoxemia May be severe and may cause up to 25% of deaths in patients with SS disease Causes include infection (e.g., viral, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Streptococcus pneumoniae*), sickling, atelectasis, fat embolism, painful bone crisis involving the ribs, and pulmonary edema from fluid overload	Careful hydration and pain management Oxygen Appropriate antibiotics (usually cefuroxime and azithromycin) Incentive spirometry Early use of partial exchange transfusion in a patient who does not improve rapidly
Sequestration crisis	Rapid accumulation of blood in spleen (or less commonly, liver) Occurs in patients <6 years of age Abdominal distension, abdominal pain, shortness of breath, tachycardia, pallor, fatigue, and shock; mortality can be high Lab findings: low Hgb; elevated reticulocytes	Supportive care Transfusion of RBCs Splenectomy recommended by some practitioners because recurrence occurs in up to 50%
Aplastic crisis	Temporary cessation of RBC production often caused by parvovirus B19 or other infectious agent Pallor, fatigue, tachycardia Lab findings: low Hgb; low reticulocytes	Supportive care Transfusion of RBCs
Hyperhemolytic crisis	Rapid hemolysis; often occurs in patients with other hemolytic diseases (e.g., G6PD deficiency) Pallor, fatigue, tachycardia, jaundice Lab findings: low Hgb; elevated reticulocytes; elevated bilirubin	Supportive care Transfusion of RBCs

1- For **anemia** → Low Hb% & Ht value.
2- For **chronic hemolysis** →↓ RBCs survival & ↑ erythropioesis.
3- For **the cause:**
- Blood film: - detect sickle cells in peripheral blood. If not detected, sickling can be enhanced by adding sodium metabisulfite (Sickling test).
- Howell–Jolly bodies (nuclear reminants) and Submembraneous pits in RBCs may be seen indicating hyposplenism.
- Hemoglobin electrophoresis: Show HbS (90%) & Hb F (2-10%).
- Neonatal screening allows early detection , adequate care and longer survival



- Diagnostic Tests:

- The best initial test is a peripheral smear. Sickle cell trait (AS disease) does not give sickled cells.

- The most accurate test is the hemoglobin electrophoresis.

- Howell-Jolly bodies are nuclear remnants of the red blood cells which are generally removed by a functional spleen; therefore, their presence in a peripheral smear suggests functional asplenia in sickle cell patients.

- Hemolytic anemias are characterized by a decreased serum haptoglobin level as well as an increased LDH and bilirubin. Haptoglobin is a serum protein that binds free hemoglobin and promotes its excretion by the reticuloendothelial system.

Usual Laboratory Findings in Sickle Cell Anemia

Red blood cell life span	10–50 days
Hemoglobin	6–9 g/dL
Hematocrit	18–27%
Reticulocyte count	5–15%
White blood cell count	12,000–20,000 cells/mm^3
Platelet count	Increased, often > 500,000 platelets/μL
Bilirubin	Increased
Blood smear	Sickled cells, target cells, Howell–Jolly bodies
Bone marrow	Erythroid hyperplasia

Treatment

1- Chronic transfusion therapy & iron chelation.
Indications: patients with strokes,splenic sequestration crises, repeated episodes of acute chest syndrome.

2- Treatment of crisises:
✧ Supportive care: Ensure ABC & remove precipitating factors(e.g. infections)
⌖ Vaso oclusive
- Hydration at 1.5-2 maintenance & alklinization.
- Analgesics (paracetamol, ibuprofen, opiates)
- If refractory → partial exchange transfusion.

⌖ Sequestration
- Blood transfusion.
- Exchange transfusion(keep sickle cells<30%)
- If refractory → emergency splenectomy.

⌖ Aplastic / hemolytic → Blood transfusion

3- Control of infection:
- Prophylactic penicillin (up to 6 years)
- Immunize against: Pneumococci & H. influenzae

4- Recent treatment:
- Hydroxyurea → induction of Hb F.
- Bone marrow transplantation.

N.B: Sickle cell trait: Heterozygous form
- The patient's blood contains mixture of (HbS = 30%) and (HbA).
- Asymptomatic but severe hypoxia may lead to ⇛ vaso occlusive crisis.
- Patients are resistant to falciparum malaria.

❖ N.B:

1. Osteonecrosis is a common complication of sickle cell anemia due to vaso-occlusion of the bone. It causes significant joint pain and functional limitation. The humerus and femur are the most frequently affected bones.
   - Treatment is pain management and limitation of weight bearing, with surgical intervention if conservative management is unsuccessful (joint reconstruction).

2. Hand-foot syndrome or dactylitis is the earliest manifestation of vaso-occlusive disease in sickle cell anemia.
   - The pathophysiology of dactylitis involves vascular necrosis of the metacarpals and metatarsals, which may be seen on plain radiographs as osteolytic lesions.

3. Patients with sickle cell anemia become functionally hyposplenic at an early age due to splenic autoinfarction. Thus, they are more susceptible than other patients to infection with encapsulated organisms, such as S. pneumoniae, H. influenzae, and N. meningitidis.
   - Vaccination with the conjugated S. pneumoniae vaccine decreases the incidence of invasive infections caused by this organism.
   - Twice daily administration of prophylactic penicillin should also be given to children with sickle cell disease until they reach five years of age.

To sum up:

Sickle cell anemia	
Pathophysiology	Autosomal recessive inheritance of sickle β globin mutation in African & Hispanic populations
Clinical features	• Hemolytic anemia • Dactylitis • Acute vasoocclusive pain crises
Laboratory findings	• ↓ Hematocrit, ↑ reticulocytes, ↑ serum low-density lipoprotein, ↑ unconjugated bilirubin • Peripheral smear: Sickled red cells, Howell-Jolly bodies
Management	**Maintenance** • Vaccination • Penicillin (until age 5) • Folic acid supplementation • Hydroxyurea (for patients with recurrent vasoocclusive events) **Acute pain crises** • Hydration • Analgesia • +/- Transfusion

Sickle cell disease	
Pathophysiology	• Beta globin mutation (Glu → Val) • Autosomal recessive
Clinical features	• Vaso-occlusive pain crises • Hemolytic anemia
Laboratory findings	• ↓ Hematocrit • ↑ Reticulocyte count • Peripheral smear: Sickled RBCs • Hemoglobin electrophoresis: ↑ HbS, ↓ HbA
Management	• Maintenance ◦ Pneumococcal vaccine ◦ Penicillin (until age 5) ◦ Folic acid supplementation ◦ Hydroxyurea • Acute pain crises ◦ Hydration ◦ Analgesia ◦ ± Transfusion

CRISIS IN SICKLE CELL DISEASE

تلخيص كل ما ورد باليوورد عن عمو sickle😊🤍

Acute severe anemia in sickle cell disease		
Cause	**Reticulocytes**	**Key features**
Aplastic crisis	↓	• Transient arrest of erythropoiesis • Secondary to infection (eg, parvovirus B19)
Splenic sequestration crisis	↑	• Splenic vaso-occlusion → rapidly enlarging spleen • Occurs in children prior to autosplenectomy

Aplastic Crisis

1. Transient arrest of erythropoiesis
    a. Leads to SEVERE anemia (<6 g/dl)
    b. Occurs before age 15 because parvovirus outbreaks are most common in school-age children
2. Decrease in RBC
    a. Reticulocyte count is low
3. Platelets and WBC are normal
4. Secondary to Parvovirus B19
    a. Although B19 symptoms are typical, aplastic crisis can occur without any preceding B19 symptoms
5. Findings
    a. Pallor
    b. Fatigue
    c. Functional systolic murmur (due to hyperdynamic blood flow)
6. Treatment is blood transfusion

Complications of Sickle Cell Trait

1. Hematuria
2. Splenic infarction at high elevations
3. Sudden death with significant exercise

Sickle cell Management

1. Vaccine
    a. Conjugate capsular polysaccharide vaccine against *S pneumoniae*
2. Penicillin
    a. Twice daily administration until age 5 years.

Differential Diagnosis of Bone Pain in Sickle Cell Disease

Differential diagnosis of bone pain in sickle cell disease			
Cause	**Vaso-occlusive crisis**	**Osteomyelitis**	**Avascular necrosis**
Clinical features	• Acute, severe pain • **Pain ≥1 site** (eg, dactylitis) • +/- Low-grade fever • Erythema & warmth • May be preceded by trigger (eg, dehydration)	• Acute or subacute pain • Focal pain at 1 site (eg, long bone) • Prolonged fever • Erythema & warmth • **Positive blood culture**	• **Chronic**, worsening pain (eg, femoral head) • Absence of fever • Absence of warmth or erythema

Hemoglobin Electrophoresis Findings in Sickle Cell and Thalassemia:

Hemoglobin electrophoresis patterns in sickle cell & beta-thalassemia				
Condition	**Hemoglobin A**	**Hemoglobin A2**	**Hemoglobin F**	**Hemoglobin S**
Normal	95%-98%	~2.5%	<1%	Absent
Beta-thalassemia minor	↓	↑	Near normal	Absent
Beta-thalassemia major	Absent	↑↑	↑↑	Absent
Sickle cell trait	↓↓	Near normal	Near normal	↑
Sickle cell disease	Absent	Near normal	↑↑	↑↑

In Low Reticulocyte count:

First/Aplatic Anemia

- Definition/Etiology:

- Aplastic anemia is an acquired deficiency of pluripotent stem cells (Damage to hematopoietic stem cells) that can result from certain exposures, viral infections, or autoimmune conditions resulting in pancytopenia (anemia, thrombocytopenia, and leukopenia) with low reticulocyte count.

- Any infection or cancer can invade the bone marrow, causing decreased production or hypoplasia. Other causes of pancytopenia are:
  - Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis.
  - Radiation and drugs (benzene, chloramphenicol, alkylating agents, antimetabolites).
  - Viral agents (parvovirus B19, EBV, HIV, hepatitis viruses).
  - Fanconi anemia (DNA repair defect causing bone marrow failure); also, short stature, ↑ incidence of tumors/leukemia, café-au-lait spots, thumb/radial defects.

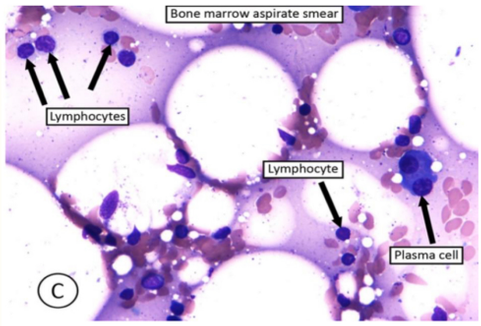
- Presentation/Diagnostic Tests:

- Patients present with the fatigue of anemia, infections from low white cell counts, and bleeding from thrombocytopenia.

- Aplastic anemia is confirmed by excluding all the causes of pancytopenia.

- The most accurate test is a bone marrow biopsy demonstrating hypocellular marrow with a few normal hematopoietic cells, no myeloid infiltration or fibrosis, and predominantly stroma and adipocytes.

- Bone marrow aspiration is usually "dry" and histopathology shows marrow replacement with fat cells and fibrous stroma.



- Treatment:

- Aplastic anemia acts as an autoimmune disorder in which the T cells attack the patient's own marrow.

- Treatment is based on medications like cyclosporine that inhibit T cells. This brings the marrow back to life.

- Besides supportive therapy such as blood transfusion for anemia, antibiotics for infection, and platelets for bleeding, you should treat any underlying cause that is identified. A true aplastic anemia is treated with allogeneic bone marrow transplantation (BMT) if the patient is young enough and there is a matched donor.

- When the patient is too old for BMT (above age 50) or there is no matched donor, the treatment is antithymocyte globulin (ATG) and cyclosporine. Tacrolimus is an alternative to cyclosporine. Alemtuzumab is an anti-CD52 agent that suppresses T cells.

.To Sum Up:

Aplastic Anemia

Aplastic anemia	
Pathogenesis	Bone marrow failure due to hematopoietic stem cell deficiency ($CD34^+$)
Causes	• Autoimmune • Infections (eg, parvovirus B19, Epstein-Barr virus) • Drugs (eg, carbamazepine, chloramphenicol, sulfonamides) • Exposure to radiation or toxins (eg, benzene, solvents)
Clinical & laboratory findings	Laboratory studies: Pancytopenia • Anemia (fatigue, weakness, pallor) • Thrombocytopenia (mucosal bleeding, easy bruising, petechiae) • Leukopenia (recurrent infections) Biopsy: Hypocellular bone marrow with fat and stromal cells

Second/Fanconi Anemia

- **Fanconi anemia** [21][22]
  - Hereditary autosomal recessive disorder due to a **DNA crosslink** repair defect resulting in bone marrow failure
  - Skeletal and organ abnormalities: short stature, hypo- and hyperpigmentation, cafe-au-lait spots, microcephaly, developmental delay, **thumb and forearm malformations**, kidney, GI, heart, eye, and ear abnormalities
  - Laboratory tests show pancytopenia and normocytic or macrocytic anemia.
  - ~ 50% of patients with Fanconi anemia will develop acute myeloid leukemia or myelodysplastic syndromes in early adulthood. [23]

❖ N.B:

- Fanconi anemia is an autosomal recessive disorder that causes congenital marrow failure, poor growth, morphologic abnormalities, and usually macrocytic anemia.
- Congenital causes of aplastic anemia are more common in children, and Fanconi anemia (FA) is the most common congenital cause. Most patients with FA are diagnosed by the age of 16 years and have a predisposition for developing cancer. Numerous genes, all believed to involve DNA repair, have been implicated.
- Diagnosis of FA is made by chromosomal breaks on genetic analysis combined with the clinical findings.

.To Sum Up:

Fanconi Anemia

1. Most common congenital cause of aplastic anemia
   a. Presents at age 4-12 years
2. It is a DNA repair defect
3. Clinical Features:
   a. Pancytopenia
      i. Macrocytic anemia
      ii. Leukopenia
      iii. Thrombocytopenia
   b. Short stature
   c. Hyper/hypo-pigmentation
   d. Hypoplastic thumbs with flattened thenar eminences or polydactyly
4. Diagnosis
   a. Positive chromosomal breakage following DNA exposure to interstrand crosslinking agents
5. Differentials
   a. Benzene exposure
      i. It can cause chromosomal breakage and aplastic anemia but no thumb and skin findings are there
   b. Diamond Blackfan Anemia
      i. Triphalangeal thumb
      ii. Pure red cell aplasia

Fanconi anemia	
Pathophysiology	• Inherited DNA repair defect • Bone marrow failure
Clinical findings	• Short stature • Hypo-/hyperpigmented macules • Abnormal thumbs • Genitourinary malformations
Laboratory findings	• Pancytopenia • Positive chromosomal breakage testing
Treatment	• Hematopoietic stem cell transplant

Third/Red blood cell Aplasia

General

- **Description**: normocytic, normochromic anemia characterized by a severe reduction in circulating reticulocytes and marked reduction or absence of erythroid precursors in the bone marrow [29]
- **Pathophysiology**: thought to be related to abnormal T-cell function and IgG antibodies that target erythroblasts and erythropoietin
- **Etiology**
  - Acquired
    - Most often idiopathic
    - Possible associated conditions
      - Thymoma
      - Myelodysplastic syndrome
      - Adverse drugs effects (e.g., from phenytoin, chloramphenicol)
      - Parvovirus B19 infection
      - Autoimmune disorders (e.g., type 1 diabetes, thyroiditis, rheumatoid arthritis)
  - Congenital: **Diamond-Blackfan anemia** (DBA): see below
- **Diagnostics**
  - **Low reticulocyte** count
  - Bone marrow biopsy shows marked reduction or absence of erythroid precursors.
- **Treatment**
  - Treatment of the underlying cause (e.g., cessation of possible offending agents, thymectomy)
  - Red blood cell transfusion for symptomatic patients
  - Immunosuppressive and/or cytotoxic agents (e.g., glucocorticoids, cyclosporine, cyclophosphamide)

.Diamond-Blackfan Anemiam

Diamond-Blackfan anemia [30]

- **Description**
  - Intrinsic defect of erythroid progenitor cells → ↑ apoptosis
  - Usually autosomal dominant inheritance or associated with impaired ribosome synthesis mutations
  - Rapid onset of **macrocytic** (nonmegaloblastic) anemia in infancy (usually diagnosed within the first year of life)
- **Additional clinical features**: physical abnormalities manifest in ~50% of affected individuals
  - Fatigue, poor feeding
  - Short stature, webbed neck
  - Upper extremity malformations (e.g., **triphalangeal thumbs**)
  - Microcephaly, micrognathia
  - Hypertelorism, flat nasal bridge, cleft palate
  - Congenital cataracts or glaucoma
  - Atrial and ventricular septal defects
- **Diagnostics**
  - Electrophoresis
    - **Elevated HbF levels**
    - Low total Hb levels
  - Specific laboratory findings
    - **Elevated erythrocyte adenosine deaminase levels** (eADA)
    - Increased expression of i antigen in RBCs
- **Treatment** [31]
  - Corticosteroids (first-line treatment)
  - Chronic red cell transfusions: individuals who do not respond to corticosteroids
  - Hematopoietic stem cell transplantation
- **Complications**
  - Increased risk of malignancy: acute myelogenous leukemia, myelodysplastic syndrome, solid tumors (e.g., colon cancer, osteogenic sarcoma)
  - Treatment-associated complications: iron overload due to repeated transfusions, corticosteroid-induced hyperglycemia
  - Endocrine dysfunction: adrenal insufficiency, hypogonadism, vitamin D deficiency



To Sum Up:

Diamond-Blackfan Anemia

1. Clinical features
   a. Macrocytic anemia
      i. Reticulocytopenia
   b. Craniofacial abnormalities
      i. Mild hypertelorism
      ii. Flat nasal bridge
   c. Triphalangeal thumbs
2. Other features include:
   a. Short stature
   b. Webbed neck
   c. Cleft palate
3. Normal platelets and WBC
4. Treatment
   a. Mainly corticosteroids
   b. RBC transfusion in refractory cases

Diamond-Blackfan anemia	
Pathogenesis	• Congenital erythroid aplasia
Clinical findings	• Craniofacial abnormalities • Triphalangeal thumbs • Increased risk of malignancy
Laboratory findings	• Macrocytic anemia • Reticulocytopenia • Normal platelets, white blood cells
Treatment	• Corticosteroids • Red blood cell transfusions

🦋.Transient Erythroblastopenia

Transient hypoplastic anemia between 6 months–3 years

– Transient **immune suppression** of erythropoiesis

– Often after nonspecific viral infection (not parvovirus B19)

Labs—decreased reticulocytes and bone-marrow precursors, normal MCV and HbF

Recovery generally **within 1–2 months**

Medication not helpful; may need one transfusion if symptomatic

Characteristics of the Red Blood Cell Aplasias

Aplasia	Etiology	Clinical Features	Laboratory Findings	Treatment
Congenital hypoplastic anemia (Diamond–Blackfan anemia)	Unknown Autosomal recessive or autosomal dominant inheritance	Anemia within the first year of life Rapid onset One-fourth to one-third have physical findings: craniofacial, renal, cardiac anomalies; short stature; triphalangeal thumbs Signs and symptoms of anemia	↓Hgb ↓Reticulocytes ↑Hgb F ↓or normal platelet count Marrow: ↓RBC precursors; other marrow elements normal	RBC transfusion Corticosteroids (up to 70% respond) Bone marrow transplant if no response to corticosteroids
TEC	Unknown Possible postviral autoimmune reaction	Anemia begins >1 year of age Slow in onset Signs and symptoms of anemia	↓Hgb ↓Reticulocytes Normal platelet count Marrow: ↓RBC precursors	Spontaneous recovery within several weeks No treatment required
Parvovirus B19–associated pure RBC aplasia*	Parvovirus B19 infection	Anemia generally not symptomatic May have associated URI symptoms and facial rash ("slapped cheeks") of fifth disease Aplastic crisis in patients with SS disease	↓Hgb ↓Reticulocytes Normal platelet count	Spontaneous recovery within 2 weeks RBC transfusions may be required for patients with aplastic crisis associated with SS disease

*Note that Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus (HIV), and drugs (e.g., chloramphenicol) may cause an acquired RBC aplasia similar to parvovirus B19.

وأخيراً ما ورد بتلخيص النصر 🦋😊

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بسم الله الرحمن الرحيم

المحاضرة ⑤ مع الدكتور اسماعيل ياسين

- Anemia -

موضوع تخص اسمها العزيزة ♥

Red urine → urine analysis :

RBC	blood	
⊕	⊕	∴ hematuria
⊖	⊕	∴ hemoglobinuria / myoglobinuria
⊖	⊖	∴ Red discoloration → rifampicin / iron / Ibuprofen

⊛ Clinical manifestation of anemia :

1. pallor 2. hypoactivity 3. poor intake 4. lethargy

if acute (due to hemolysis) → 5. Signs of HF :

لو صارت الـ anemia على فترة طويلة → Sweaty → tachycardia

مثلاً مثلاً القلب يعوض بالتاكيد 5. اللي بعده → dyspnea → Gallop rhythm

Signs of HF → Cardiomegaly in CXR

6. poor School performance

7. Jaundice if hemolysis

→ Normal Hgb in pediatric should be ≥ 11 if < 11 ∴ anemia (نقرة معقدة نقول 10)

هذا ينطبق على كل الأعمار

- at birth Hgb = 18-20 (normal till 13.8)

Hgb < 13.8 in neonal age = anemia

- [8-10] weeks after birth Hgb decrease بشكل كبير

وهاي تسمى Physiological anemia ، اليوم كم بتصير؟

✓ Preterm baby Hgb = 7-9

✓ full term baby Hgb = 9-11

؟ يعني نزل الشغب في سحريه !! ما السبب إلك على كدة

⊛ fetal RBC life span = 70 days

(adult RBC life span = 120)

⊛ Intrauterine Saturation 50% → hypoxic → EPO عالي

عند أمك تنفس بدالها → O_2 sat = 99% → EPO بقل بشكل كبير

⊛ greatest growth occur in first 3 months

at birth 3Kg → at 4th Month

Duplication of wt.

هاي فترة حياة الإنسان بيصير فيها زيادة الطول في هاي

بعد فترة بيرجع الـ Hgb يزيد

- at 1 year → Hgb = 11

⊛ Normal MCV in pediatric = 70-80 fL (femtoliter) $= 10^{-3}$ L

after 1 year MCV = 70 + Age x 3

⊛ Classification of anemia according to MCV :

Microcytic	Normocytic	Macrocytic
		لو اجالك مريض
		Pallor
		low Hgb
		MCV = 75
		∴ Normocytic anemia

بدي أحدد نوعها ، فلازم أعمل جدول أشياء :

Normocytic anemia

- hemolytic
  - intrinsic (RBC defect)
  - Extrinsic
    - AIHA
    - MAHA
    - macroangio
- NON-hemolytic = bone marrow suppression
  - aplastic anemia
  - chronic kidney dz

① أول شي عم أفرق فيه إنيميا ناتجة عن hemolysis or BM supression

Reticulocyte count : normally ≤ 2%

Reticulocyte count

low < 2%	inappropriately low (يعني أقل من طبيعي بالنسبة لـ Hgb و Retic)	high > 2%
أسبابها		4-5%
① BM dz : leukemia		in hemolytic anemia
myelofibrosis		∴ investigation :
② chronic Dz		- serum bilirubin
③ Drug induce		- lactate dehydrogenase
④ Aplastic anemia		- Hepatoglobin
⑤ Acute infection		

Reticulocyte count in normocytic anemia

< 2%		> 2% (destruction / blood loss)	
isolated anemia	Pancytopenia	Hemolysis	
= BM hypoplasia	= Aplasia	intrinsic (# RBC Defect)	extrinsic
- acute viral infection	- aplastic anemia		- AIHA
- TEC*	- leukemia		- MAHA ← DIC / USP / TTP
- renal dz	- Drug induced		- liver dz
- hypothyroidism			- hypersplenism
- Drugs [chloramphinicol Subs.]			- wilson dz
			- metabolic

⊛ TEC = Transient Erythroblastopenia of Childhood

- mild to moderate Normocytic anemia
- age [6 months → 3 years]
- once blood transfusion ، إذا احتاج أكثر من مرة بشك بشيء آخر
- No Skeletal anomalies

⊛ DDx of isolated Normocytic anemia : (one line is affected)

1. TEC
2. Drug : chloramphenicol
3. viral infection → transient hypoplasia of BM (Bone marrow hypoplasia / aplasia)
4. Chronic renal dz : 2 causes : ↓ EPO / ↑ urea is toxic to BM

⊛ hemolysis = pallor + Jaundice (↑ indirect bilirubin)

non immune vs immune بدي أفرق هلأ بينهم

Coombs test إذن

⊕ Direct ⊕ : AIHA (autoimmune) = Coombs

⊖ Indirect ⊕ : Newborn (isoimmune) = high Retics

antibodies from mother

- mother Rh ⊖ / baby Rh ⊕
- mother O / baby A/B

MCV normal

↑ indirect bilirubin

RBC defect

- membrane
- Hgb (SC)
- enzyme (G6PD)

Thalassemia

⊛ Direct coombs ⊕ : AIHA

warm → extravascular hemolysis in spleen (No Red Urine)

cold → intravascular hemolysis → hemoglobinuria → Saturation of Haptoglobin → urine → Dark Urine (Red Urine)

---

① أول اشي من CBC شفت الـ Hgb و MCV ∴ normocytic Anemia الـ خطوة حلك على خزعة

② تاني اشي لعلمت Retics count عشان أشوف هل high أم low

③ لو طلعت high ⇐ RBC destruction إذن

عشان أعرف سبب الـ destruction الـ أعمل الـ investigations التالية :

- LDH (lactate dehydrogenase)
- indirect bilirubin
- haptoglobin
- coombs test

↑ LDH
↑ bilirubin
haptoglobin ≤ 2.5 mg/dL
⊕ coombs
∴ hemolysis

---

② Retics count أشوف

high → ③ ↑ destruction of RBCs (الفحوصات السابقة)

- hemolysis
- hypersplenism
- MAHA
- liver dz wilson dz

④ عشان أعرف نوع الـ hemolysis

Coombs test

⊕ → ∴ immune
⊖ → ∴ RBC defect

MAHA:
- HUS (عند الأطفال)
- DIC (severe sepsis, shock)
- TTP (adult عند الـ)

⊛ MAHA has specific blood film : ① Schistocytes fragmented ② Helminth cells

⊛ wilson dz → copper intoxication of RBC → destruction

⊛ Spherocytosis → osmolarity fragility test

Hemolytic Anemia + Red Urine ∴ intravascular hemolysis

① G6PD
② MAHA
③ AIHA cold type
④ Clostridial sepsis
⑤ Thermal / mechanical injury [Burns, prosthetic valve ...]

G6PD : non immune hemolytic anemia

- x-linked Recessive
- defect in pentose pathway

G-6-P-D
G-6-P → 6-PG
NADP + → NADPH used to reduce Glut

⊛ female عشان يكون عندها G6PD لازم عند الـ carrier mother & affected father

- Turner (45,XO)
- loiNization → X-inhibition

[Strong antioxidant]

stress الـ اللي بسبب الـ hemolysis

① infection : أكثر اشي
② Drug : sulfa drug
③ Fava beans : أقل اشي

إذا تعرضت لـ oxidant ⇐ onset of oxidant خلال 48 ساعة

⊛ الـ severity تختلف من شخص لآخر :

① level of enzyme deficiency
② oxidant type & amount

enzyme activity في حالة الـ mutations الـ تؤثر على الـ G6PD ، أحياناً تكون

⊛ enzyme level الـ عند الشخص الـ طبيعي G6PD عشان نشخص الشخص متى أعمله ؟

لو عملت له at time of presentation ⇐ normal

Reticulocyte count الـ بيكون عالي نتيجة الـ hemolysis . enzyme activity الـ بيكون normal in Reticulocytes لأنه لسه بدأ يكون في الـ old RBCs أقل شغلة في الـ

∴ if normal G6PD level You can't exclude G6PD

لازم تعيده بعد أسبوعين .

⊛ G6PD level at presentation ⇐ متى بنعمل أعمل ؟

in low Retics count

⊛ managment :

[Blood transfusion] :

① if Hgb < 7 ② Hgb 7-8 ③ if Hgb > 8

hemolysis الـ بنعمل فيه بناء على الـ مزاج الطبيب

- hemolysis stopped → Stable Hgb, Urinanalysis ⊖ blood → No need for transfusion
- ongoing process → decrease Hgb, Urinanalysis ⊕ blood → blood transfusion

Blood film ⇐ G6PD ⊛ لما بدي أعمل الـ

أشوف Heinz body, due to denaturation of RBC DNA

وبتم after onset of hemolysis بـ 48h

Approach to a Case of Anemia

A. History

* Onset: - Neonatal e.g. G6PD, spherocytosis
  - After 6 month e.g. β thalassemia, sickle cell anemia.
* Past history:
  - Hemorrhage
  - Drugs which may induce (aplasia, acute hemolysis in G6PD deficiency).
  - Infection or fava beans → G6PD deficiency.
  - Family history → similar cases & consanguinity for inherited causes.

B. Clinical approach

- Features of bone marrow failure(pallor,purpura,pyrexia)
- Features of hemolytic anemia: - Acute hemolysis(see page 219)
  - Chronic hemolysis(see page 222)
- Anemia with congenital anomalies: - Fanconi anemia.
  - Diammond Blackfan anemia.
- Anemia with: - GIT upset → Folic acid deficiency
  - Neurologic disorders → B_{12} deficiency

C. Laboratory approach

1. Confirm Anemia → ↓ Hb% & ↓ RBCs count.

2. Anemia with other hematologic abnormalities(e.g.purpura):

Consider: - Aplastic anemia
- Leukemia
- Other bone marrow replacement disorders.

3. Anemia without other hematologic abnormalities⇒Assess reticulcytic count

a. Low / normal reticulocytic count ⇒ check RBCs size :

- MCV < 70 fl→ **microcytic anemia** (for differential diagnosis ;see page 215)
- MCV > 85 fl → **macrocytic anemia;**

Causes:

With megaloblastic changes	Without megaloblastic changes
- Folic acid and B12 deficiency - Thiamine responsive megaloblastic anemia - Orotic aciduria - Lesch Nyhan syndrome	- Normal newborn - Reticulocytosis - Postsplenectomy - Aplastic anemia - Diamond Blackfan syndrome - Liver disease - Hypothyroidism - Paroxysmal nocturnal hemoglobinuria.

✧Normal MCV(72-79 fL) → **normocytic anemia**

Causes: - Acute blood loss
- Bone marrow infilteration
- Anemia of chronic disease(infection,connective tissue disorder)
- Chronic renal failure
- Hemolysis(enzyme deficiency,membrane defect)

b. High reticulocytic count ⇒ check for serum bilirubin:

✧ Normal → hemorrhagic anemia

✧ High → hemolytic anemias

4- Cases with hemolytic anemia is subjected to Coomb's test:

✧ Positive Coomb's test: Immune hemolytic anemia .

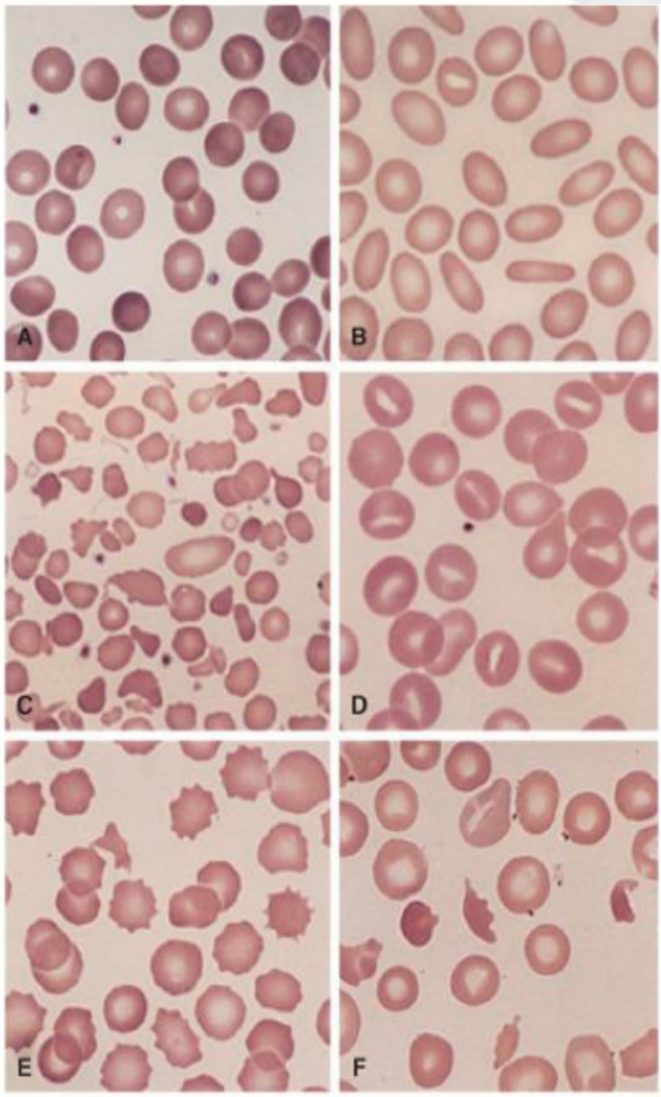
✧ Negative Coomb's test : Other causes of hemolytic anemia(see page 210)

5- Detailed peripheral blood smear :

⌖Sherocytosis:
- Hereditary sherocytosis
- Pyruvate kinase deficiency
- Auto immune hemolytic anemia
- ABO incompitability
- Microangiopathic hemolytic anemia
- Hypersplenism
- Burn
- Sickle cell disease
- Severe hypophosphatemia

⌖Target cells:
- Thalassemia
- Severe iron deficiency
- Hyposplenism
- Hemoglobinopathy; Hb SC, Hb E

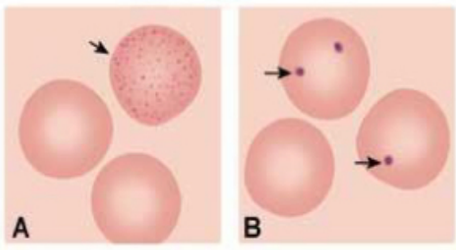
⌖Blister cells(area under membrane free of hemoglobin): G6PD deficiency .



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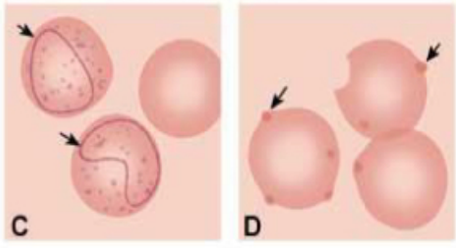
Figure 458-3 Morphology of abnormal red cells. *A,* Hereditary sphe-rocytosis; *B,* hereditary elliptocytosis; *C,* hereditary pyropoikilocytosis; *D,* hereditary stomatocytosis; *E,* acanthocytosis; *F,* fragmentation hemolysis

Basophilic stippling
Representing aggregated ribosomes
1. thalassemia syndromes
2. iron deficiency
3. lead poisoning



Howell- jolly bodies
Nuclear remnants
1. asplenia
2. pernicious anemia
3. severe iron deficiency

Cabots ring bodies
Nuclear remnants
1. lead toxicity
2. pernicious anemia
3. hemolytic anemias



Heinzs bodies
Denatured aggregated hemoglobin
1. thalassemia,
2. asplenia
3. G6PD disease
4. chronic liver disease

Approach to assessing the common causes of anemia in children.

Historical Clues in Evaluation of Anemia

Variable	Comments
Age	Iron deficiency rare in the absence of blood loss before 6 mo in term or before doubling birth weight in preterm infants
	Neonatal anemia with reticulocytosis suggests hemolysis or blood loss; with reticulocytopenia, suggests bone marrow failure
	Sickle cell anemia and β-thalassemia appear as fetal hemoglobin disappears (4-8 mo of age)
Family history and genetic considerations	X-linked: G6PD deficiency Autosomal dominant: spherocytosis Autosomal recessive: sickle cell anemia, Fanconi anemia
	Family member with early age of cholecystectomy (bilirubin stones) or splenectomy
	Ethnicity (thalassemia in individuals of Mediterranean origin; G6PD deficiency in blacks, Greeks, and Middle Eastern individuals)
	Race (β-thalassemia in individuals of Mediterranean, African, or Asian descent; α-thalassemia in blacks and those of Asian descent; SC and SS in blacks)
Nutrition	Cow's milk diet: iron deficiency
	Strict vegetarian: vitamin B_{12} deficiency
	Goat's milk: folate deficiency
	Pica: plumbism, iron deficiency
	Cholestasis, malabsorption: vitamin E deficiency
Drugs	G6PD: oxidants (e.g., nitrofurantoin, antimalarials)
	Immune-mediated hemolysis (e.g., penicillin)
	Bone marrow suppression (e.g., chemotherapy)
	Phenytoin, increasing folate requirements
Diarrhea	Malabsorption of vitamins B_{12} or E or iron
	Inflammatory bowel disease and anemia of chronic disease with or without blood loss
	Milk protein intolerance-induced blood loss
	Intestinal resection: vitamin B_{12} deficiency
Infection	*Giardia:* iron malabsorption
	Intestinal bacterial overgrowth (blind loop): vitamin B_{12} deficiency
	Fish tapeworm: vitamin B_{12} deficiency
	Epstein-Barr virus, cytomegalovirus: bone marrow suppression, hemophagocytic syndromes
	Mycoplasma: hemolysis
	Parvovirus: bone marrow suppression
	HIV
	Chronic infection
	Endocarditis
	Malaria: hemolysis
	Hepatitis: aplastic anemia

Physical Findings in the Evaluation of Anemia

System	Observation	Significance
Skin	Hyperpigmentation	Fanconi anemia, dyskeratosis congenita
	Café-au-lait spots	Fanconi anemia
	Vitiligo	Vitamin B_{12} deficiency
	Partial oculocutaneous albinism	Chédiak-Higashi syndrome
	Jaundice	Hemolysis
	Petechiae, purpura	Bone marrow infiltration, autoimmune hemolysis with autoimmune thrombocytopenia, hemolytic uremic syndrome, hemophagocytic syndromes
	Erythematous rash	Parvovirus, Epstein-Barr virus
	Butterfly rash	SLE antibodies
Head	Frontal bossing	Thalassemia major, severe iron deficiency, chronic subdural hematoma
	Microcephaly	Fanconi anemia
Eyes	Microphthalmia	Fanconi anemia
	Retinopathy	Hemoglobin SS, SC disease
	Optic atrophy	Osteopetrosis
	Blocked lacrimal gland	Dyskeratosis congenita
	Kayser-Fleischer ring	Wilson disease
	Blue sclera	Iron deficiency
Ears	Deafness	Osteopetrosis
Mouth	Glossitis	Vitamin B_{12} deficiency, iron deficiency
	Angular stomatitis	Iron deficiency
	Cleft lip	Diamond-Blackfan syndrome
	Pigmentation	Peutz-Jeghers syndrome (intestinal blood loss)
	Telangiectasia	Osler-Weber-Rendu syndrome (blood loss)
	Leukoplakia	Dyskeratosis congenita
Chest	Shield chest or widespread nipples	Diamond-Blackfan syndrome
	Murmur	Endocarditis: prosthetic valve hemolysis; severe anemia
Abdomen	Hepatomegaly	Hemolysis, infiltrative tumor, chronic disease, hemangioma, cholecystitis, extramedullary hematopoiesis
	Splenomegaly	Hemolysis, sickle cell disease, (early) thalassemia, malaria, lymphoma, Epstein-Barr virus, portal hypertension
	Nephromegaly	Fanconi anemia
	Absent kidney	Fanconi anemia
Extremities	Absent thumbs	Fanconi anemia
	Triphalangeal thumb	Diamond-Blackfan syndrome
	Spoon nails	Iron deficiency
	Beau line (nails)	Heavy metal intoxication, severe illness
	Mees line (nails)	Heavy metals, severe illness, sickle cell anemia
	Dystrophic nails	Dyskeratosis congenita
Rectal	Hemorrhoids	Portal hypertension
	Heme-positive stool	Gastrointestinal bleeding
Nerves	Irritable, apathy	Iron deficiency
	Peripheral neuropathy	Deficiency of vitamins B_1, B_{12}, and E, lead poisoning
	Dementia	Deficiency of vitamins B_{12} and E
	Ataxia, posterior column signs	Vitamin B_{12} deficiency
	Stroke	Sickle cell anemia, paroxysmal nocturnal hemoglobinuria
General	Small stature	Fanconi anemia, HIV, malnutrition