HLS

SHEET NO. 2

PATHOLOGY

كتابة: دكتور 021

تدقيق: زينة أبو ذياب و أحمد الكاشف

الدكتور: طارق العديلي

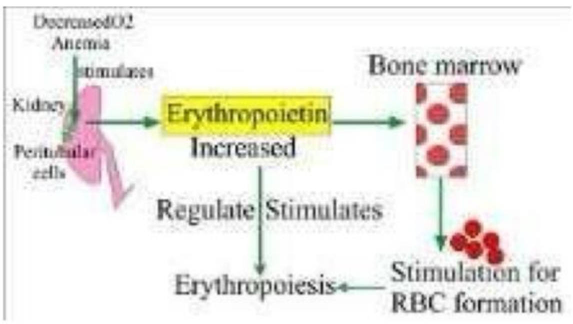
ANEMIA

Definition (the opposite of polycythemia)

- **Anemia is Reduction of oxygen carrying capacity of blood secondary to decrease in red cell mass** (the blood is no longer capable of delivering oxygen)
- **Leads to tissue hypoxia**
- **Practically, measured by Hemoglobin concentration, and Hematocrit,** they become below normal level.

Anemia and erythropoietin (What is the pathophysiology of anemia?)

- **Anemia** (leading to hypoxia) **triggers production of erythropoietin,** many organs will suffer from hypoxia including the kidney which will secrete more erythropoietin when it senses the hypoxia, that **activates the erythropiosis in bone marrow**
- **Causes compensatory erythroid hyperplasia in bone marrow (BM)**
- **In acute anemia, production can increase by 5x or more in healthy people,** Erythropoietin production can increase RBC production 5 folds in acute anemia, it's a potent hormone and in healthy patients the compensation is fast and complete, so we have good reserve and efficiency in the production of RBCs in acute anemia
- **In severe cases** (anemia is persistent for a long time, so erythropoietin is high for along time too) **causes extramedullary hematopoiesis in secondary hematopoietic organs** "reticuloendothelial organs" **(spleen, liver, and lymph nodes)**, here we have production of RBCs "hematopoiesis" outside the bone marrow
- **<u>Anemia is associated with increased erythropoietin but with</u>** <u>**exceptions**</u>:



1. **anemia of renal failure** (kidney is the organ responsible for erythropoietin production, so simply the kidneys can't function well)

2. **anemia of chronic Inflammation**,

here in the two cases the erythropoietin is suppressed

Classification according to cause (etiology)

3 main categories

1- Blood loss

2- Diminished (decreased) RBC production (Decreased bone marrow production, MOST COMMON anemias, and usually it's nutritional)

- **Iron deficiency anemia**
- **Anemia of chronic inflammation**
- **Megaloblastic anemia**
- **Aplastic anemia**
- **Pure red cell aplasia**
- **Myelophthisic anemia**
- **Myelodysplastic syndrome**
- **Anemia of renal failure**
- **Anemia of hypothyroidism**

3- Increased destruction (hemolytic anemia)

normal bone marrow, but RBCS die early outside the bone marrow, there is problem in the RBCs itself, abnormal shape or defect, so they are destroyed easily

- **Extrinsic factors**
  (infection, antibody, mechanical)
- **Intrinsic RBC abnormalities:**
  1)Hereditary (membrane, enzyme, Hg abnormalities)
  2)Acquired (Paroxysmal nocturnal hematuria

Destruction either happens outside of the RBCs (induced by other factors e.g., malaria induced hemolysis or (mechanical damage), Or it happens inside the RBC due to a preexisting defect

Classification according to morphology blood film

Blood smear (examination of blood samples via microscope).

We use this classification to reach to a diagnosis (How we decide what kind of anemia the patient has). We preform a blood smear then use automated devices for testing. This how we preform a CBC (complete blood count).
Normal values differ slightly between different testing devices.

- **Size: Normo, Micro, Macrocytic (MCV =mean cell volume)**

  normal diameter of RBCs is 7 µm but if we do not have measurement how should we know? We usually compare the RBC to a lymphocyte nucleus to judge on its size (the size of one RBC is similar in diameter to a lymphocyte's nucleus), if they were in the same size then it is normocytic anemia, smaller = microcytic anemia, bigger = macrocytic anemia.
  We can use MCV, without looking at the blood smear this value can reflect the size of the cells, normal range from 80 to 100 fL, if the value was less than 80 fL = microcytic, more than 100 fL= macrocytic) fL=fimtoleters

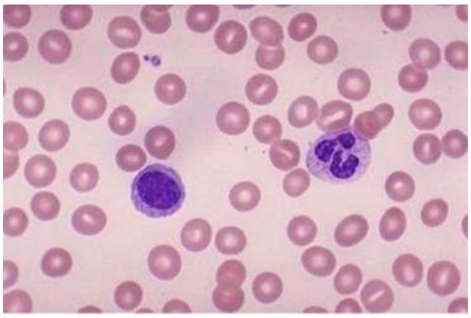
- **Color: Normo, Hypochromic (MCH)**

  - reflects the content of hemoglobin, if it was low and below normal = hypochromic anemia, higher=hyperchromic)
  - normally the RBCs are biconcave in shape, the center is thin, so it appears pale (central pallor) and occupies 1/3 of the total diameter. If the RBCs still have this shape, then it is called normochromic anemia (no changing in the content), if all of it was white and little red hemoglobin= hypochromic anemia, if all of it was red with no central pallor=hyperchromic anemia
  - usually normocytic goes with normochromic anemia, microcytic with hypochromic anemia, macrocytic with hyperchromic anemia (with some exceptions)

- **Shape, we see if the cells similar in shape or there is abnormal figures "Anisopoikelocytosis" (An= non, iso=similar, poikelo=shape) like (spherocytes, sickle, schistiocytes), we can use (RBC distribution width "RDW' which Reflects Anisopoikelocytosis, if it was High = abnormal shapes, different from each other)**

In general, Hypochromic microcytic anemia usually reflects impaired Hg synthesis, Hg contains (iron) and globulin(protein), so patients with iron deficiency or thalassemia or have problems with globulin synthesis, will give identical picture, hypochromic microcytic anemia

Macrocytic anemia reflects stem cell disease and defect in maturation



RBC indices

In the good old days poor physicians had to do everything manually even counting RBCs and WBCs - thank God for technology- back then a physician could barely get the results for 10 patients in a day, now we can get thousands in a way shorter time

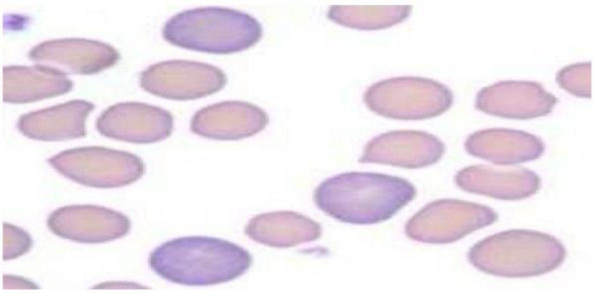
- **Can be directly measured, or automated**

- **Slight variation is present between labs** (they are close to each other but sometimes there's slight variation)**, geographic areas (in high altitude, normally there is higher Hb conc.)**

- **Sex** (males typically have higher Hb concentrations due to androgens, while females may have lower levels during menstruation), **age** (infants has low Hb then increases to reach adults ranges), **race** (African populations may have lower Hb levels compared to others due to genetic factors)**, and mobility status** (less physical activity like elderly can be associated with lower Hb concentrations)

- **Reticulocyte count**(normally 1-2% of total RBCs , the life span is almost one day then they get smaller and become mature RBCs) **is used to distinguish between hemolytic anemia** (where there is an increased destruction of red blood cells, prompting the bone marrow to produce more reticulocytes (immature red blood cells that doesn't have nucleus) meaning high reticulocyte count) **and aregenerative anemia** (occurs when the bone marrow fails to produce an adequate number of red blood cells, resulting in a low reticulocyte count.) So, the reticulocyte count reflects the status of bone marrow, if it's functioning or not
  - **Anemia with high reticulocyte levels = bone marrow is functioning**
  - **Anemia with low reticulocyte levels= bone marrow is not functioning**

-Reticulocytes in morphology are bigger than RBCs and have slight blue color, they have DNA streaks which make it slightly basophilic.



	Units	Men	Women
Hemoglobin (Hb)	g/dL	13.2–16.7	11.9–15.0
Hematocrit (Hct)	%	38–48	35–44
Red cell count	$\times 10^6/\mu L$	4.2–5.6	3.8–5.0
Reticulocyte count	%	0.5–1.5	0.5–1.5
Mean cell volume (MCV)	fL	81–97	81–97
Mean cell Hb (MCH)	pg	28–34	28–34
Mean cell Hb concentration (MCHC)	g/dL	33–35	33–35
Red cell distribution width (RDW)		11.5–14.8	

*Reference ranges vary among laboratories. The reference ranges for the laboratory providing the result should always be used in interpreting a laboratory test.

As we said before there's always a slight variation so always looks at the normal range, There's also a slight difference due to different ages races and sex and there's always exceptions e.g., in pregnancy (lower hb), neonates (higher hb).

Here is a brief summary for the main ideas of the first part of this lecture, amazingly easy!!

Category	Details
Definition	- Reduction in oxygen-carrying capacity of blood due to decreased RBC mass, leading to tissue hypoxia.
Pathophysiology	- **Tissue Hypoxia**: Decreased oxygen delivery to tissues due to insufficient hemoglobin (Hb) or red blood cells (RBCs).
	- **Erythropoietin Response**: Hypoxia stimulates kidneys to produce erythropoietin, a hormone that promotes RBC production in the bone marrow.
	- **Bone Marrow Activation**: Erythropoietin activates erythropoiesis in the bone marrow, leading to increased production of red blood cells.
	- **Acute vs. Chronic Response**: In acute anemia, erythropoietin levels can rise rapidly (up to 5x) to compensate for blood loss.
	- **Extramedullary Hematopoiesis**: In chronic cases, if anemia persists, the body may start producing RBCs in other organs (spleen, liver) due to prolonged high erythropoietin levels.
	- **Bone Marrow Reserve**: Healthy individuals have a good reserve and efficiency in producing RBCs; however, persistent anemia may exhaust this reserve.
	- **Exceptions**: In anemia of renal failure, erythropoietin production is low due to impaired kidney function. In anemia of chronic inflammation, erythropoietin production is suppressed despite tissue hypoxia.
Classification by Cause	1. **Blood Loss** (e.g., trauma, GI bleeding)
	2. **Decreased RBC Production** (e.g., iron deficiency, chronic inflammation, renal failure, hypothyroidism)
	3. **Increased RBC Destruction (Hemolytic)** (e.g., hereditary spherocytosis, sickle cell disease, mechanical damage)
Morphological Classification	**Size**: Normocytic, Microcytic, Macrocytic
	Color: Normochromic, Hypochromic Hyperchromic
	Shape: Abnormal shapes (Anisopoikilocytosis) – e.g., Spherocytes, Sickle Cells, Schistocytes
Blood Smear	- Examines RBC size, color, and shape to classify anemia types.
	- Uses a Complete Blood Count (CBC) and reticulocyte count to further diagnose.
Reticulocyte Count	- **High reticulocyte count**: indicates bone marrow is functioning (e.g., hemolytic anemia).
	- **Low reticulocyte count**: indicates bone marrow dysfunction (e.g., aplastic anemia).
Additional Factors	- Variations in normal ranges due to sex, age, race, geography (e.g., higher Hb levels at high altitudes, lower in women due to menstruation).

Clinical features of anemia

- All anemia cause **Hypoxia** (Systemic Hypoxia)
- **Dizziness** due to hypotension
- **Fatigue** due to hypoxia
- **Pallor** obvious when examining the conjunctiva, nail-beds, sclera of the eye.
- **Headache** due to the hypotension

Adaptive changes: (with prolonged hypoxia)

- **Tachycardia**
- **Tachypnea** (faster respiration to bring more oxygen)
- **Increased red cell 2,3-diphosphoglycerate.** Facilitates the delivery of O2 (This molecule binds to hemoglobin and, in doing so, effectively displaces oxygen molecules, making it easier for hemoglobin to unload oxygen where it's needed most)

If the patient has heart or lung diseases, symptoms will be worse

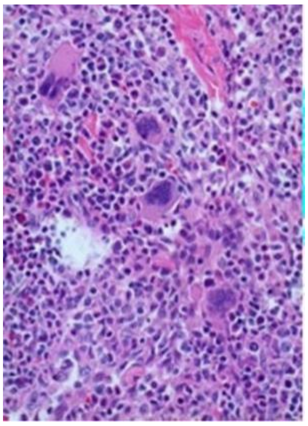
Cinical symptoms in special types of anemia

1- Chronic hemolytic anemia: jaundice, pigmented gall bladder stones, red urine

Hemolysis-> degradation of hemoglobin-> turns to bilirubin which is not soluble and gets deposited in tissue and causes the yellowish discoloration (jaundice)
It also forms pigmented (dark) gallbladder stones different from the cholesterol white stones,
Hemoglobin also after RBCs hemolysis could pass through the kidney and cause red coloration of the urine (not bleeding)
All of that are symptoms of anemia in addition of the general symptoms

2- **Extramedullary hematopoiesis: splenomegaly, hepatomegaly**

3- **Thalassemia major and sickle cell anemia: growth retardation, bone deformity (prominent cheeks and jaw), secondary hemochromatosis (damage to heart, endocrine glands)** **Due to prolonged exposure to high levels of erythropoietin**



Prolonged exposure to erythropoietin can also suppress the hormone hepcidin, which plays a crucial role in blocking iron absorption. As a result, patients may absorb excessive amounts of iron from their diet, and since the body has limited mechanisms to excrete iron (primarily through the normal shedding of epithelial cells), it can accumulate in tissues, including the heart (leading to cardiomegaly and potentially heart failure) and endocrine glands, causing physical damage and in this phase it's usually fatal (secondary hemochromatosis).

These patients do not grow normally due to hypoxia, have enlarged abdomen (enlarged spleen and liver : if you take a tissue biopsy they'll look like bone marrow and you'll see Megakaryocytes, myeloid, erythroyed cells, They also have a distinctive bone shape : short structure, special skull shape called sickle face (large cheeks and forehead because of the increase of hematopoietic cells)

Anemia of acute blood loss

Sudden and fast, could cause brain and major organ tissue necrosis leading to death

-Symptoms are related to decreased intravascular volume (hypovolemia and hypotension)

-If loss is >20% of blood volume, patient might have hypovolemic shock and die **We worry the most of shock so we could give fluids and depend on bone marrow to compensate the RBCs loss**

- If a patient survived blood loss, the body responds by shifting fluid from interstitial to intravascular space, causing dilutional anemia and worse hypoxia (stays 2-3days)

Dilutional anemia occurs when a patient experiences bleeding that is subsequently stopped. For example, if a patient initially had a hemoglobin (Hb) concentration of 14 g/dL before bleeding, and it decreased to 10 g/dL due to the bleeding, it's not uncommon to find that the Hb concentration may decrease further to 8 g/dL after a few days. This decline does not necessarily indicate ongoing bleeding but is a result of a normal physiological response – the body shifts fluids from surrounding tissues into the bloodstream to restore blood volume, leading to a dilution effect on Hb concentration.

-Erythropoietin secretion is stimulated, activating BM erythropoiesis (needs 5-7days)

-In internal hemorrhage, iron is reclaimed from extravasated RBCs and used again in erythropoiesis

-In external and GIT hemorrhage, iron is lost (iron deficiency**), which complicates anemia**

-The anemia is normochromic, normocytic, with reticulocytosis **(bone marrow is active**

Anemia of chronic blood loss (it is always external)

Rises from the gradual loss of blood in small amounts over an extended period

- **Occurs when the rate of RBC loss exceeds regeneration**
- **Mostly occurs in gastrointestinal diseases (**Peptic ulcers, hemorrhoids, colon cancer, small bowel inflammation), **also in excessive menstruation**
- **Results in iron deficiency, anemia appears hypochromic and microcytic, low reticulocytes** (decreased production).

In this case there's always iron deficiency unlike acute blood loss anemia (deficiency only happens with external bleeding).

TEST YOURSELF

1. In anemia, what stimulates the production of erythropoietin in response to decreased oxygen-carrying capacity?

A) High iron levels

B) Low reticulocyte count

C) Tissue hypoxia

D) Elevated bilirubin levels

2. In patients with extramedullary hematopoiesis, which organs are most likely to become enlarged?

A) Lungs and kidneys

B) Spleen and liver

C) Heart and brain

D) Stomach and pancreas

3. Reticulocyte count is used to distinguish between:

A) Hypothyroidism and hyperthyroidism

B) Hemolytic anemia and aregenerative anemia

C) Iron-deficiency anemia and megaloblastic anemia

D) Sickle cell anemia and thalassemia major

4. What is a typical clinical feature of chronic hemolytic anemia?

A) Cyanosis

B) Jaundice

C) Hypertension

D) Increased platelet count

5. which clinical symptom is commonly associated with anemia with prolonged hypoxia?

A) High blood pressure

B) Tachycardia

C) Increased oxygen saturation

D) Improved exercise tolerance

6. What is the term for the physiological response that leads to a decrease in hemoglobin concentration after bleeding has stopped?

A) Hypoxia

B) Dilutional anemia

C) Reticulocytosis

D) Hemolysis

Answers: 1)C / 2)B / 3)B / 4)B / 5)B / 6)B