**Anemia (I)**

Hematopoiesis is defined as the process of formation and development of blood cells. The pluripotent hematopoietic stem cell (HSC) maintains itself by self-renewal and undergoes multilineage differentiation to generate the appropriate numbers and types of cells in the circulating blood compartment.

The bone marrow must have the capacity to produce cells to compensate for the normal rapid turnover of hematopoietic cells resulting from senescence, normal use, and migration into tissue spaces. It must have a reserve capacity to produce additional cells in response to unusual demands that arise from bleeding, infection, or other stresses.

Early in life, all fetal bones contain regenerative bone marrow, but the marrow becomes progressively replaced by fat with age. In adults, active marrow resides only in the axial skeleton (i.e., Sternum, vertebrae, pelvis, and ribs) and in the proximal ends of the femur and humerus. Consequently, bone marrow samples, which are needed for many hematologic diagnoses, are usually obtained from the iliac crest or sternum. The amount of hemoglobin is maintained by erythropoietin, the hormone secreted by renal peritubular cells which is responsible for stimulating the bone marrow to synthesize RBC.

Under pathological conditions that stress the capacity of the marrow space, as in severe inherited hemolytic anemia (e.g., Thalassemia major), extramedullary hematopoiesis may be reestablished in sites of fetal hematopoiesis, especially the spleen.

**Function and structure of RBCs**

The main function of red blood cells (RBCs), or erythrocytes, is to deliver oxygen to tissues in the body and carry carbon dioxide back to the lungs for excretion. The erythrocyte has a biconcave disk shape that maximizes the membrane surface area for gas exchange, and it has a cytoskeleton and membrane structure that allows it to deform sufficiently to pass through the microvasculature. An RBC has the ability to pass through capillaries whose diameter may be one fourth the resting diameter of it.

**Hemoglobin**

Hemoglobin is a protein specially adapted for oxygen transport. It is composed of four globin chains, each surrounding an iron-containing porphyrin pigment molecule termed haem. Globin chains are a combination of two alpha and two non-alpha chains; there are several different types of globin chains, named alpha, beta, delta, and gamma.

Normal hemoglobin types include:

- Hemoglobin A (Hb A): makes up about 95%-98% of hemoglobin found in adults; it contains two alpha (α) chains and two beta (β) protein chains.

- Hemoglobin A2 (Hb A2): makes up about 2%-3% of hemoglobin found in adults; it has two alpha (α) and two delta (δ) protein chains.

- Hemoglobin F (Hb F, fetal hemoglobin): makes up to 1%-2% of hemoglobin found in adults; it has two alpha (α) and two gamma (γ) protein chains. It is the primary hemoglobin produced by the fetus during pregnancy; its production usually falls shortly after birth and reaches the adult level within 1-2 years.

Each haem molecule contains a ferrous ion (Fe2+) to which oxygen reversibly binds; the affinity for oxygen increases as successive oxygen molecules bind. When oxygen is bound, the beta chains ‘swing’ closer together; they move apart as oxygen is lost.

Anemia

Anemia is strictly defined as a decrease in RBC mass. It will lead to diminish the ability of blood to transport oxygen and carbon dioxide.

Anemia is, with no doubt, a sign of an underlying condition and should never be treated before the diagnosis of this condition.

In general, the causes of anemia can be divided into:

 ***1- blood loss (whether acute or chronic)***

 ***2- Increased destruction of RBCs (hemolysis)***

 ***3- Decreased production of RBCs.***

Each of the above three causes includes multiple medical conditions of various etiology:

 **1- Genetic etiology:**

A- Hemoglobinopathies (Thalassemia, Sickle cell anemia)

B- Hereditary spherocytosis

C- Sideroblastic anemia

 **2- Dietary etiology:**

A- Iron deficiency

B- Vitamin B-12 deficiency

C- Folate deficiency

 **3- Physical etiology**

A- Trauma

B- Burn

 **4- Chronic disease and malignant etiologies include the following:**

A- Chronic renal disease

B- Chronic hepatic disease

C- Chronic infections

**Signs and symptoms**

Symptoms of anemia depend on the following factors:

1. severity of anemia
2. rapidity of decrease of RBC mass
3. the underlying cause of anemia
4. Presence of comorbid diseases

The main clinical features of anemia include:

1- Fatigue

2- Decreased exercise tolerance.

3- Dyspnea

4- Palpitations

5- In patients with coronary artery disease, anemia may precipitate angina.

6- a hypovolemic shock in case of acute and severe hemorrhage

7- lack of concentration and impaired memory

8- anorexia

On physical examination:

1- Pallor is the major sign of anemia.

2- Tachycardia

3- Audible flow murmurs.

4- Jaundice and splenomegaly in patients with hemolysis.

Oral manifestation of anemia

1- Glossitis

2- Angular stomatitis

3- Recurrent periodontitis

4- Pallor of mucous membranes

**Approach to a patient with anemia**

Because of the wide range of medical conditions that might be associated with anemia, a careful and scientific approach is mandatory before making a correct diagnosis.

The physician should never start any treatment for anemia before a clear diagnosis is made as serious medical conditions might be missed.

Beside the presenting signs and symptoms of the patients, laboratory investigations are crucial for making a correct diagnosis.

- Measurement of hemoglobin (Hb) and/or packed cell volume (PCV) are the most common initial laboratory test used to confirm the presence of anemia.

The normal range of Hb. for an adult is:

Male: 13–18 g/dL

Female: 11.5–16.5 g/dL

- A rational approach to determining etiology is to begin by examining the peripheral smear and laboratory values obtained on the blood count.

According to mean corpuscular volume (MCV), anemia is divided into:

**1- Microcytic anemia (anemia with low MCV):**

Causes: A- Iron deficiency

 B- Thalassemia

 C- Lead poisoning

 D- Sideroblastic anemia

**2- Normocytic anemia (anemia with normal MCV):**

Causes: A- Chronic disease

 B- Chronic renal failure

 C- Aplastic anemia

**3- Macrocytic anemia (anemia with high MCV)**

Causes: A- Megaloblastic anemia

 - B12 deficiency

 - Folate deficiency

 B- Nonmegaloblastic

 - Chronic liver disease

 - Hypothyroidism

 - Alcoholism

There is another large group of causes of anemia called hemolytic anemia. The most important initial lab. test for the diagnosis of hemolytic anemia is the measurement of reticulocyte count which is expected to be high in these conditions. Hemolytic anemia is characterized by the presence of jaundice (high TSB).

Examples of hemolytic anemia include:

 A- G6PD deficiency

 B- Sickle cell anemia

***Reticulocytes* are defined as immature red blood cells, composing about 1% of the red blood cells in normal condition. During the process of  erythropoiesis, reticulocytes develop and mature in the  bone marrow and then circulate for about a day in the blood stream before developing into mature red blood cells. Like mature red blood cells, reticulocytes do not have a cell nucleus. They are called reticulocytes because of a reticular (mesh-like) network of ribosomal RNA.**

 C- Hereditary spherocytosis

 D- Eclampsia



Iron Deficiency Anemia (IDA)

Around 30% of the total world population is anemic and half of these, some 600 million people, have an iron deficiency.

It occurs when iron losses or physiological requirements exceed absorption. The most common explanation in men and post-menopausal women is gastrointestinal blood loss.

In premenopausal women, iron deficiency is most frequently related to loss of iron with menstruation (about 15 mg per month) and during pregnancy (about 900 mg per pregnancy).

Iron is acquired in the diet from heme sources (i.e., meat) and from nonheme sources (e.g., vegetables such as spinach).

**Risk factors for the development of IDA**

1- Being a female (menstruation, lactation, pregnancy, and delivery)

2- Peptic ulcer

3- Vegetarians

4- Major surgery or physical trauma

5- Bariatric procedures, especially gastric bypass operations

6- Malabsorption

Accordingly, the causes of IDA are:

1. Blood loss

a. Acute blood loss: accident and surgery

b. Chronic blood loss: gastritis, peptic ulcer, hookworm infestation, hemorrhoids, and menstrual loss.

2. Increased demand: Infancy, adolescence, and pregnancy

3. Malabsorption: Postgastrectomy and Crohn’s disease

4. Inadequate diet

Physical signs of IDA are similar to other types of anemia, but there are specific signs and symptoms that characterize IDA which includes:

1- Koilonychia (spoon nails)

2- Pica (unusual desire for nonfood items, such as ice, dirt, paint)

3- Glossitis

1. Mild splenpmegaly might occur although it is uncommon

**Laboratory findings**

The mainstay of the diagnosis of iron deficiency is the peripheral blood iron indices. These include:

|  |  |
| --- | --- |
| **Expected findings** | **Lab. test** |
| Low  | Serum iron |
| Low  | Serum ferritin  |
| High  | Total iron-binding capacity (TIBC) |
| Low  | Transferrin saturation  |

In general, all or part of the following investigations are required:

a. The general blood picture: microcytic hypochromic.

b. Serum iron and ferritin are low while total iron-binding capacity (TIBC) is increased. Transferrin saturation is below 16%.

c. Bone marrow stains for iron reveal decreased or absent iron stores.

d. Stool examination for parasites and occult blood is useful for detection of the cause of iron deficiency.

e. Endoscopic and radiological examination of gastrointestinal tract is needed to detect the source of bleeding.

If the indirect measurement of iron indices does not definitively confirm or refute a diagnosis of iron deficiency, a therapeutic trial of iron supplementation may be considered. Alternatively, a bone marrow examination can be performed to provide a direct assessment of marrow iron stores.

**Treatment**

Unless the patient has angina, heart failure or evidence of cerebral hypoxia, blood transfusion is not necessary and oral iron supplementation is appropriate.

Ferrous sulphate 200 mg 8-hourly is a good choice.

The hemoglobin should rise by 10 g/L every 7–10 days and a reticulocyte response will be evident within a week. A failure to respond adequately may be due to non-compliance, continued blood loss, malabsorption or an incorrect diagnosis.

Parenteral iron should be reserved for patients who are either unable to absorb oral iron or who have increasing anemia despite adequate doses of oral iron. It is expensive and has greater morbidity than oral preparations of iron.

It should be mentioned that any surgical dental procedure should not be performed for a patient whose Hb. is less than 10 g/dl.

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