Anemia

Introduction

1-Anemia is a group of diseases characterized by a **decrease** in either hemoglobin (Hb) or the volume of red blood cells (RBCs), resulting in **decreased oxygen-carrying capacity of blood**.

2-The World Health Organization defines anemia as Hb less than **13** g/dL in men or less than **12** g/dL in women.

Pathophysiology

1-The functional classification of anemias is found in Fig. -1.

2- Morphologic classifications are based on **cell size**.

A-Macrocytic cells are larger than normal and are associated with deficiencies of vitamin B12 or folic acid.

B-Microcytic cells are smaller than normal and are associated with iron deficiency, whereas **normocytic anemia** may be associated with recent blood loss or chronic disease.

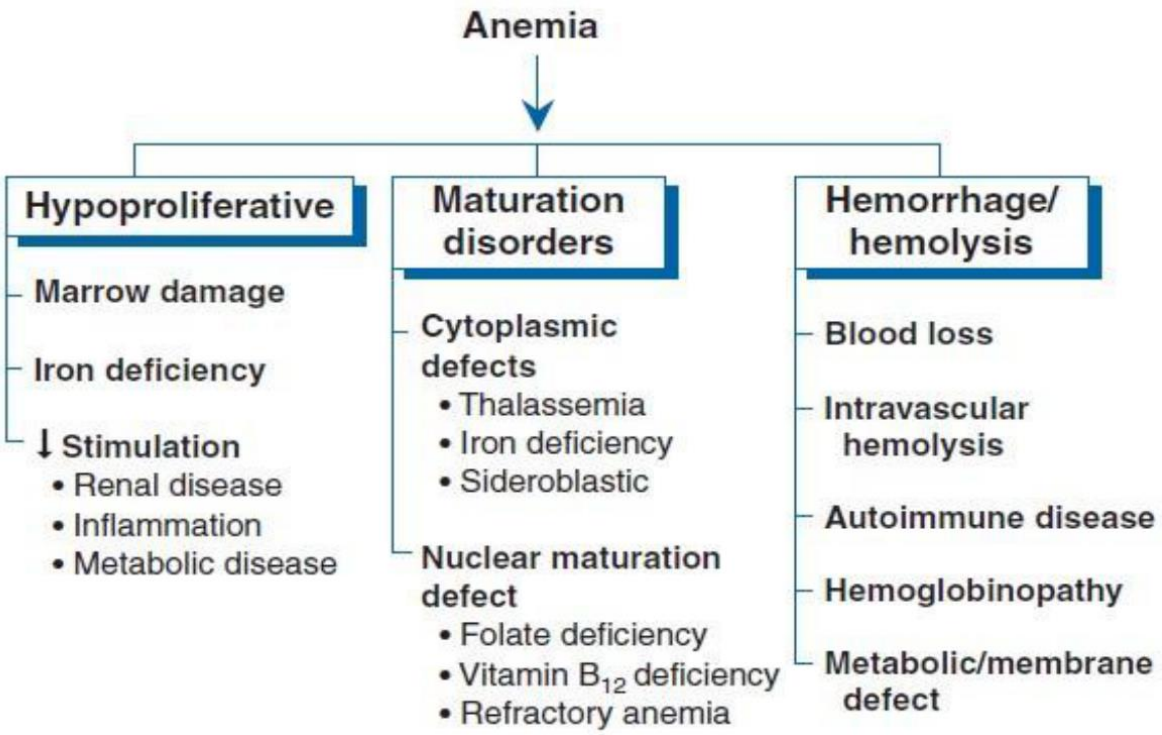

Figure-1. Functional classification of anemia

Hypo proliferative Anemia
➞ Problem: the bone marrow is not producing enough RBCs
Main mechanisms:
1. Marrow damage
Aplastic anemia
Marrow infiltration (leukemia, fibrosis, cancer)
2. Iron deficiency
Lack of iron → ↓ hemoglobin synthesis → ↓ RBC production
3. Decreased stimulation of marrow
Renal disease → ↓ erythropoietin
Chronic inflammation (anemia of chronic disease)
Metabolic diseases
The marrow is *capable*, but it is **under stimulated or lacks raw materials**

Maturation Disorders
➞ Problem: RBCs are produced but do not mature properly
1. Cytoplasmic defects (Hemoglobin synthesis problem)
Thalassemia
Iron deficiency
Sideroblastic anemia
(Leads mainly to **microcytic anemia**)
2. Nuclear maturation defects (DNA synthesis problem)
Folate deficiency
Vitamin B_{12} deficiency
Refractory anemia
(Leads to **macrocytic (megaloblastic) anemia**)
RBCs are made, but they are **abnormal in size or structure due to faulty maturation**

Hemorrhage / Hemolysis
➞ Problem: RBCs are lost or destroyed faster than they are made
Causes:
1. Blood loss (Acute or chronic hemorrhage)
2. Intravascular hemolysis
3. Autoimmune hemolytic anemia
4. Hemoglobinopathies (e.g., sickle cell disease)
5. Membrane or metabolic defects (G6PD deficiency, Hereditary spherocytosis)
The marrow may be normal or even hyperactive, but **RBC loss/destruction exceeds production**

3-Iron-deficiency anemia (IDA), characterized by decreased levels of ferritin (**most sensitive marker**) and serum iron, and decreased transferrin saturation, can be caused by inadequate dietary intake, inadequate gastrointestinal (GI) absorption, increased iron demand (e.g., pregnancy), blood loss, and chronic diseases.

4-Vitamin B12– and folic acid–deficiency anemias, macrocytic in nature, can be caused by inadequate dietary intake, malabsorption syndromes, and inadequate utilization.

A-Deficiency of intrinsic factor causes decreased absorption of vitamin B12 (i.e., pernicious anemia).

B-Folic acid–deficiency anemia can be caused by hyperutilization due to **pregnancy**, **hemolytic anemia**, **malignancy**, **chronic inflammatory disorders**, **long-term dialysis**, or **growth spurt**.

C-**Drugs** can cause anemia by **reducing absorption of folate** (e.g., phenytoin) or through **folate antagonism** (e.g., methotrexate).

5-Anemia of inflammation (AI) is a newer term used to describe both **anemia of chronic disease** and **anemia of critical illness**.

A-**AI** is an anemia that traditionally has been associated with malignant, infectious, or inflammatory processes, tissue injury, and conditions associated with release of proinflammatory cytokines.

Malignant, infectious, inflammatory diseases, and tissue injury cause anemia by **activating the immune system**, which releases **pro-inflammatory cytokines** (especially **IL-6**). These cytokines:
1. **Increase hepcidin** → iron is trapped in macrophages and ↓ intestinal iron absorption
2. **Reduce erythropoietin (EPO) production and response**
3. **Suppress bone marrow erythropoiesis**
4. **Shorten red blood cell lifespan**

➞ Result: **anemia of inflammation (hypo proliferative anemia)**, usually **normocytic or mildly microcytic**, with **low serum iron but normal/high ferritin**.

B-**Serum iron is decreased** but in contrast to IDA, the serum ferritin concentration is normal or increased.

1. Inflammation → ↑ IL-6 → ↑ hepcidin (from the liver)
Hepcidin blocks **ferroportin**, the iron-export channel.
2. Iron gets trapped in storage sites
Iron cannot leave **macrophages** or **liver**
Intestinal iron absorption is reduced
➞ **Serum iron** ↓ (little iron reaches the blood)
3. Ferritin behaves differently
Ferritin = iron storage protein
Ferritin is also an acute-phase reactant
Inflammation causes:
↑ iron storage inside cells
↑ ferritin production due to cytokines
➞ **Ferritin is normal or increased**, despite low serum iron

Clinical presentation

1-Acute-onset anemia is characterized by cardiorespiratory symptoms such as palpitations, angina, orthostatic light-headedness, and breathlessness.

2-Chronic anemia is characterized by weakness, fatigue, headache, orthopnea, dyspnea on exertion, vertigo, faintness, cold sensitivity, and pallor.

3-**IDA** is characterized by glossal pain, smooth tongue, reduced salivary flow, pica (compulsive eating of nonfood items), and pagophagia (compulsive eating of ice).

Glossal pain & smooth tongue (atrophic glossitis):
Iron is essential for **epithelial cell turnover,** iron deficiency → **atrophy of tongue papillae.** Loss of papillae makes the tongue **smooth, shiny and painful or burning.**

Reduced salivary flow (xerostomia):
Iron deficiency impairs **salivary gland enzyme activity that will** Leads to ↓ saliva production, dry mouth **and** oral discomfort

4-Neurologic effects (e.g., numbness and paraesthesisas) of **vitamin B12 deficiency** may **precede** hematologic changes. Psychiatric findings, including irritability, depression, and memory impairment, may also occur with vitamin B12 deficiency. **Anemia with folate deficiency is not associated with neurologic symptoms**.

Vitamin B12 is essential for **myelin synthesis,** deficiency → **demyelination of peripheral nerves and spinal cord and** nerve signal transmission become abnormal and this will lead to:
Paresthesias first (irritation of nerves) {**abnormal sensation without an external stimulus** like Tingling, Pins-and-needles, Crawling sensation}
Numbness second (loss of nerve function) {**loss or reduction of normal sensation**}. Patient feels the area is **"dead," "asleep," or less sensitive.** Commonly affects **hands, feet, fingers, toes**

Diagnosis

1-Rapid diagnosis is essential because anemia is **often** a sign of underlying pathology. Severity of symptoms **does not always** correlate with the degree of anemia.

2-Initial evaluation of anemia involves **a complete blood cell count (CBC)**, **reticulocyte index**, and **examination of the stool for occult blood**.

- Is **the bone marrow responding appropriately?** → ***Reticulocyte index.***
- Is **there ongoing blood loss (especially hidden GI bleeding)?** → ***Occult blood in stool.***

Reticulocytes are **young red blood cells** that is released from the **bone marrow and** mature into normal RBCs in **1–2 days.** So:
More reticulocytes = bone marrow is working harder.
So, if anemia occur, the reticulocyte index must be high to indicate that bone marrow tries to produce more RBC to compensate the anemia but if the reticulocyte index is normal or low despite the anemia this means that there is an inadequate response by the bone marrow (possible reasons like Iron deficiency, B12 deficiency, folate deficiency, anemia of inflammation, bone marrow failure)
Anemia + low reticulocyte index = underproduction anemia
Anemia + high reticulocyte index = loss or destruction of RBCs

3-The **earliest** and **most sensitive** laboratory change for **IDA** is **decreased serum ferritin (storage iron)**.

4-**In macrocytic anemias**, mean corpuscular volume is usually elevated. Vitamin B12 and folate concentrations can be measured to differentiate between the two deficiency anemias.

Mean Corpuscular Volume (MCV) = the **average size (volume)** of a red blood cell. Vitamin B12 and folate are required for DNA synthesis (DNA synthesis → normal cell division at the right time → normal-sized RBC).
B12 / folate deficiency: DNA synthesis is impaired→ Cell division is delayed→ Cytoplasm continues to grow → Nucleus matures slowly
Result: **Large cells that fail to divide on time**

5-In AI, serum iron is usually decreased, but, unlike IDA, serum ferritin is normal or increased. The peripheral smear reveals normocytic anemia.

➢ Treatment

Goals of Treatment: The goals are to return hematologic parameters to normal, restore normal function and quality of life, and prevent long-term complications.

❖ Iron-deficiency anemia

1-Oral iron therapy with soluble ferrous iron salts, which are not enteric coated and not slow or sustained release, is recommended at a daily dosage of 150–200 mg **elemental iron** in two or three divided doses.

2-Iron is best absorbed from meat, fish, and poultry. Administer iron at least **1 hour before meals** because food interferes with absorption, but administration with food may be needed to improve **tolerability**.

3-Consider parenteral iron for patients with **iron malabsorption**, **intolerance** of oral iron therapy, or **nonadherence**.

4-Iron dextran, sodium ferric gluconate, iron sucrose, ferumoxytol, and ferric carboxymaltose are available parenteral iron preparations with similar efficacy but different pharmacokinetics, bioavailability, and adverse effect profiles.

❖ Vitamin B12–deficiency anemia

1-Oral vitamin B12 supplementation is as **effective** as **parenteral**, even in patients with pernicious anemia, because the alternate vitamin B12 absorption pathway is independent of intrinsic factor.

the alternate pathway for vitamin B12 absorption occurs via **passive diffusion** of this vitamin across the intestinal mucosa. This pathway does not require intrinsic factor or receptor but it is **very inefficient** (Only **~1%** of an oral B12 dose is absorbed passively). To compensate this problem, high oral doses are administered.
Example: Oral dose = **1000 µg**
Absorbed passively ≈ **10 µg**
Daily requirement ≈ **2–3 µg**

2-Parenteral therapy acts more **rapidly** than **oral** therapy and is recommended if neurologic symptoms are present. Initiate daily oral cobalamin administration after symptoms resolve.

3-Continue vitamin B12 for life in patients with pernicious anemia.

❖ Folate-deficiency anemia

1-Oral folic acid, **1 mg daily for 4 months**, is usually sufficient for treatment of folic acid–deficiency anemia, unless the etiology cannot be corrected.

2-If malabsorption is present, a dose of **1–5 mg daily** may be necessary. Parenteral folic acid is available but **rarely** necessary.

❖ Anemia of inflammation

1-Treatment of AI is less specific than that of other anemias and should focus on **correcting reversible causes**. Reserve iron therapy for an established IDA; iron is not effective when inflammation is present. RBC transfusions are effective but should be limited to Hb of 7–8 g/dL.

2-Erythropoiesis-stimulating agents (ESAs) can be considered, but **response** can be impaired in patients with **AI**. Iron, cobalamin, and folic acid supplementation may **improve response** to ESA treatment.

ESA are drugs that **stimulate the bone marrow to produce red blood cells**, by acting like (or increasing the effect of) **erythropoietin (EPO) like epoetin alfa and darbepoetin alfa**. EPO is a hormone that is produced mainly by the **kidney** in response to **hypoxia/anemia to** stimulates **erythroid progenitor cells** in bone marrow.
In **anemia of inflammation (AI),** inflammatory cytokines ↓ endogenous EPO production and ↓ bone marrow responsiveness to EPO. Giving an ESA **pushes the marrow to make RBCs** but RBC production needs **raw materials (iron, cobalamin and folic)** and if those are missing → ESA response is **blunted. This why supplementation with these agents may improve response of ESAs**

3-Potential toxicities of **exogenous ESA** administration include increases in blood pressure, nausea, headache, fever, bone pain, and fatigue. Hb must be monitored during ESA therapy. An increase in Hb greater than 12 g/dL with treatment or a rise of greater than 1 g/dL every 2 weeks has been associated with **increased mortality and cardiovascular events**.

4-In patients with anemia of **critical illness**, **parenteral iron** is often used but is associated with a theoretical risk of infection.

❖ Anemia in pediatric populations

1-**Infants aged 9–12 months**: Administer ferrous sulfate 3–6 mg/kg/day (**elemental iron**) divided once or twice daily between meals for 4 weeks. Continue for **two additional months** in responders to **replace storage iron pools**.

2-The dose and schedule of vitamin B12 should be titrated according to clinical and laboratory response. The daily dose of folic acid is 1 mg.

➢ Evaluation of therapeutic outcomes

1-**IDA**: Positive response to oral iron therapy is characterized by an increase in Hb seen at 2 weeks. Hb should return to normal after 2 months; **continue** iron therapy until iron stores are replenished and serum ferritin normalized (**up to 12 months**).

2-**Megaloblastic anemia**: Signs and symptoms usually improve within a few days after starting vitamin B12 or folic acid therapy.