

ANEMIA

- Anemia is defined as the reduction of the red blood cells (RBC^S) volume or the hemoglobin (Hb) concentration below the range of values occurring in healthy persons.
- There may be racial differences in Hb levels. Black children have levels about 0.5 g/dl lower than whites & Asians, possibly, in part because of the high incidence of α -thalassemia in blacks.
- \downarrow Hb \rightarrow \downarrow O₂ carrying capacity of the RBC.

■ Physiological response to anemia

1. \uparrow cardiac output.
2. Shunting of the blood flow towards vital organs & tissues.
3. \uparrow 2,3-DPG (diphosphoglycerate) \rightarrow \downarrow affinity of Hb to O₂.
4. With \uparrow severity of anemia \rightarrow weakness, tachycardia, tachypnea, dyspnea on exertion, cardiac dilatation, & may be congestive heart failure (CHF).
5. \uparrow Erythropoietin (EPO) \rightarrow \uparrow RBC^S production by bone marrow \rightarrow \uparrow absolute reticulocyte count, but sometimes bone marrow losses it's usual capacity for RBC production due to bone marrow failure or ineffective erythropoiesis (e.g. megaloblastic anemia or thalassemia) \rightarrow normal or \downarrow absolute reticulocyte count or reticulocyte percentage.

■ *Normal RBC^S count* is about $4 \times 10^6 / \text{mm}^3$.

Normal absolute reticulocyte count is about 40,000 / mm^3 .

Normal reticulocyte % is about 1%.

Normal Hb level: Cord blood: Mean: 16.8 g/dl, Range: 13.7-20.1 g/dl, at 2 wk: 16.5(13-20), at 3 mo: 12(9.5-14.5), at 6 mo to 6 yr: 12(10.5-14), at 7-12 yr: 13(11-16), Adult: female: 14(12-16), male: 16(14-18)

■ Approach to common causes of anemia in children

1. Anemia associated with other hematologic abnormalities as that due to *aplastic anemia, leukemia, & other bone marrow replacement failure*.
2. Anemia associated with reticulocytosis as that due to *bleeding & ongoing hemolysis*.
3. Anemia associated with hyperbilirubinemia or \uparrow serum lactate dehydrogenase (LDH) is usually due to " *hemolysis* " \rightarrow review of peripheral blood smear as follows :
 - Spherocytes \rightarrow hereditary spherocytosis, autoimmune hemolytic anemia, Wilson disease.
 - Sickle forms \rightarrow sickle cell anemia, SC- β -thalassemia.
 - Target cells \rightarrow Hb-SC disease.
 - Hypochromic & nucleated RBC^S \rightarrow homozygous β -thalassemia.
 - Microangiopathy \rightarrow HUS, thrombotic thrombocytopenia.
 - Bite cells / blister cells \rightarrow G6PD deficiency.

4. Anemia associated with lower than appropriate reticulocyte response → assess RBC size as follows :
- Microcytic RBC → *iron deficiency anemia (IDA), α or β -thalassemia, Hb-E disease, lead poisoning.*
 - Macrocytic RBC → assess whether there is or there is no neutrophil hypersegmentation as follows :
 - +ve neutrophil hypersegmentation → *folate deficiency, B12 deficiency, inborn error of metabolism.*
 - -ve neutrophil hypersegmentation → *Diamond-Blackfan syndrome, congenital dyserythropoietic anemia, pearson syndrome.*

IRON DEFICIENCY ANEMIA (IDA)

- It is the most widespread & common nutritional disorder in the world.
- It is estimated that 30% of the global population suffers from IDA, & most of them live in developing countries.
- In the USA, 9% of children ages 12-36 mo are iron deficient, & 30% of them will develop IDA.
- The body content of iron is about 0.5 g in newborn & about 5 g in adult.
- About 1 mg of iron must be absorbed by GIT each day.
- Because of the absorption of the dietary iron in the proximal small intestine is about 10% of the eaten amount → a diet containing 8-10 mg of iron is required daily.
- During the 1st year of life, there are relative small quantities of iron-rich food → their may be deficiency of iron, so it is important that the diet should be fortified with iron.
- Adolescents are also susceptible to iron deficiency because of ↑ requirements due to growth spurt, dietary deficiency, & menstrual blood loss (about 2% of adolescent girls have IDA).

Etiology

1. *Low birthweight & unusual perinatal hemorrhage*
2. *Dietary deficiency* : failure of breast feeding, delayed or improper weaning, ingestion of large amount of cows milk, ingestion of little amount of iron-rich diet as iron-fortified milk, meat, green vegetables e.t.c..
 - In term, IDA due to dietary loss is unusual < 6 months of age & usually occurs at 9-24 months of age (the incidence ↓ after that).
 - The usual dietary pattern in infants with IDA is the consumption of a large amount of cow's milk (low iron content & blood loss from milk protein colitis) & of food not supplemented with iron.

3. *Blood loss* → particularly in older children as peptic ulcer, meckel's diverticulum, intestinal polyps or hemangiomas, inflammatory bowel diseases(IBD), hookworm infestation, *Trichuris trichiura*, *plasmodium*, *Helicobacter pylori* , pulmonary hemsiderosis, menstruation (adolescents), chronic diarrhea, & cow's milk allergy.
4. Intense exercise conditioning, as occurs in competitive athletics in high school, may result in iron depletion in girls; this occurs less commonly in boys.

Clinical manifestations

- Most children with iron deficiency are asymptomatic & are identified by investigations.
- *Pallor* is the most important sign of IDA but is not usually visible until the Hb falls to 7-8 g/dL (pallor of the palms, palmar creases, nail beds, or conjunctivae).
- In mild to moderate IDA (Hb: 6-10 g/dL), compensatory mechanisms, including increased levels of 2,3-DPG & a shift of the oxygen dissociation curve, may be so effective that few symptoms of anemia aside from mild irritability are noted.
- When Hb level falls to <5 g/Dl, irritability, anorexia & lethargy develop, & systolic flow murmurs are often heard. As Hb continues to fall, tachycardia & high output cardiac failure can occur.
- Iron deficiency has nonhematologic systemic effects. The most important effects are impaired intellectual & motor function that can occur early in iron deficiency before anemia develops. There is evidence that these changes might not be completely reversible after treatment with iron, increasing the importance of prevention.
- Pica, the desire to ingest non-nutritive substances(can result in ingestion of lead-containing substances leading to plumbism) & pagophagia, the desire to ingest ice, are other symptoms of IDA.
- IDA may lead to decreased cell mediated immunity & impaired neutrophil activity.

Laboratory findings

In progressive IDA, a sequence of biochemical & hematological events occur as follows :

1. Disappearance of bone marrow hemosiderin, & ↓ serum ferritin followed by :
 2. ↓ serum iron, ↑ serum total iron binding capacity (TIBC or serum transferrin), & ↓ transferrin saturation followed by :
 3. ↓ MCV, ↓ MCH (hypochromic microcytic RBC^s) followed by :
 4. RBC count decreases& blood smear reveals hypochromic, microcytic red cells with substantial variation in cell size (anisocytosis which can be revealed as increasing RBC distribution width (RDW)).
- Reticulocyte % may be normal or moderately ↑ , but absolute reticulocyte count shows insufficient response to anemia.
 - Elliptocyte or cigar-shaped RBC are often seen.
 - Detection of increased transferrin receptor & decreased reticulocyte hemoglobin concentration provides supporting diagnostic information when these studies are available.

- WBC count is normal.
- Platelets count may show thrombocytosis , but in severe cases, there may be thrombocytopenia.
- Bone marrow examination → hypercellular with erythroid hyperplasia.
- Occult blood in stool is seen in about 1/3 of cases.
- In most instances, a CBC demonstrating a microcytic anemia with high RDW, reduced RBC, normal WBC, & normal or elevated platelet count is sufficient for a presumptive diagnosis. Other laboratory studies as reduced ferritin, reduced serum iron & increased TIBC, are not usually necessary for diagnosis unless severe anemia requires more rapid diagnosis, other complicating clinical factors are present, or the anemia does not respond to iron therapy.

Differential diagnosis

1. *β-thalassemia trait* : It is a mild microcytic anemia which occurs in the people of Mediterranean area, Africa, & Asia. It is characterized by ↑ HbA₂ &/or ↑ HbF. Serum iron , TIBC, & serum ferritin are normal. There are ↑ RBC count (↓ in IDA), normal RDW (↑ in IDA).
2. *α-thalassemia trait* : (↑ in blacks, Chinese, & south-east Asia).
3. *Hemoglobinopathies as Hb-H , Hb E, & Hb C disease*.
4. *Anemia of chronic diseases & infections* : It is usually normocytic anemia but may slightly microcytic (about 20%). There are ↓ serum iron, ↓ serum TIBC, & normal or ↑ serum ferritin.
5. *Lead poisoning* : There are ↑ FEP (free erythrocyte protoporphyrin), coarse basophilic stippling of the RBC^S, & ↑ blood lead level.
6. *Sideroblastic anemia* : They are acquired or hereditary disorders of heme synthesis → dimorphic anemia (hypochromic microcytic & normal RBC^S) & mostly occur in adulthood.

Prevention

- Iron deficiency is best prevented to avoid both its systemic manifestations & the anemia.
- Breast feeding should be encouraged, with the addition of iron-fortified cereals after 4-6 mo of age.
- Infants who are not breast-fed should only receive iron fortified formula (12 mg of iron per liter) for the first year, & thereafter bovine milk should be limited to < 20-24 oz daily. This approach encourages the ingestion of foods richer in iron & prevents blood loss due to bovine milk-induced enteropathy.
- When these preventive measures fail, routine screening helps prevent the development of severe anemia. Routine screening using Hb or Hematocrit is done at 12 mo of age, or earlier if at 4 mo of age the child is assessed to be at high risk for iron deficiency.

Treatment

- The regular response of IDA to adequate amount of iron is a critical diagnostic & therapeutic feature.
- **Oral administration of simple ferrous salts** (most often ferrous sulfate) provide inexpensive & effective therapy. A daily total dose of 3-6 mg/kg of elemental iron in 3 divided doses is adequate (ferrous sulfate has 20% elemental iron & is ideally given between meals with juice) for 8 wks after blood values normalize to reestablish iron stores. Intolerance to oral iron is uncommon in young child but older children & adolescents may have GIT complaints.
- **Parenteral iron** preparation are only used when malabsorption is present or when compliance is poor, because oral therapy is otherwise as fast, as effective, & much less expensive & less toxic. When necessary, parenteral iron sucrose & ferric gluconate complex have a lower risk of serious reactions than iron dextran.
- **Dietary counseling** is usually necessary. Excessive intake of milk, particularly bovine milk, should be limited. Iron deficiency in adolescent girls secondary to abnormal uterine blood flow loss is treated with iron & hormone therapy.
- **Follow-up:** If anemia is mild, the only additional study is to repeat the blood count 4 wk after initiating therapy at which Hb has usually risen by at least 1-2 g/Dl & has often normalized. If the anemia is more severe, earlier confirmation of the diagnosis can be made by the appearance of reticulocytosis usually within 48-96 hr of treatment. The Hb will then begin to increase 0.1-0.4 g/dL per day depending on the severity of the anemia.
- **When the anemia respond poorly** or not at all to iron therapy, there are multiple consideration like poor compliance, incorrect dose or medication, malabsorption, ongoing blood loss, concurrent infection or inflammatory disorder, concurrent vitamin B 12 or folate deficiency or diagnosis other than IDA.
- **Blood transfusion** is rarely necessary. It should only be used when congestive heart failure is eminent or if the anemia is severe with evidence of substantial ongoing blood loss (usually with partial correction the starting oral therapy).