بسم الله الرحمن الرحيم

ANEMIA in CHILDREN

M.Golpayegani MD
Pediatric Hematologist&Oncologist
K.U.M.S

Definition of Anemia

- Reduction in red cell mass or blood hemoglobin concentration
- Normal limit at 2 standard deviations below the mean for the normal population

Evaluation of Anemia in Practice

- History
- Physical Examination
- CBC
- Peripheral Blood Smear
- Additional Laboratory Tests

Anemia-Initial Investigation

history:

- PMHx, FmHx
- social
- dietary
- exposures
- blood loss
- recent infection

physical:

- pallor, petechiae
- jaundice
- spleen, liver, nodes
- hemolytic facies
- cardiovascular

Laboratory Evaluation of Anemia

- Complete blood count
- Reticulocyte count
- Peripheral smear

Red blood cell indices.

- The MCV shows the size of the red blood cells. Normal range is 80 - 98 femtoliters.
- The MCH value is the amount of hemoglobin in an average red blood cell. Normal range is 27 - 32 picograms.
- MCHC, The average concentration of hemoglobin in a given volume of red cells. This is a calculated volume derived from the hemoglobin measurement and the hematocrit. Normal range is 32 - 36%.
- RDW a measurement of the variability of red cell size. Higher numbers indicate greater variation in size. Normal range is 11 - 15.

Complete Blood Count

- Directly measured indices:
  - Hb (more reliable, more directly related to O2 carrying capacity)
  - MCV
  - RBC count
- Calculated indices:
  - Hct = MCV x RBC
  - MCH = Hb / RBC
  - MCHC = Hb / Hct = Hb / (MCV x RBC)
- RDW:
  - Coefficient of variation of the erythrocyte volume distribution = cell size variability

Eosinophil

Neutrophil

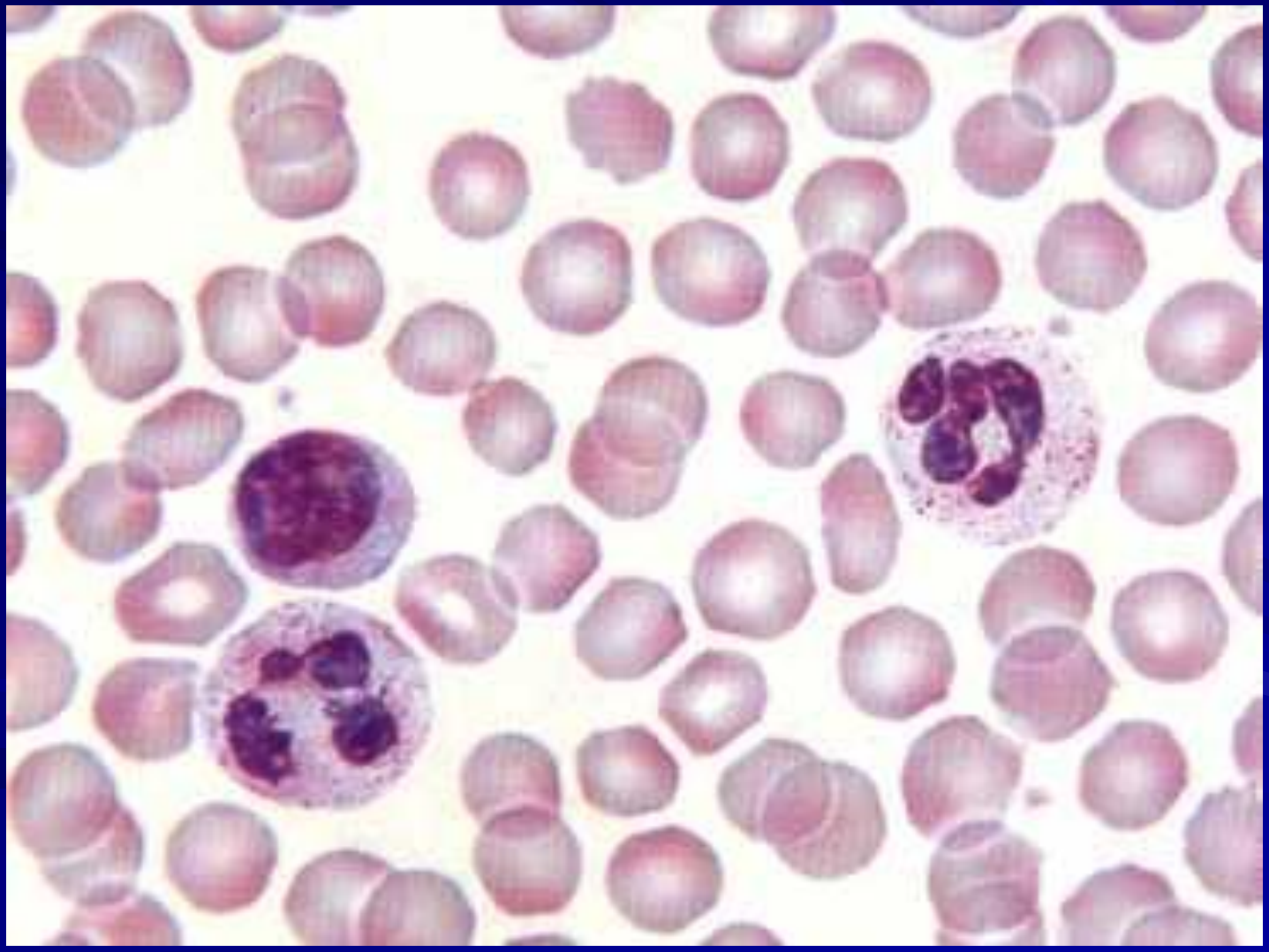
Band cell

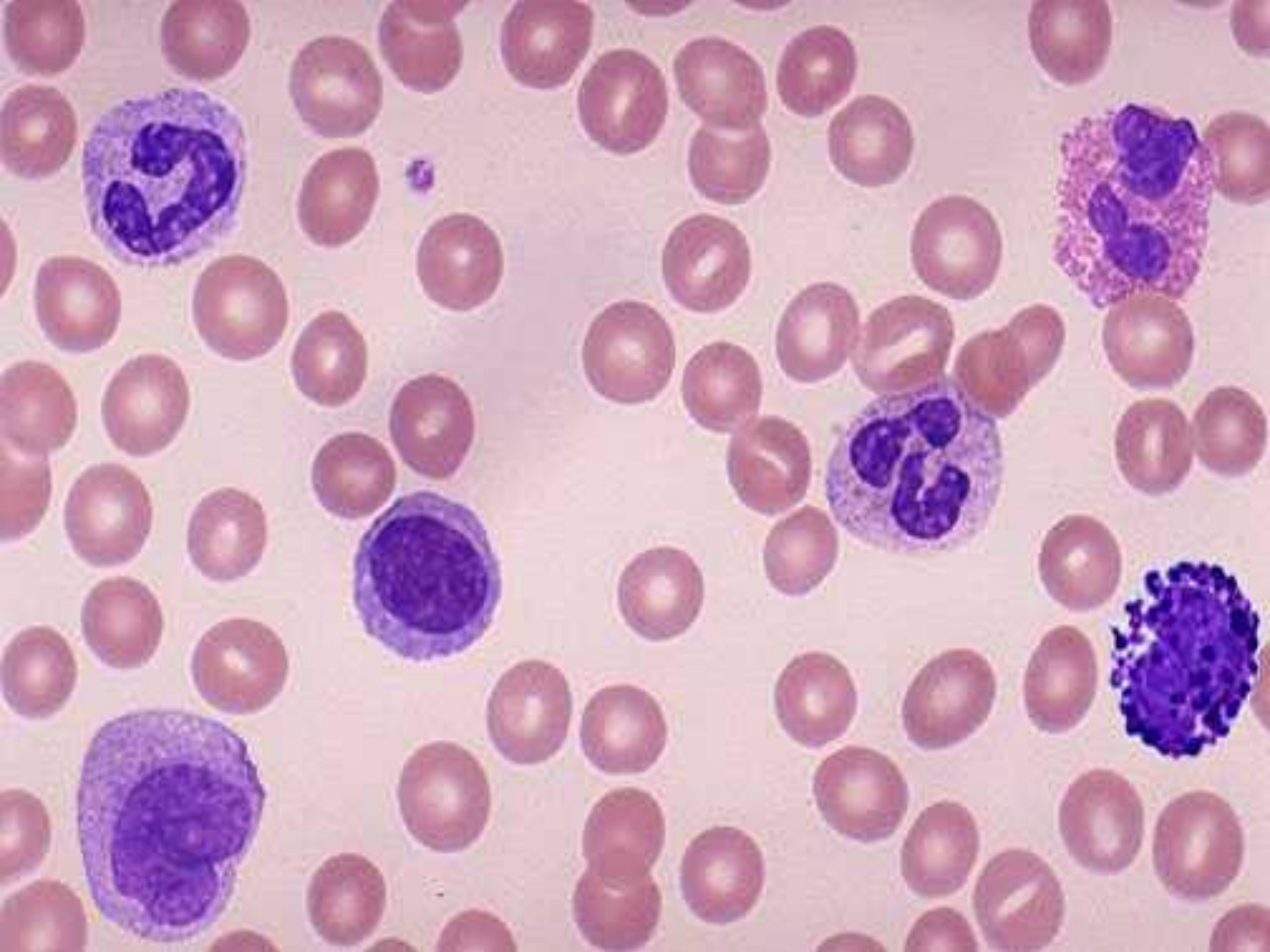
Red blood cell

Lymphocyte

Monocyte

Blood Smear - Normal





Physiologic Classification of Anemia

- Disorders of Red Cell Production
- Disorders of Increased Red Cell Destruction
- Loss

ANEMIA

HEMOGLOBIN AND INDICES
RETIC COUNT AND MORPHOLOGY

Inadequate response (RPI <2)

Hypochromic, Microcytic

Iron deficiency
- Chronic blood loss
- Poor diet
- Cow's milk protein intolerance
- Menstruation

Thalassemia
- β major, minor
- α minor

Chronic inflammatory disease

Cooper deficiency

Sideroblastic anemia

Aluminum, (?) lead intoxication

Hereditary pyropoikilocytoses

Hemoglobin CC

Hemoglobin EE

Normochromic, Normocytic

Chronic inflammatory disease
- Infection
- Collagen-vascular disease
- Inflammatory bowel disease

Recent blood loss

Malignancy/marrow infiltration

Chronic renal failure

Transient erythroblastopenia of childhood

Marrow aplasia/hypoplasia

HIV infection

Hemophagocytic syndrome

Macrocytic

Vitamin B_{12} deficiency
- Pernicious anemia
- Ileal resection
- Strict vegetarian
- Abnormal intestinal transport
- Congenital intrinsic factor or transcobalamin deficiency

Folate deficiency
- Malnutrition
- Malabsorption
- Antimetabolite
- Chronic hemolysis
- Phenytoin
- Trimethoprim/sulfa

Hypothyroidism
Oroticaciduria
Chronic liver disease
Lesch-Nyhan syndrome
Down syndrome

Marrow failure
- Myelodysplasia
- Fanconi anemia
- Congenital dyserythropoietic anemia
- Aplastic anemia
- Pearson syndrome (mitochondrial disorder)
- Diamond-Blackfan syndrome

Drugs
- Alcohol
- Azidothymidine (zidovudine)

Adequate response (RPI >3) R/O blood loss

Hemolytic Disorders

Hemoglobinopathy
- Hemoglobin SS, S-C, S-β thalassemia

Enzymopathy
- G6PD deficiency (loite cells)
- Pyruvate kinase deficiency

Membranopathy
- Hereditary spherocytosis
- Elliptocytosis
- Ovalocytosis

Extrinsic factors
- DIC, HUS, TTP
- Abetalipoproteinemia
- Burns
- Wilson disease
- Vitamin E deficiency

Immune hemolytic anemia
- Autoimmune
- Isoimmune
- Drug-induced

Macrocytic Anemia

- The RBCs are larger than normal at every stage of development and an asynchrony between the maturation of nucleus and cytoplasm.

- Almost all cases of childhood megaloblastic anemia result from a deficiency of folic acid or vitamin B12;rarely, they may be caused by inborn errors of metabolism.

- Both vitamin BI2 and folate are required in the synthesis of nucleoproteins; deficiencies result in defective synthesis of DNA and, to a lesser extent, RNA and protein.

FOLIC ACID DEFICIENCY

- Folates are abundant in many foods, including green vegetables,fruits, and animal organs (e.g., liver, kidney).
- Folate conjugase activity in the intestinal brush border aids the conversion of polyglutamates to the monoglutamate and thereby enhances absorption. Folic acid is absorbed throughout the small intestine,

- Body stores of folate are limited, and megaloblastic anemia occurs after 2-3 mo on a folate-free diet.

CLINICAL MANIFESTATIONMS

- peak incidence at 4-7 mo of age, somewhat earlier than iron deficiency anemia
- affected infants with folate deficiency are irritable, have inadequate weight gain, and have chronic diarrhea.
- Hemorrhages from thrombocytopenia occur in advanced cases.

- Folic acid deficiency can occur as a consequence of inadequate folate intake, decreased folate absorption, or acquired and congenital disorders of folate metabolism.

LABORATORY FINDINGS

- The anemia is macrocytic (mean corpuscular
- volume> 100 fL). *The reticulocyte count is low*. Neutropenia and thrombocytopenia rarely may be present. The neutrophils are large, some with hypersegmented nuclei.
- Levels of iron and vitamin BI2 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.

TREATMEN

- When the diagnosis of folate deficiency is established, folic acid may be administered orally or parenterally at 0.5-1.0 mg/day. If the specific diagnosis is in doubt, smaller doses of folate (0.1 mg/day) may be used for 1 week as a diagnostic test, because a hematologic response can be expected within72 hr. Doses of folate >0.1 mg can correct the anemia of vitaminBI2 deficiency but may aggravate any associated neurologic abnormalities.

- 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.

VITAMIN B12 (COBALAMIN) DEFICIENCY

- Vitamin BI2 is derived from cobalamin in food (mainly animal sources) secondary to production by microorganisms
- The cobalamins are released by the acidity of the stomach and combine there with R proteins and intrinsic factor (IF); and are absorbed in the distal ileum via specific receptors for IF-cobalamin. In the plasma, cobalamin binds to a transport protein, transcobalamin II (TC-II), which carries the vitamin Bl2 to the liver, bone marrow, and other tissue storage sites.

- In contrast to folate stores, older children and adults have sufficient vitamin Bl2stores to last 3-5 yr.
- However, in young infants born to mothers with low vitamin Bl2 stores, clinical signs of cobalamin deficiency can become apparent in the first 6-18 months of life.

ETIOLOGY

- Vitamin Bl2 deficiency may result from inadequate dietary intake of vitamin, lack of IF secretion by the stomach,impaired intestinal absorption of IF-cobalamin, or absence of vitamin Bl2 transport protein.

CLINICAL MANIFESTATION

Nonspecific manifestations such as weakness,fatigue, failure to thrive, or irritability. Other common findings include pallor, glossitis, vomiting, diarrhea, and icterus. Neurologic symptoms also occur, and these can include paresthesias,sensory deficits, hypotonia, seizures, developmental delay, developmental regression, and neuropsychiatric changes.

Neurologic problems from vitamin Bl2 deficiency can occur in the absence of any hematologic abnormalities.

LABORATORY FINDINGS

- The hematologic manifestations of folate and cobalamin deficiency are identical.
- 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.

TREATMENT

- Parenteral administration of vitamin B12 (25-100micro)
- 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 BI2 is sufficient.

Iron Deficiency Anemia

- Iron deficiency is the most widespread and common nutritional disorder in the world.
- the most common hematologic disease of infancy and childhood.
- 30% of the global population suffers from iron-deficiency anemia;
- In the USA, 9% of children ages 12-36 mo are iron deficient, and 30% of this group have progressed to iron-deficiency anemia.

- 1 mg of iron must be absorbed each day.
- Because < 10% of dietary iron usually is absorbed, a dietary intake of 8-10 mg of iron daily is necessary to maintain iron levels.

- Absorption of dietary iron is assumed to be about 10%; a diet containing 8-10 mg of iron daily is necessary for optimal nutrition.
- Iron is absorbed in the proximal small intestine.
- Iron is absorbed 2 to3 times more efficiently from human milk than from cow's milk.

- In term infants, anemia caused solely by inadequate dietary iron usually occurs at 9-24 mo of age and is relatively uncommon thereafter.

ETIOLOGY

- Nutritional
- Blood loss:

  peptic ulcer,Meckel diverticulum, polyp, hemangioma, or inflammatory bowel disease.

  infections with hookworm, *Trichuris trichiura, Plasmodium,*and *Helicobacter pylori* .

CLINICAL MANIFESTATIONS

- Asymptomatic and are identified by recommended laboratory screening at 12 months of age or sooner if at high risk.
- Pallor is the most important clinical sign
- irritability ,anorexia, and lethargy,systolic flow murmurs.
- As the hemoglobin continues to fall, tachycardia and high output cardiac failure

- impaired intellectual and motor function.
- Pica, the desire to ingest non-nutritive substances,
- pagophagia, the desire to ingest ice,

LABORATORY FINDINGS

- First, tissue iron stores are depleted. This depletion is reflected by reduced serum ferritin, which provides an estimate of body iron stores in the absence of inflammatory disease.
- Next, serum iron levels decrease, the iron-binding capacity of the serum (serum transferrin) increases, and the transferrin saturation falls below normal.

- As iron stores decrease, iron becomes unavailable to complex with protoporphyrin to form heme. Free erythrocyte protoporphyrins (FEPs) accumulate, and hemoglobin synthesis is impaired.
- With less available hemoglobin in each cell, the red cells become smaller. This morphologic characteristic is best quantified by the decrease in (MCV) and (MCH).

- Elevated RBC distribution width (RDW)
- (RBC) also decreases
- reticulocyte percentage may be normal or moderately elevated, but absolute reticulocyte counts indicate an insufficient response to the degree of anemia.
- Thrombocytosis,Thrombocytopenia is occasionally seen with very severe iron deficiency,

DIFFERENTIAL DIAGNOSIS

- The most common alternative causes of microcytic anemia are thalassemia and hemoglobinopathies, including hemoglobin

  E and C

  Lead poisoning

PREVENTION

- 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, and thereafter
- bovine milk should be limited to <20-24 oz daily.

Table 449-3 DIFFERENTIAL DIAGNOSIS OF MICROCYTIC ANEMIA THAT FAILS TO RESPOND TO ORAL IRON

Poor compliance (true intolerance of Fe is uncommon)
Incorrect dose or medication
Malabsorption of administered iron
Ongoing blood loss including gastrointestinal, menstrual, and pulmonary
Concurrent infection or inflammatory disorder inhibiting the response to iron
Concurrent vitamin B_{12} or folate deficiency
Diagnosis other than iron deficiency

- Thalassemias
- Hemoglobin C and E disorders
- Anemia of chronic disease
- Lead poisoning
- Sickle thalassemias, hemoglobin SC disease
- Rare microcytic anemias (Chapter 450)

TREATMENT

- A daily total dose of 3-6 mglkg of elemental iron in 3divided doses is adequate, with the higher dose used in more severe cases. Ferrous sulfate is 20% elemental iron ideally given between meals with juice
- Excessive intake of milk, particularly bovine milk, should be limited

- If the anemia is mild, the only additional study is to repeat the blood count approximately 4 wk after initiating therapy. At this point the hemoglobin has usually risen by at least 1-2

- If the anemia is more severe,earlier confirmation of the diagnosis can be made by the appearance of a reticulocytosis usually within 48-96 hr of instituting treatment. The hemoglobin will then begin to increase 0.1-0.4 gIdL per day depending on the severity of the anemia. Iron medication should be continued for 8 wk after blood values normalize to re-establish iron stores.

ANEMIA OF CHRONIC DISEASE (ACD)

- There is a relative failure of bone marrow to respond adequately to the anemia.

LABORATORY FINDINGS

- Hemoglobin concentrations usually are 6-9 g/dL. The anemia usually is normochromic and normocytic,
- Absolute reticulocyte counts are normal or low,
- The serum iron level is low, without the increase in total iron-binding capacity (serum transferrin) that occurs in iron deficiency. This pattern of low serum iron and low to normal iron-binding protein (serum transferrin) is a regular and valuable diagnostic feature. The serum ferritin level may be elevated.
- TfRlferritin

- Recombinant human EPo

Thank You