Anemia in PEDs
Hgb/Hct Values

Background
1. Definitions
   - Anemia:
     - Hemoglobin (Hgb) <2 SD below the mean for age
     - See Hgb / Hct values
   - Iron deficiency anemia (IDA)
     - Anemia + ferritin <10 ng/mL
   - Iron deficiency (ID)
     - Abnormal labs (ferritin, iron studies, FEP, RDW) without anemia

Pathophysiology
1. Pathology of disease
   - IDA
     - Iron required for Hgb synthesis and enzymes (cytochromes)
     - Lack of cytochrome iron can lead to GI mucosal damage
   - Non-ID Anemia
     - Pathology varies with etiology
2. Prevalence
   - 1-2 yo
     - IDA 2-3% (1% higher in blacks)
     - ID 9%
   - 3-5 yo
     - IDA <1%
     - ID 3%
   - 6-11 yo
     - IDA <1%
     - ID 2%
   - Females 12-19 yo
     - IDA 2-3%
     - ID 9-11%
   - Males 12-15 yo
     - IDA <1%
     - ID 1%
   - WIC population: IDA 11%
     - Ages 6-11 mo: 16.2%
     - Ages 12-17 mo: 15.8%
     - African American infants: 19%
3. Risk factors
   - Iron deficiency anemia
     - High cow's milk intake (>24 oz/day) without iron containing food
     - Low iron formula
     - Low income, WIC
     - Native American, African American, recent immigrant
     - Cow's milk allergy (controversial)
     - IBD, celiac dz
     - Maternal anemia during pregnancy
• Prematurity, low birth weight
  o Non-iron deficiency
    ▪ Dietary deficiencies
      • Folate (goat's milk)
      • B12 (vegan)
    ▪ Prolonged neonatal hyperbilirubinemia
    ▪ Mediterranean, African or South Asian descent
    ▪ Family hx
      • Spherocytosis, splenectomy, hemoglobinopathy, G6PD
  ▪ Lead exposure
  ▪ Thyroid dz
  ▪ Leukemia, metastatic malignancy
  ▪ Chronic renal disease
  ▪ Chronic inflammatory dz
    • JRA, connective tissue dz

4. Morbidity, mortality
  o Cognitive and psychomotor abnormalities
  o Poor school performance (esp. math)
  o Diminished growth
  o Fatigue, irritability
  o Cholelithiasis (if anemia assoc w/chronic hemolysis)

Diagnosis
  1. History
    o Irritability, fatigue, dyspnea (if severe)
    o Nutritional content
      ▪ Early introduction of cow's milk (<12 mo)
      ▪ Exclusive breast feeding without iron supplementation after 6 mo
    o Bleeding diathesis
    o GI bleeding
      ▪ Hematochezia, melena
    o Travel outside US
      ▪ Parasite exposure (malaria, hookworm, roundworm)
    o Excessive menses
      ▪ >80 mL/month
        • 30-40 mL is normal
      ▪ Changing pads (or tampons) at <3 hr intervals
      ▪ >21 pads/cycle
      ▪ Clots >1 inch and need to change pad at night
    o Pregnancy
    o Eating disorder, obesity
    o Drugs
      ▪ Dilantin, chloramphenicol
    o Recent infections (EBV, hepatitis, parvovirus)
    o Chronic renal disease
    o Pica
    o Heavy metal / lead exposure
    o Hx of G6PD and / or hematuria or pallor with food, infections or drugs
    o Family hx of anemia
2. Physical exam
   o Skin
     ▪ Pallor (conjunctivae and palmar creases), jaundice, petechiae, bruising, purpura, mucous membrane bleeding
   o HEENT
     ▪ Prominent cheek bones, bossing, dental malocclusion (from increased marrow production in chronic hemolytic anemia)
   o Cardiovascular
     ▪ Tachycardia, systolic murmur, signs of heart failure
   o GI/Hematopoietic
     ▪ Hepato-splenomegaly, lymphadenopathy

3. Diagnostic testing
   o Venous (vs. capillary) sample preferred for confirmation
     ▪ Only test necessary if hx consistent with IDA and pt <3 yo
   o If concern is for something other than IDA or if no or incomplete response to iron therapy:
     ▪ CBC with diff
       • 1/3 of IDA pts have normal MCV because RBC size diminishes slowly, increased RDW
     ▪ Reticulocyte count
       • <2% = underproduction of RBCs, >2% = overproduction of RBCs [hemolysis, blood loss]
     ▪ Peripheral smear:
       • Target cells
         o IDA, hemoglobinopathies, thalassemia
       • Basophilic stippling
         o Lead
       • Spherocytes
         o Immune-mediated hemolytic anemia from drugs or infections, and spherocytosis
       • Elliptocytes
         o IDA, hereditary elliptocytosis
       • Heinz bodies, "bite cells"
         o G6PD
       • Irreversibly sickled cells, variation in size and shape
         o SS, SC
       • Howell-Jolly bodies
         o Asplenia
       • Intraerythrocyte parasites
         o Malaria
   o Other tests to consider:
     ▪ Ferritin
       • Estimate of body iron stores (acute phase reactant, so increases in chronic and acute inflammation)
     ▪ Stool for occult blood (especially if <9 mo or >3 yr)
     ▪ Serum iron, TIBC, % sat vs. ferritin vs. fetal erythrocyte protoporphyrin to confirm iron deficiency (no one of these tests is better)
     ▪ G6PD screen if evidence of hemolysis
- Direct and indirect Coombs if evidence of hemolysis
- Osmotic fragility (spherocytosis; elliptocytosis)
- Bone marrow biopsy (occasionally used, mainly for malignancies, Diamond-Blackfan, transient erythroblastopenia of childhood, aplastic anemia, sideroblastic anemia)
- Hemoglobin electrophoresis (may have already been done on state newborn screen)

**Differential Diagnosis**

1. Key DDx
   - Iron deficiency anemia
   - Hemoglobinopathy
   - G6PD
   - Anemia of chronic disease
   - Transient erythroblastopenia of childhood
   - Parasitic infection

2. Disorders of effective red cell production
   - Marrow failure
     - Aplastic anemia
       - Congenital
       - Acquired
     - Pure red cell aplasia
       - Congenital: Diamond-Blackfan Syndrome
       - Acquired: transient erythroblastopenia of childhood
     - Marrow replacement
       - Malignancies
       - Osteopetrosis
       - Myelofibrosis
       - Chronic renal disease
       - Vitamin D deficiency
       - Infection
       - Tuberculosis
       - Pancreatic insufficiency - marrow hypoplasia syndrome
   - Impaired erythropoietin production
     - Chronic renal disease
     - Hypothyroidism, hypopituitarism
     - Chronic inflammation (anemia of chronic dz)
     - Protein malnutrition
   - Abnormalities of cytoplasmic maturation
     - Iron deficiency
     - Thalassemia syndromes
     - Sideroblastic anemias
     - Lead poisoning
   - Abnormalities of nuclear maturation
     - Vitamin B12 deficiency
     - Folic acid deficiency
     - Thiamine-responsive megaloblastic anemia
     - Hereditary abnormalities in folate metabolism
     - Orotic aciduria
3. **Disorders of increased red cell destruction or loss**
   - Defects of hemoglobin
     - Structural mutants (HbSS, HbSC, HbS-beta thal)
     - Diminished production (thalassemias)
   - Defects of RBC membrane (spherocytosis)
   - Defects of RBC metabolism (pyruvate kinase deficiency)
   - Antibody-mediated (Parvovirus and others, underlying immunologic dysfunction (HIV, Lymphoma), drugs)
   - Mechanical injury to the erythrocyte
     - Hemolytic uremic syndrome
     - Thrombotic thrombocytopenic purpura
     - Disseminated intravascular coagulation
   - Thermal injury to the erythrocyte
   - Oxidant-induced RBC injury (G6PD def)
   - Paroxysmal nocturnal hemoglobinuria
   - Plasma-lipid-induced abnormalities of the red cell membrane
   - Acute/Chronic blood loss (Meckel's diverticulum, menstrual loss, inflammatory bowel disease, parasitic infection)
   - Hypersplenism
     - Hereditary spherocytosis

**Acute Treatment**
1. Dependent upon cause of anemia
2. IDA treated with iron, reduction in cow’s milk and encouraging solid foods with iron
3. Therapeutic trial of iron (3-6mg/kg/day of elemental iron); no difference in iron formulations
   - Increase in retic count within 1 w and increase Hgb level of 1g/dL within 4 weeks is diagnostic of IDA
     - Hgb should return to normal in 4-6 w
   - Treat with iron until 3 m after Hgb normalizes, to replenish stores
4. Iron-containing foods:
   - Meats - beef, pork, lamb, and liver and other meats
   - Poultry - chicken, duck, and turkey, especially dark meat; liver
   - Fish - shellfish, like clams, mussels, and oysters; sardines; anchovies; other fish
   - Leafy greens of cabbage family - broccoli, kale, turnip greens, collards
   - Legumes, such as lima beans and green peas; dry beans and peas, such as pinto beans, black-eyed peas, and canned baked beans
   - Yeast-leavened whole-wheat bread and rolls
   - Iron-enriched white bread, pasta, rice, and cereals
5. Other nutritional deficiencies treated with folate or B12 and diet management
6. Acute or chronic blood loss:
   - Supportive care until found found and treated
7. Depending on hemoglobinopathy, no treatment may be necessary (beta and alpha thalassemia traits), or bone marrow transplant or splenectomy and/or lifelong
treatment (Beta thal major, alpha thal major [HbH or 3 gene deletion disease], SS disease)

8. Antibody mediated anemia may require Prednisone or simple observation

**Long-term Care**

1. Chronic hemolytic anemia, incl. thalassemia major, spherocytosis and elliptocytosis: Folic acid supplementation
2. HbSC, HbSS, Sbeta, or hypersplenism (spherocytosis, elliptocytosis, some autoimmune hemolytic anemias):
   - Influenza, meningococcal, and pneumococcal vaccinations
3. HbSC, HbSS or Sbeta:
   - Penicillin prophylaxis (62.5 mg BID <3 kg, 125 mg BID to age 3; 250 BID until at least age 5)
4. Consider repeat Hgb electrophoresis after 6 mo if newborn screen is positive to define exact distribution of Hgb types
5. Genetic counseling for any hereditary diagnoses

**Follow-Up**

1. Return to office
   - In IDA, repeat Hgb 1-4 weeks after initiating iron depending on severity of anemia and need to assess adherence to iron
   - If no improvement, consider non-adherence or failure to treat (continuing blood loss or other etiology)
   - Iron therapy continued until 3 months after Hgb is normal
   - Earlier follow-up if severe anemia or symptoms worsening
2. Refer to specialist
   - Most conditions requiring genetic counseling
   - Hemoglobinopathies needing treatment
   - Thalassemia major
   - Hereditary spherocytosis for Dx and suspicion of aplastic crisis with parvovirus infection
   - If Dx not clear after iron deficiency Tx
     - Peripheral smear evaluation
     - Hgb electrophoresis
     - Occult blood loss testing
3. Admit to hospital
   - Extremely low Hgb (<8) with acute symptoms, hypotension, signs of CHF, or aplastic crisis

**Prognosis**

1. Depends on etiology and severity of condition

**Prevention**

1. Iron deficiency
   - See Diagnostics and Risk factors as to what etiologies can be prevented
   - Screening for IDA is only indicated in high risk groups
2. Preterm infants:
   - Supplementation with oral iron
3. Lead poisoning:
   - Avoidance and cleanup of environment
4. G6PD deficiency:
   - Avoidance of drugs and foods that can cause hemolysis

References

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