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

Diagnosis

1. History
    - Irritability, fatigue, dyspnea (if severe)
    - Nutritional content
        - Early introduction of cow's milk (<12 mo)
        - Exclusive breast feeding without iron supplementation after 6 mo
    - Bleeding diathesis
    - GI bleeding
        - Hematochezia, melena
    - Travel outside US
        - Parasite exposure (malaria, hookworm, roundworm)
    - 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
    - Pregnancy
    - Eating disorder, obesity
    - Drugs
        - Dilantin, chloramphenicol
    - Recent infections (EBV, hepatitis, parvovirus)
    - Chronic renal disease
    - Pica
    - Heavy metal / lead exposure
    - Hx of G6PD and / or hematuria or pallor with food, infections or drugs
    - Family hx of anemia

2. Physical exam
    - Skin
        - Pallor (conjunctivae and palmar creases), jaundice, petechiae, bruising, purpura, mucous membrane bleeding
    - HEENT
        - Prominent cheek bones, bossing, dental malocclusion (from increased marrow production in chronic hemolytic anemia)
    - Cardiovascular
        - Tachycardia, systolic murmur, signs of heart failure
    - GI/Hematopoietic
        - Hepato-splenomegaly, lymphadenopathy
3. Diagnostic testing
    - Venous (vs. capillary) sample preferred for confirmation
        - Only test necessary if hx consistent with IDA and pt <3 yo
    - 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
                - IDA, hemoglobinopathies, thalassemia
            - Basophilic stippling
                - Lead
            - Spherocytes
                - Immune-mediated hemolytic anemia from drugs or infections, and spherocytosis
            - Elliptocytes
                - IDA, hereditary elliptocytosis
            - Heinz bodies, "bite cells"
                - G6PD
            - Irreversibly sickled cells, variation in size and shape
                - SS, SC
            - Howell-Jolly bodies
                - Asplenia
            - Intraerythrocyte parasites
                - Malaria
    - 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

- Primary dyserythropoietic anemias
- Erythropoietic protoporphyria
- Refractory sideroblastic anemia

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

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