Iron Deficiency Anemia

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I do begin to have bloody thoughts. —William Shakespeare

Learning Objectives:
1. Understand the diagnostic evaluation of an anemic child
2. Describe common reasons for iron depletion/deficiency in US children
3. Outline the diagnosis and treatment of iron deficiency anemia and the next steps of management if a trial of supplemental iron has failed
4. Know the screening guidelines for anemia recommended by the American Academy of Pediatrics

Primary Reference:

Author’s Note: This module is intended to review the most common cause of anemia in children, iron deficiency anemia. While it touches upon other causes of microcytic anemia, it does not highlight causes of anemia related to inadequate production or hemolysis.

The following four patients have the CBC results listed:

<table>
<thead>
<tr>
<th>WBC</th>
<th>RBC</th>
<th>MCV</th>
<th>RDW</th>
<th>RBC Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.1</td>
<td>9.6</td>
<td>89</td>
<td>16</td>
<td>4.5</td>
</tr>
</tbody>
</table>

CASE ONE:
A 2-month-old presents to the Emergency Department (ED) with a fever of 102. A CBC, blood culture, urinalysis, urine culture, and cerebrospinal fluid (CSF) sample are obtained. (This patient’s CBC has an MCV of 90.)

CASE TWO:
A 13-month-old girl with no significant past medical history has a screening CBC checked at a well-child visit. She was breastfed for the first 7 months of life. Her physical exam, growth, and development are normal.

CASE THREE:
A 3-year-old presents to the ED with a fever of 104. He has a prior history of a urinary tract infection. A CBC, blood culture, urinalysis, and urine culture are obtained.

CASE FOUR:
A 15-year-old female with menarche at age 12 has a screening CBC checked at a health maintenance visit.
1. Are all of the above patients anemic? Why or why not?

No. The 2-month-old’s CBC likely reflects physiologic anemia of infancy. Within the first week of life, a progressive decline in hemoglobin (Hb) level begins and reaches a nadir at 6-8 weeks. Several factors contribute:

- erythropoiesis temporarily ceases with the onset of respiration at birth
- erythropoietin has a shorter half-life and larger volume of distribution in newborns
- fetal red blood cells (RBCs) have a shortened life-span

Always interpret CBC results based on normal values for age, as can be found in references such as the Harriet Lane Handbook. It is important to note that these norms for age are for postnatal, uncorrected, age. Remember that in children 12 months and older, the lower limit of normal Hb starts at 11 g/dL. A rule of thumb for children ages 12 months to 6 years:

$$11 + (0.1 \times \text{age in years}) = \text{lower limit of normal for Hb}$$

From 6-12 years the lower limit of normal Hb is 11.5 g/dL and from 12-18 years, the lower limit is 12 g/dL for females and 13 g/dL for males. Preterm infants require increased iron supplementation at an early age because they are likely to experience frequent blood draws, and do not benefit from the increased iron absorption from maternal supply that occurs throughout the third trimester.

2. What further information would you obtain from the anemic children above? How do you categorize the anemia based on the CBC results? What is the most likely cause of the anemia and why?

The initial approach should focus on a detailed history (age, gender, ethnicity, diet, medications, recent illnesses, and past/family/social history) and physical exam (vital signs, general appearance, skin and mucous membranes, lymph nodes, cardiovascular exam, abdominal exam to evaluate for masses or hepatosplenomegaly). In an otherwise healthy child who only had a capillary Hb level checked at a well-child visit, lab testing should include a CBC, reticulocyte count, and evaluation of peripheral blood smear, preferably by venipuncture. If the initial test documenting anemia had been a CBC, most providers would not perform a repeat blood draw immediately simply to check a reticulocyte count. The anemia should be classified as microcytic, normocytic, or macrocytic, and further evaluation can be guided by the differential diagnosis (see review chart below).

Except for the 2-month-old in case 1, the CBC shows a microcytic anemia based on the low mean corpuscular volume (MCV). RDW reports red blood cell distribution, or variation in the size of RBCs. A high RDW is a hallmark of iron deficiency. The RDW is typically normal in thalassemia minor helping to differentiate thalassemia minor from iron deficiency in some cases. The RDW becomes significantly elevated during iron replacement (25-35%).

The Mentzer index, equal to the MCV divided by the RBC count, can help to pinpoint the diagnosis of iron deficiency. An index >13.5 is suggestive of iron deficiency, <11.5 is suggestive of thalassemia minor. Understanding the concept behind the Mentzer index is more important than memorizing the formula: in both thalassemia minor and iron deficiency the MCV is low, but in thalassemia minor, RBC production is preserved so the ratio is low (large denominator), and in iron deficiency, the bone marrow cannot produce RBCs normally so the RBC count is lower and the ratio is higher (small denominator). The Mentzer index is 15.3 in the above cases 2, 3 and 4.

The three stages of iron deficiency are (1) depletion of iron stores (decreased ferritin), (2) decreased Hb and finally, (3) decreased MCV. Mild to moderate thrombocytosis may also be seen in the setting of iron deficiency.
Classification of Anemia

<table>
<thead>
<tr>
<th>Microcytic</th>
<th>Normocytic</th>
<th>Macrocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Deficiency</td>
<td>Bone Marrow Replacement</td>
<td>Normal newborn (spurious)</td>
</tr>
<tr>
<td>Thalassemias</td>
<td>Leukemia</td>
<td>Reticulocytosis (spurious)</td>
</tr>
<tr>
<td>Lead Poisoning</td>
<td>Tumors</td>
<td>Vitamin B12 Deficiency</td>
</tr>
<tr>
<td>Vitamin B6 Responsive</td>
<td>Storage Diseases</td>
<td>Folate Deficiency</td>
</tr>
<tr>
<td>Copper Deficiency</td>
<td>Osteopetrosis</td>
<td>Hereditary orotic aciduria</td>
</tr>
<tr>
<td>Sideroblastic Anemia (some)</td>
<td>Myelofibrosis</td>
<td>Myelodysplasia</td>
</tr>
<tr>
<td></td>
<td>Blood loss</td>
<td>Liver Disease</td>
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<td></td>
<td>Sequestration</td>
<td>Hypothyroidism (some)</td>
</tr>
<tr>
<td></td>
<td>Hemolysis: Intrinsic RBC Abnl</td>
<td>Vitamin B6 Deficiency (some)</td>
</tr>
<tr>
<td></td>
<td>Hemoglobinopathy</td>
<td>Thiamine Deficiency</td>
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<td></td>
<td>Enzymopathy</td>
<td>Aplastic Anemia</td>
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<td>Membrane Disorder</td>
<td>Diamond Blackfan Anemia</td>
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<tr>
<td></td>
<td>Hemolysis: Extrinsic RBC Abnl</td>
<td>Dyserythropoietic Anemia</td>
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<td>Immunologic</td>
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<td></td>
<td>Toxins</td>
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<td>Infections</td>
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<td></td>
<td>Microangiopathic</td>
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<td>DIC</td>
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<td></td>
<td>HUS</td>
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<td></td>
<td>Hypertension</td>
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<td></td>
<td>Cardiac disease</td>
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<tr>
<td>Chronic Disease</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Inflammation</td>
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<tr>
<td>Renal Disease</td>
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</tbody>
</table>

3. Could the 13-month-old’s anemia have been prevented?

During the first year of life, infants require the absorption of 0.8 mg/day of iron (0.6 mg for growth and 0.2 mg to replace ongoing losses). Human milk and cow’s milk contain 0.5 mg/L, but 50% of iron from human milk is absorbed and 10% of iron from cow’s milk is absorbed. Formula fed infants should be on iron-fortified formula, though less than 5% of iron from iron-fortified formula, which contains 10-30 mg/L of iron, is absorbed. After 6 months, the AAP recommends supplementation of the diet with iron-rich foods, such as fortified infant cereals, for infants fed both breast-milk and artificial milk. Iron-rich meat can also be introduced at this age.

Iron-deficiency anemia is still common in children without notable dietary extremes. A 2016 analysis of the National Health and Nutrition Examination Survey found that 14% of one-year-olds and 4% of preschool children (3 to 5-year-olds) were iron-deficient; an older analysis of the dataset identified 9% of adolescent females (12 to 19-year-olds) and 9% of women of childbearing age (20 to 49-year-olds) as iron deficient. Infants, toddlers, adolescents, and pregnant women are especially at risk secondary to their relative rapid growth and increased demand for iron. Menstruating females need additional iron to replace losses from menstruation. Dietary counseling regarding iron-fortified cereals and iron-rich foods should be discussed at the 6-18 month visits and in adolescence.

The AAP recommends universal screening for anemia at 12 months of age with measurement of Hb, followed by regular risk-assessment with selective screening thereafter, and this approach represents standard practice. However in a 2015 report, the US Preventive Services Task Force notes that the evidence is insufficient to recommend routine screening for iron deficiency in asymptomatic children aged 6-24 months, and calls for additional studies to demonstrate that screening and early treatment result in improved growth and neurocognitive outcomes. The situation is made more complicated because available screening tests, including commonly used point-of-care measurements of Hb, have
poor test characteristics in identifying iron-deficiency anemia. A Hb level itself is neither sensitive nor specific for iron deficiency, since many other conditions can cause anemia, and iron deficiency often exists without anemia. Serum ferritin, a marker of iron stores, has been proposed as a better screening test. However, it is more expensive and cannot be done with a capillary blood sample (fingerstick). Screening with Hb at 12 months of age remains the pediatric standard.

CASE continued:

Once the acute infection is addressed, you inquire about the diet of the 3-year-old in case 3. His family's description of the child's diet is common among children with iron deficiency.

4. What are you likely to hear? What dietary changes can you suggest? Why might it be difficult to assess this child's iron stores?

Toddlers often have diets that do not contain enough iron-rich foods. Dietary risk factors include early introduction of cow's milk (before 1 year of age) and consumption of greater than 24 oz/day of cow's milk. Cow's milk is low in iron, interferes with iron absorption, and may cause occult gastrointestinal bleeding. Occult bleeding caused by consumption of large amounts of cow's milk, and milk hypersensitivity with pulmonary hemosiderosis (Heiner Syndrome), is a rare cause of iron deficiency and may be seen in younger children.

Increased juice intake may decrease appetite for iron-rich foods. Iron-rich foods include meat, fish, legumes, and leafy green vegetables as well as fortified bread, noodles, and cereals.

Iron absorption takes place in the duodenum. Its absorption is enhanced by an acidic environment and Vitamin C, and is inhibited by phytate, tannins, egg yolk, antacids and the fiber of cereal grains.

Ferritin is also an acute phase reactant and may be elevated in the setting of infection and inflammation. Conversely, the serum iron concentration and total iron binding capacity (TIBC) may be decreased during active infection, making these levels difficult to interpret.

5. What will you do next for the two toddlers (cases two and three)? How will you follow the response to treatment? Why are you bothering to treat?

One should presumptively treat the 13-month-old and the 3-year-old for iron deficiency anemia with ferrous sulfate. The traditional dosing regimen is 3 to 6 mg/kg of elemental iron divided twice daily. Studies in adults have shown that lower doses of iron (3 mg/kg) not only have improved tolerance, but are better absorbed and result in improved increases in Hb measurements compared to higher doses of iron. Giving an iron supplement every other day instead of daily may also lead to improved absorption. Parents should be warned about the possible side effects of constipation, dark stools, dental staining, nausea, and epigastric pain. Less gastrointestinal irritation is reported if the iron drops are given after meals. Taking it with an acidic beverage (e.g., a small amount of orange juice) may enhance absorption. Liquid oral iron preparations such as Fer-In-Sol 15mg/ml liquid drops or flavored alternatives (such as NovaFerrum liquid iron drops 15mg/ml) are some options for treatment in this age group.

Repeat the CBC in 1 month. An increase of 1 g/dl of Hb confirms the diagnosis of iron deficiency. First evidence of response to iron therapy would be an increased reticulocyte count 7-10 days after starting treatment, though it is not necessary to check this routinely. If there is evidence of response, continue the iron therapy for 1 month after the normalization of the Hb level to fully replete iron stores. After discontinuing iron therapy, it is reasonable to check Hb levels in 6-12 months if the cause of iron-deficiency has been corrected or if the child/adolescent has entered a period of decreased rate of growth with decreased iron demand.

Not only is one treating to prevent the symptoms of fatigue, exercise intolerance, irritability, and anorexia, but also to prevent the more serious complications of anemia, which include tachycardia and cardiac dilatation. There is also a growing body of evidence suggesting that iron deficiency early in life can have measurable effects on cognitive achievement. Carter and colleagues found iron deficiency...
and iron deficiency anemia to be associated with poorer age appropriate cognitive performance including object permanence and short-term memory in infants compared with iron sufficient infants. Numerous other studies suggest an association of iron deficiency (with or without anemia) with decreased cognitive performance, which has prompted interest in screening for iron deficiency without anemia [e.g., ferritin, zinc protoporphyrin (ZPP)]. As noted above, an optimal test has yet to be identified, and data are lacking to support that early intervention impacts cognitive outcomes.

CASE continued:

You repeat a CBC on the 13-month-old after several months of treatment with iron. It is unchanged.

6. What diagnoses are you now considering? What should you do next?

One must first ensure adequate adherence to therapy. In children with microcytic anemia who do not respond to iron therapy, you must consider hemoglobinopathies or lead poisoning.

Understanding iron and heme physiology underlies understanding the significance of the following lab studies. In brief, iron is absorbed in the proximal small intestine bound to transferrin, which mediates its uptake into RBC precursors through the transferrin receptor. The iron is released and incorporated into heme. Iron outside of Hb-producing cells is stored in ferritin. 60-70% of total iron is found in Hb. A small amount is found in heme and nonheme enzymes and myoglobin. The remainder is stored in ferritin, located primarily in the liver, bone marrow, spleen, and muscle.

Laboratory studies to consider:

- CBC - repeat to evaluate current status, and to rule out laboratory error.
- Reticulocyte count - to evaluate RBC production in response to anemia.
- Serum ferritin - storage form of iron, earliest marker of iron deficiency, and highly specific (but not sensitive because it is an acute phase reactant).
- Serum iron concentration - decreases as stores are depleted, but may be affected by meals, infection, inflammation, and diurnal variation
- TIBC - indirectly measures transferrin, a specific carrier protein for iron. TIBC may also be decreased with malnutrition, inflammation, and chronic infection.
- ZPP - formed when zinc is incorporated into protoporphyrin instead of iron in final step of heme biosynthesis. Detects iron deficiency before onset of anemia, but may also be elevated with lead poisoning and chronic disease.
- Lead level - The AAP and CDC guidelines recommend assessing risk for lead poisoning at 9-12 months of age and 24 months of age and screening all Medicaid-eligible children at those ages.
- Hemoglobin electrophoresis - to determine if hemoglobinopathy is the cause of microcytic anemia. Two caveats related to hemoglobin electrophoresis: 1) it may not be accurate in the setting of iron deficiency due to decreased hemoglobin A2 synthesis; beta thalassemia trait cannot be excluded as the etiology for microcytosis unless iron stores are replete. 2) hemoglobin suggestive of alpha-thalassemia trait cannot be identified on a hemoglobin electrophoresis after the newborn period and would be a diagnosis of exclusion or may be formally diagnosed by alpha globin gene testing.

7. How would you manage the teenager in case 4? What are the AAP screening guidelines for anemia in adolescents?

Case 4 highlights that adolescents are at risk for iron deficiency. Risk factors in adolescence include rapid growth and blood loss (such as that due to menstruation, gastrointestinal loss, hematuria, or Helicobacter pylori infection). Evaluation for anemia with Hb should occur in any adolescent with a positive risk assessment including those with iron poor diets or females with heavy menses. Also consider a bleeding evaluation in females with menorrhagia (refer to the module on Adolescent Menstrual Disorders for a more detailed discussion on the evaluation of menorrhagia).

Dosing for iron replacement in adolescents with iron deficiency (which can be applied to any patient over 20 kg) ranges from 60-100 mg of elemental iron divided twice daily. Ferrous sulfate 325 mg tablets contain 65 mg of elemental iron/tablet and should be given once to twice daily depending on the
severity of iron deficiency and anemia. Once again, absorption is enhanced by an acidic environment (e.g., taking it with a small amount of orange juice). Combination vitamin C/iron preparations are available for adolescents.

Patients and parents should be warned about the possible side effects of constipation, dark stools, dental staining, nausea, and epigastric pain. Less gastrointestinal irritation is reported if the iron is taken after meals.

Monitoring for treatment response is similar across age groups in childhood and adolescence, though therapy may need to be of longer duration in adolescents with ongoing blood loss.

**Additional References:**

**Resource:**