Iron deficiency Anemia
UW Pediatrics Outpatient Clinical Guidelines

Sources:
• AAP Clinical Report—Diagnosis and Prevention of Iron Deficiency and Iron-Deficiency Anemia in Infants and Young Children (0–3 Years of Age), 2010
• Screening and Management of Anemia at HMC Pediatric Clinic, 2013
• Screening for Iron Deficiency – Pediatrics in Review 2002
• UpToDate Iron Deficiency Anemia pediatric guidelines, accessed Feb 2018

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Summary:

1. Screening for iron deficiency anemia (IDA) is recommended by the American Academy of Pediatric (AAP) to be done as universal screening for all children between ages 9-12 months with Hgb or Hct. Some have recommended an adjunct screening (such as ferritin or zinc protoporphyrin to heme ratio, ZPPH) to assess for iron deficiency without anemia. (Note, however, the USPSTF has found inconclusive evidence to recommend for or against routine screening among young children in the US. Other countries including the UK and Canada do not have a universal screening recommendation.)

2. Rescreening is recommended 6-12 months later in communities and populations that have a high prevalence of IDA, including children eligible for WIC, children of migrant workers, or recently arrived refugee children. In communities that have low rates of anemia overall, selective rescreening is recommended for children at risk for iron deficiency. WIC eligibility requires annual rescreening.

3. Risk of IDA is increased for preterm or low-birthweight infants, poor growth or failure to thrive, lead exposure, infants consuming cow milk before age 12 months, breastfed infants who are receiving low amounts of iron-rich foods (<2 servings per day), prior anemia, and children who consume more than 24 oz of cow milk per day.

4. Additional screening for IDA should be considered for adolescent females within a year of onset of menses, and children with special health considerations including restricted diet, GI dysfunction, BMI >95th percentile, and restless leg syndrome.

Background:

1. Iron deficiency anemia (IDA) is the most common nutritional deficiency worldwide. Rates decreased in the US since the 1970's, but IDA remains relatively common and
has been found in 6.6% to 15.2% of toddlers, depending on ethnicity and socioeconomic status.

2. Many studies have demonstrated an association between IDA in infancy and later cognitive deficits. However, it is noted that a USPSTF statement published in Sept 2015 concluded that there was not sufficient evidence to recommend for or against iron deficiency anemia screening in 6-24 month old children in the US: “Few well-designed long-term studies on the effects of iron deficiency anemia in infancy and childhood on these health outcomes are available. Based primarily on observational data, studies have found an association between iron deficiency (with or without anemia) in infancy and childhood and impaired neurodevelopment in older children. Cognitive and behavioral delays in children have also been found to be associated with iron deficiency anemia. However, these observational studies have limitations due to the types of measures reported and confounding with nutritional and socioeconomic factors, making causation difficult to determine.” Despite this inconclusive data, the AAP recommends screening given worldwide evidence of the potential harm of IDA on development outcomes.

3. Eligibility for the Women, Infant and Children’s nutritional program (WIC) requires annual evaluation for IDA, given higher overall rates among low-income children.

4. There are many causes for anemia other than iron deficiency. One that is particularly common, and also associated with microcytic anemia like IDA, is thalassemia trait, which is not reliably identified on the newborn screen (unlike Beta-thalassemia major), and may require hemoglobin electrophoresis to diagnose. Individuals with thalassemia trait may have concurrent IDA which responds to iron therapy; empiric treatment with iron is reasonable to confirm they are iron sufficient. It is common for residual microcytic anemia to persist after iron treatment for these individuals. Iron studies can be used to determine when patients have sufficient iron stores.

Definitions

- **Anemia** – generally defined as hemoglobin concentration 2 standard deviations below the mean (below the 5th percentile) for a normal, equivalent population
  - For children 6 months-5 years, the WHO defines this as Hgb < 11.0 g/dL
  - WHO definitions: Children 5-11 years Hgb < 11.5, Hct < 34
  - WHO definitions: Children 12-13 years Hgb < 12.0, Hct < 36
- **Iron deficiency** – **insufficient** iron to maintain normal physiologic function.
  - One definition from the WHO is ferritin < 12 mcg/L in children up to age 5, and < 15 mcg/L in those 5 years and older.
- **Iron deficiency anemia** – anemia that results from iron deficiency

Screening

There is no one test considered to be the gold standard for diagnosing iron deficiency or IDA, so official recommendations and clinical practice varies. Screening available includes
Dietary history:
- Because of the low specificity of dietary history for iron deficiency anemia, dietary screening cannot eliminate the need for further laboratory testing. However, dietary history may be useful in identifying children at low risk for iron deficiency because it has a higher negative predictive value. In one study of healthy 15-60 month old children in an urban area, the negative predictive value was 97% if they did not meet criteria for dietary iron deficiency, as defined as: 1) fewer than 5 servings per week each of meat, cereals or bread, vegetables, and fruit; 2) more than 16 oz per day of milk; or 3) daily intake of fatty snacks or sweets or greater than 16 oz of soda.
- The AAP dietary risk assessment includes 1) Use of non-formula cow’s milk, goat’s milk, or soy milk before 12 months of age, 2) Fewer than two servings/day of iron-rich foods (eg, meats or fortified infant cereal) from 6-12 months of age. 3) For children 12 months and older: Milk intake greater than 24 oz daily; 4) Fewer than three servings daily of iron-rich foods (eg, iron-fortified cereal or meats).

Hematologic markers:
- Hgb and Hct are the most commonly used screening tests for iron deficiency. Both measurements are inexpensive, readily available tests for anemia and are the most commonly used screening tests for iron deficiency. Disadvantages include that they are late markers of iron deficiency, are not specific for IDA, and are less predictive as IDA prevalence decreases (like in the US population).
  - Hgb, the concentration of oxygen-carrying protein, is a more sensitive and direct test for anemia than Hct, the percentage of whole blood that is occupied by RBCs.
- The mean corpuscular volume (MCV) is the average volume of RBCs. MCV is useful for categorizing anemia as microcytic, normocytic, and macrocytic.
- The red blood cell distribution width (RDW) measures variations in the size of RBCs. RDW increases with iron deficiency. RDW has relatively low specificity, so is not as useful as a single screening test, but it is used frequently in conjunction with MCV to differentiate among various causes of anemia. For example, RDW is high in IDA, but low in thalassemia minor.
- Ferritin binds iron atoms, and stores iron mostly within cells. A small fraction circulates in the serum, and is related to tissue iron stores.
  - Ferritin is an acute phase reactant so it can be falsely normal/elevated (i.e., negative) in the context of chronic inflammation, infection, malignancy, and liver disease. Measuring a CRP with the ferritin can be used to help rule out inflammation (this can be added on later if ferritin is elevated):
    - If ferritin is decreased, this indicates low iron, so CRP is irrelevant
    - If ferritin is normal to high with normal CRP -> no ID
    - If ferritin is normal to high with high CRP -> more tests needed
  - Clinical tip: if you have already drawn a ferritin level, additional iron studies can be added on to the tube of blood drawn for ferritin, as well as CRP
  - In some major labs, obtaining ferritin and full iron panel costs the same.
- Zinc Protoporphyrin to Heme ratio (ZPPH)
  - Protoporphyrin IX is found in red blood cells, and is the immediate precursor
of heme. In the setting of iron deficiency or lead toxicity, rather than incorporating a ferrous ion, protoporphyrin incorporates a zinc ion, forming Zinc protoporphyrin, or ZPP.

- In the past, ZPP levels have been measured indirectly by a testing process that removed the Zinc ion and measured what is called the free erythrocyte protoporphyrin, or erythrocyte protoporphyrin. This was used to screen for lead toxicity (prior to using blood lead levels) and for iron deficiency.
- ZPPH has become more widely used in part because it can be measured quickly, at low cost, and with a small blood volume.
- Lab levels vary, but the UW labs consider ZPP to be normal when <80mcg/dL but some pediatric studies have used lower cut-off levels.
- An advantage of ZPPH is that it is not an acute phase reactant like ferritin.

- Additional labs to consider when anemia is more severe (e.g., Hgb <10 or Hct <30) to evaluate for other diagnoses:
  - Serum Iron, TIBC, Transferrin Saturation
  - CBC with differential
  - Reticulocyte count
  - Thalassemia screen (especially when MCV/ferritin/ZPPH are normal)
  - Newborn screen (may check hemoglobinopathy screen only) for children born outside of US
  - B12 and folate for strict vegetarians
  - Stool for occult blood
  - IgA-TTG antibodies for celiac disease

- Blood sampling options
  - When available, a finger or a toe stick can be used to obtain a Hgb or a Hct (and in some cases can also be used for the ZPPH measure), which may be preferable over a venipuncture blood draw. However, venous draw is needed for more extensive testing including ferritin or other iron studies.
  - Consider early lab screening (at 4-6 months of age) for premature infants, infants with failure to thrive, or for breastfed infants with maternal anemia.

**Prevention of IDA**
- The nutritional goal for infants is 10mg of iron daily.
- By 4 months of age, the natural supply of iron decreases with the physiologic nadir. We should recommend dietary support with iron-rich solids and/or multi-vitamin with iron, especially for breastfed infants. Breastfed infants should have iron-rich foods offered beginning at the time of solid food introduction, around 4-6 months.
- Consider prescribing iron-fortified vitamins, especially for those not yet taking solid foods with iron.
- Premature infants are at higher risk when most of the iron is transferred in the 3rd trimester. Infants <32 weeks should be supplemented with iron.
- Provide anticipatory guidance and handouts on iron-rich foods.

**Treatment**
- Presumptive iron deficiency is treated with oral iron salts, most commonly over-the-
counter ferrous sulfate, which is inexpensive and relatively well absorbed.
  o Response to a clinical trial of iron therapy is often used as a practical method of confirming the diagnosis of IDA.

- Recommended dosages of iron salts are based on elemental iron
  o Children receive 3 to 6 mg/kg per day (daily or twice daily)
  o Adolescents receive 60 mg/dose (daily or twice daily).
- If not tolerated, consider more expensive formulations (such as Nova-Ferrum, which is generally better tasting and better tolerated).
- Provide counseling on administration
  o Iron is best absorbed with concurrent intake of vitamin C (such as orange juice). Milk interferes with absorption, so should be avoided around time of administration.
  o Give concurrently with foods that blunt the taste. For example, a tip from a clinical pharmacist is mixing with jam and giving with crackers.
  o Brush teeth afterwards to avoid stained teeth. If tooth staining does occur, baking soda and water can help to remove it.
  o Consider giving the medication in the bathtub given the potential for staining clothing.
- Parenteral iron rarely is considered if oral iron is not tolerated; intramuscular iron injections usually are not appropriate.

**Follow-up**

- If the iron deficiency is nutritional, the response to iron typically is rapid.
- Support families with initiating iron therapy, which may include
  o Calling pharmacy to ensure prescription was picked up (if given as a prescription vs OTC formulation)
  o Calling family to check in about how it is going with giving medication
- After 1 month of therapy, the Hgb measurement should be repeated. An increase of 1 g/dL (10 g/L) or greater confirms the diagnosis of iron deficiency anemia. No improvement in Hgb should prompt further evaluation of the anemia with additional laboratory tests, including MCV, RDW, and serum ferritin, and a search for possible sources of blood loss.
- When there is no lab response to iron supplementation, thalassemia screening should be considered if not performed through newborn screening (or to evaluate for thalassemia trait).
- Iron therapy should be continued for an additional 2 to 3 months after Hgb has returned to a normal level, and Hgb (and/or ZPPH or ferritin) should be remeasured.