

# Iron deficiency anemia in toddlers to teens: How to manage when prevention fails

JACQUELYN M POWERS, MD, AND GEORGE R BUCHANAN, MD

**Dr Powers** is a fellow, Pediatric Hematology-Oncology, University of Texas Southwestern Medical Center, Dallas. She has nothing to disclose in regard to affiliations with or financial interests in any organizations that may have an interest in any part of this article.

**Dr Buchanan** is professor of pediatrics, Pediatric Hematology-Oncology, University of Texas Southwestern Medical Center, Dallas. He reports contracted research for Gensavis Pharmaceuticals LLC.

Despite recommendations for universal screening of children for iron deficiency, there is heightened concern about prevalence, especially among young children and teenaged girls. It is imperative that pediatricians identify and correct the cause; educate the family regarding the diagnosis; and prescribe iron therapy.

Iron deficiency anemia (IDA) is the most common hematologic condition, affecting millions of children in the United States and worldwide. For decades efforts have focused on prevention of IDA, but little emphasis has been placed on the optimal management of children in whom prevention has failed.<sup>1</sup> Despite recommendations for universal screening at 1 year of age, the prevalence of IDA remains at 3% to 7%, with a disproportionately high risk in lower socioeconomic groups.<sup>2-4</sup> Although screening is not recommended for adolescent females, patients in this age group often have IDA as well, with an estimated prevalence of 9%.<sup>5</sup>

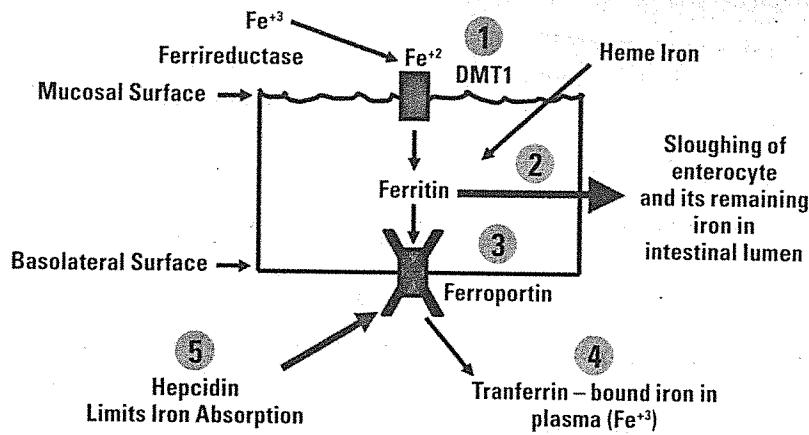
## Pathophysiology

Iron is utilized by all cells in the body, so iron homeostasis is tightly regulated. In a

person with normal iron status, approximately 1 mg to 2 mg of iron (10% of the iron in a normal diet) is absorbed each day from the duodenal lumen into the intestinal mucosal cell (enterocyte), usually in the ferrous (Fe<sup>2+</sup>) state. Except for heme-bound iron derived from meat, this process requires a divalent metal transporter 1 which also transports other metal ions including lead.<sup>6</sup> In persons with iron deficiency, iron absorption is increased. Because iron absorption is accompanied by the intake of other elements as well as children with pica, which commonly results from iron deficiency, are at higher risk for lead ingestion and intoxication if their environments are contaminated with lead.

Iron in the enterocyte is either retained (and subsequently sloughed and excreted in the stool) or carried across its basolateral

**FIGURE MECHANISM OF IRON ABSORPTION IN THE INTESTINE**



**▲ Absorption of iron by the duodenal enterocyte and regulation by hepcidin:**  
 ① Iron is absorbed in the ferrous (Fe+2) state from the duodenal lumen into the enterocyte via divalent metal transporter 1 (DMT1). ② Iron is retained as ferritin and subsequently sloughed or ③ carried across the basolateral surface into the plasma via ferroportin. ④ In the bloodstream, iron is bound and transported to the bone marrow or storage sites via transferrin. ⑤ During states of iron excess or inflammation, hepcidin levels increase and block ferroportin, limiting the ability to mobilize iron into plasma.

membrane into the plasma by the transport protein ferroportin. It is this process of intestinal iron absorption that serves as the primary mechanism of iron homeostasis, which is tightly regulated by the small peptide hepcidin. Hepcidin is produced in the liver and upregulated in states of inflammation.

When iron deficiency is present, hepcidin is decreased, thus fostering enhanced absorption of iron. In contrast, during states of iron excess or inflammation, hepcidin levels are usually increased, thereby blocking ferroportin and limiting its ability to mobilize iron into the plasma from enterocytes and storage sites (Figure).

In the bloodstream, iron is bound to transferrin and transported to the bone marrow for the production of hemoglobin, which constitutes more than half of the body's total

iron packaged within erythrocytes. Some iron is required to produce myoglobin, and a small but important fraction helps promote DNA synthesis in all cells and is necessary for optimal function of key oxidative enzymes in mitochondria. The remainder of the body's iron is stored in macrophages and liver parenchymal cells.

Physiologic iron loss from the body in sloughed mucosal cells, skin sweat, and external blood loss (especially menstruation) averages 1 mg to 2 mg per day, balancing its normal rate of absorption. Reduction in dietary intake or excessive blood loss results in a net negative iron balance, which over time leads to iron deficiency and eventually anemia. Such changes can be exacerbated during periods of increased growth and demand, as in young children and adolescents, thus placing them at highest risk of iron deficiency.

**Incidence/etiology**

In young children, the primary etiology of IDA is nutritional deficiency due to excessive milk intake and/or prolonged breastfeeding without adequate iron supplementation (Table 1).<sup>7</sup> In the United

**TABLE 1 RISK FACTORS FOR NUTRITIONAL IDA IN YOUNG CHILDREN**

- Prematurity
- Exclusive breastfeeding >6 months of age without iron supplementation
- Hispanic ethnicity or Asian race
- Prolonged bottle use
- Obesity
- Low socioeconomic status
- Early, excessive, or prolonged intake of cow milk
- Not in day care

Abbreviations: IDA, iron deficiency anemia. Brotanek JM, et al.<sup>2,3,7</sup>

**TABLE 2 LABORATORY DEFINITIONS**

LABORATORY MEASURE	DEFINITION
<b>Hemoglobin</b>	Measure of the protein within red blood cells that carries iron and transports oxygen
<b>Hematocrit</b>	Percentage of the volume of red blood cells in the blood
<b>MCV</b>	Measure of the average volume of a red blood cell
<b>RDW</b>	Measure of the variation of red blood cell volume
<b>Reticulocyte</b>	Measure of the most immature red blood cells, in circulation 1-2 days prior to becoming mature red blood cells
<b>Ret-He, CHR</b>	Measure of the hemoglobin content in reticulocytes, the most immature red blood cells in circulation
<b>Serum iron</b>	Measure of circulating iron that is bound to transferrin
<b>Serum ferritin</b>	Measure of the intracellular protein that stores iron
<b>TIBC</b>	Measure of the body's capacity to bind iron with transferrin
<b>Transferrin</b>	Measure of iron-binding protein found in the plasma
<b>Transferrin saturation</b>	Percentage of the serum iron that is bound to transferrin

Abbreviations: CHR, reticulocyte hemoglobin content; MCV, mean corpuscular volume; RDW, red cell distribution width; Ret-He, reticulocyte hemoglobin equivalent; TIBC, total iron binding capacity.

States, emphasis on the convenience of cow milk-based formulas led to decreased breastfeeding during the 1940s. This, in turn, resulted in "cow milk anemia" because of iron deficiency in up to 15% of infants and young children. Iron-fortified formula was thus recommended by the American Academy of Pediatrics (AAP) in 1969 and later adopted by the Women, Infants, and Children program during the 1970s. These improvements along with a shift back to the benefits of breastfeeding fostered a decline in iron deficiency in some high-risk populations.<sup>2</sup> Yet IDA continues as a common problem for those children aged 9 to 48 months, especially in lower income groups.

Iron in cow milk has lower bioavailability than human breast milk (5%-10% vs 50% absorption, respectively), and milk potentially interferes with absorption of iron present in other foods. When consumed in excessive quantities, proteins in cow milk can sometimes damage the intestinal mucosa, leading to occult blood loss and occasionally frank protein-losing enteropathy.<sup>8</sup> Such patients present with periorbital or even generalized edema due to low serum albumin. Adolescent girls, in contrast to young children, develop IDA primarily from acute and/or chronic heavy menstrual bleeding.

### Effects of IDA

Concerted efforts to prevent IDA

largely result from its association with lower test scores of mental and motor development in young children, at least some of which are long lasting.<sup>9-11</sup> Such deficits may result from reduced activity of key iron-containing enzymes in the brain. Less appreciated are the similar effects in older pediatric patients with IDA. For example, iron-deficient adolescent girls without anemia have improved verbal learning and memory after taking ferrous sulfate for 8 weeks compared with those receiving placebo.<sup>12</sup> Moreover, young women with menorrhagia and decreased ferritin levels have elevated fatigue scores relative to those with normal menses.<sup>13</sup>

### Shortfalls of prevention and screening

Because IDA, at least in infants and young children, is usually preventable, research has focused on defining risk factors and means to ensure early diagnosis. Strategies to prevent iron deficiency are often unsuccessful, however, as evidenced by only modest decreases in its prevalence in the United States during the past several decades. Indeed, this failure of prevention has resulted in the AAP's Committee on Nutrition recommendation that screening be performed in all young children at approximately 1 year of age.<sup>14</sup>

Unfortunately, the timing of such "screening" often falls prior to the transition to cow milk for most children, thus missing the opportunity to diagnose and treat iron deficiency before its potentially damaging effects occur. Infants who are primarily formula fed during the first year of life are at low risk of IDA at 12 months of age, given that

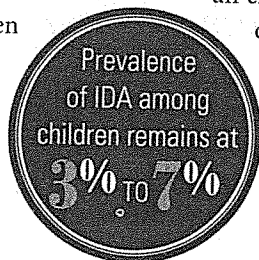
virtually all commercially available formulas are supplemented with the 10 mg to 12 mg of iron per liter necessary to meet the growing baby's needs. The subsequent transition to cow milk, however, often administered in large quantities, increases the risk for IDA during the second year of life when rapid growth rate requires substantial iron intake.<sup>15</sup>

Although the AAP recommends screening for iron deficiency whenever risk factors are present, no formal screening recommendations exist for this age group, or for the other high-risk group, adolescent females. Nonetheless, in all young women who have reached menarche, it is important to obtain a thorough menstrual history and consider testing for iron deficiency in those who appear to have excessive bleeding.

### Confirmation of the diagnosis

Screening typically consists of a complete blood count (CBC) or measurement of the hematocrit or hemoglobin concentration alone. A CBC is preferable because it provides information about red cell indices, the most important of which are mean corpuscular volume and red cell distribution width (Tables 2, 3). Given that approximately 60% of anemia is caused by factors other than IDA, virtually all etiologies of anemia—including hemolysis and bone marrow failure (eg, leukemia)—should initially be included in the differential diagnosis.<sup>14</sup>

In patients whose history is consistent with iron deficiency and who have mild microcytic anemia



(hemoglobin >9 g/dL), it is reasonable to prescribe a therapeutic trial of oral iron and reassess 4 weeks to 6 weeks later to confirm an increase (and ideally normalization) of the hemoglobin concentration.<sup>16</sup> In children with no or limited response to an empiric trial of iron therapy or whose laboratory tests for IDA are normal, other etiologies of microcytic anemia should be considered (Table 4). For patients with anemia that is more severe (hemoglobin <9 g/dL), confirmation of IDA by history, review of the other CBC parameters, and/or iron studies are prudent to ensure appropriate management.

Unfortunately, there is no ideal

test or even combination of tests to firmly establish the diagnosis of IDA in all patients.<sup>17</sup> Serum ferritin level will usually provide an accurate assessment of total iron stores in an otherwise well child. With acute inflammation, however, ferritin values will be elevated and the transferrin saturation may be reduced or normal. The reticulocyte hemoglobin content is the first peripheral blood count measurement that becomes abnormal in iron deficiency, but it is also reduced in thalassemia trait. Thus, all the clinical information and laboratory data should be taken into account to ensure a correct diagnosis.

**Education and etiology**  
Whether IDA is identified through

**TABLE 3** TYPICAL LABORATORY TEST RESULTS IN CHILDREN WITH IDA

LABORATORY TEST	UNITS	NORMAL VALUES		IDA VALUES	
		ALL TODDLERS	ADOLESCENT FEMALES	ALL TODDLERS	ADOLESCENT FEMALES
Hb	g/dL	>11	>12	<11	<12
MCV	fL	>70	>80	<70	<80
RDW	%	<15	<15	>15	>15
Ret-He, CHr	pg	>25	>25	<25	<25
Serum iron concentration <sup>a</sup>	mcg/dL	>40	>40	<40	<40
Serum ferritin concentration <sup>a</sup>	ng/dL	>10	>10	<10	<10
TIBC <sup>a</sup>	mcg/dL	<400	<400	>400	>400
Transferrin saturation <sup>a</sup>	%	>20	>20	<20	<20

<sup>a</sup>Concomitant inflammation may increase serum ferritin and/or decrease serum iron and TIBC. Abbreviations: CHr, reticulocyte hemoglobin content; Hb, hemoglobin concentration; IDA, iron deficiency anemia; MCV, mean corpuscular volume; RDW, red cell distribution width; Ret-He, reticulocyte hemoglobin equivalent; TIBC, total iron binding capacity.

**TABLE 4**  
**MOST COMMON CAUSES OF MICROCYTIC ANEMIA**

- Iron deficiency anemia
- Thalassemia trait (alpha or beta)
- Anemia of inflammation (if moderate or severe)
- Hemoglobin C disorder<sup>a</sup>
- Hemoglobin E disorder<sup>a</sup>

<sup>a</sup>With or without concomitant thalassemia trait

screening, as a result of specific signs/symptoms, or by “accident” when a CBC is performed for another reason, it is important to identify and correct the cause; educate the family regarding the diagnosis; and prescribe iron therapy. In young children, a thorough dietary history and education about the benefits of limiting cow milk intake and providing a well-balanced diet are required. Emphasis should be placed on limiting milk intake to 20 ounces per 24-hour period, which will allow the child’s diet to diversify and likely include foods with higher iron content (eg, virtually all forms of meat, fish, and beans), while continuing to provide adequate dietary calcium and vitamin D. In toddlers who continue to drink from the bottle, transition to a sippy cup or regular cup should be strongly encouraged.

For teenaged girls with heavy menstrual bleeding responsible for IDA, institution of appropriate

hormonal regulation is often necessary to reduce continuing excessive blood loss. Moreover, evaluation for a generalized hemorrhagic disorder should be undertaken if other bleeding sites or a positive family history are identified.

In patients who have IDA that is not clearly due to poor nutrition or heavy menstruation (ie, boys aged older than 4 years or girls who have not reached menarche), other etiologies must be considered. Specific possibilities are gastrointestinal blood loss due to inflammatory bowel disease or discrete lesions such as ulcer or hemangioma and/or malabsorption resulting from celiac disease or iron refractory iron deficiency anemia. In some patients with recurrent IDA of unknown cause, intrapulmonary bleeding or intravascular hemolysis causing occult urinary iron loss may need to be considered.

### Iron therapy

Countless iron preparations and formulations exist, many of them available over the counter.<sup>18</sup> These are often labeled (according to US Food and Drug Administration [FDA] regulations) as supplements and marketed based on slight differences in other added vitamins (eg, B<sub>12</sub>, folate) and minerals, with or without extended-release properties. Ferrous sulfate, the first formulation developed to treat iron deficiency, is among the least expensive and perhaps most effective.<sup>19</sup> To date, iron salts such as ferrous sulfate, gluconate, or fumarate are the most frequently employed iron preparations,

with ferrous sulfate remaining most popular. It is important to note that multivitamin drops with iron (10 mg elemental iron/1 mL), although an appropriate supplement for children who do not have IDA but are potentially at risk, usually do not provide sufficient iron for the treatment of IDA.

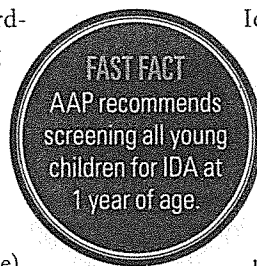
Regarding IDA treatment, these basic tenets are essential: adequate dose and sufficient duration.<sup>19</sup> The most widely cited dosing range in children is 3 mg/kg/day to 6 mg/kg/day of elemental iron divided 1 to 3 times daily. Although no clinical trials have compared the efficacy of different dosing regimens, 3 mg/kg/day of elemental iron was effective in a well-designed clinical trial; may minimize adverse gastrointestinal effects; and is recommended by the Centers for Disease Control and Prevention.<sup>20,21</sup> In teenagers, it may be more convenient to base dosing on the number of tablets daily, depending on the patient’s weight and degree of anemia.

Patients must be instructed about administering iron medication.

Ideally, it is taken on an empty stomach or at least 1 to 2 hours before or after meals to maximize absorption. In young children, parents must be specifically instructed not to give milk with the

iron medication because this will interfere with absorption. Administering iron with vitamin C (eg, juice) may improve absorption but is not critical to successful therapy.

Adverse effects commonly associated with oral iron therapy include poor taste, stained teeth, dark stools,



mild abdominal discomfort, and constipation. Iron may cause fewer adverse gastrointestinal effects if given in low dosages on an empty stomach at night, although this approach has not been validated by formal studies. Adherence is critical to successful therapy, and deficiencies thereof are the most common reason for treatment failure.

Duration of iron therapy is guided by the patient's response, measured by resolution of anemia and repletion of iron stores, typically requiring a minimum of 3 months. In response to treatment, the anemia will resolve first, but iron must be continued beyond the achievement of a normal hemoglobin concentration to ensure repletion of iron stores.

After the planned 3-month treatment duration, it is reasonable to assess the serum ferritin level to confirm the apparent resolution of IDA based on improved blood count findings. Children with ongoing blood loss and/or malabsorption (or any primary etiology not under control) must continue iron therapy and ongoing follow-up to monitor for recurrence.

### Intravenous iron therapy: future standard of care?

Pediatricians frustrated by unsuccessfully treating IDA with oral iron should be aware that new intravenous iron preparations with improved safety profiles have been recently introduced. The advantages of intravenous iron include the possible use of a single total dose infusion (TDI), which in theory eliminates the need for a prolonged course of oral iron and its well-known problems of poor

adherence and adverse effects.

The principal disadvantages of intravenous iron are high cost in comparison to oral iron and concerns about serious adverse effects. Most literature describing intravenous iron involves adults, but several recent studies in children have established that it may be safely administered when oral iron is ineffective.<sup>22,23</sup>

At present, most intravenous iron agents are not FDA approved for use in children. Thus, well-designed studies of initial intravenous versus oral iron therapy in young children and adolescents that evaluate treatment response and quality-of-life measures will be necessary to determine whether this new option is practical, safe, and affordable.<sup>24</sup> ■

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