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HOW I APPROACH

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How I approach iron deficiency with and without anemia

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Abstract

Iron deficiency anemia remains a common referral to the pediatric hematology–oncology subspecialist. Improved understanding of iron homeostasis, including the effects of the regulatory hormone hepcidin, recent adult and pediatric clinical trial data, as well as the availability of safer formulations of intravenous iron, have resulted in additional considerations when making treatment recommendations in such patients. Young children and adolescent females remain the most commonly affected groups, but children with complex medical or chronic inflammatory conditions including comorbid gastrointestinal disorders also require special consideration.

KEYWORDS

hepcidin, inflammation, intravenous, nutritional, therapy

1 | INTRODUCTION

Iron deficiency anemia (IDA) is the most common hematologic condition in the world and the leading cause of anemia globally.[1] According to the World Health Organization, iron deficiency (ID) is the 10th most common modifiable risk factor for early death worldwide.[2] In the United States, it affects approximately 3% of children age 1 to 2 years and 5% of adolescent females.[3] ID alone is estimated at 10% to 13% in these groups. IDA has been associated with lower scores on tests of mental and motor development, which may persist over time.[4–6] Pediatric hematology–oncology subspecialists often see patients with IDA in consultation at initial presentation or later in their clinical course due to persistence of anemia or overt treatment failure. This review discusses iron physiology, iron replacement therapy, and approaches for patients with severe or refractory IDA, mixed conditions of ID and inflammation, and clinical conditions associated with ID without anemia. For the purposes of this review, we utilize the following definitions:

Iron deficiency: Serum ferritin < 15 ng/mL
Mild anemia: Hgb ≥ 9 g/dL but < lower limit of normal for age
Moderate anemia: Hgb 7 to <9 g/dL
Severe anemia: Hgb < 7 g/dL

1.1 | Iron homeostasis

Iron is a critical micronutrient involved in DNA synthesis, energy production, erythropoiesis, and neuronal myelination.[7] It plays a key role in neurodevelopment, neurotransmitter synthesis and packaging, as a structural component of myoglobin, and in cytochromes and enzymes within the mitochondrial citric acid cycle and electron transport chain. Its role in oxygen transport is its most important function.[8] As iron is prioritized to erythrocytes, ID causes hepatic stores to be depleted first, followed by other lower-priority tissues, such as skeletal muscle and intestine.[7] With worsening ID, cardiac iron is compromised, followed by brain iron, and lastly erythrocyte iron. IDA represents a severe form of ID.

Adults with normal iron status have 3 to 5 grams of total body iron, the majority found in circulating erythrocytes and bone marrow.[9] Efficient recycling of iron occurs from senescent erythrocytes via the reticuloendothelial system to form new red blood cells or to be stored in the liver to support growth. Due to its efficient recycling, only 1 to 2 mg of elemental iron intake per day is required to maintain balance in someone with normal iron status. Although heme iron found in meat is efficiently absorbed, the mechanisms affecting its regulation are largely unknown. In contrast, absorption of the nonheme iron found in other foods, as well as many oral iron preparations, occurs within the duodenum (Figure 1A).[7] After export into the capillaries, transferrin-bound iron is transported to other tissues and efficiently taken into the bone marrow by erythrocyte precursors. If not needed for marrow erythrocytes, it is taken up by hepatocytes and macrophages for storage. As in enterocytes, storage iron is exported from hepatocytes via ferroportin.

As there is no physiologic method for iron excretion, intestinal absorption is the primary site of its regulation, and trafficking between transport, storage, and cells utilizing iron is regulated by the hepatic peptide hormone hepcidin (Figure 1B).[10] In states of normal iron status, hepcidin induces internalization and degradation of ferroportin,

Abbreviations: GI, gastrointestinal; IBD, inflammatory bowel disease; ID, iron deficiency; IDA, iron deficiency anemia; IRIDA, iron refractory iron deficiency anemia; sTfR1, serum/soluble transferrin receptor

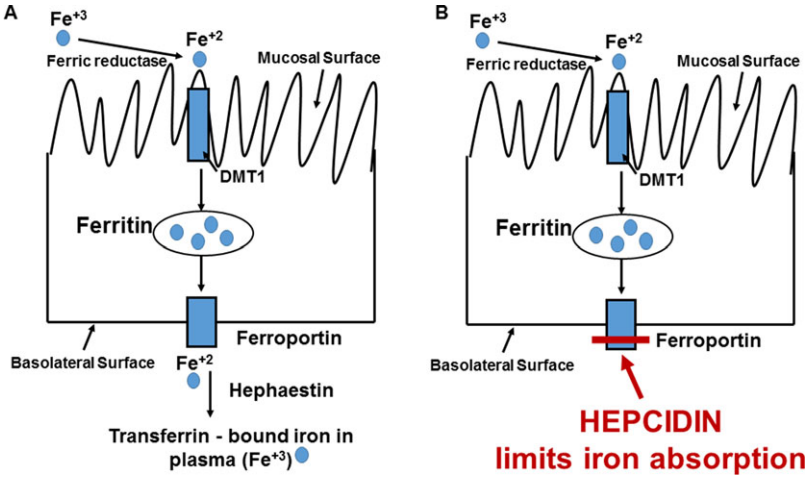

FIGURE 1 A, Nonheme iron absorption at the duodenal enterocyte. B, Regulatory effect of hepcidin on ferroportin, thereby inhibiting iron absorption

thereby limiting iron export from storage sites. During iron-deficient states, hepcidin expression is downregulated, allowing for upregulation of ferroportin, which facilitates iron absorption and release from macrophages to allow for erythropoiesis.

1.1.1 | Anemia of inflammation/excessive hepcidin

Elevated production of hepcidin occurs with acute inflammation or tissue damage and results in impaired iron absorption and release, thus decreasing iron availability for cellular functions.[11] Chronic inflammation with long-standing iron-restricted erythropoiesis can result in a microcytic anemia over time that mimics IDA but may be distinguished by differences in the iron profile (Table 1). Genetic mutations affecting the TMPRSS6 gene result in overexpression of hepcidin[12] and a rare clinical entity known as iron refractory iron deficiency anemia (IRIDA),[13] which is characterized by nonresponse to oral iron therapy and limited response to intravenous iron.[14]

1.2 | Principles of IDA management

A systematic approach to patients with IDA facilitates the correct diagnosis and treatment success.

1.2.1 | Confirm diagnosis

In patients with a microcytic anemia, a clinical history consistent with IDA (i.e., poor or limited iron intake or excessive external blood loss), and characteristic peripheral smear, additional laboratory studies are often unnecessary to confirm the diagnosis. If the history is inconsistent or limited, iron measures may be informative. Although no gold-standard tests exist for ID, an understanding of associated laboratory changes, as well as limitations of each individual test (Table 1), will help support or exclude the diagnosis.[15]

Low serum ferritin (<15 ng/mL) is always consistent with ID. In patients with concomitant chronic conditions, serum ferritin may be falsely normalized. Such patients will often have low transferrin saturation (<15%), which may be more consistent with anemia of inflammation or chronic disease. Assessment of the serum or soluble transferrin receptor (sTfR1) and/or the sTfR/ferritin index may be helpful in differentiating IDA versus anemia of inflammation, with an elevated index (>2) indicative of ID.[16] Patients with persistent microcytic anemia and normal iron panel should be assessed for thalassemia trait or other hemoglobinopathies.

1.2.2 | Identify and correct or manage primary cause (Table 2)

In patients with IDA, the underlying etiology must be elicited. IDA results from either insufficient intake (i.e., low dietary iron content or poor iron absorption) or excessive loss (i.e., external blood loss). Infants and children with history of prematurity are at particular risk for ID given that the majority of iron transfer from mother to fetus occurs during the third trimester of pregnancy. In young children, nutritional IDA results from insufficient dietary iron coupled with increased demand during periods of rapid growth. Excessive cow milk intake is the most common dietary history elicited in affected patients of this age. In addition to limiting consumption of iron-rich foods, when consumed in excessive quantities, cow milk proteins can damage the intestinal mucosa and lead to microvascular gastrointestinal (GI) blood loss. Depending on the amount of milk intake, some children present with milk protein enteropathy that results in intestinal protein loss and anasarca.[17,18] In young children whose diets include appropriate iron intake and limited milk, evaluation for GI blood loss should be pursued.

In adolescent females, chronic menstrual blood loss, particularly in adolescents with abnormal uterine bleeding, is the most common etiology.[19–21] Approximately 0.4 to 0.5 mg of iron is lost along with every 1 mL of blood, so heavy menstrual blood loss may result in IDA that persists or recurs.[22] In females whose clinical history is inconsistent with excessive menstrual bleeding, dietary history and assessment for GI blood loss is necessary.

Once the primary etiology is identified, steps should be taken to address the cause while initiating iron therapy. Dietary counseling, including decreased milk intake to less than 16 ounces per day (regardless of transition to or substitution of soy or almond milk in lieu of cow milk) for young children, is necessary. Adolescent females should be referred for management of excessive menstrual blood loss, which can often be achieved with hormonal therapy or, alternatively, antifibrinolytic medications. Patients with history

TABLE 1 Findings in iron laboratory measurements by iron status

Parameter	Iron overload	Depleted iron stores (stage I)	ID without anemia (stage II)	IDA (stage III)	Anemia of inflammation
Hemoglobin concentration	Normal	Normal	Normal	↓	↓
Mean corpuscular volume	Normal	Normal	Normal	↓	↓
CHr or Ret-He	Normal	Normal	↓	↓	↓
Serum ferritin	↑	↓	↓	↓↓	↑↑
Transferrin saturation	↑↑	Normal	↓	↓	↓
sTfR1	↓	↑	↑↑	↑↑↑	↑↑↑
Hepcidin*	↑	Normal	↓	↓	↑

Abbreviations: CHr or RET-He, reticulocyte hemoglobin content or reticulocyte hemoglobin equivalent; sTfR1, soluble or serum transferrin receptor.

TABLE 2 Clinical history and risk factors for IDA based on patient age and gender

Patient population	Primary etiology	Important clinical history
Infants and young children	Nutritional	History of prematurity Low iron diet Exclusive breastfeeding beyond 6 months of age without iron supplementation Excessive cow milk intake (>16 ounces/day)
Adolescent females	Excessive menstrual blood loss	Menstrual history consistent with excessive blood loss Duration > 7 days >5 sanitary products per day, double production or product change at night Passage of large clots (>size of quarter), sensation of gushing Clinical assessment for bleeding disorder Personal/family history of bruising without trauma Prolonged duration of bleeding (i.e., epistaxis > 10 minutes, minor wounds > 5 minutes, post-dental extractions or surgery) Low iron diet Vegetarian/vegan diet High-carbohydrate diet (i.e., bread, pasta, "junk food"), low in meat/vegetables Skipped meals (breakfast or during school day)
School-aged children and adolescent males	Gastrointestinal blood loss	Gastrointestinal history Failure to thrive Gross blood, dark stools

of GI blood loss or guaiac positive stools should be referred to a GI specialist.

1.2.3 | Provide iron replacement therapy

Therapeutic dosing of iron is required to correct the anemia and replenish iron stores. In addition to considering the underlying etiology, decision-making on the benefits and risks of oral versus intravenous iron should be reviewed with the family, particularly in patients with persistent or refractory IDA despite attempts at appropriately dosed oral iron therapy.

1.2.4 | Oral iron

A large number of oral iron therapy options exist (Supporting Information Table S1). Iron salts, particularly ferrous sulfate, are the most common initial therapy for patients with IDA. Alternatives include iron polysaccharide complex and carbonyl iron. However, data support more efficient absorption of iron salts compared with other formulations and should be considered first line.[23,24]

Dosing recommendations vary considerably. Studies in iron-deficient, nonanemic women comparing oral iron dosing regimens found that lower and less frequent dosing maximizes the fractional amount of iron absorbed per dose.[25,26] Clinical trials utilizing low-dose regimens have also demonstrated efficacy in both adults and children.[24,27] Therefore, in young children we recommend dosing of 3 mg/kg elemental iron administered once daily, preferably as ferrous sulfate. Oral iron administration should occur at least two hours before or after meals and without dairy products. In adolescents, we recommend 65 to 130 mg elemental administered once daily, again preferably as ferrous sulfate. Once-daily dosing maximizes the amount of iron absorbed per dose and may also promote adherence while decreasing side effects such as GI intolerance.

1.2.5 | Intravenous iron

Initial formulations of intravenous iron in the mid-20th century resulted in high rates of serious adverse effects, limiting its use to exceptional circumstances. Formulations developed since 2000 have improved safety profiles, allowing for greater use of this form of iron replacement therapy. All five intravenous iron formulations available in the United States (Table 3) share a common structure of an iron core stabilized by a carbohydrate shell, which slows the release into the plasma after administration. The size of the iron core and type as well as carbohydrate shell density determine the total quantity of iron that may be administered in a single infusion. A "total-dose-infusion," in which a patient's entire iron deficit may be administered with a

TABLE 3 Intravenous iron preparations approved in the United States or Europe

Generic name	Ferric gluconate	Iron sucrose	Low-molecular-weight iron dextran	Ferumoxytol	Ferric carboxymaltose	Iron isomaltoside[a]
FDA indication (adult)	Chronic kidney disease on dialysis + erythropoiesis-stimulating agents	Chronic kidney disease	Oral iron administration is unsatisfactory or impossible	Chronic kidney disease	Intolerance or unsatisfactory response to oral iron; nondialysis-dependent chronic kidney disease	Ineffective response to or inability to use oral iron; Clinical need for rapid iron delivery (Europe)
FDA approved (pediatrics)	Yes, >6 years	Yes, >2 years	Yes, >4 months	No	No	No
[b]Maximum dose per infusion	125 mg	7 mg/kg or 300 mg	20 mg/kg or 1000 mg	510 mg	15 mg/kg or 750 mg	20 mg/kg
Infusion time	60 minutes	60–90 minutes	60 minutes	15–60 minutes	15 minutes (undiluted)	30–60 minutes
Test dose required	No	No	Yes	No	No	No
Black box warning	No	No	Yes	Yes	No	No
Iron Concentration	12.5 mg/mL	20 mg/mL	50 mg/mL	30 mg/mL	50 mg/mL	100 mg/mL

[a]Approved only in Europe. Not FDA approved.
[b]Total required iron dose and number of infusions for a complete treatment course are determined based on the degree of anemia/iron deficiency and formulation utilized.

single infusion, is possible with three formulations: low-molecular-weight iron dextran, ferumoxytol, and ferric carboxymaltose. The principal benefit of intravenous iron therapy is the avoidance of adherence challenges related to taste and GI side effects.[28] Cost varies widely for the various formulations, and all are substantially higher compared with oral iron therapy.

Adult literature on the safety and efficacy of intravenous iron is extensive. Published cohorts have demonstrated efficacy of various intravenous iron formulations in diverse groups of children and adolescents with ID and IDA.[29–34] Most observed adverse effects are transient and include nausea, vomiting, abdominal pain, headache, flushing, pruritus, and urticaria, which typically occur during or immediately after infusion.[35,36] Extravasation of iron into the subcutaneous tissue will result in iron staining of the skin. Anaphylaxis is rare, though "pseudo-allergic" reactions as a result of free iron release into the plasma are difficult to distinguish from the former. Despite the very low risk of serious adverse effects,[37,38] administration should be performed at centers with trained staff to provide appropriate care in the event of an adverse reaction.[39]

1.2.6 | Confirm therapy success

The final step in successful treatment is appropriate follow-up to confirm both resolution of IDA and that the underlying etiology has been addressed. Children with severe IDA should be followed closely (within 7–10 days) to ensure initial response with reticulocytosis and incremental increase in hemoglobin. Subsequent follow-up at the 1- and 3-month time frame is considered within standard of care. In children with history of blood loss, additional follow-up after cessation of iron therapy is prudent to ensure there has not been recurrence.

2 | CONSULTATIONS TO THE PEDIATRIC HEMATOLOGY–ONCOLOGY SPECIALIST

2.1 | Case 1: Initial presentation of severe IDA

A 20-month-old male presents to his primary provider appearing pale and tired. The child took formula during his first year but now drinks 4 to 5 bottles of milk per day and often chews on his cardboard books. A complete blood count at 12 months of age was normal. He is found to have a severe microcytic anemia and is referred to the emergency department.

2.1.1 | Management considerations

This is a typical presentation of a young child with severe nutritional IDA due to excessive milk intake. Initial management, including whether to administer red cell transfusion, should focus on the patient's clinical stability (Figure 2). Transfusion is first-line therapy in patients with hemodynamic changes (tachycardia, orthostatic hypotension) to prevent severe complications such as stroke. In such patients, small aliquots should be administered over several hours to allow for gradual increment in hemoglobin and prevention of volume overload and congestive heart failure. Iron replacement therapy in the form of oral iron should be initiated in addition to red cell transfusion as the iron in transfused red cells is not immediately available for erythropoiesis. If the child is clinically stable and transfusion is deferred, initiation of oral iron therapy necessitates close follow-up (7–10 days) to ensure adherence and appropriate response to therapy (i.e., reticulocytosis with incremental increase in hemoglobin).

Similar to young children, the initial management of an adolescent patient with severe IDA depends on accompanying symptoms.

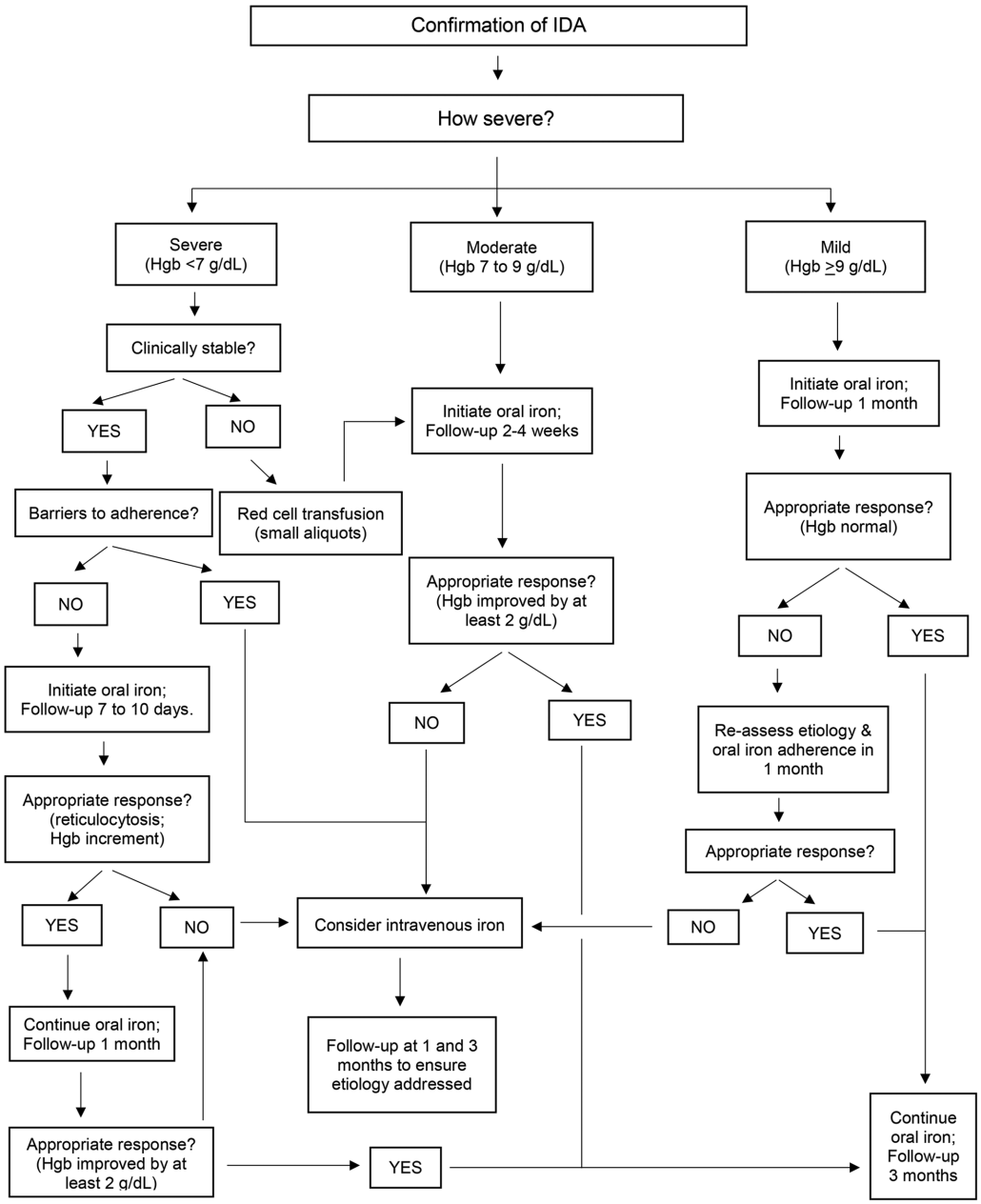

FIGURE 2 Algorithm for the initial management and subsequent follow-up of children with IDA based on degree of anemia at presentation

It is important to consider that an adolescent is unlikely to be able to tolerate the same degree of anemia as the typical toddler with nutritional IDA. It also requires some additional considerations, most notably a detailed history of menstrual blood loss and control of acute menstrual hemorrhage, if present (Table 2). Once the anemia is fully treated, it is important to consider evaluation for a bleeding disorder in patients with heavy menses prior to discharge from hematologic care.[22,40,41] Dietary history must also be considered in adolescent females, as well as increased iron utilization or losses due to high levels of athletic activity (see "Runner's or athlete's anemia").[42] Oral iron therapy is the typical initial therapy, although for patients experiencing substantial fatigue, headaches, and/or exercise intolerance, intravenous iron may be considered to achieve a faster response.

2.2 | Case 2: Persistent or refractory IDA

A 14-year-old female presents with persistent moderate IDA despite six months of oral iron therapy. She was initially diagnosed when her mother noticed her incessant chewing of ice. She admits to inconsistent adherence to iron pills. She also reports having heavy periods that last for more than a week, occurring every 3 to 4 weeks.

2.2.1 | Management considerations

Poor adherence to oral iron therapy is a common cause of persistent IDA in adolescents, but such history may be difficult to obtain when the parent is unaware or the adolescent is embarrassed to share. Acknowledging the difficulty of daily medication adherence or frequency of side effects may allow the patient to be more forthcoming. A 2015

meta-analysis found that 70% of adults prescribed oral iron reported significant GI side effects.[43] In adolescents who are adherent to oral iron therapy, a common cause of persistent ID is poorly controlled excessive menstrual blood loss (see "Identify and correct or manage primary cause"). After fully addressing the underlying etiology, reassessment of iron replacement therapy is warranted. In patients with GI upset, lowering the dose of iron may decrease symptoms. Patients on proton-pump inhibitors or H2 acid blockers may have poor absorption of oral iron therapy. For patients who fail oral iron, the alternative of intravenous iron therapy should be considered.

2.3 | Case 3: Complex patients with IDA

A now six-year-old ex-25 week premature infant with history of necrotizing enterocolitis requiring bowel resection and parenteral nutrition dependence is referred for persistent IDA. His mother reports that despite "always" having been on iron supplementation via G-tube, his years-long microcytic anemia is worsening.

2.3.1 | Management considerations

Any abnormality in the GI tract can alter iron absorption and result in IDA. Iron malabsorption is commonly seen after certain GI surgeries, particularly those involving resection of the proximal small intestine. Micronutrient deficiencies, including ID, are highly prevalent among children with short bowel syndrome/intestinal failure receiving parenteral nutrition and persist even in patients transitioned to enteral feeds.[44,45] Screening for IDA should occur routinely in this patient population. These patients are also at increased risk of vitamin B12 deficiency, so IDA may occur without evident microcytosis. Bariatric surgery, increasingly performed in the older adolescent population, is another cause of ID due to impaired absorption, as is celiac disease.[46] Although celiac disease can occur at any age, adolescents are more likely to present with extraintestinal symptoms, with IDA being the most common.[47] Screening is performed with tissue transglutaminase antibodies.

Inflammatory bowel disease (IBD) affects approximately 70 000 children and adolescents in the United States.[48] IBD is more likely to appear in adolescents than in younger children, with anemia being the most common extraintestinal symptom and present in up to three quarters of patients.[49] Anemia in IBD is complex and multifactorial, commonly representing a combination of GI blood loss and poor absorption resulting in IDA combined with anemia of chronic disease or inflammation.[50] The most common mechanism for ID is iron losses from chronic intestinal bleeding, which may exceed the amount of dietary iron that can be absorbed. Although iron absorption in IBD is not generally abnormal, it may occasionally be impaired in Crohn disease affecting the duodenum. Initial screening considerations may include erythrocyte sedimentation rate, C-reactive protein, or assessment of stools for occult blood.

For patients with IDA due to malabsorption or GI inflammation, intravenous iron is an appealing management strategy, as patients may not absorb oral iron or be more prone to GI side effects.[51,52] The use of intravenous iron has been described in adults receiving long-term parenteral nutrition[53] and is the preferred route of iron replacement in European guidelines for management of IDA in patients with IBD.[54]

2.3.2 | Concomitant inflammation

Anemia resulting from inflammation and ID can be seen in a variety of other inflammatory illnesses such as chronic kidney disease, rheumatologic conditions, and obesity.[55,56] In epidermolysis bullosa, chronic blood and iron loss from open wounds on the skin and erosions in the GI tract can lead to IDA with transfusion dependence.[57] Such patients often fail to respond to oral iron but may become transfusion independent with intravenous iron therapy.[58] ID is increasingly becoming recognized in patients with heart failure[59–62] resulting from a combination of poorer nutritional status, failure to thrive, and decreased intestinal iron absorption. Treatment of ID with intravenous iron in adult heart failure patients has demonstrated clinical improvement, including reduction of all-cause mortality and cardiovascular hospital readmission.[63–65] In any chronic inflammatory condition, elevation of hepcidin results in a functional reduction in iron availability due to both decreased absorption and impaired release of storage iron. Therefore, in the majority of patients with mixed ID and anemia of chronic inflammation, intravenous iron should be considered early in treatment.

2.4 | Case 4: Symptomatic ID without anemia

A 17-year-old female is referred for consideration of iron therapy for persistently low ferritin, without anemia. The patient reports fatigue and poor concentration in class. She also endorses symptoms consistent with restless legs syndrome.

2.4.1 | Management considerations

Given iron's critical role in cellular functions, ID, even in the absence of anemia, negatively affects tissues including the musculoskeletal and nervous systems. ID is associated with fatigue, pica, neurologic symptoms such as restless legs syndrome, and sleep disorders.

The most common symptom of ID without anemia is fatigue. Depletion of tissue iron stores correlate with decreased skeletal muscle capacity for aerobic metabolism, increased lactate accumulation, and muscle fatiguability.[66–68] Iron supplementation mitigates such effects. A randomized double-blinded placebo-controlled study demonstrated the efficacy of intravenous iron in nonanemic iron-deficient premenopausal adult women with fatigue.[69] A smaller single-arm study of adolescent females with ID and mild/no anemia demonstrated improved fatigue and quality of life after a course of intravenous iron.[70]

Several neurologic and sleep conditions have been associated with ID, particularly in adolescents. Pediatric restless legs syndrome, characterized by the strong urge to move the legs and accompanied by uncomfortable and unpleasant sensations, is strongly associated with ID.[71,72] Periodic limb movement disorder, characterized by repetitive, stereotyped movements involving the lower limbs and resulting in sleep disturbance, is associated with ID as well. Patients with both conditions have benefited from improved symptom management with iron therapy.[73,74] At least one study has found that children with neurally

mediated syncope (i.e., simple faint) had a higher prevalence of ID compared with children with other forms of syncope.[75] Adolescents with postural tachycardia syndrome, an autonomic disorder of orthostatic tolerance, also have higher prevalence of ID and anemia compared with the normal US pediatric population and may have symptomatic improvement with iron therapy.[76] Iron therapy has also demonstrated some benefit in small case series and studies of breath-holding spells as well as idiopathic intracranial hypertension.[77,78]

2.4.2 | Runner's or athlete's anemia

Best described in long-distance runners, "runner's anemia" is another etiology for ID and results from a combination of plasma volume expansion, trace GI bleeding, as well as repetitive forceful foot striking that causes red cell lysis in the feet and intravascular hemolysis.[79,80] Other contributors include insufficient dietary iron intake, losses through sweat, and exercise-induced acute inflammation.[81,82] In our clinical experience, "athlete's anemia" is a more appropriate term, as we have cared for similarly affected patients active in crew, soccer, volleyball, and basketball. Female athletes are at higher risk for athlete's anemia due to increased risk of insufficient caloric intake and concomitant menstrual losses. A nutrition referral can be helpful in assessing appropriateness of athletes' overall caloric intake and iron content with the goal of minimizing the need for iron supplementation. Outside the context of confirmed ID, iron replacement therapy in athletes has not demonstrated beneficial effects in endurance and/or performance.[83]

3 | SUMMARY

- IDA occurs most commonly in young children and adolescent females. Patients with primary GI conditions, who are status post GI or gastric bypass surgery, and with chronic inflammatory conditions are also at risk for developing ID.
- Iron homeostasis is regulated by the peptide hormone hepcidin, primarily at the site of intestinal absorption. States of excessive hepcidin (i.e., inflammation) limit both intestinal iron absorption and release of iron from reticuloendothelial stores.
- Principles of IDA management include confirmation of the diagnosis, identification and correction of underlying etiologies, initiation of iron replacement therapy, and appropriate follow-up to ensure resolution.
- Iron replacement therapy may consist of either oral iron or intravenous iron.
  - Low-dose oral iron therapy administered once daily is sufficient for most patients with IDA.
  - Intravenous iron therapy may be considered in patients with oral iron intolerance or nonadherence, as well as initial therapy for patients with ID and anemia of inflammation.
- Many clinical conditions are associated with ID without anemia and may benefit from iron therapy including fatigue, sleep and neurologic disorders, GI or other chronic inflammatory conditions, heart failure, and high-endurance athletes.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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