

Anemia in Children With Inflammatory Bowel Disease: A Position Paper by the IBD Committee of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition

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ABSTRACT

Anemia is one of the most common extraintestinal manifestations of inflammatory bowel disease (IBD). It can be asymptomatic or associated with nonspecific symptoms, such as irritability, headaches, fatigue, dizziness, and anorexia. In IBD patients, the etiology of anemia is often multifactorial. Various causes include iron deficiency, anemia of inflammation and chronic disease, vitamin deficiencies, hemolysis, or myelosuppressive effect of drugs. Anemia and iron deficiency in these patients may be underestimated because of their insidious onset, lack of standardized screening practices, and possibly underappreciation that treatment of anemia is also required when treating IBD. Practitioners may hesitate to use oral preparations because of their intolerance whereas intravenous preparations are underutilized because of fear of adverse events, availability, and cost. Several publications in recent years have documented the safety and comparative efficacy of various intravenous preparations. This article reviews management of anemia in children with IBD, including diagnosis, etiopathogenesis, evaluation of a patient, protocol to screen and monitor patients for early detection and response to therapy, treatment including parenteral iron therapy, and newer approaches in management of anemia of chronic disease. This report has been compiled by a group of pediatric gastroenterologists serving on the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) IBD committee, in collaboration with a pediatric hematologist, pharmacist, and a registered dietician who specializes in pediatric IBD (IBD Anemia Working Group), after an extensive review of the current literature. The purpose of this review is to raise awareness of under-diagnosis of anemia in children with IBD and make recommendations for screening, testing, and treatment in this population.

Key Words: Crohn disease, iron deficiency anemia, iron dextran, parenteral iron, pediatric, recommendations, ulcerative colitis

An infographic for this article is available at: <http://links.lww.com/MPG/B904>.

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What Is Known

- Anemia is a common extraintestinal manifestation of inflammatory bowel disease.
- Clinical guidelines on the diagnosis and management of anemia in children with inflammatory bowel disease are lacking.

What Is New

- Guidelines for recognition, diagnostic testing, monitoring, and treatment of anemia in children with inflammatory bowel disease.
- Microbiome alterations with oral iron therapy in inflammatory bowel disease.
- Overview and cost comparison of current Food and Drug Administration-approved and currently used oral and parenteral preparations in children.

In patients with inflammatory bowel disease (IBD), anemia can be both a biomarker of disease activity and a subtle or debilitating extraintestinal manifestation. A recent review of care pathways in adult IBD patients reported significant variability among gastroenterologists' approach towards diagnosis and management of anemia. The authors recognized a need for clinical guidelines on the diagnosis and management of anemia in patients with IBD. Consensus among gastroenterologists is lacking on screening protocols, type of diagnostic tests utilized, definition of iron deficiency, recognition of nonanemic iron deficiency (NAID), and need for treatment of anemia alongside IBD (1). Pels et al (2) noted that newly diagnosed children with IBD are more likely to have iron

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deficiency anemia (IDA) in contrast to anemia of chronic disease (ACD). No significant improvement in the hemoglobin (Hgb) levels was observed when patients were assessed after 13 weeks of induction therapy with conventional drugs that included nutritional therapy, azathioprine, steroids, and 5-aminosalicylates. Antitumor necrosis factor (TNF- α) agents were not used in that cohort. Despite the recognition of anemia, fewer than half of anemic patients received indicated iron therapy (3,4). Promising data now show the safety and efficacy of intravenous iron (IV) in the treatment of anemia in children with IBD. Additionally, exciting data now document the use of newer treatment approaches in ACD, which can be refractory to iron replacement alone. Currently, no guidelines exist for screening, diagnosis, and management of anemia in children with IBD. In this position paper, we provide an overview of the current understanding of etiology and pathogenesis of anemia in children with IBD and propose guidelines for their screening, diagnosis, and management.

DEFINITION

Anemia is defined as low Hgb or red cell mass that can result in lowered oxygen-carrying capacity. Hgb is expressed as grams per deciliter (g/dL) or millimoles/liter (mmol/L) and red cell mass as hematocrit (HCT). The guidelines for the definition of anemia were first outlined in a World Health Organization (WHO) paper from 1968 (5). The normal ranges for Hgb vary with age, gender, race, and pregnancy status in women (Table 1). Hgb levels are similar in preteen boys and girls; however, after menarche, the cutoff Hgb in girls is lower than in boys and is even lower in pregnant versus nonpregnant women. The African American population tends to have lower Hgb concentration compared with Caucasians (6,7). Although the normal range of Hgb varies with age, gender, and race, a Hgb level below 10 g/dL is considered to be consistent with moderate anemia and below 8 g/dL as severe anemia, whereas in young children below the age of 5 years and pregnant women, a Hgb level below 7 g/dL is deemed as severe anemia (8).

INCIDENCE AND PREVALENCE OF ANEMIA IN INFLAMMATORY BOWEL DISEASE

Several studies have evaluated the prevalence of anemia in pediatric patients with IBD, both at diagnosis and follow-up. Using the WHO definition of anemia, prevalence ranges from 44% to 74% at diagnosis and 25% to 58% at 1-year follow-up (4,9–17). Pels et al (2) reported a 78% incidence of anemia in newly diagnosed children with IBD, of whom 58% had exclusive IDA. They found persistent anemia in one-third of the patients at follow-up, 1 year after diagnosis. Wiskin et al (17) reported a 75% prevalence of anemia in newly diagnosed children with IBD (both ulcerative colitis [UC] and Crohn disease [CD]), dropping to 42% and 32% at 1 and 2 years, respectively. The reported incidence of anemia and iron deficiency is higher in children compared with adults among

various studies. Sjöberg et al (4) reported a prevalence of anemia at diagnosis and 1-year follow-up (diagnosis: 55% vs 27%, $P < 0.0001$; follow-up 28% vs 16%, $P < 0.05$) in children compared with adults, respectively. Similarly, Goodhand et al reported higher prevalence of anemia in children (3–17 years) compared with adolescents (16–26 years) and adults (18–89 years). Anemia as defined by WHO criteria was found in 70% versus 42% versus 40%, in children, adolescents, and adult patients with IBD, respectively, in this cross-sectional study (11).

Several retrospective case series have reported persistent anemia despite medical therapy for IBD [Pels et al (2), 33% at 1-year follow-up, Gerasimidis et al (10), 68% at 1-year follow-up, Wiskin et al, 42% at 1-year and 32% at 2-year follow-up (17)]. A recent cross-sectional study in children with IBD demonstrated a prevalence of 32% and 68% for anemia and iron deficiency, respectively (18). Aljomah et al (19) performed a retrospective analysis in 153 children with IBD and reported that while 67.3% of patients were found to be anemic at diagnosis, 20.5% were still anemic at 1-year follow-up despite a majority of them being in clinical remission. Iron deficiency is reported to be the most common cause of anemia in IBD, with reports of iron deficiency with/without anemia in 76.8% and 68.1% children at diagnosis and 1-year follow-up, respectively (9,20). In a retrospective study examining racial differences in IBD, anemia (defined as Hgb < 10 g/dL) was more likely (39% vs 17%) in African American compared with non-African American children (21). These studies indicate that anemia and iron deficiency are significant comorbid conditions in patients with IBD and may not resolve unless treated specifically.

RISK FACTORS ASSOCIATED WITH ANEMIA IN INFLAMMATORY BOWEL DISEASE

A number of risk factors have been associated with the development and persistence of anemia in pediatric IBD patients. Low albumin, high C reactive protein (CRP) or erythrocyte sedimentation rate (ESR) values, low body mass index (BMI), acute onset with severe disease at presentation, and extensive colitis in children were most significant. Severe anemia was found to be more common in girls, whereas gender differences were not seen with mild anemia (10). Sjöberg et al (4) reported additional risk factors for anemia that included diagnosis of CD versus UC, extensive disease in UC, or colonic CD at diagnosis. The association between anemia and elevated calprotectin levels has not been systematically investigated.

CLINICAL RELEVANCE OF ANEMIA

Anemia and iron deficiency are not only comorbid conditions but can also serve as objective measures of underlying disease activity in IBD and, in some cases, may be the only signs of ongoing active disease (22,23). Persistent or recurrent anemia may also be associated with a more severe phenotype. Wiskin et al (17) reported

TABLE 1. Normal hemoglobin by age

Age	Healthy Hgb, g/dL	Mild anemia Hgb, g/dL	Moderate anemia Hgb, g/dL	Severe anemia Hgb, g/dL
0.5 to under 5 years	≥ 11	10–10.9	7–9.9	<7
5–11 years	≥ 11.5	11–11.4	8–10.9	<8
12–14 years	≥ 12.0	11–11.9	8–10.9	<8
Adult males, ≥ 15 years	≥ 13	11–12.9	8–10.9	<8
Adult females, nonpregnant (≥ 15 years)	≥ 12	11–11.9	8–10.9	<8
Pregnant women	≥ 11	10–10.9	7–9.9	<7

Adapted from (5,8). Hgb = hemoglobin.

TABLE 2. Symptoms of iron deficiency anemia

Organ system	Symptoms
Cardiovascular	Reduced exercise capacity Exertional dyspnea Tachycardia, palpitations Systolic murmur Cardiac failure Skin pallor
General symptoms	Hypothermia Fatigue Pica, Pagophagia Hair loss
Gastrointestinal	Anorexia Nausea Angular stomatitis Motility disturbances Glossitis
Central nervous system	Restless leg syndrome Impaired cognitive function Depression
Immune system	Dysfunction of innate and adaptive immunity
Genitourinary	Menstrual irregularity Loss of libido

Adapted from (20,22,31,32).

that patients with persistent anemia at 1- and 2-year follow-up had a greater likelihood of having a higher CRP, and Sjöberg et al (4) found an association between persistent anemia and high use of steroids and/or anti-TNF- α agents. Koutroubakis et al (24) found that persistent or recurrent anemia in adults correlated with increased likelihood of emergency department and clinic visits, hospitalizations, and surgeries. Patients with persistent anemia lasting for 3 or more years were noted to have a higher prevalence of more severe and complicated disease (stricturing and penetrating phenotype) with a greater need for surgical intervention (25).

Chronic anemia and iron deficiency are not only associated with disabling symptoms but may even have a subtle impact on quality of life. Whether quality of life, cognitive function, or disease activities scores improve upon treatment of iron deficiency and anemia in children is not clear. In a study of children with IBD, Danko and Weidkamp observed that anemia had a significant impact on health-related quality-of-life scores (HRQoL) regardless of disease activity. In this study, 19 pediatric patients were noted to be in clinical remission, of whom 42% still had anemia. The HRQoL scores were assessed in 6 domains. A significantly higher percentage of patients with anemia than without anemia were found to have low HRQoL scores in at least 1 domain (62.5% vs 9%) while controlling for disease activity (26). Studies performed in adults also demonstrate improvement in quality of life, albeit not in cognitive function, following treatment of IDA regardless of disease activity (27–29).

CLINICAL PRESENTATION OF ANEMIA

Anemia can cause a variety of symptoms that depend on severity, rate at which Hgb has dropped, and comorbid conditions. A sudden acute drop in Hgb can cause hypoxia and significantly impact the circulatory and cardiovascular systems. In severe cases, patients can have tachycardia, syncope, functional systolic murmur, or even cardiovascular failure. Symptoms of chronic anemia may include dizziness, fatigue, poor exercise capacity, nausea,

TABLE 3. Symptoms of nonanemic iron deficiency

Fatigue
Reduced exercise tolerance
Sleep disorders
Impaired cognitive function
Attention deficit
Restless leg syndrome
Pica, pagophagia

Adapted from (34,36–38).

irritability, poor concentration, attention deficit, pica, pagophagia (craving for ice), agitation, and female infertility. Chronic and long-standing iron deficiency may also cause epithelial alterations resulting in dry mouth, cheilitis, atrophic glossitis, hair loss, and rarely Plummer–Vinson syndrome (22,30). Iron in the form of Hgb not only plays an important role in oxygen-carrying capacity in the red blood cells but also is an important component of cytochromes and several other enzymes that are vital for the functioning of various organ systems. Symptoms of iron deficiency can, therefore, be nonspecific and may include impairment of cognitive function, headaches, anorexia, hair loss, pica, pagophagia, fatigue, irritability, lightheadedness, exercise intolerance, immune system abnormalities, hair loss, infertility, or even sleep disorders including restless leg syndrome (20,30–32). Iron deficiency in the absence of anemia often remains unrecognized and may respond to iron supplementation (20,30–38) (Tables 2 and 3).

PATHOPHYSIOLOGY OF ANEMIA IN INFLAMMATORY BOWEL DISEASE

Anemia in IBD has a complex and multifactorial etiology but most often occurs because of a combination of IDA and ACD. Iron deficiency can result from multiple factors that include inadequate iron intake, excessive blood loss, poor iron absorption, and inflammation-driven blockage in reutilization of stored iron. In addition, anemia can also result from vitamin deficiencies (such as vitamin B12 and folate deficiency), hemolysis, or myelosuppression from drugs used for IBD therapy (31,39–44) (Table 4).

Iron absorption takes place at the intestinal enterocytes, mainly in the duodenum. Dietary iron obtained from plants and fortified foods (nonheme) is released in the ferric form (Fe^{3+}). It is first reduced to ferrous (Fe^{2+}) iron by the gastric acid or duodenal

TABLE 4. Causes of anemia in inflammatory bowel disease

Most common	Iron deficiency Anemia of chronic disease Combined iron deficiency and chronic disease
Vitamin deficiency	Vitamin B12 deficiency Folate deficiency Possible: vitamin A, D, B6, copper
Drug-induced	Mercaptopurine: bone marrow suppression, myelodysplasia Methotrexate: folate deficiency, bone marrow suppression Sulfasalazine: folate deficiency, bone marrow suppression, hemolysis
Immune-mediated	Hemolysis
Inherited causes	Hemoglobinopathy Disorders of erythropoiesis Glucose-6-phosphate dehydrogenase deficiency

Adapted from (31,39–44).

cytochrome b (DcytB) and subsequently transported into the cytoplasm via the divalent metal transporter 1 (DMT1). In contrast, iron in animal meats is released as a heme molecule and can be absorbed directly by the heme carrier protein 1 (HCP1) using receptor-mediated endocytosis. Intracellularly, free ferrous iron is oxidized by hephaestin and either transported into the plasma via a transport protein ferroportin (FP), or stored as ferritin within the enterocytes or macrophages of the reticuloendothelial system. Once in circulation, transferrin-bound ferric iron is available for exchange and utilization throughout the body (20).

Iron homeostasis is tightly regulated by hepcidin, an acute phase peptide hormone produced by the liver. It has receptors on villus enterocytes, hepatocytes, and reticuloendothelial macrophages. Hepcidin synthesis is induced in the liver by inflammatory signals mediated by interleukin-6 and high iron levels mediated by bone morphogenetic protein-6 (BMP-6). Conversely, hepcidin synthesis is suppressed by iron deficiency, anemia, oxidative stress, or hypoxia. Hepcidin inhibits the export of intracellular iron into the plasma by binding to and thus inactivating ferroportin, which is the

key transport protein responsible for iron transport from intracellular compartment to the plasma for peripheral utilization. As a result of ferroportin inactivation, the trapped iron accumulates in the enterocytes or macrophages. The excess intracellular iron further downregulates iron absorption by inhibiting expression of key mediators like DcytB and DMT1 on villus enterocytes (44,45). Furthermore, hepcidin also exerts a direct inhibitory effect on iron absorption by the enterocytes (46,47) (Fig. 1).

IDA is the most common cause of anemia in children with IBD. True iron deficiency results from a number of factors, including chronic blood loss secondary to gastrointestinal bleeding, decreased iron absorption because of tissue or systemic inflammation and from reduced absorptive surface area. Other factors include decreased dietary iron intake because of reduced appetite or dietary restrictions (20,31).

Functional iron deficiency (FID) results from high levels of circulating hepcidin, which binds to and disables the iron transporter, ferroportin. Under the influence of hepcidin, ferroportin-mediated export of intracellular iron is stalled, leaving the iron

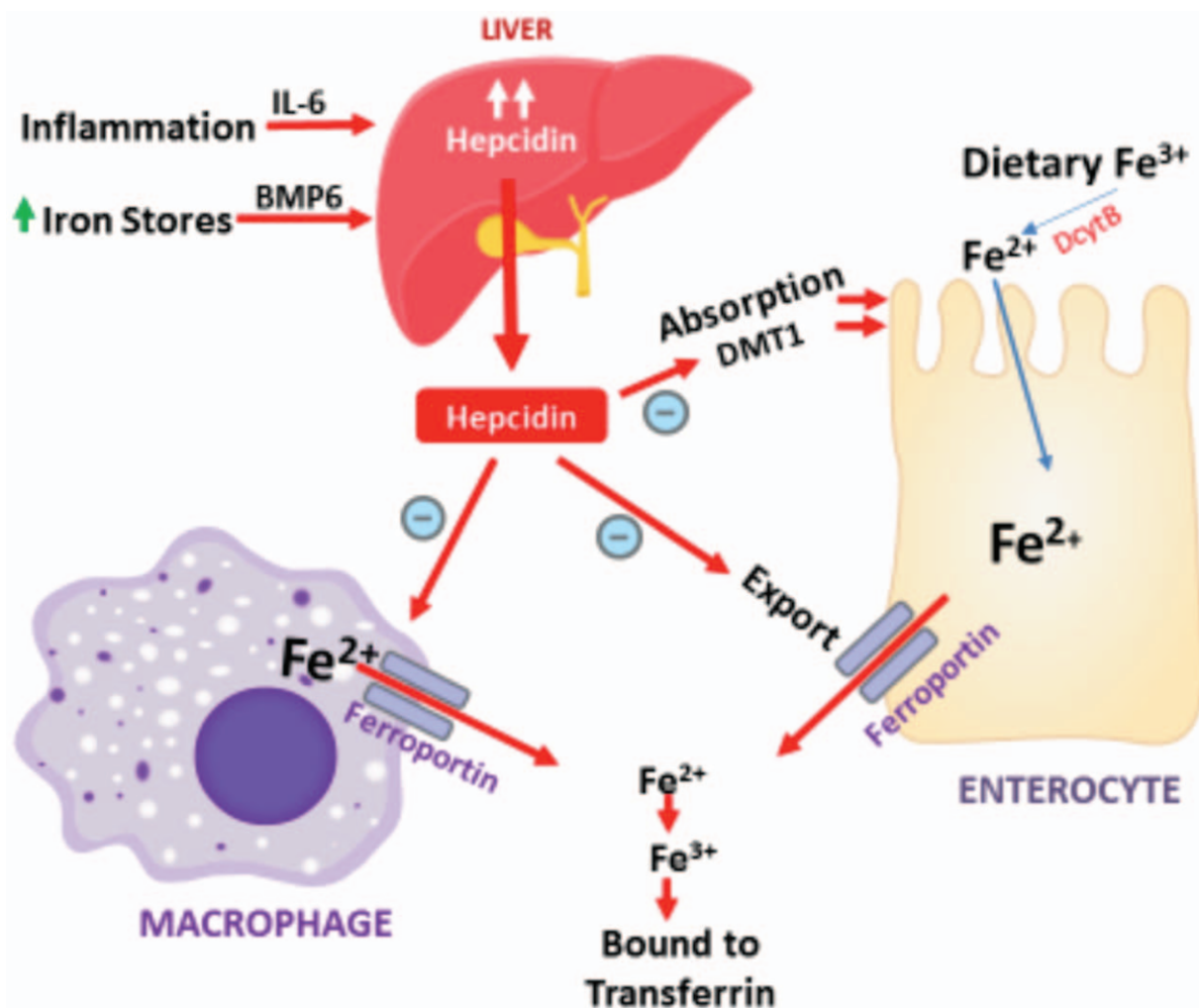


FIGURE 1. Hepcidin tightly regulates iron homeostasis. Hepcidin, produced by the liver, has receptors on villus enterocytes, hepatocytes, and reticuloendothelial macrophages. Hepcidin synthesis is induced in the liver by elevated iron levels and inflammatory signals, that is, interleukin-6 (IL-6) and bone morphogenetic protein-6 (BMP6). Hepcidin inhibits both iron release and iron absorption by the enterocytes in the duodenum. It acts by binding and inactivating ferroportin, a cellular iron exporter, leading to reduced efflux of cellular iron into the plasma. High intracellular iron inhibits divalent metal transporter (DMT1), further inhibiting iron absorption.

trapped within the enterocytes and macrophages. Therefore, insufficient utilizable iron is available for erythropoiesis despite adequate iron stores. In patients with IBD, the underlying inflammation, which induces hepcidin production can result in anemia secondary to FID, which closely mimics IDA (20,31).

ACD occurs from various downstream pathways secondary to inflammation. Elevated cytokine levels, such as interleukin-1 (IL-1), IL-6, TNF- α , interferon-alpha (IFN- α), and IFN- γ eventually inhibit erythropoiesis despite iron availability. It is the second most common cause of anemia in children with IBD and often coexists with IDA. The pathophysiology of ACD involves several mechanisms that include: reduced iron absorption from enterocytes; FID; downregulation of erythropoiesis caused by a combination of inhibited erythropoietin (EPO) release and decreased density of its receptors ("EPO resistance"); enhanced erythrophagocytosis by the activated macrophages resulting in a shortened erythrocyte lifespan; and premature apoptosis of the earliest erythroid committed precursor BFU-e (burst forming unit-erythrocyte) (31,40).

Deficiency of vitamins: A deficiency of vitamin B12 and/or folic acid usually presents with macrocytic anemia because of an impairment of nucleic acid metabolism affecting cell division in erythroid and myeloid precursors. Vitamin B12 absorption requires both the presence of stomach-derived intrinsic factor and healthy mucosa in the distal ileum; a risk of deficiency in children with IBD is overall low but can occur secondary to extensive terminal ileum

resection, dietary restriction in vegans, intestinal inflammation, or secondary bacterial overgrowth. Folic acid is primarily absorbed in the duodenum and jejunum. Folic acid deficiency is also uncommon and mostly occurs secondary to drugs including sulfasalazine and methotrexate. Vitamin B12 and/or folic acid deficiency should be suspected based on clinical suspicion and laboratory results including macrocytic anemia, megakaryocytosis, and low vitamin levels (48–51).

Myelosuppression can be an adverse effect of certain medications, such as thiopurine analogs, sulfasalazine, and methotrexate; most of these can also inhibit erythropoiesis directly. Thiopurine analogs, such as 6-mercaptopurine (6-MP) and azathioprine can also be occasionally associated with direct myelotoxicity as well as myelodysplasia. Therefore, close monitoring of blood counts is essential in these patients (31,40,41) (Fig. 2).

Autoimmune hemolytic anemia is rare and has been described in up to 1.7% of patients with UC, usually in association with extensive colitis, whereas it is less common in CD (52). It results from the development of erythrocyte autoantibodies that further cross react between red cells and colon. Hemolysis can also result from drugs like sulfasalazine in patients with glucose-6-phosphate dehydrogenase deficiency (31,39–43).

Other rare causes of anemia in IBD include pre-existing hemoglobinopathies, inherited disorders of erythropoiesis, and hypothyroidism. Hypothyroidism can result in ACD and iron or

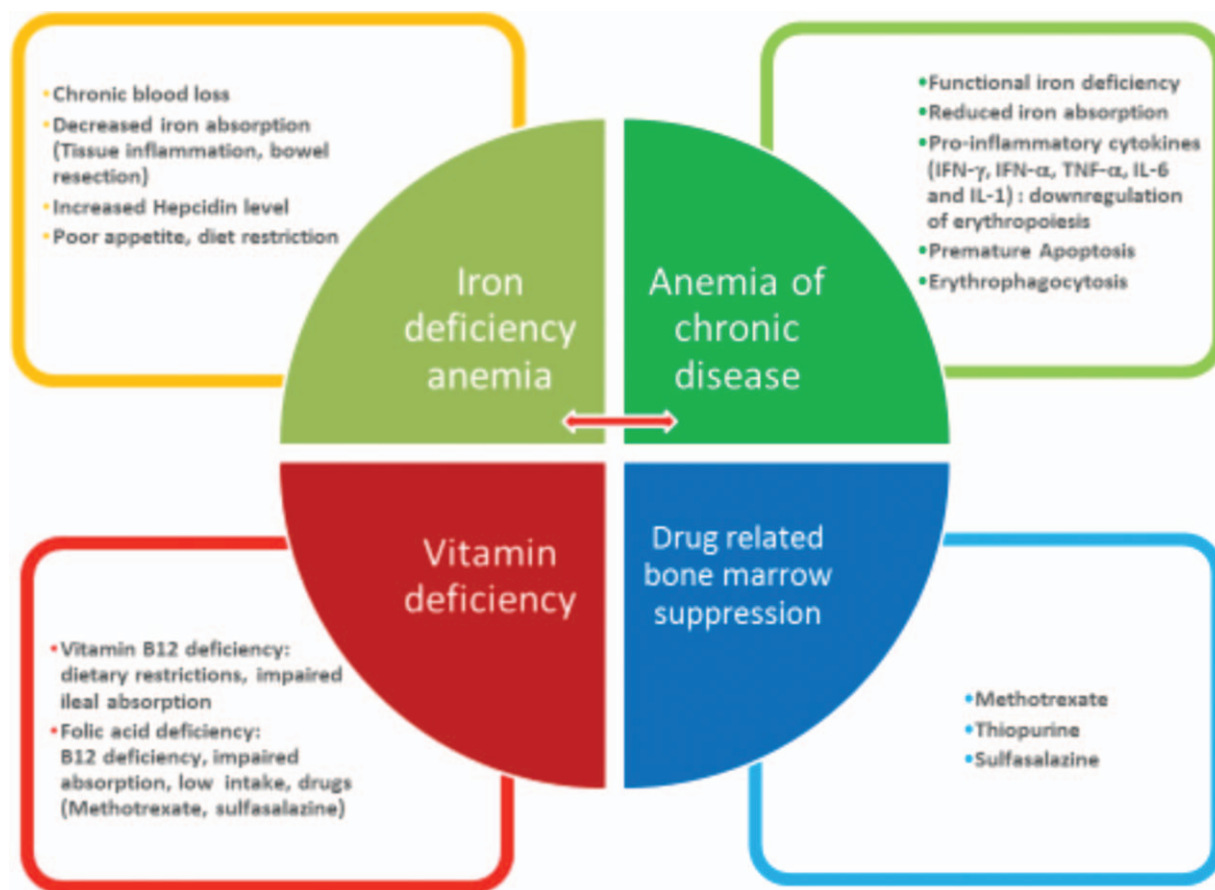


FIGURE 2. Mechanism of anemia in inflammatory bowel disease patients. Anemia is a frequent complication seen in patients with inflammatory bowel disease. It has a complex and multifactorial etiology with many patients having a combination of iron deficiency anemia (IDA) and anemia of chronic disease (ACD). In addition, anemia can also result from vitamin deficiencies (such as B12 and folate deficiency) or from drug-related bone marrow suppression.

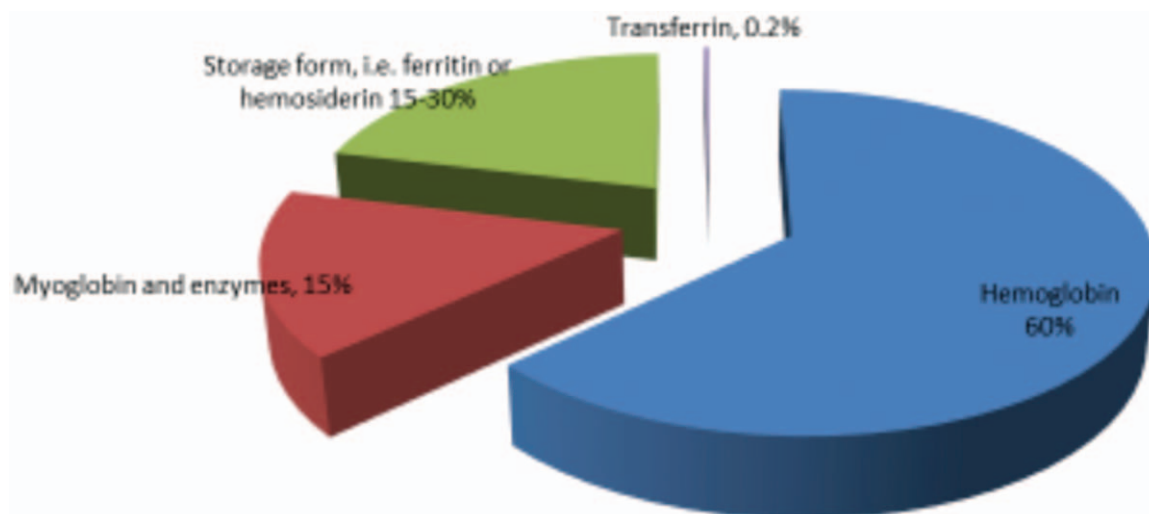


FIGURE 3. Iron distribution in human body. The human body has a total of about 3 to 4 g of iron that corresponds to 40 to 50 mg iron/kg body weight, of which 60% is incorporated in hemoglobin and only a small fraction (6–7 mg/kg) is present in myoglobin, and enzymes.

vitamin deficiencies and can present as macrocytic, normocytic, or microcytic anemia depending on etiology (53) (Table 4).

ASSESSMENT AND DIAGNOSIS

For appropriate management, the severity and cause of anemia needs to be determined. The adult human body has a total of about 3 to 4 g of iron that corresponds to 40 to 50 mg iron/kg body weight, of which 60% is incorporated in Hgb, and approximately 15 to 30% is stored mostly as ferritin in the cytoplasm or as hemosiderin in the lysosomes. A small fraction (6–7 mg/kg) is present in myoglobin and various enzymes. The iron bound to the transport protein transferrin, constitutes less than 0.2% of total body iron. Free and transferrin-bound iron levels can fluctuate because of the ongoing shift of iron in and out of the plasma (54) (Fig. 3).

Screening guidelines

Anemia is the most common extraintestinal complication of IBD and is associated with considerable morbidity if left untreated. Therefore, all patients with IBD should be regularly monitored and treated for anemia. The European Crohn's and Colitis Organization (ECCO) guidelines for adults with IBD were established by a committee of selected experts who made recommendations after a systematic literature review and graded them according to the Oxford Center for Evidence-Based Medicine. The final guidelines were established after subsequent discussions and voting process (31). The IBD Anemia Working Group agreed that the screening guidelines recommended by ECCO are also applicable to children. The initial screening tests (described below) should be done at the time of diagnosis and repeated at every 3-month interval for patients with active disease and every 6 to 12 months with inactive disease. All patients should be screened annually for folic acid and vitamin B12 status, whereas those at risk of vitamin deficiency (patients with bowel resection, ileal pouch, bacterial overgrowth, extensive ileal disease) should be tested every 3 to 6 months (31,40).

Assessment and diagnostic testing

This section will outline the screening guidelines by ECCO and covers some details on various conventional and newer tests that can be utilized in the work-up of anemia.

Screening Tests

Initially a complete blood count (CBC), CRP, and ferritin levels should be performed. If a patient is found to be anemic, then testing should include CBC with differential, including mean corpuscular volume (MCV), mean corpuscular Hgb concentration (MCHC), red cell distribution width (RDW), reticulocyte count, CRP, serum ferritin, and transferrin saturation (TSAT) (31).

MCV and MCHC: In patients with IDA and FID, anemia is more likely to be microcytic and hypochromic (Low MCV and MCHC), whereas in ACD the anemia is more likely to be normocytic and normochromic.

Macrocytic anemia may be seen in association with vitamin B12 or folic acid deficiency or drug therapy including sulfasalazine, methotrexate, 6-MP, and azathioprine. Other conditions that can lead to macrocytosis include hemolysis or rapid red cell turnover, which results in increased reticulocytes, which have a higher MCV than mature red cells.

In IBD, the picture can be mixed as a combination of macrocytic and microcytic anemia can occur in the same patient because of different etiologies, for example, iron deficiency along with drug side-effects or vitamin deficiency (31).

Red blood cell distribution width (RDW) is a measure of variability in the size of red blood cells (anisocytosis). Therefore, a high RDW in the presence of microcytosis suggests iron deficiency. This index mainly depends on the bone marrow erythropoietic activity and has a high sensitivity of about 93% for the diagnosis of iron deficiency (54,55).

The reticulocyte count is a useful marker of bone marrow response to anemia. A low reticulocyte count indicates insufficient response to anemia because of suppression of erythropoiesis, as seen with IDA, FID, ACD, or bone marrow failure. Conversely, a high initial reticulocyte count raises suspicion for ongoing hemolysis rather than iron deficiency. In that case, further evaluation for hemolysis should be initiated including a peripheral blood cell smear, serum haptoglobin, bilirubin, lactate dehydrogenase, and Coomb test (31).

If the platelet count is high, iron deficiency and/or inflammation is more likely (55).

A pancytopenia would be concerning for bone marrow failure from drug side effects or other causes of anemia associated with a suppressed marrow (31).

Serum ferritin is a measure of iron stores in the body. The main storage sites are the liver, spleen, and skeletal muscle. A serum ferritin of 100 $\mu\text{g/L}$ correlates with 1000 mg of stored iron. Ferritin is an acute phase reactant and can be elevated in patients with acute or chronic inflammation, malignancy, liver or tissue damage, whereas it can be artificially low in patients with hypothyroidism and vitamin C deficiency. Investigating other inflammatory markers, such as CRP and/or disease activity assessment is required to interpret ferritin levels in IBD. The normal values vary with age. The WHO and American Academy of Pediatrics (AAP) have defined iron deficiency as ferritin levels below 12 and 15 $\mu\text{g/L}$ in otherwise healthy children under and above 5 years, respectively (20,30,56). According to the ECCO guidelines for adults with IBD, serum ferritin levels below 30 $\mu\text{g/L}$ are highly suggestive of iron deficiency, whereas levels above 100 $\mu\text{g/L}$ are unlikely to be associated with iron deficiency. Ferritin levels between 30 and 100 $\mu\text{g/L}$ could still be seen with iron deficiency in the presence of inflammation (31,43). The IBD Anemia Working Group recommends the diagnosis of iron deficiency be considered in children with IBD when serum ferritin levels are below 100 $\mu\text{g/L}$ with active inflammation, or below 15 $\mu\text{g/L}$ without evidence of underlying inflammation. Serum ferritin can be misleadingly high because of enhanced synthesis after receiving IV iron and may not reflect the true iron status for up to 8 weeks after an infusion (31,57). When serum ferritin levels are very high, hemophagocytic lymphohistiocytosis (HLH)-associated anemia should be considered, which could occur because of underlying genetic predisposition to both IBD and HLH (eg, X-linked inhibitor of apoptosis protein deficiency), drug therapy (eg, 6-MP, azathioprine), or infections (eg, Epstein-Barr Virus).

Serum iron level reflects the flow of iron in and out of the plasma pool. It is, however, unreliable in the assessment of iron deficiency as the level fluctuates with several variables including a rapid red blood cell turnover and diurnal fluctuations (45).

Transferrin (TRF) is a transport protein that binds to free iron in the plasma and mediates iron exchange between body tissues. Normal values can vary between 200 and 400 mg/dL. Transferrin levels are not commonly used to assess anemia. Transferrin levels are elevated in true iron deficiency, during pregnancy, and with the use of oral contraceptives, whereas levels decrease with iron overload, inflammation, infection, liver disease, malignancy, nephrotic syndrome, and malnutrition (19,45,48).

Transferrin saturation (TSAT) is a measure of the iron content in the circulating transferrin and reflects the availability of utilizable iron. It is reported as a percentage (quotient of iron levels $\mu\text{moles/L}$ divided by TRF mg/dL $\times 70.9$). Normal transferrin saturation ranges from 16% to 45%. A saturation below 16% indicates suboptimal iron available for erythropoiesis and levels above 50% suggest iron overload. Transferrin saturation should be interpreted cautiously in conditions where the transferrin levels are elevated as the percentage saturation can be proportionately reduced even without iron deficiency. TSAT has a sensitivity of 59% to 88% and specificity of 63% to 78% in diagnosis of iron deficiency based on studies in renal failure patients (58–60). The advantages include high sensitivity, wide availability, and a quick turnaround time to screen for utilizable iron, whereas disadvantages include variability secondary to transferrin levels and diurnal fluctuation as well as its inability to predict iron stores or distinguish between IDA and FID.

Total iron binding capacity (TIBC) is the amount of iron needed to saturate the plasma transferrin. TIBC can overestimate the binding capacity of transferrin as iron also binds to other proteins like albumin. It is high in patients with functional or true iron deficiency and has been reported to have a diagnostic sensitivity of 36% and specificity of 97% (61).

When the etiology of anemia is not apparent based on standard screening, various other tests may be used, including soluble transferrin receptor level (sTfR), sTfR-log ferritin index (sTfR-F), zinc protoporphyrin, red blood cell size factor (RSF), Hgb content in reticulocytes (Chr), and hepcidin levels.

Soluble transferrin receptor (sTfR) is a truncated soluble form of transferrin receptor. It is shed into the plasma and can be measured as sTfR levels that are proportional to the total number of transferrin receptors on erythroid precursor cells of the bone marrow. It is not directly affected by chronic inflammation or hepatic disease. It is upregulated with enhanced cellular erythropoietic activity coupled with insufficient iron availability, as seen in hemolysis or anemia (IDA or FID). The normal values range from 5 to 8 mg/L but are dependent on the assay used (15,62). It is low in conditions associated with suppression of erythropoiesis, including ACD. A level greater than 8 mg/L is suggestive of iron deficiency or hemolysis. The sTfR level has still not been adopted for routine use because of paucity of data on international standards and the assay being not as widely available.

sTfR log ferritin index (sTfR-F) is calculated by sTfR in mg/L divided by ferritin in $\mu\text{g/L}$ (log refers to base-10 log). An elevation of sTfR (seen with iron deficiency) coupled with a low serum ferritin will result in a higher sTfR-F (ratio >2) with true IDA, whereas levels <1 suggest ACD and excludes IDA. As patients with FID are likely to have higher ferritin levels, the sTfR-F may not be as high when compared with true IDA. Using the sTfR-F compared with ferritin alone increases the sensitivity for differentiating IDA from ACD from 41% to 92%, and therefore, is considered to be a better test to distinguish between ACD and IDA (54,62,63).

Hemoglobin content in reticulocytes (Chr) can provide a measure of more recent availability of iron for erythropoiesis compared with standard indices, such as MCV and MCHC that are affected by the long lifespan of erythrocytes (about 120 days). Normal Chr can range from 23 to 29 pg and is expected to be low in IDA and FID. A recent study in children with IBD found Chr to be affected by inflammation and found that Chr levels were higher in children with IBD compared with a healthy population. Levels below 31 pg (unadjusted) or less than 34 pg (adjusted) for inflammation could predict iron deficiency (18).

Red blood cell size factor (RSF) is the square root of MCV multiplied by mean reticulocyte volume (MRV) and has also been found to have a good correlation with Chr. It is yet another early marker of bone marrow erythropoietic activity. A low RSF indicates IDA; a level below 98.6 fL was found to be 83% sensitive and 82% specific, with a positive-predictive value of 67% and negative-predictive value of 92% (54,64). High RDW along with low RSF is highly predictive of iron deficiency, with no significant difference between active and inactive disease (54).

Immature reticulocyte fraction (IRF) is an early and sensitive index of erythropoiesis and could help in identifying anemia secondary to increased versus decreased erythropoietic activity (54).

Zinc protoporphyrin is elevated in IDA when zinc (instead of iron) is incorporated into protoporphyrin IX because of iron-deficient erythropoiesis. An elevated zinc protoporphyrin level (>40) indicates IDA, whereas a level >80 is observed in a more severe symptomatic IDA (54). It should, however, be interpreted with caution, as zinc deficiency is not uncommon in patients with IBD.

Hepcidin is a circulating peptide that is induced secondary to inflammation and iron overload, whereas iron deficiency inhibits hepcidin production. Hepcidin levels below 79.4 ng/mL are 81% sensitive and 45% specific in diagnosing IDA but are not widely used (54). Conflicting data, however, indicate that low-serum hepcidin levels can be seen in iron-deficient anemic patients with

active IBD, which may suggest that low iron status could inhibit hepcidin production and override the stimulus secondary to inflammation (65). Syed et al found that hepcidin levels poorly correlated with anemia in children with IBD, with a sensitivity of 44% and specificity of 54% (18).

Vitamin B12 and folate levels are helpful when vitamin deficiency is suspected. Red blood cell (RBC) folate and vitamin B12 levels along with another functional marker like methylmalonic acid or homocysteine are recommended (40,41,66). Even when isolated folate deficiency is suspected, a concurrent vitamin B12 deficiency should be ruled out as it mediates the conversion of an inactive methyltetrahydrofolic acid to active tetrahydrofolic acid. Vitamin B12 levels below 200 pg/mL and serum folate levels below 7 nmol/L or RBC folate levels below 340 nmol/L are suggestive of deficiency (67).

Determination of Iron Deficiency Anemia Versus Anemia of Chronic Disease

Patients with IBD often have a combination of both iron deficiency and anemia of chronic inflammation. It can be especially hard to distinguish between true and FID. A CBC with differential is often helpful. A patient with low Hgb and microcytosis is likely to have either true or FID, whereas normocytic anemia is more common with ACD. Low MCHC is seen mainly with IDA, whereas ACD is normochromic. According to ECCO guidelines, a combination of TSAT and ferritin can be used to determine the etiology of anemia. The TSAT is usually below 20% in true or FID. A ferritin level below 15 µg/L is a reliable marker for true iron deficiency but being an acute phase reactant, it is usually high in FID or ACD. A low ferritin (below 15 µg/L) in conjunction with a low TSAT (below 20%) is suggestive of true IDA, whereas a low TSAT with normal or high ferritin may reflect FID associated with ACD. In patients with ACD without FID, TSAT may be normal but ferritin will still be high (31). Thomas et al suggested using both sTfR-F and Chr to distinguish between IDA and ACD, though Chr is not widely available. When both Chr and sTfR-F are low, FID is more likely, whereas in IDA, low Chr but a high sTfR-F will be more likely (68,69). Serum erythropoietin (EPO) levels, which are lower in ACD than in IDA with comparable degrees of anemia, scatter too broadly to be of diagnostic value in distinguishing IDA from ACD (31). Despite the availability of various tests, a single test or even multiple tests may not always distinguish IDA from ACD (45,70) (Table 5). One must, therefore, use clinical judgment and consider an adequate trial of iron therapy first; if unsuccessful, the patient is more likely to have ACD (18).

Nonanemic Iron Deficiency

NAID can be detected by routine screening for anemia in patients with IBD. A ferritin level below 15 µg/L is considered to be diagnostic for iron deficiency in children, whereas in active disease, levels of up to 100 µg/L can still be consistent with iron-deficient state. A low transferrin saturation (< 20%) coupled with a low ferritin will be observed with iron deficiency, whereas high ferritin and low TSAT will be observed in FID, even without anemia. Other early changes that can be observed in NAID include a high RDW and low or borderline MCH (37).

TREATMENT OF ANEMIA

The treatment of anemia depends on the etiology and severity. The goals of therapy are to normalize Hgb, replenish iron stores, correct vitamin deficiencies, and improve quality of life. Various considerations include severity of anemia, presence of iron

TABLE 5. Various tests used to differentiate iron deficiency anemia from anemia of chronic disease

	IDA	ACD	FID
Hgb	↓	↓	↓
MCV	↓	Normal	↓ or normal
Ferritin	↓	↑	↑ or normal
Iron level (unreliable)	↓	↓	↓
Transferrin	↑	↓	↓
Transferrin saturation	↓	↓/↑	↓
sTfR	↑	↓ or normal	↑ or normal
sTfR-F	>2	<1	<2, variable
Zinc Protoporphyrin	>40	<40	>40
CRP	normal	↑	↑
Hepcidin	↓	↑	↑ or ↓
STfR-F/Chr	↑/↓	↓/↑	↓/↓

ACD = anemia of chronic disease; Chr = hemoglobin content in reticulocytes; CRP = C reactive protein; FID = functional iron deficiency; Hgb = hemoglobin; IDA = iron deficiency anemia; MVC = mean corpuscular volume; sTfR = soluble transferrin receptor level; STfR-F = STfR log ferritin index. Adapted from (40,61).

deficiency versus ACD, disease activity, cost and availability of drugs, as well as the patient's tolerance for a given drug therapy. For anemia that is secondary to drug side effects, the offending drug should be stopped, and the patient carefully monitored for improvement or recovery. In patients with macrocytic anemia, vitamin B12 and folic acid deficiency should also be ruled out and treated accordingly. The anemia in IBD is often a combination of iron deficiency and chronic inflammation. It is especially difficult to distinguish between iron deficiency alone and FID. A trial of iron therapy is often required to make that distinction. It is important that a simultaneous IBD disease activity assessment and treatment escalation be implemented while managing anemia.

IDA should be treated with iron supplementation, optimizing dietary intake, and controlling the disease activity. In mild anemia (Hgb ≥ 10 g/dL) and/or quiescent disease, oral iron should be tried first. The response to iron therapy should be determined by repeating Hgb in 2 to 4 weeks, or even earlier by assessing reticulocyte count. The criteria for adequate response with iron therapy is an increase in Hgb level by 1 g/dL in 2 weeks or 2 g/dL in 4 weeks. Reticulocyte response can be observed as early as 4 days, with maximal response at 7 to 10 days (42,71,72). Parenteral iron is indicated when oral iron is ineffective or poorly tolerated, in patients with moderate-severe anemia and/or with active inflammation. In patients with active disease, oral iron therapy may not be as efficacious because of poor absorption and iron entrapment in the enterocytes secondary to elevated hepcidin levels combined with gastrointestinal intolerance, so IV therapy is preferred. The dose required for IV iron replacement depends on total iron deficit, calculated based on weight, current Hgb, and the goal of Hgb after correction. According to ECCO guidelines, an IV replacement goal of achieving of ferritin level of up to 400 µg/L is more likely to prevent recurrence of anemia. The risk of iron overload is relatively low in patients with IBD because of their ongoing blood loss; however, a transferrin saturation of 50% and serum ferritin of 800 µg/L should not be exceeded (31).

When there is inadequate response with IV iron, ACD may be the underlying cause and a stronger emphasis should focus on escalating treatment targeted to underlying IBD. Inflammatory markers may not always reflect the underlying disease activity and a careful clinical, radiographic, or endoscopic reassessment of disease status may be required. The use of biological agents,

especially TNF inhibitors, may be helpful in optimizing therapy in the presence of active disease. Other considerations are attention to vitamin deficiencies, drug toxicity, or other causes of anemia. Please refer to the section dedicated to iron refractory anemia.

Currently no consensus exists on treatment of patients who suffer from NAID. These patients should also be assessed for underlying disease activity since anemia and iron deficiency may be the earliest signs of active disease. The patients should be treated with iron supplementation, especially when they have symptoms, such as fatigue, poor concentration, or sleep difficulties, and so forth (31). Please refer to the section on treatment of NAID.

Role of Diet in Treatment of Anemia

For a child with IBD and anemia, the goal is to provide a balanced diet that includes a variety of iron-rich foods, enhancing iron absorption via thoughtful food pairing while simultaneously addressing nutritional management for optimization of growth. Iron is absorbed primarily from the duodenum and partially from the proximal jejunum and ileum. Self-reported food intolerances because of nausea, diarrhea, and abdominal discomfort are common in IBD patients. Avoidance of iron-rich foods that may aggravate gastrointestinal symptoms, including beans, red meat, spinach, and seeds, may lead to limited dietary oral iron intake (32). Dietary consumption of iron-rich foods and a balanced diet could, however, not only improve overall health and quality of life for the patients but may also prevent recurrence or even provide medical intervention in patients with mild anemia.

Dietary iron can be classified into 2 forms: heme and nonheme (73). Heme iron is derived from ingestion of meats, poultry, and fish, all which are highly bioavailable and absorbed more efficiently than nonheme sources. Non-heme iron sources are mostly plant-based and include iron-fortified products and dark green leafy vegetables, such as spinach, kale, and Swiss chard. Absorption of iron from nonheme iron sources is more variable (74). Therefore, simple dietary modifications like pairing nonheme iron sources with foods high in ascorbic acid, such as melons and citrus fruits, or vegetables, such as bell pepper, broccoli, beans, carrots, tomatoes, and sweet potato, can lead to enhanced absorption (73). Certain foods may decrease iron absorption. These include soybeans, cereals, or dietary fiber; animal proteins like milk, egg, and albumin; those containing tannins (coffee and teas), polyphenols, or phytates; and calcium products (75).

Children should consume a well-balanced diet constituted of at least 3 servings per day of iron-rich foods from sources including fortified cereals, 3 ounces red meat, or 4 ounces of tofu. Recommended daily intake of iron for healthy children ranges from 7 to 11 mg daily.

Microbiome Alterations Associated With Oral Iron Therapy for Anemia

The pathogenesis of IBD involves an inappropriate inflammatory response to commensal gut microbes in a genetically susceptible individual. Host genetics, however, explains only a minority of the variance in disease risk, suggesting the importance of environmental factors, such as gut microbiota (76).

In recent years, interest in evaluating the impact of diet on the gut microbiota has increased. Oral iron is a dietary supplement that is sometimes poorly tolerated by patients because of gastrointestinal side effects. This intolerance has led to studies, both in animals and humans, evaluating the impact of oral iron on the composition of the gut microbiota. IBD patients are more likely to have a higher burden of intraluminal colonic iron concentration

secondary to bleeding from mucosal ulcers, which can be of further exacerbated by an excess load of unabsorbed iron because oral iron therapy. The unabsorbed luminal iron can further worsen dysbiosis, as it is essential for the growth of many pathogenic enterobacteria, and additionally leads to the expression of key virulence factors in others, including Gram-negative enteric pathogens. An increase in unabsorbed intraluminal iron in the gut could thus favor the growth of opportunistic pathogens in preference to the beneficial mucosal barrier-maintaining species like lactobacilli, which do not require iron. Perhaps some of the most important evidence that oral iron may have a negative effect on the composition of the gut microbiota comes from studies of infants and children in Kenya and other areas in Africa, where the malnourished iron fortified cohort experienced a surge in the pre-existing higher baseline fecal calprotectin and enterobacterial count, while favorable bacterial colonies like lactobacilli declined (77). In contrast, a randomized controlled trial of iron supplements in South African children with better hygiene and a normal diversity at baseline did not demonstrate a similar effect on the gut microbiota (using qPCR rather than 16S sequencing), concentration of fecal short-chain fatty acids (SCFA) or fecal calprotectin (78). These studies suggest that environment and baseline microbiota composition are important factors affecting dysbiosis secondary to oral iron.

Overall, several animal studies also demonstrate alterations in the composition of the gut microbiota when animals were fed iron-supplemented or deficient diets. Taken together, the results of these studies suggest that nonabsorbed iron may further worsen gut inflammation in animal models of IBD. Potential mechanisms include iron-induced alterations in the composition of the gut microbiota, including preferential enrichment of bacterial species that require iron to grow (79–83). Etreiki et al (84) also showed that ferrous and not the ferric forms are more harmful, though they did not report the effects of ferrous iron on the composition of the microbiota. Multiple mechanisms and factors could be responsible for these observations. A potential mechanism is the Fenton reaction, whereby ferrous iron generates a hydroxyl radical and hydroxyl ion from hydrogen peroxide, potentially contributing to oxidative stress (85). It may also be important to consider that other molecules, such as sulfide could be responsible for the development of ileitis from ferrous sulfate, as seen in the Werner study (83,86,87). In addition, it should be noted that some of the studies of oral iron supplementation in animals used very high doses.

To date, only 1 study has investigated the impact of oral iron on the composition of the gut microbiota in humans with IBD. In 2017, Lee and colleagues performed a randomized trial of oral ferrous sulfate versus IV iron sucrose in adults with IBD (UC or CD) versus controls with anemia but without underlying inflammation (NI). In this small study, shifts in the metabolome, gut microbiota composition, and diversity were differentially affected by the route of administration (oral vs IV iron). The shifts were more pronounced in subjects with IBD (especially CD) receiving oral iron, regardless of the underlying disease activity, as compared with NI subjects (88).

In summary, iron clearly has a significant impact on composition of the gut microbiota. This connection is more relevant because of the association between the gut microbiota and IBD. So far, studies indicate that dysbiosis at baseline worsens the unfavorable shifts in microbiome with oral iron therapy. This information is particularly important as patients with IBD are known to have a “dysbiotic” composition of the gut microbiota at baseline. The data presented in these studies have led some providers to avoid oral iron supplementation in patients with IBD. Our position, however, is that further studies are required in humans before any reliable conclusions can be drawn.

TABLE 6. Price comparison and highlights of various iron preparations*

Product (intravenous)	Cost per vial (vial size) cost per mg	Comments
Iron dextran	\$33.74 = 100 mg (2 mL vial) \$0.34/mg	FDA-approved for ages 4 months and older -Black box warning for anaphylaxis: Test dose -Drugs for anaphylaxis at bedside -Total dose (50 mg/mL): $\text{mL} = 0.0442 (\text{Hbn}-\text{Hbo}) \times \text{LBW} + (0.26 \times \text{LBW})$ -Compatible with parenteral nutrition, not lipids -Higher risk of adverse events with total dose
Iron sucrose	\$44.99=100 mg (5 mL vial) \$0.45/mg	FDA-approved for ages 2 y and older -Total dose (mg) = $0.6 \times \text{wt (kg)} \times [100 - (\text{actual Hgb}/12 \times 100)]$ (for hemoglobin goal of 12 mg/dL, or as required) -Maximum initial dose = 5 mg/kg up to 100 mg -Subsequent doses = 5–7 mg/kg up to 300 mg/wk.
Sodium ferric gluconate	\$17.69 = 62.5 mg (5 mL vial) \$0.28/mg	-FDA approved for ages 6 y and older -1–1.5 mg/kg/dose (up to 125 mg per dose per week.) -Maximum 8 doses
Ferumoxytol	\$715.38 = 510 mg (17 mL vial) \$1.40/mg	-More data in pediatric kidney disease -Not FDA-approved in pediatrics -Pediatric dose: (10 mg/kg), total 510 mg \times 2 doses -Black box warning for hypersensitivity reactions and anaphylaxis despite tolerating previous doses
Ferric carboxymaltose	\$903.39 = 750 mg (15 mL vial): \$1.20/mg	Not FDA-approved in pediatrics -Pediatric dose: (15 mg/kg), total 750 mg \times 2–3 doses up to 1 week apart -May have more hypophosphatemia than other iron preparations
Ferric derisomaltose†	Not currently marketed; pricing not available	-No test dose required -Allows for total dose infusion – not FDA-approved in pediatrics
Products (oral)	Cost per tablet/cost elemental iron	Comments*,\$,‡,
Ferrous sulphate	Tablet: 325 mg (65 mg E) = \$0.0003/mg Elixir (E=8.8 mg/mL) = \$0.001 per mg Oral solution (E=15 mg/mL) = \$0.006/mg	Elixir version contains alcohol‡,\$,
Ferrous gluconate	Tablet: 324 mg (37.4 mg E) = \$0.001/mg	§,
Ferrous fumarate	Tablet: 324 mg (106 mg E) = \$0.002/mg	‡,\$,
Polysaccharide Iron Complex	Tablet: (150 mg E) = \$0.28–0.5/mg liquid: 15 mg/mL E = \$0.01–0.02/mg	‡,\$,

E = elemental iron; FDA = Food and Drug Administration; Hbn = hemoglobin desired; Hbo = hemoglobin observed; Hgb = hemoglobin; lbw = lean body weight.

Oral iron product dosing: Dose: 2–3 mg/kg elemental iron/day in a single dose, maximum 100 mg elemental Iron/day. Alternate day dosing maybe better tolerated. Price comparisons from <https://online.lexi.com> (for US products).

*These are available over the counter (OTC) in many different formulation (tablets, controlled release tablets, solutions, etc.). Prices will vary with the dosage form and brand purchased. For comparison, the lowest price/mg for the regular release tablets is displayed (pricing is given for US products only).

†Ferric derisomaltoside (MonoFerric) was approved by the US FDA in January of 2020 for use in adults. At the time of writing, it has not been marketed in the United States. Pricing and pediatric dosing is not available.

‡Brush teeth after using liquid formulations.

§Absorption improved when given with vitamin C.

||Extended release version may be suboptimal in inflammatory bowel disease (IBD) patients.

Iron Replacement Products

In North America, a variety of different iron replacement products are available. Both oral and IV forms are marketed (Tables 6–8). This section will examine the advantages and disadvantages of various iron replacement products approved for use in the United States, Mexico and Canada.

Oral/Enteral Iron Products

The choice between oral versus parenteral iron is not always straightforward. Oral iron preparations have the advantage of being inexpensive, easily available, and not requiring infusions. They are also, however, known to cause gastrointestinal distress including constipation, diarrhea, abdominal pain, and nausea,

TABLE 7. Additional iron products available in Canada

Generic name	Brand name	Dosage form/pearls
Iron isomaltoside (recently approved by FDA for adults in the United States)	MONOFER	Intravenous infusion -Same as ferric derisomaltoside (available in the United States) -No test dose required -Total dose infusion

Courtesy of the International Drug Information Center at the Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University. Personal Communication. Recently approved in the United States.

TABLE 8. Additional iron products available in Mexico*

Generic name	Brand name (elemental iron)	Dosage form/pearls
Proteinsuccinato de hierro (Iron protein succinylate, contains Fe^{3+})	FERXAL (E:266.66 mg/100 mL)	Oral solution
Hierro aminoquelado (Iron amino acid chelate)	Ferrivax F folic acid 350 μg ; Iron 40 mg	Oral capsule
Hierro polimaltosado (Iron polymaltose complex)	FERRANINA IM (100 mg)	Intramuscular injection
Hierro polimaltosado (Iron polymaltose, contains Fe^{3+})	FERRANINA GTS Drops: 50 mg/mL Solution 10 mg/mL	Solution/drops
Complejo polimaltosado férrico (Iron polymaltose complex)	FERRANINA oral Oral solution 10 mg/mL	Oral solution
Complejo de hidróxido férrico polimaltosado [Iron (III) hydroxide polymaltose complex]	DUNOX SOL Oral drops 50 mg/mL Solution: 10 mg/mL	Oral solution
Hierro aminoquelado (iron amino acid chelate)	INTRAFER TF PEDIATRIC 8.55 mg/mL	Oral suspension

E = elemental iron.

Courtesy of the International Drug Information Center at the Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University. Personal Communication. March 20, 2020.

Oral iron product dosing: Dose: 2 to 3 mg/kg elemental iron/day in single dose, maximum 100 mg elemental Iron/day Alternate day dosing may be better tolerated.

*These are available over the counter (OTC) in many different formulation (tablets, controlled release tablets, solutions, etc.). Prices will vary with the dosage form and brand purchased.

adding to an existing symptom burden secondary to IBD. Iron absorption can be affected by presence of inflammation, which is associated with high hepcidin levels. When choosing oral iron therapy, considerations should include not only the severity of anemia but also the dose and frequency of oral iron administration, as unabsorbed iron in the gut lumen could result in unfavorable microbiome shifts as well as other potential consequences. Studies in adults have found better efficacy, lowered incidence of side effects, and reduced gastrointestinal exposure to unabsorbed iron when oral iron is given at a lower dose (40–80 mg/day) or on alternate days. It has been found that multiple doses per day can paradoxically decrease iron absorption (89,90). In children, the recommended dose is approximately 2 to 3 mg/kg/day, and based on ECCO guidelines, the oral adult dose of 100 mg of elemental iron per day should not be exceeded (31,91,92).

In a recent study of adolescents and adults with IBD and mild anemia, Rampton et al found that a high CRP was associated with poor response, whereas lower baseline Hgb was associated with better results following oral iron therapy. In their study, subjects with combined ACD and IDA showed a trend towards lower response to oral iron when compared with IDA alone (93). Lee et al conducted a meta-analysis of iron replacement therapy in adult patients with IBD, to compare outcomes with oral and parenteral preparations. They found more adverse events with oral iron compared with IV iron, whereas improvements in both Hgb and serum ferritin were significantly better with IV iron. Both groups had improvements in quality of life (88). Similarly, another meta-analysis by Avni et al (94) that included 973 adult patients with IBD reported that IV iron was superior in achieving an increase in Hgb compared with oral iron, had a lower risk of discontinuation, with no serious adverse events.

Oral iron should still be tried in patients with mild anemia, especially in those with Hgb ≥ 10 g/dL, inactive disease, or if a patient prefers to try oral iron therapy first despite moderate anemia as long as they are otherwise well. A follow-up Hgb and reticulocyte count should be checked in 14 to 28 days to assess the adequacy of response, which is defined as an increase in Hgb of 1 g/dL in 2 weeks or 2 g/dL in 4 weeks (31). The treatment can be switched to

parenteral iron if there are side effects and/or poor response to oral iron therapy.

Although various ferrous salts of oral iron products are available, these salts vary in terms of the amount of elemental iron they contain. The elemental iron content is 33%, 20% and 11.6% in ferrous fumarate, ferrous sulfate and ferrous gluconate, respectively. Iron polysaccharide preparations are marketed in various strengths, which are equal to the amount of elemental iron they contain. Ferrous fumarate is available only in the tablet form whereas ferrous sulfate, ferrous gluconate, and iron polysaccharide complex are available both as tablet and liquid preparations. Ferrous sulfate is available as regular and extended release tablets. The liquid preparations are preferred in younger patients or when iron is given through an enteral tube. Some liquid preparations may need to be diluted with water immediately before administration if they are too viscous for administration. Additionally, the iron product may be given after enteral feedings to reduce adverse effects, like gastrointestinal (GI) irritation. Ferric maltol was recently shown to be well tolerated and efficacious in adult patients with IBD and mild anemia who had previously failed therapy with ferrous salts (95,96). Ferric maltol was approved by the Food and Drug Administration (FDA) in July of 2019 for adult patients but has not been approved in Mexico or Canada. Powers et al conducted a double-blind randomized trial in 80 pediatric patients (9–48 months), comparing ferrous sulfate (FS) with iron polysaccharide complex (IPC) at a single daily dose of 3 mg/kg/day of elemental iron for 12 weeks. They found a more favorable rise in Hgb (average of 1 g/dL), and thus a higher rate of successful resolution of anemia in 29% versus 6% of children receiving FS compared with IPC. Diarrhea was more frequent with IPC, while vomiting occurred more often with FS. Therefore, an overall combined adverse events profile was not different between the 2 groups (92). Once Hgb is normalized, the oral therapy should continue for about 3 additional months to replenish iron stores.

Absorption of oral or enteral iron may be affected by ingestion of foods, dietary supplements, and certain medications. Protein snacks can reduce absorption, whereas ascorbic acid, citrus fruit, or vegetable juice can enhance it. Liquid iron preparations can

stain the teeth temporarily, so parents should be advised to brush the child's teeth after ingestion of iron. Oral/enteral iron supplements may cause side effects like nausea, vomiting, stomach pain, constipation, and darkening of stools.

Intravenous Iron Replacement Products

IV iron products are indicated in patients with active inflammation and in patients with moderate-to-severe anemia, including those who require a blood transfusion to replenish iron stores. They are also recommended in patients who are intolerant or unresponsive to oral iron products, and if erythropoiesis-stimulating agents are administered. The IV iron preparations are relatively safe and unlikely to cause iron overload. A TSAT of 50% and ferritin levels above 800 µg/L should serve as markers to discontinue further iron infusions (31). Parenteral iron preparations are greatly underused because of safety concerns, particularly regarding anaphylaxis, which was observed mainly with the older iron dextran preparation that is no longer available; the newer low-molecular-weight dextran is safer. Chertow et al analyzed the data recorded in the FDA registry between 2001 and 2003 and reported a rate of 3.3 versus 11.3 life-threatening adverse events per million doses attributed to the use of low versus high-molecular-weight iron dextran (97).

The hypersensitivity reactions to parenteral iron are mostly secondary to iron nanoparticles that trigger complement activation-related pseudo-allergy (CARPA). The reaction results from release of anaphylatoxins (C3a and C5a) that further activate mast cells, basophils, and macrophages upon binding via specific receptors leading to the release of vasoactive mediators (histamine, thromboxane, leukotrienes, and platelet-activating factor). Most reactions are mild and transient, they might manifest as a rash, injection site pain, nausea, vomiting, pruritus, headache, and flushing. Reactions generally resolve after the infusion is completed or interrupted. For mild reactions, stopping the infusion for a few minutes, monitoring closely and restarting at a slower rate when the patient recovers is sufficient. If the patient tolerates a slower infusion rate and has no further events, the same protocol is recommended for subsequent infusions (similar to Redman syndrome with vancomycin). If the reaction does not resolve on stopping/slowing the iron infusion, or vital sign changes, such as tachycardia, hypotension, urticarial rash, or shortness of breath are observed, a normal saline bolus along with IV hydrocortisone is recommended. Future iron infusions should be administered with caution and a different IV iron product is recommended. In the rare case of severe reaction with cardiac/respiratory compromise or arrest, cyanosis, loss of consciousness, and so forth, subcutaneous epinephrine, normal saline bolus, intravenous steroids, and oxygen can be used, and all future iron infusions should be cancelled. The use of antihistamines for iron infusion reactions is controversial (98,99) (Fig. 4).

It is important that parenteral iron be administered by trained personnel. Emergency medications and resuscitative equipment should be available during these infusions. Iron infusions should be used with caution in patients with severe allergies and asthma, ongoing severe inflammation or sepsis, systemic mastocytosis, first trimester of pregnancy, current therapy with beta blockers or angiotensin converting enzyme (ACE) inhibitor, severe cardiac or respiratory disease and conditions associated with iron overload (98). Product-specific details and adverse effects are discussed in the section below.

The FDA has approved 6 IV iron products for use in the United States. Only 3 of these products have been, however, approved for use in pediatric patients: low-molecular-weight iron dextran (LMW-ID), iron sucrose (IS), and ferric gluconate (FG). In addition to these, ferric carboxymaltose (FCM) and ferumoxytol

have been in use throughout North America. Ferric derisomaltose is an intravenous iron product that was being used in Canada and now has also been recently approved by the FDA in January 2020 for adults in the United States.

All the IV iron products are iron-carbohydrate complexes (ICC) and consist of colloids or spherical iron-carbohydrate nanoparticles. The core of each particle is a polynuclear-iron-oxyhydroxide gel. The carbohydrate shell is required to stabilize the core and slow down the release of bioactive iron while maintaining the colloidal suspension. The size and composition of the carbohydrate shell varies between products and is believed to contribute to the different side effect profiles of each agent. Following IV administration, the ICC is taken up by macrophages via endocytosis and is further degraded in the endolysosomes. Following lysosomal degradation, iron is released to the intracellular labile iron pool, which could either be exported via ferroportin and bound to transferrin or delivered to mitochondria and/or other target proteins. The unused iron is stored as ferritin (44).

IS and FG are less stable complexes, and therefore are mostly dissociated in the blood, resulting in release of some labile iron into the plasma, which can bind to transferrin. Once transferrin is saturated, the nontransferrin bound iron (NTBI) can be taken up, especially by highly vascular tissue, resulting in oxidative stress; therefore, these agents should be infused slowly and administered at a lower dose per infusion compared with newer preparations. After dissociation in the blood (IS and FG), the carbohydrate shell is excreted by the kidneys, and the polynuclear iron core enters the macrophages and is subjected to further degradation in the endolysosomes. The carbohydrate shell in dextran-free products like FCM is first partially broken up in the plasma by α -amylase before being taken up by the macrophage for endolysosomal degradation. Therefore, the labile iron is released only into the cytoplasm of the macrophages, allowing a larger dose to be administered as a single infusion. On the other hand, the dextran-containing complexes like iron dextran (IDX) are taken up intact by the macrophages. They undergo a slower degradation in the endolysosomes, and the retained iron-carbohydrate complex can further lead to oxidative stress within the macrophages (44,100). Ferumoxytol has a superparamagnetic iron oxide nanoparticle core due to which it can be used as an enhancing agent in magnetic resonance imaging (MRI). It may be pertinent to inform the radiologist if an MRI is to be performed within 3 months of Ferumoxytol administration.

Various studies comparing different iron products have shown superior response to IV compared with oral iron products. In a recent meta-analysis of mainly adults and older teenagers ($n = 1143$ patients), Askan et al noted that Hgb response was mostly superior with IV iron compared with oral iron therapy. The tolerability of parenteral iron was also superior to oral iron therapy. They found IV iron to be overall safe, though adverse events were noted to occur in a few patients. They noted response rates of 79%, 68%, and 42% with FCM, IS, and LMW-ID, respectively. Of the 543 patients treated with FCM, 12% had adverse events, including transient increase in liver enzymes (2.2%), headaches (1.7%), hypophosphatemia (1.7%), and hyperferritinemia (1.3%). Among 471 patients who received IS, 15.3% had adverse events, with burning at the site of venipuncture (1.5%) being the most commonly observed. Of the 83 patients treated with LMW-ID, 12% were noted to have adverse events, of which nausea and anaphylactoid reactions (3.6%) were the most common. One drug-related serious adverse event (SAE) was noted with FCM (pulmonary embolism), and another possible SAE with IS (thrombocytopenia) (101). Evstatiev et al also found FCM to be superior to IS in adults with IBD, demonstrating response rates of 65.8% versus 53.6%, respectively (102). A recent randomized, multicenter, double-blind trial comparing FCM with Ferumoxytol in about 2000 adult patients



FIGURE 4. Algorithm for grading the severity and management of hypersensitivity reactions to intravenous iron infusions. Reproduced with permission from Rampton et al and Hematologica.

with IDA of any etiology found them to be comparable in efficacy and adverse events. Patients receiving FCM, however, had a 38.7% incidence of significant hypophosphatemia (<2.0 mg/dL). They also noted comparable incidence of other adverse events in 3.5% of the patients in both study arms, including headache, nausea, dizziness, and fatigue (103).

In a US study using health administrative data, Akhuemonkhan et al performed a retrospective analysis of 37 168 infusions in 6151 adult IBD patients. They investigated occurrence of anaphylactic shock, hypotension, and bronchospasm within 7 days of receiving parenteral iron. They found 1.3% of patients with adverse events (2.48 events/1000 infusions), with the highest number occurring with ferumoxytol, followed by FG, IS, and LMW-ID, and none with FCM. Hypotension was the most common, followed by anaphylactic shock (0.24 events/1000 infusions), which was noted primarily with ferumoxytol infusions, whereas none were seen with

LMW-ID. They also noted that it is safe to administer biologics and iron infusions on the same day (104).

Mamula et al studied 70 children with IBD who received LMW-ID and found that 9% had hypersensitivity reactions. They noted significant improvement in Hgb of 34 subjects who were evaluable for efficacy (105). Plummer et al performed an observational prospective study of LMW-ID in 31 children (9 months to 18 years) with anemia of diverse etiology and who had failed oral iron therapy. Adverse events were noted in 29% (9/31 subjects), of whom 7/9 were unable to tolerate the test dose, so the infusions had to be discontinued. Of the remaining 24 subjects who were evaluated for efficacy in this study, 67% and 33% were noted to have either a complete or partial response, respectively (106).

Stein et al retrospectively reviewed their experience in 72 pediatric patients with IBD who received IS. They noted adverse

events in 6.6% of the infusions, of which the most common symptom was IV injection site pain. Only 43/72 patients were evaluable for efficacy, with an overall response noted in 41.9% (18/43) of children, whereas Hgb normalized in only 52.3% of the subjects who were able to receive their full calculated deficit (107). Kaneva et al reported their experience in 142 children (7 months to 22 years) receiving IS for various causes of anemia. Only 1 patient developed cough and wheezing, which resolved on stopping the infusion. They noted significant improvements in Hgb, MCV, serum iron, ferritin, TIBC, and iron saturation values (108). Papadopoulos et al published their experience in 41 children with IBD who received IV iron for anemia. Thirty-five children above 12 years received FCM, while 7 patients under 12 years of age received IS. They noted a self-limited rash during infusion in 2/35 patients receiving FCM and 1/7 in those receiving IS. They reported significant improvement in Hgb of all patients and also noted that response was not related to disease activity (109). Powers et al recently published a retrospective study on efficacy of FCM in 72 children (11 months to 18 years), among whom 17 were below 2 years of age. They noted normalization of Hgb in 68% and partial response in 30% patients. They reported no serious adverse events, and only minor adverse events in 16% (7/72) patients, the most common of which was urticaria that was treated with oral or IV diphenhydramine (110). Carman et al recently reported results of an uncontrolled prospective trial using FCM in children with IBD, finding resolution in 64% and 81% of children with IDA or iron deficiency, respectively. They noted only injection site pain and urticarial rash but did not observe any serious adverse events (111).

Only a few reports are available on the use of ferumoxyl in children. Hassan et al conducted a retrospective review in 54 children (age range 1 month to 19 years) with anemia of diverse etiologies, who altogether received 110 infusions of ferumoxyl administered at the dose of 10 mg/kg with a maximum dose or 510 mg/dose over 1 hour. They found significant improvements in both Hgb and ferritin, whereas an even larger increase was noted in those who had received concomitant erythropoietin. Adverse events were noted in 4.5% of the infusions; 3 patients (2.7% infusions) had moderately severe hypersensitivity reactions requiring immediate discontinuation of the infusion (112).

Ferric derisomaltose is the newest intravenous iron product that was approved in January 2020. Although data are limited so far, a recent report documented negligible incidence of hypophosphatemia compared with ferric carboxymaltose. At the time of this writing, ferric derisomaltose is not yet available in the US market (113).

Calculation of Iron Deficit

To fully assess the iron requirements of a patient, the iron deficit must be calculated. This value provides an estimation of how much iron needs to be given to replete deficit in iron stores. Many iron deficit equations have been validated for use; all equations use the desired Hgb goal, current Hgb values, and patient's weight for calculation. The dose calculation in children differs among each preparation. These equations have been provided with individual product descriptions in this section.

Iron Dextran

Low-molecular-weight iron dextran is FDA-approved for IDA in children over 4 months old. Although the carbohydrate shell is smaller for this product compared with the older preparations, and theoretically carries less risk of anaphylactic reactions, it still carries the same black box warning.

A test dose is required before using iron dextran to assess if the patient will have an anaphylactic reaction. The test dose varies in pediatric patients by weight (<10 kg: 10 mg, 10–20 kg: 15 mg, >20 kg, and adults: 25 mg). If the test dose is tolerated, it is relatively safe to proceed with the remainder of calculated iron deficit that can be given as a total dose infusion (TDI) (ie, iron deficit – test dose = dose of iron dextran) or as an incremental daily dose (split dose option). According to FDA guidelines, total daily dose should not exceed 100 mg. When giving a test dose, close monitoring and resuscitative equipment at the bedside are required in case an anaphylactic reaction occurs. Concomitant use of ACE inhibitor may increase the risk of anaphylaxis. Large IV dose as used in TDI are associated with increased risk of adverse events that are seen as delayed reactions, 1 to 2 days after infusion. These include arthralgias, back pain, chills, dizziness, moderate-to-high fever, headaches, malaise, nausea, and vomiting, and may take 3 to 4 days to subside. Iron dextran is unique in that it is compatible with 2-in-1 parenteral nutrition. It has, however, a destabilizing effect on IV lipids, and therefore, cannot be given as 3-in-1 infusion. Iron dextran is also the only IV iron product that can be given intramuscularly through the Z-track method, though it is not used this way as it may cause permanent dyeing of the skin, is painful, and only a small volume can be given.

Repletion dose calculation for iron dextran

Available at: http://online.lexi.com/lco/action/doc/retrieve/docid/pdh_f/128848?hl=6403 (subscription required for access).

Recommended daily dose should be limited to 100 mg (2 mL).

Dose (mL) = $0.0442 (Hb_n - Hb_o) \times LBW + (0.26 \times LBW)$
Where Hb_n (desired Hgb), Hb_o (measured Hgb), LBW (lean body weight)

Children 5 to 15 kg; LBW = actual body weight, $Hb_n = 12$ g/dL

Children >15 kg and adults; use calculated LBW, $Hb_n = 14.8$ g/dL

\square LBW (kg) ≤ 14 years old: boy/girl = $3.8 \times 0.0215 \times (\text{total wt. in kg})^{0.646} \times (\text{height in cm})^{0.7236}$

≥ 18 years old (boys) = $1.1 \times \text{total weight} - 128$ (weight/height)²

≥ 18 years old (girls) = $1.07 \times \text{total weight} - 148$ (weight/height)²

(no validated formulas for ages 15–17, therefore, use clinical judgement)

Use total body weight if LBW calculation yields a higher number.

Electronic calculators for all of the above LBW values may be found at

<http://www.calculator.net/lean-body-mass-calculator.html>.

Iron Sucrose

Iron sucrose is FDA-approved for patients over 2 years of age and does not have a black box warning or require a test dose. It is, however, advisable to monitor and observe the patient during the infusion and up to 30 minutes after it is completed. As total dose infusion is not an option with iron sucrose, the iron deficit is replaced in a series of doses. The first dose is 5 mg/kg up to a maximum of 100 mg. Subsequent doses are 5 to 7 mg/kg per dose at weekly intervals but should not exceed 300 mg/dose.

Iron sucrose can be given undiluted as a slow IV injection over 2 to 5 minutes but preferably should be diluted in normal saline and given over 15 minutes to 2.5 hours, with higher doses requiring

a longer infusion time. For the treatment of nonrenal IDA, it is advisable to dilute to a 1 mg/mL solution and administer at a rate of 1–1.3 mL/minute.

Repletion Dose Calculation for Iron Sucrose

Dose (mg) = $0.6 \times \text{wt. (in Kg)} \times [100 - \{(\text{observed Hgb} / \text{desired Hgb}) \times 100\}]$

desired Hgb typically 12, but a different target may be used (114).

Sodium Ferric Gluconate

Sodium ferric gluconate is FDA-approved for patients 6 years and older, it does not carry a black box warning, and also has a low risk of adverse reactions.

Repletion Dose Calculation for Sodium Ferric Gluconate

Dose is not dependent on the iron deficit. Patients are given 0.75 to 1.5 mg/kg elemental iron per dose of sodium ferric gluconate (with a maximum dose of 125 mg per session) in a series of 8 weekly doses. Doses over 125 mg have been associated with increased incidence and severity of adverse effects. In children, sodium ferric gluconate must be diluted before administration with at least 25 mL of normal saline and given over 1 hour (115).

Ferumoxytol

Ferumoxytol is a newer agent that was approved for the treatment of IDA in adult patients with chronic kidney disease. It is a superparamagnetic iron oxide coated with a polyglucose sorbitol carboxymethyl ether shell and can also be used as a contrast agent for cardiac and venous MRI. This medication can only be given intravenously and is not known to be compatible with parenteral nutrition solutions. It has been FDA approved for use in adults since 2009 but has been used off-label in pediatric patients. A test dose is not required; Safety studies showed increased risk of moderate-to-severe symptomatic hypotension with an acute decrease (>30% of baseline) in systolic blood pressure and hypersensitivity reactions. Because of this risk, the FDA strengthened a warning about these adverse effects and placed a black box warning on the label for ferumoxytol.

Repletion Dose Calculation for Ferumoxytol

In adults, a dose of 510 mg elemental iron can be followed by a second dose of 510 mg elemental iron 3 to 8 days later. Doses can be diluted in 50 to 200 mL of normal saline or 5% dextrose and given over at least 15 minutes.

Pediatric data are lacking; 1 retrospective case series in children described 1 to 2 doses of 10 mg/kg per dose (up to a dose of 510 mg) of elemental iron given over 60 minutes (112).

Hypersensitivity reactions to ferumoxytol have occurred in patients who had previously tolerated it well. Therefore, it is imperative that patients be monitored for at least 30 to 60 minutes after each dose.

Ferric Carboxymaltose

Ferric carboxymaltose is the newest agent available for the treatment of IDA and was approved for use in adults by the FDA in

TABLE 9. Dosing guidelines for ferric carboxymaltose

Adult Patients		
Hemoglobin	Weight	Total Dose in mg
7–10 gm/dL	Below 70 kg	1500 mg
	Above 70 kg	2000 mg
Above 10 gm/dl	Below 70 kg	1000 mg
	Above 70 kg	1500 mg
Children*		
Hemoglobin		
7–10 gm/dL	15 mg/kg	Total dose/infusion 750 mg (up to 2 infusions)
Above 10 gm/dL	15 mg/kg	Maximum dose/infusion 750 mg (single dose)

gm: grams, dl: deciliter, Kg: kilograms, mg: milligrams.

*This drug has not been FDA- approved for use in children. On the basis of pediatric studies, can be used with physician discretion.

Adapted from (102,110).

2013. It has a stable carbohydrate complex, which minimizes the release of free labile iron, and therefore can be given in larger doses. It has a lower risk of hypersensitivity reactions as it is dextran-free. This medication has no black box warnings and does not require a test dose. It can be given only intravenously and is not known to be compatible with parenteral nutrition solutions. This medication should not be used if there is known hypersensitivity to any of its components. FCM carries a higher risk of hypophosphatemia with FCM compared with other parental iron preparations. Hypophosphatemia may occur within 2 months of an infusion and can present with pain, nausea, or asthenia. Rarely in severe cases, muscle weakness, rhabdomyolysis, hemolytic anemia, or cardiac dysrhythmias may occur (103). Routine monitoring of phosphate level is not indicated unless a patient has symptoms. FCM can be given undiluted by IV push at approximately 100 mg/minute but preferably should be diluted to concentrations greater than or equal to 2 mg/mL and given by IV infusion over at least 15 minutes. Patient should be monitored for at least 30 minutes after receiving a dose.

This drug is not yet FDA-approved for children under the age of 18 years, though it is being used off-label in pediatric patients. Published studies document safety and efficacy in children (109,100,111,116). We suggest physician discretion for its use in children below 18 years of age.

Repletion Dose Calculation Guidelines for Ferric Carboxymaltose (Based on Pediatric Studies)

Children: 15 mg/kg, max 750 mg per dose up to 2 doses 1 week apart, maximum amount of iron per course is 1500 mg (110,111,116).

Adults: Patients are stratified according to Hgb and body weight. The maximum dose per session for a patient below 70 kg is 750 mg and above 70 kg is 1000 mg. For mild anemia, the total doses are 1000 and 1500 mg for below and above 70 kg, respectively. For severe anemia, the dose is 1500 and 2000 mg for below and above 70 kg, respectively (31,102) (Table 9).

Follow-up and Prevention of Recurrence of Anemia and Iron Deficiency

It is important to maintain adequate follow-up after treatment of anemia as recurrence can occur in up to 50% of treated

patients within the following year. A post-treatment ferritin level of 400 µg/L is predictive of low likelihood of recurrence of anemia within the subsequent 1–5 years of follow-up. It is important to monitor the CBC, ferritin, TSAT, and CRP every 3 months for up to 1 year, and then every 6 months if the disease is inactive (31). Concurrent treatment of IBD is also important to prevent recurrence. Iron deficiency should serve as a warning sign for possible recurrence of active disease even in the absence of clinical symptoms or anemia. Iron treatment can be promptly started if the Hgb or ferritin levels drop below the normal range.

Product Selection Considerations

Many elements should be considered when selecting an agent for treating iron deficiency in a pediatric patient. First, assessing the history for prior allergic reactions is essential. Some cross-reactivity exists between LMW-ID, IS, and FG, but not between these 3 products and ferumoxylol or FCM (44). Clinical considerations, like severity of disease, ongoing blood loss, sepsis, iron status, travel distance from the hospital or infusion center, use of IV biologicals (so it can be coordinated), time available for infusions, and need for parenteral nutrition should all be considered. Medication cost and availability or other important considerations, as financial barriers may exist for some patients. The price of each medication in the United States is listed in Table 6 (note: prices may vary based on institutional contracts).

TREATMENT OF NONANEMIC IRON DEFICIENCY

NAID often presents with vague symptoms and can be missed if patients are not being monitored. No guidelines exist for the treatment of NAID in children with IBD. Several studies report on iron deficiency in young athletes and adolescent girls who benefit from parenteral iron supplementation (117,118). A consensus statement for NAID with IBD in adults (>18 years) was recently published by a European panel of experts with 16 gastroenterologists and a hematologist, who universally recommended treatment of NAID along with escalation of medical therapy in patients with active disease. According to their recommendations, oral iron was suggested as the initial therapy in patients with inactive disease or if patients had successfully tolerated oral iron previously. Patients who are intolerant or unresponsive to oral iron should receive IV iron. Initially IS (low dose) can be tried but if not successful than FCM (high dose) is recommended. There was a stronger consensus on the use of parenteral versus oral iron in patients with clinically active compared with quiescent disease. The goal of iron therapy is to keep ferritin at or above 100 µg/L (35).

INDICATIONS FOR BLOOD TRANSFUSION

The literature is sparse on guidelines for blood transfusion, specifically for children with IBD. Before the more prevalent use of parental iron, blood transfusions were given more commonly. Various factors that should be considered include the general condition and stability of the patient, vital signs, ongoing blood loss, and rapidity of development of anemia. On the basis of review of current literature and practice patterns in various institutions in North America, the IBD Anemia Working Group suggests a red cell transfusion when the Hgb drops to below 7 to 8 g/dL. Blood transfusion should not be given if Hgb is 10 g/dL or above (31,35,119). Other strategies, such as IV iron therapy should be, however, considered when correction of anemia is indicated in a hemodynamically stable patient with adequate tissue perfusion.

REFRACTORY ANEMIA

As noted previously, in the majority of children with IBD, the most common causes of anemia are IDA and ACD. Anemia in these patients should respond to iron replacement therapy along with treatment of IBD. If the patient does not show adequate response with a rise in Hgb and increase in reticulocyte count following a 2-to 4-week trial of an adequate iron therapy, one or more of the following factors could be playing a role.

Oral iron: Poor iron absorption. The patient may not be taking oral iron because of adverse effects, or nonadherence. In patients with ongoing inflammation or with inappropriate food pairing as described above, iron absorption can be significantly impaired.

Ongoing blood loss from menorrhagia, or a bleeding diathesis, such as Von Willebrand disease, use of anticoagulant therapy, or low platelet count.

Inflammation: The patient may not be able to incorporate iron for erythropoiesis because of active IBD-associated inflammation, extraintestinal infections, or other sources of inflammation mimicking IBD.

Other nutrient deficiencies: Examples include folic acid and vitamin B12 deficiency. Patients with malabsorption related to small bowel involvement, intestinal resection, ileal pouch, poor nutritional status, and those taking sulfasalazine or methotrexate are particularly more susceptible.

Drug-induced anemia: sulfasalazine, 6-MP, azathioprine, methotrexate, and trimethoprim-sulfamethoxazole can be associated with folate deficiency, bone marrow suppression, or hemolysis.

Cause is not directly related to IBD or its therapy: individuals with thalassemia trait can have a disproportionate degree of red cell microcytosis with a relatively mild anemia. Their Hgb or MCV will not normalize after correction of iron deficiency. Lead toxicity also leads to low MCV and mild anemia. A rare inherited disorder called iron-refractory iron-deficiency anemia (IRIDA) can lead to failure of oral iron therapy. IRIDA is caused by loss-of-function mutations of the *TMPRSS6* gene, which encodes a serine protease matrilysin 2 that functions by cleaving membrane-bound hemojuvelin, thereby reducing hepcidin synthesis under normal conditions. Loss of *TMPRSS6* function causes iron deficiency because of inappropriately high hepcidin levels, with markedly reduced absorption of iron from the gastrointestinal tract and refractory anemia (120).

Hematology consultation should be sought for patients with inadequate response to a trial of adequate iron and IBD-directed therapy if no other treatable cause(s) are detectable.

ROLE OF ERYTHROPOIETIN AND HEPcidIN INHIBITORS

As discussed under pathophysiology, anemia occurs because of ongoing blood loss, poor absorption, and reduced red blood cell production in the bone marrow because of several factors. Other factors include reduced absorption of iron from the gastrointestinal tract, trapping of iron in macrophages, and a relative decrease in erythropoietin (EPO) production.

EPO is a hematopoietic cytokine produced by kidney cells in response to hypoxia. It functions by preventing apoptosis, while promoting induction of proliferation and differentiation of the erythroid precursors, thereby maintaining a renewable pool of mature functional red blood cells in circulation.

Recombinant human EPO is approved by the FDA for patients whose anemia is associated with chronic renal failure, HIV, and chemotherapy. EPO has also been used to treat ACD in patients with rheumatoid arthritis and IBD. Several small studies in adults with IBD have shown treatment responses with increase in Hgb levels and improvement in quality of life. Katsanos et al

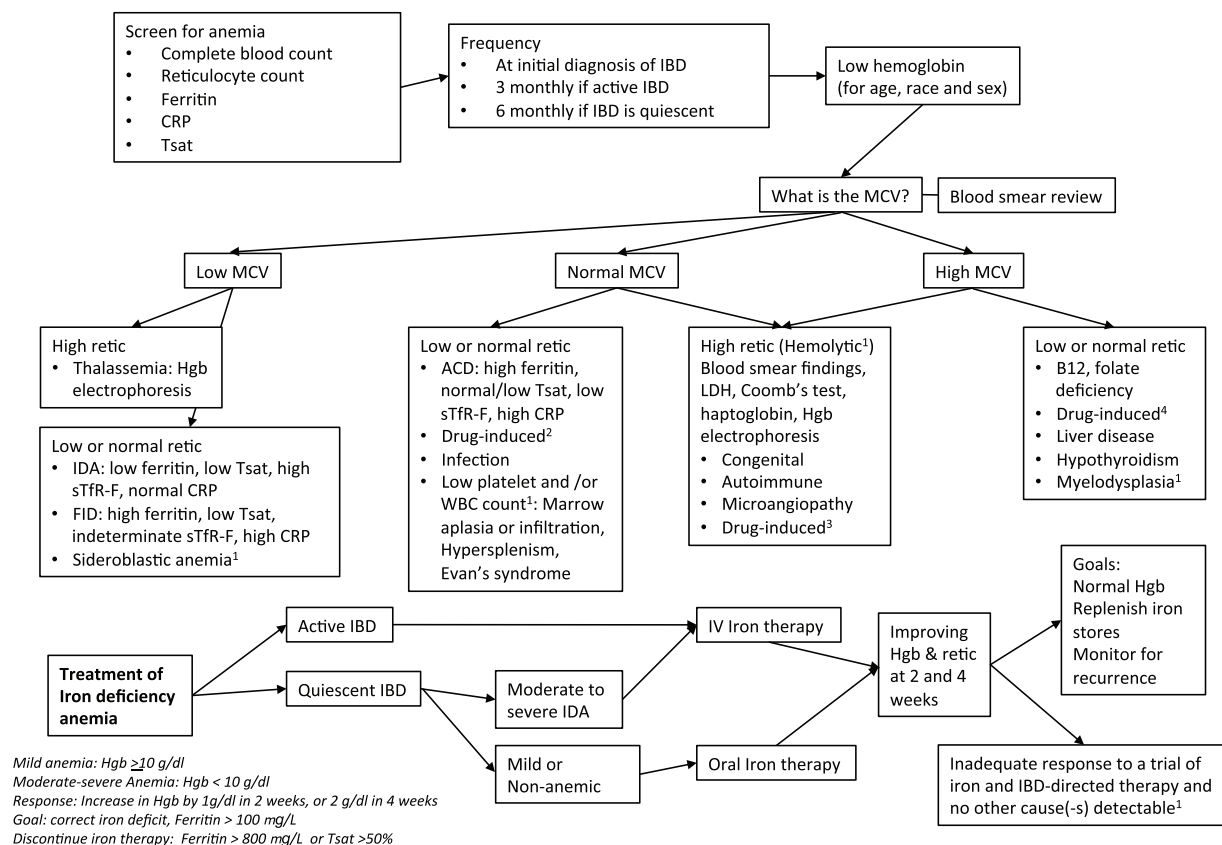


FIGURE 5. Suggested algorithm for diagnosis and management of anemia in children with inflammatory bowel disease. ACD = anemia of chronic disease; CRP = C-reactive protein; FID = functional iron deficiency; Hgb = hemoglobin; IBD = inflammatory bowel disease; IDA = iron deficiency anemia; LDH = lactic dehydrogenase; MCV = mean corpuscular volume; sTfR-F = soluble transferrin receptor -ferritin index; Tsat = transferrin saturation; WBC = white blood count. ¹Hematology consultation may be indicated; ²Azathioprine, 6-mercaptopurine, mesalamine, sulfasalazine; ³Sulfasalazine, trimethoprim-sulfamethoxazole; ⁴Methotrexate, azathioprine, 6-mercaptopurine.

described their 15-year experience in 78 patients who had failed IV iron therapy. They noted an increase in Hgb by 2 g/dL or more in 61.5% and a partial response in another 23.1% patients with EPO therapy. No adverse events were noted in their analysis (121). In a 2015 guideline, ECCO included a recommendation on use of EPO in patients with ACD that is poorly responsive to anti-TNF and IV iron. Concomitant IV iron should be given in patients on EPO therapy to maintain a TSAT $\geq 20\%$ and a serum ferritin ≥ 200 μ g/L (31).

Adverse effects of EPO treatment in patients with ACD have not been rigorously studied. Limited data are available on the use of EPO in children with IBD. In our view, EPO should be reserved for symptomatic patients who have not responded to IV iron despite aggressive management of IBD (including anti-TNF therapy) and may otherwise require repeated blood transfusions. On the basis of data in patients with cancer or renal insufficiency, it would be prudent not to exceed Hgb levels above 12 g/dL with EPO therapy to minimize risks of venous thrombosis and cardiovascular events.

Excessive hepcidin expression inhibits dietary iron absorption and leads to iron retention within tissue macrophages, thereby contributing to the development of anemia with iron-restricted erythropoiesis (such as FID and IRIDA, as discussed). Considerable interest is directed at therapeutic strategies targeted to inhibit the hepcidin-ferroportin axis to treat these disorders. Treatment with IL-6 inhibitor (tocilizumab) in patients with Castleman disease and

TNF-inhibitor (infliximab) in those with rheumatoid arthritis and IBD has been shown to reduce serum hepcidin levels with concurrent improvement in ACD (122,123). Neutralizing antibodies or small molecule antagonists that directly inhibit hepcidin are also under development. An early phase trial of hepcidin inhibitor NOX-H94, a structured mirror-image RNA oligonucleotide of hepcidin, has been completed for ACD in patients with cancer (NCT 01691040). A clinical trial of PRS-080, a PEGylated anticalin protein that specifically binds to hepcidin and inhibits its activity in patients with chronic kidney disease is underway (NCDT03325621) (122).

In summary, anemia is the most common extraintestinal manifestation of IBD and should be routinely monitored and treated alongside IBD. Patients not tolerating or responding to oral iron and those with active disease having moderate-to-severe anemia should receive parenteral iron even after a blood transfusion. If patients are not responding to iron replacement, consider other etiologies like ACD, drug toxicity, vitamin deficiency, and other rare causes. We encourage pediatric IBD centers to implement diagnosis and treatment care pathways to support proper screening and therapy (Fig. 5). Refractory cases should be referred to a hematologist.

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