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Iron: Not Too Much and Not Too Little

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Disorders of iron metabolism are frequently encountered in gastroenterology practice and include deficiency or excess. The limited intestinal uptake of iron slows response in deficiency, and no pathway exists for excretion in overload states. This article reviews iron disorders commonly seen in GI practice, describing common clinical tools for diagnosis and treatment.

IRON DEFICIENCY

Conditions associated with insufficient iron stores range from depletion to frank iron deficiency anemia. Iron depletion refers to diminished body stores, yet serum iron and blood hemoglobin (Hgb) levels remain normal as there is still enough iron for normal erythropoesis. Iron deficiency anemia (IDA) occurs when absent marrow iron limits red blood cell (RBC) production. IDA affects 1% to 4% of adult men, 5% to 11% of adult women (1), and up to 29% of low-income pregnant women (2). Fifteen percent of hospitalized patients over 65-years of age will have IDA (3). Pathologic causes of iron deficiency are usually related to inadequate iron intake, bleeding, or iron malabsorption. Physiological deficiency occurs when demand outstrips availability, such as during rapid childhood growth and pregnancy.

The gold standard to establish the absence of iron is the bone marrow biopsy; however, the expense and discomfort of bone marrow biopsy do not allow it to be used to follow patients over time. Routine lab reports of absent marrow hemosiderin, an insoluble iron storage protein, may be inaccurate in 30% of cases (4).

Serum ferritin is the preferred serologic marker of iron stores. A ferritin less than 15 ng/mL is virtually diagnostic of IDA with a specificity of 99% (5). Unfortunately, serum ferritin is elevated in chronic inflammation (Table 1). In 259 anemic patients whose bone marrow and iron serologies were studied, only two out of 49 patients with a serum ferritin <18 did not

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Table 1
Factors Influencing Ferritin Levels

- Total Body Iron
- Infection or Inflammation {↑}
- Female Gender {↓}
- Alcohol Consumption {↑} (70)
- Fatty Liver {↓} (71)

have IDA, while only eight out of 116 with a serum ferritin >100 had IDA. Between 18 and 100, 40% had IDA, although only one had a serum ferritin >45. The authors suggested that a ferritin of less than 40 can diagnose IDA in patients without inflammation and less than 70 was indicative of deficiency for those with an inflammatory condition (5). The average ferritin values for adult men and women are 100 ng/mL and 30 ng/mL, respectively (6).

Transferrin (Tf) is the major iron transport protein in the blood. The ratio between iron and Tf decreases in iron deficiency since there is less iron to transport. Transferrin saturation (TS) is obtained by the formula: (serum iron × 100)/TIBC, where TIBC is a surrogate marker for circulating transferrin. Most laboratories report the transferrin saturation when the tests are ordered together. Iron deficiency is associated with TS less than 18%; normal is 25% to 50%. In the anemia of chronic disease, now referred to as, "anemia of inflammation," iron is sequestered from the circulation while transferrin levels drop, causing a near-normal TS, confounding its use. Thus, underlying iron deficiency can be present in anemic patients with normal TS who have an underlying inflammatory disease process.

CLINICAL CONDITIONS CAUSING IRON DEFICIENCY

Any lesion within the gastrointestinal tract can cause occult bleeding and iron loss, with upper tract lesions as likely as colon cancers to be responsible (7–9). Table 2 lists the most common causes of GI blood loss. In refractory IDA, occult lesions that should be considered include Cameron ulcers, watermelon stomach, portal gastropathy, and vascular ectasias. Only about 5% of all bleeding arises between the ligament of Treitz and the terminal ileum (10), with angiodysplasia (small vascular malformation) accounting for 30%–40% of these cases (11). Endoscopic examination is not failsafe; up to 25% of patients who have a negative EGD and colonoscopy are found to have upper GI tract lesions at the time of repeat EGD (12). Prior to small bowel evaluation for occult bleeding, colonoscopy and EGD should be repeated, as up to 64% of lesions identified with a push enteroscope could have been seen with an upper endoscope (13).

Table 2
Causes of Gastrointestinal Bleeding

Carcinoma
Large Adenoma (>1.5 cm)
Inflammation
- Erosive esophagitis
- Ulcer
- Cameron lesion
- Erosive gastritis
- Celiac sprue
- Crohn's disease
- Ulcerative colitis
- Colitis
- Idiopathic cecal ulcer

Vascular
- Vascular ectasia
- Portal gastropathy
- Watermelon stomach
- Dieulafoy's lesion

Infectious
- Hookworm
- Whipworm
- Tuberculosis

Miscellaneous
- Hemosuccus pancreaticus
- Hemobilia
- Hemoptysis
- Oropharyngeal

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Malabsorption of iron is a common cause of iron deficiency, such as in celiac disease. In 190 patients with IDA, 13.7% were diagnosed with celiac disease by duodenal biopsy (14). Iron deficiency in celiac disease can also occur from occult gastrointestinal bleeding (15,16). *Helicobacter pylori* infection has also been linked to iron malabsorption, from occult bleeding from erosive gastritis and decreased absorption from hypochlorhydria. A positive serology supports a "test and treat" strategy for *H. pylori* in the unexplained IDA patient (17). Both autoimmune and environmental atrophic gastritis cause IDA due to a lack of gastric acid to solubilize dietary iron (18). Gastric or bariatric surgery patients also develop iron deficiency. IDA occurs in 55% of Roux-en-Y gastric bypass patients within three years post-op (19) due to reduced overall intake, impaired reduction of ferric iron to the more absorbable ferrous form, quicker gastrojejunal transit and duodenal bypass, the primary site of absorption (20). IDA is estimated to occur between 10% and 34% in post-gastrectomy patients (21).

TREATMENT OF IRON DEFICIENCY STATES

Treating IDA consists of addressing the underlying disorder and supplementing iron. Oral iron therapy is preferred over IV iron infusion. Common side effects of nausea and epigastric discomfort may be minimized by taking iron with food, but this reduces absorption by about two-thirds (22). In some patients, decreasing the dose is wiser rather than risking non-compliance. Ferrous sulfate and ferrous gluconate are the preferred oral forms due to low cost and high bioavailability. Enteric-coated preparations should be avoided as the iron is released beyond the primary site of intestinal absorption (duodenum). Optimal daily doses should be between 150 and 200 mg of elemental iron which translates into three 325 mg (60 mg of elemental iron each) tablets of ferrous sulfate per day (23). Absorption of iron may be enhanced by co-administration with 500 mg of ascorbic acid or a vitamin C containing beverage (24). In contrast, phenols, contained in some teas, coffee, and wine, may inhibit iron absorption (25) (Table 3). Dietary repletion is not practical; a 3 ounce serving of steak only supplies 3mg of elemental iron (6).

The major indications for parenteral iron administration are failure of oral therapy, ongoing iron malabsorption, and high iron losses as seen in hemodialysis patients. The dose of parenteral iron required can be determined by:

$$\text{Replacement dose (mg)} = 0.3 \times \text{Weight (lbs)} \times (100 - [\text{actual Hgb} \times 100/\text{desired Hgb}])$$ (23).

The three parenteral preparations available include iron dextran, iron gluconate, and iron sucrase. Anaphylactic reactions to these drugs, particularly iron dextran, have led some clinicians to be reluctant to replete with IV iron infusions.

Regardless of the route used, there is little difference in the rate of hemoglobin (Hgb) increase, unless iron malabsorption is present (22); 1–2 g/dL improvement in Hgb every two weeks is expected (21). An inadequate or slow response to oral iron may be due to non-compliance, inadequate dosing, malabsorption, blood loss, or administration with food. In severe deficiency, it may be three-to-four months before full restoration of iron stores and normalization of Hgb occurs (21). Once Hgb returns to normal, many physicians opt to discontinue iron; however, we and others

Table 3
Factors Influencing Iron Absorption

Enhancers of iron absorption
- Ascorbic acid (24)
- Meat/fish/poultry
- Fermented soy products
- Organic acids (citrate, lactic)

Inhibitors of iron absorption
- Phytate
- Polyphenols (tea, coffee, red wine)
- Calcium
- Oxalic acid (in spinach)
- Soy protein
- Avidin (in eggs)

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Table 4
Dietary Reference Intakes (DRI) for Iron

Life Stage Group	*mg iron*
Infants and Children	
0–6 months	0.27
7–12 months	11
1–3 years	7
4–8 years	10
Males	
9–13 years	8
14–18 years	11
19+ years	8
Females	
9–13 years	8
14–18 years	15
19–50 years	18
51+ years	8
Pregnancy	
≤18 years	27
18+ years	27
Lactation	
≤18 years	10
18+ years	9

National Academy of Sciences. 2001. Dietary Reference Intakes. Washington, D.C., National Academy Press.

recommend supplementation for another six-to-12 months to replenish iron stores to a ferritin level >40 in a non-acute phase setting (6,26,27). For a list of Dietary Reference Intakes (DRI) for iron see Table 4.

IRON OVERLOAD STATES

A single packed red cell transfusion (PRBC) contains 200 mg of elemental iron. Without a mechanism for excretion, this iron is retained in the body after RBC lysis. For example, if a patient requires 2 units of PRBC every month and is not bleeding, he is receiving an additional 4.8 grams (4800 mg!) of iron per year. Normal total body iron is approximately 3.5 grams; organ dysfunction begins to develop when total body iron accumulates in the range of 20 to 40 grams (28).

Hemochromatosis

Hereditary hemochromatosis (HH) is a genetic disease of uncontrolled intestinal iron uptake that occurs in approximately 1 in 200 (0.5%) in the U.S. It is the most common cause of iron overload and can cause cirrhosis, cardiomyopathy, diabetes mellitus and arthritis. Several primary (or idiopathic) forms of hemochromatosis exist. A genetic test, (HFE), is available for the most common form. Secondary hemochromatosis results from iron overload in otherwise normal hosts. This can occur from excess blood transfusions for anemias *without* blood loss. Examples include ineffective erythropoiesis in chronic hemolytic anemias, or unmonitored, or self-imposed, iron supplementation.

Determining the cause of iron overload requires genetic testing, iron studies, and clinical judgment. Screening for HH should occur among first degree relatives of those with known HH, individuals discovered to have abnormal iron markers, unexplained elevation of liver enzymes, hepatomegaly, or enhanced attenuation of the liver on CT (even if asymptomatic). Symptoms of overall poor health, arthropathy, arrhythmia, or impotence are no more common among identified homozygotes than among controls (29). Current guidelines do not support testing for HFE gene mutations in the general population (30).

A TS greater than 50% in women or 60% in men, or a ferritin >200 in women and >300 in men, in a non-acute phase setting, can identify candidates for HH testing, such as HFE gene testing or liver biopsies for age-adjusted quantitative iron (28,31,32). The HFE gene test is reasonable unless liver biopsy is indicated (such as those with an abnormal AST and ALT, where a liver biopsy is recommended), as over 90% of patients with HH are homozygous for the major C282Y mutation, and a C282Y/H63D (minor allele) accounts for 3%–5% more (31). Clinical penetrance of less than 1% has been described among hereditary homozygotes, and is even lower among females (29,33). Studies suggest that C282Y patients with serum ferritin >1000 are most at risk for developing cirrhosis (34,35). Phlebotomy before cirrhosis develops significantly reduces the morbidity and mortality of HH, with the non-cirrhotic HH patient having the same life span as the general population (36). Phlebotomy is a convenient way

Table 5
Iron Overload States

Hereditary Hemochromatosis
- HFE gene test related
- Non-HFE related

Juvenile hemochromatosis
Secondary hemochromatosis
- Iron loading anemias
  - Thalassemia major
  - Sideroblastic anemia
  - Hemolytic anemia

Dietary iron overload
Chronic liver disease
- Hepatitis B and C
- Alcohol induced liver disease
- Fatty liver disease
- Porphyria cutanea tarda

Miscellaneous
- African iron overload
- Aceruloplasminemia
- Neonatal iron overload

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to mobilize iron from body stores and can be performed weekly. It may take two-to-three years to achieve the desired endpoint of a ferritin <50 ng/mL (28,29).

Secondary hemochromatosis occurs in the setting of ineffective erythropoiesis, chronic liver disease, or excessive administration of iron. Patients on total parenteral nutrition with unmonitored iron supplementation are one group at risk. The clinical presentation of these conditions can be indistinguishable from primary hemochromatosis. In secondary hemochromatosis, anemia and other features of the underlying disorder are normally present (see Table 5 for types of iron overload syndromes). Those patients with transfusion related iron overload of thalassemia or other diseases of ineffective erythropoiesis are not candidates for phlebotomy due to their underlying anemia. These patients require chelation therapy with deferoxamine or the newly available oral agents, deferiprone or deferasirox. The iron chelates formed are excreted primarily in the urine.

ANEMIA AND INFLAMMATORY BOWEL DISEASE

In inflammatory bowel disease (IBD), iron deficiency occurs in 36% of cases (37,38). Iron deficiency may result from gastrointestinal blood loss due to ongoing disease activity, reduced iron intake, and malabsorption of iron (39).

IBD poses unique challenges: oxidation of ferrous iron can form hydroxyl radicals that can exacerbate gastrointestinal symptoms (40,41). Iron absorption may be impaired in small intestinal Crohn's Disease, which is worsened by hepcidin. Hepcidin, a peptide hormone produced by the liver, appears in the blood in response to inflammation to decrease duodenal iron absorption through the degradation of the enterocyte iron export protein ferroportin and to sequester iron in macrophages, thereby limiting marrow iron for erythropoiesis (42). Oral iron supplementation is not well tolerated in 21% of Crohn's cases and must be discontinued (43).

Intravenous iron preparations have shown greater clinical efficacy in IBD, especially in restoration of ferritin stores (44,45). However, as mentioned previously, anaphylactic reactions have occurred with administration via this route, hence, test dosing and capability of treating anaphylactic shock is required. Current indications for the use of IV iron include severe anemia, intolerance of oral formulations, inappropriate response, severe intestinal disease activity, concomitant therapy with an erythropoietic agent, or patient preference. The goals of anemia treatment are to increase the Hgb, ferritin, and TS above the lower threshold of normal (46).

ANEMIA AND THE ICU

Anemia is common in ICU patients. In a study of 4,892 patients, the mean Hgb was 11.0 at admission and decreased during the ICU stay to a mean of 8.6 (47). In non-bleeding ICU patients, Hgb concentrations drop by 0.5 g/dL/day over the first three days, with further decreases with sepsis or high APACHE II

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scores (48); phlebotomy removes an average of 41 mL of blood per 24-hour period (49).

Anemia in the ICU is multifactorial: severe gastrointestinal hemorrhage (defined as >300 mL/24 hour period), occurs in 21% of ICU patients (50), reduced red cell survival and production also play a role (51), and hemodilution can occur from increased plasma volume. Additional factors for anemia include inappropriately low erythropoietin levels and abnormal red cell maturation (52,53). Management of anemia with transfusion in this population is controversial due to: concerns regarding the questionable need for a higher Hgb concentration for tissue perfusion (especially in heart failure), the evidence for clinically relevant immune suppression, nosocomial infections in those receiving transfusions, and functional impairment of transfused red cells (54–56).

"Restrictive" transfusion strategies have been proposed for ICU patients. The Transfusion Requirement in Critical Care (TRICC) study randomized over 400 patients to a restrictive strategy when transfusions were given below a Hgb value of 7, or a liberal strategy where transfusions were given for a Hgb <10. There were no differences in overall mortality rate. However, among patients less than 55-years-old or with APACHE II score <20, 30-day mortality rates were significantly improved in the restrictive group (57). Erythropoietin has also been studied in the ICU population, but the expense and lack of survival benefit, have hindered its expansion into standard clinical practice (58). The decision to transfuse requires consideration of the patient's current condition, comorbidity, and risk factors for impaired tissue oxygenation.

The use of intravenous iron has not been studied extensively in the ICU population. However, in ICU situations where correction of iron deficiency anemia is desired, red blood cell transfusion is the preferred method as it allows for correction of the anemia within hours as opposed to weeks with iron infusion alone (20). Intravenous iron infusion may also enhance infectious processes through leukocyte dysfunction, although this has not been studied extensively within the ICU (59). That parenteral iron could increase the risk of infection was first seen in neonates: intramuscular iron-dextran given to Polynesian infants increased the risk of death from *E. coli* sepsis by preventing bacterial killing from serum and leukocyte migration (60). We urge restraint in using parenteral iron for patients with ongoing, or at high-risk for, infections such as those with burns, open wounds, or multi-organ failure.

ANEMIA AND CHRONIC KIDNEY DISEASE (CKD)

The association between chronic kidney disease and anemia is well-documented. Anemia frequently develops when glomerular filtration rate (GFR) drops below 60 mL/min. The prevalence of anemia among those 60-years or older varies from approximately 1% among those with a normal GFR to 33% among men and 66% among women with a GFR of 15 mL/min (61). Anemia in CKD is usually normochromic and normoctyic (62). The predisposition to develop anemia stems from reduced interstitial kidney erythropoietin synthesis (63), and is worsened with blood loss associated with hemodialysis.

In a study of the bone marrow of 47 CKD patients with Hgb <12, all but one was found to be iron deficient (64). Reduced serum ferritin (<25) or transferrin saturation (<16%) may be used to define iron deficient erythropoiesis (65). These parameters are less useful in the hemodialysis (HD) dependent group. Once iron deficiency is identified, iron supplementation should be initiated. In HD-dependent patients, IV iron therapy is strongly recommended due to greater efficacy (66); non-HD dependent patients may use oral therapy. The goal of therapy is to restore the storage compartment, avoid the development of iron deficiency that might be unmasked with erythropoietin-stimulating agents, and to achieve and maintain Hgb levels. Target markers of satisfactory replacement in the HD dependent group include ferritin >200 and transferrin saturation (TS) >20%. In the pre-dialysis patient with renal insufficiency, a ferritin >100 and TS >100 may be used. Iron status tests alone are inadequate in defining appropriate supplementation, as Hgb values and erythropoietin dosing must also be considered.

Recombinant erythropoietin drugs decreased transfusion requirements and improved quality of life in HD patients receiving these drugs (65,66). Two subsequent, well-chronicled studies entitled Cardiovascular Risk Reduction by Early Anemia Treatment with Epo-

etin Beta (CREATE) and Correction of Hgb and Outcomes in Renal Insufficiency (CHOIR) demonstrated that erythropoietin drugs may pose greater risk than benefit (67,68). A large, double-blinded, placebo-controlled trial is currently underway to further examine this issue. Current guidelines recommend the use of erythropoietin stimulating agents to a target Hgb of 11 to 12 mg, not to exceed 13 (69).

SUMMARY

Disorders of iron are commonly encountered in GI practice. Familiarity with the parameters used to define iron deficiency and the appropriate endoscopic and non-endoscopic evaluation are integral to the practice of gastroenterology. Within the IBD, ICU and chronic renal disease patient populations, iron related disorders are especially common and it is incumbent upon the gastroenterologist to understand the unique measures used to define, interpret, and treat these conditions. ■

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