Diagnosis and management of iron deficiency anemia in the 21st century

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***Abstract*:** Iron deficiency is the single most prevalent nutritional deficiency worldwide. It accounts for anemia in 5% of American women and 2% of American men. The goal of this review article is to assist practitioners in understanding the physiology of iron metabolism and to aid in accurately diagnosing iron deficiency anemia. The current first line of therapy for patients with iron deficiency anemia is oral iron supplementation. Oral supplementation is cheap, safe, and effective at correcting iron deficiency anemia; however, it is not tolerated by some patients and in a subset of patients it is insufficient. Patients in whom the gastrointestinal blood loss exceeds the intestinal ability to absorb iron (e.g. intestinal angiodysplasia) may develop iron deficiency anemia refractory to oral iron supplementation. This population of patients proves to be the most challenging to manage. Historically, these patients have required numerous and frequent blood transfusions and suffer end-organ damage resultant from their refractory anemia. Intravenous iron supplementation fell out of favor secondary to the presence of infrequent but serious side effects. Newer and safer intravenous iron preparations are now available and are likely currently underutilized. This article discusses the possible use of intravenous iron supplementation in the management of patients with severe iron deficiency anemia and those who have failed oral iron supplementation.

***Keywords*:** anemia, blood loss, intravenous iron, iron deficiency, therapy

Introduction

Anemia (from the ancient Greek ἀναιμία, *anaimia*, meaning 'lack of blood') is defined by a decrease in the total amount of hemoglobin or the number of red blood cells. Iron deficiency anemia is a form of anemia due to the lack of sufficient iron to form normal red blood cells. Iron deficiency anemia is typically caused by inadequate intake of iron, chronic blood loss, or a combination of both. Iron deficiency anemia is the most common cause of anemia in the world. Approximately 5% and 2% of American women and men, respectively, have iron deficiency anemia [Clark, 2009; Looker *et al.* 1997].

Iron metabolism

Iron is a trace element that is required for numerous cellular metabolic functions. As iron is toxic when present in abundance, tight regulation is required to avoid iron deficiency or iron overload [Anderson *et al.* 2009; Byrnes *et al.* 2002]. The adult body contains 3–4 g of iron. The usual Western diet contains approximately 7 mg of iron per 1000 kcal; however, only 1–2 mg is normally absorbed each day. The human diet contains two forms of iron: heme iron and nonheme iron. Heme iron is derived from meat and is well absorbed. Pancreatic enzymes digest heme to free it from the globin molecule in the intestinal lumen. Iron is then absorbed into the enterocytes as metalloporphyrin and degraded by heme oxygenase-1 to release nonheme iron. Subsequently, iron is exported by ferroportin located on the basolateral aspect of the enterocyte. Nonheme dietary iron, which is found in cereals, beans, and some vegetables, is less well absorbed. Nonheme iron is present as either ferric (Fe^{+2}) or ferrous (Fe^{+3}) iron. The acidic environment of the stomach and certain foods are known to increase the bioavailability of dietary iron [Zhang and Enns, 2009; Schmaier and Petruzzelli, 2003; Conrad and Umbreit, 1993]. Vitamin C, for example, functions to prevent precipitation of ferric iron in the duodenum. Other foods containing plant phytates (grains) and tannins (nonherbal tea) are known to decrease the absorption of nonheme iron [Schmaier and Petruzzelli, 2003; Conrad and Umbreit, 1993].

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After entry of ferric iron into the duodenum it must first be reduced to the ferrous form by duodenal cytochrome b prior to absorption. Duodenal cytochrome b is a reductase located in the brush border of the duodenum and proximal jejunum. Once reduced, the divalent metal transporter 1, the only currently known intestinal iron importer, transports ferrous iron from the proximal small intestinal lumen into the apical membrane of the enterocyte [Zhang and Enns, 2009]. After entry into the cell, ferrous iron may either be stored as ferritin or transverses the cell to the basolateral aspect of the enterocyte where the ferroportin is located. Ferroportin is present in the mucosa of the proximal small intestine, macrophages, hepatocytes, and syncytiotrophoblasts of the placenta. Ferroportin, along with ceruloplasmin and hephaestin, facilitates the reoxidation of ferrous iron to ferric iron, which must occur prior to exportation. Transferrin has a high affinity for ferric iron and binds it so quickly that there is essentially no free iron circulating in the plasma. Binding of iron to transferrin occurs via the apotransferrin receptor pathway [Conrad, 2009; Zhang and Enns, 2009].

Once in the plasma the iron is transported by transferrin to the bone marrow for synthesis of hemoglobin and incorporation into the erythrocytes. Normal erythrocytes circulate for roughly 120 days before being degraded. Senescent red blood cells are engulfed by macrophages in the reticuloendothelial system, primarily in the spleen and liver where they are degraded and catabolized by the cytosolic hemeoxygenase-1 to release the bound iron. Recycling of heme iron from senescent red blood cells is the primary source of iron for erythropoiesis and accounts for delivery of 40–60 mg iron/day to the bone marrow [Hillman and Henderson, 1969]. Some of the iron from senescent red blood cells is also stored in macrophages as ferritin (the major storage form of iron) or hemosiderin (the water-soluble form of iron), and the majority of it is released via ferroportin into the plasma bound to transferrin for recycling. Around 70% of the total body iron is in heme compounds (e.g. hemoglobin and myoglobin), 29% is stored as ferritin and hemosiderin, <1% is incorporated into heme-containing enzymes (e.g. cytochromes, catalase, peroxidase), and <0.2% is found circulating in the plasma bound to transferrin [Zhang and Enns, 2009; Schmaier and Petruzzelli, 2003]. During states of intravascular hemolysis, red blood cells are destroyed and hemoglobin is released into the plasma. Haptoglobin is a protein synthesized primarily in the liver and functions to bind free hemoglobin. The hemoglobin–haptoglobin complex is then removed by the reticuloendothelial system and the iron salvaged. The binding potential of haptoglobin is limited by the amount of circulating molecules and quickly becomes saturated in moderate to severe hemolytic states.

No physiologic mechanism for iron excretion exists and only 1–2 mg of iron is lost each day as a result of sloughing of cells (i.e. from the mucosal lining of the gastrointestinal tract, skin, and renal tubules). In women, approximately 0.006 mg iron/kg/day is lost during normal menstruation [Schmaier and Petruzzelli, 2003]. Thus, normally iron loss and gain is in balance with the amount lost daily being equal to the amount absorbed daily. The body has the ability to increase intestinal iron absorption dependent on the body iron needs. When the pendulum swings towards more iron being lost than is absorbed, iron stores become depleted and the patient develops iron deficiency. If the process continues the patient develops iron deficiency anemia. Iron deficiency is associated with upregulation of iron absorption from the gut by way of an increase in the production of key proteins, such as duodenal cytochrome b, divalent metal transporter 1, and ferroportin. Hypoxia-inducible, factor-mediated signaling and iron regulatory proteins also play critical roles in the local regulation of iron absorption. Hypoxia-inducible factor-signaling upregulates the expression of duodenal cytochrome b and divalent metal transporter 1; iron regulatory proteins upregulate the expression of divalent metal transporter 1 and ferroportin. These two pathways are vital for the enhancement of iron absorption associated with iron deficiency [Zhang and Enns, 2009]. Within limits, iron absorption enhancement is proportional to the degree of iron deficiency (i.e. the synthesis of key proteins, such as transferrin receptor, divalent metal transporter 1, ferritin, and ferroportin, is regulated in an iron-dependent manner) [Byrnes *et al.* 2002]. This system is checked by hepcidin, a hormone that is synthesized in the liver, secreted into the blood, and systemically controls the rate of iron absorption as well as its mobilization from stores (Figure 1). Hepcidin binds to, and negatively modulates, the function of ferroportin. Janus kinase 2 is activated upon binding of hepcidin to ferroportin and results in the internalization,

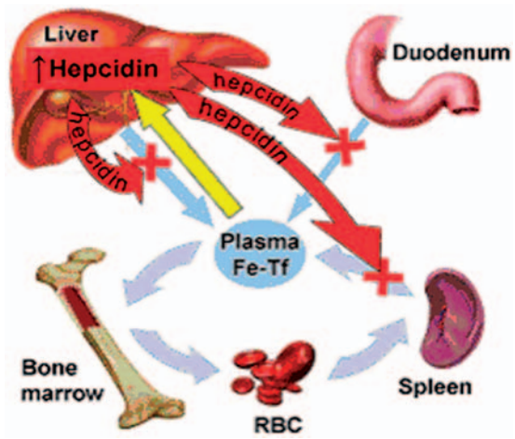


Figure 1. The role of hepcidin in normal iron homeostasis: an increase in plasma iron causes an increase in hepcidin production (yellow arrow). Elevated hepcidin inhibits iron flow into the plasma from the macrophages, hepatocytes, and the duodenum. As the plasma iron continues to be consumed for hemoglobin synthesis, the plasma iron levels decrease and hepcidin production abates, completing the homeostatic loop. (Reprinted with permission from Intrinsic LifeSciences LLC, La Jolla, CA, USA: http://www.intrinsiclifesciences.com/iron_reg/).

ubiquitination, and degradation of ferroportin. Thus, activation of Janus kinase 2 is associated with limiting iron exportation and ultimately decreasing erythropoiesis [De Domenico *et al.* 2009]. Hepcidin expression is most notably suppressed by hypoxia, erythropoietin (a hormone essential for erythrocyte differentiation), twisted gastrulation (a protein secreted by immature red blood cell precursors during the early stages of erythropoiesis), and growth differentiation factor 15 (a protein secreted by erythroblasts during the final stages of erythropoiesis). The synthesis of hepcidin is upregulated by inflammatory cytokines (particularly interleukin-6), irrespective of the total level of iron in the body. This relationship most likely accounts for the development of anemia of chronic disease. The anemia of chronic disease is outside the scope of this discussion [Zhang and Enns, 2009; Schmaier and Petruzzelli, 2003].

Laboratory diagnosis of iron deficiency anemia

The World Health Organization defines anemia as blood hemoglobin values of less than 7.7 mmol/l (13 g/dl) in men and 7.4 mmol/l (12 g/dl) in women. Typically, the evaluation of the cause of anemia includes a complete blood cell count, peripheral smear, reticulocyte count, and serum iron indices. The severity of anemia is based on the patient's hemoglobin/hematocrit level. Iron deficiency anemia is characterized by microcytic, hypochromic erythrocytes and low iron stores. The mean corpuscular volume is the measure of the average red blood cell volume and mean corpuscular hemoglobin concentration is the measure of the concentration of hemoglobin in a given volume of packed red blood cells. The normal reference ranges for mean corpuscular volume is 80–100 fL and mean corpuscular hemoglobin concentration is 320–360 g/l. The patient's cells are said to be microcytic and hypochromic, respectively, when these values are less than the normal reference range. Of note, up to 40% of patients with true iron deficiency anemia will have normocytic erthrocytes (i.e. a normal mean corpuscular volume does not rule out iron deficiency anemia) [Bermejo and Garcia-Lopez, 2009]. The red cell distribution width is a measure of the variation of red blood cell width and is used in combination with the mean corpuscular volume to distinguish an anemia of mixed cause from that of a single cause. The normal reference range is 11–14%; an elevated red cell distribution width value signifies a variation in red cell size, which is known as anisocytosis. The red cell distribution width may be elevated in the early stages of iron deficiency anemia or when a patient has both iron deficiency anemia and folate with or without vitamin B12 deficiencies, which both produce macrocytic anemia. It is not uncommon for the platelet count to be greater than 450,000/μl in the presence of iron deficiency anemia. Upon examination of a patient's peripheral smear with chronic iron deficiency anemia one will typically see hypochromic, microcytic erythrocytes; thrombocytosis may also be apparent. It is important to note that microcytosis visible on the peripheral smear may be seen prior to abnormalities on the complete blood cell count. If the patient has coexistent folate or vitamin B12 deficiency, the peripheral smear will be a mixture of macrocytic and microcytic hypochromic erythrocytes, along with normalization of the mean corpuscular volume.

Iron studies diagnostic for iron deficiency anemia consist of a low hemoglobin (<7.7 mmol/l in men and 7.4 mmol/l in women), a low serum iron (<7.1 μg/l), a low serum ferritin (storage form of iron) (<30 ng/l), a low transferrin saturation (<15%), and a high total iron-binding capacity

(>13.1 μmol/l) [Bermejo and Garcia-Lopez, 2009; Clark, 2009]. The ferritin level may be misleading in the presence of acute or chronic inflammation as ferritin is also an acute phase reactant and thus one cannot exclude iron deficiency as the cause of anemia when the serum ferritin is normal or even elevated in the presence of an inflammatory process [Bermejo and Garcia-Lopez, 2009; Conrad and Umbreit, 1993]. In the presence of an underlying infection or inflammation other iron markers may be useful including the reticulocyte hemoglobin content which, because reticulocytes are only 1–2 days old, is reflective of the iron available in the bone marrow for erythropoiesis. The alternative, which is likely to be more readily available, is the measurement of soluble transferrin receptor. In the setting of iron deficiency with increased erythroid activity (e.g. following administration of exogenous erythropoiesis stimulating agents), there is increased expression of membrane transferrin receptors in the bone marrow and some of these receptors are detectable in the serum. The limitations are that it is not as reliable as ferritin, it is not yet widely available, and the clinician must exclude other causes of elevated erythroid activity [Wish, 2006]. When all else fails and it is important to establish whether iron deficiency is present, demonstration of the absence of stainable iron via a bone marrow biopsy remains the gold standard for diagnosis.

Causes of iron deficiency anemia

In developing countries, low iron bioavailability of the diet is the primary cause of iron deficiency anemia [Berger and Dillon, 2002; Yip and Ramakrishnan, 2002]; however, in developed countries, decreased iron absorption and blood loss account for the more likely etiologies of iron deficiency. Decreased iron absorption may also be the result of atrophic gastritis or malabsorption syndromes especially celiac disease [Bermejo and Garcia-Lopez, 2009]. Postsurgical gastrectomy (partial or total) and intestinal resection or bypass may also produce iron deficiency anemia secondary to decreased iron absorption. Chronic blood loss from genitourinary, gynecological, or gastrointestinal tracts accounts for the majority of causes for iron deficiency anemia. The most common etiology of iron deficiency anemia in premenopausal women is excessive menstruation.

Gastrointestinal bleeding is a common cause of iron deficiency anemia, whether the bleeding is acute or chronic. Patients may present with maroon-colored stools or blood in their stools with brisk bleeding but more often the blood loss is unrecognized by the patient as blood loss up to 100 ml/day from the gastrointestinal tract may be associated with normal-appearing stools [Rockey, 2005]. The physiologic response of the small bowel to bleeding will be to increase iron absorption by twofold to threefold by upregulation of proteins duodenal cytochrome b, divalent metal transporter 1, ferroportin, and downregulation of hepcidin. However, iron loss greater than 5 mg/day over a prolonged period of time exceeds this compensatory response; the patient's iron stores will become depleted and iron deficiency anemia ensues [Rockey, 1999]. Chronic gastrointestinal bleeding is associated with a variety of lesions and can occur at any location within the gastrointestinal tract. Iron deficiency anemia is especially prone to occur in those taking aspirin or nonsteroidal anti-inflammatory drugs chronically. For those with angiodysplasia or other structural lesions, the site can often be visualized by endoscopic evaluation (e.g. video capsule endoscopy) of the gastrointestinal tract. However, in 10–40% of patients with occult gastrointestinal bleeding the cause remains obscure [Till and Grundman, 1997; Rockey and Cello, 1993].

Oral iron therapy and its limitations

Traditionally hemodynamically stable patients with iron deficiency anemia resultant from chronic blood loss from the gut are prescribed oral iron therapy. The two categories of iron supplements are those containing the ferrous form of iron and those containing the ferric form of iron. The most widely used iron supplements are those that contain the ferrous form of iron given that it is the better absorbed of the two. The three commonly administered types of ferrous iron supplements: ferrous fumarate, ferrous sulfate, and ferrous gluconate, which differ in the amount of elemental iron (the form of iron in the supplement that is available for absorption by the body), and contain 33%, 20%, and 12% iron, respectively (NIH, 2010). Recent studies have suggested that these iron preparations are essentially equivalent in terms of bioavailability [Harrington *et al.* 2011; Navas-Carretero *et al.* 2007; Lysionek *et al.* 2003]. The recommended daily dose of treatment by the Centers for Disease Control and Prevention (CDC) ranges from 150 mg/day to 180 mg/day of elemental iron administered in divided doses two to three times a day [CDC, 1998]. The reticulocyte count

begins to increase within the first week of iron therapy, whereas the hemoglobin usually trails by 1–2 weeks [National Institutes of Health, 2010; Provenzano *et al.* 2009]. Oral iron supplements are desirable as first-line therapy as they are safe, cheap, and effective in restoring iron balance in the average chronic gastrointestinal bleeder.

Therapy with iron supplements may be limited by gastrointestinal side effects, such as abdominal discomfort, nausea, vomiting, constipation, and dark colored stools. Enteric-coated and delayed-release iron supplements have been developed to increase compliance as they are associated with fewer side effects; however, they are not as well absorbed as the nonenteric-coated preparations [Provenzano *et al.* 2009].

Physicians are often faced with the challenge of managing iron deficiency anemia with oral iron when a patient's iron losses exceed the maximum amount of iron that the gut is able to absorb. It is this group of patients that generally requires repeated transfusions and suffers end-organ damage as the patients are not able to replenish their iron stores with oral supplementation alone. One of the most challenging groups of patients is those patients that suffer from chronic gastrointestinal bleeding secondary to vascular angiodysplasias. These patients typically have multiple lesions that occur in clusters and/or scattered throughout the gastrointestinal tract, and frequently rebleed resulting in chronic iron deficiency anemia [Boley *et al.* 1979; Clouse *et al.* 1985]. When the patient's gastrointestinal blood loss results in more iron loss than that which they are able to absorb from the gut, these patients develop anemia that is clinically refractory to oral iron therapy. It is then that physicians are faced with starting the patient on parenteral iron therapy.

Intravenous iron therapy and its limitations

Intravenously administered iron is one approach to replacing iron losses in patients with chronic gastrointestinal bleeding in which blood loss exceeds 10 ml/day (around 5 mg iron). With the use of intravenous iron the desired serum iron levels, in which the marrow production can increase by fourfold to eightfold, can be achieved [Werner *et al.* 1977]. Hillman and Henderson previously showed that the maximum iron delivery from reticuloendothelial iron stores is 40–60 mg of iron/day to the bone marrow for erythropoesis [Hillman and Henderson, 1969]. Supplementation with oral iron provides 60–80 mg iron/day, whereas intravenous iron or nonviable red cells provide 80–160 mg iron/day. They found that the maximum red blood cell production achieved by patients with a mean serum iron less than 70 μg/100 ml was between 2.5 and 3.5 times normal. With oral iron supplementation, patients were able to achieve serum iron values between 70 μg/100 ml and 150 μg/100 ml, and red blood cell production was able to increase to four to five times normal. Only when nonviable red cells or intravenous iron dextran was administered was the iron supply sufficient to increase the serum iron to values greater than 200 μg/100 ml with a concomitant increase in marrow production to 4.5–7.8 times normal (Figure 2). It is important to note that this response was transient lasting only 7–10 days as the excess iron was subsequently sequestered in the reticuloendothelial system. The physician can

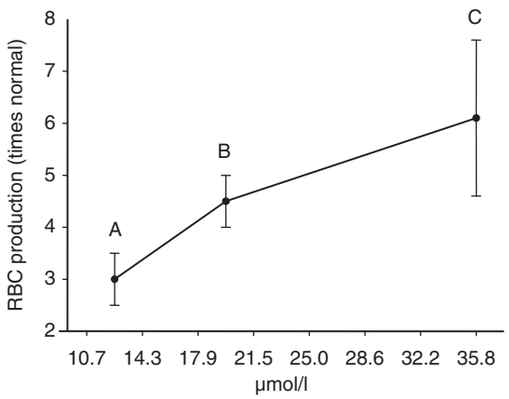


Figure 2. Response of the bone marrow in relation to the level of serum iron. The marrow response is directly associated to the serum iron level (based on a hematocrit level of 25–27%). A is the response of the bone marrow to the body's physiological increase in iron absorption from the gut in response to iron deficiency. A mean serum iron level <12.5 μmol/l is associated with an increase in RBC production, which ranges from 2.5 to 3.5 times the normal marrow response. B indicates a serum iron level of 12.5–26.8 μmol/l can be achieved with oral iron supplementation (i.e. 300 mg of ferrous gluconate every 2 h while awake), which is associated with an increase in bone marrow production of RBCs 4–5 times normal. C indicates a serum iron level >35.8 μmol/l was achieved by administration of intravenous iron dextran or nonviable red cells. This resulted in an increase in RBC production 4.5–7.8 times the normal marrow response. RBC, red blood cell.

estimate a patient's total iron deficit and then decide how much to administer intravenously (Table 1).

Iron dextran has since been replaced by newer safer iron preparations. Available intravenous iron preparations in the USA include iron dextran (INFeD® or DexFerrum®), iron sucrose (Venofer®), sodium ferric gluconate (Ferrlecit®), and ferumoxytol (Feraheme®). Iron dextran is the oldest of these and has the advantage of total dose infusion (ability to infuse the patient's total iron requirement in one administration) and lowest cost. It fell out of favor because of its association with fatalities secondary to anaphylactic reactions, with an incidence of 0.6–0.7%. Sodium ferric gluconate and iron sucrose are more bioavailable and have a lower incidence of life-threatening anaphylaxis (0.04% and 0.002%, respectively); these preparations are significantly more expensive than iron dextran and require repeated infusions to replace the lost iron stores. However, it is important to note that the administration of repeated injections has the potential advantage of allowing one to tailor the dose to maintain red blood cell production at a maximum with limited sequestration in the reticuloendothelial system. Some of the additional reported adverse events associated with each of the iron preparations are hypotension, arthralgias, myalgias, malaise, abdominal pain, nausea, and vomiting. These nonlife-threatening adverse reactions are also more commonly associated with iron dextran and less so with iron sucrose or sodium ferric gluconate (50%, 36%, 35%, respectively) (Table 2) [Silverstein and Rodgers, 2004]. Ferumoxytol provides 510 mg of iron per infusion and thus allows the physician to give patients large doses of iron with fewer infusions [De Domenico *et al.* 2009]. Intravenous iron formulations are now most commonly used in hemodialysis patients and there is a great deal of literature regarding the use of intravenous iron in patients with endstage renal disease. Regular infusions of intravenous iron may also allow improved management of patients with iron deficiency anemia refractory to oral iron therapy, especially those with anemia as a result of chronic gastrointestinal blood loss. However, there is a scarcity of

Table 1. Formula to calculate iron requirement to replete iron stores in adults.

Formula*
Elemental iron (mg) = 50 × [0.442 (desired Hgb g/L minus observed Hgb g/L) × lean body weight (see below for men and women) + 0.26 × lean body weight]
Lean body weight
For men: lean body weight = 50 kg + 2.3 kg for each inch in height over 60 inches
For women: lean body weight = 45.5 kg + 2.3 kg for each inch in height over 60 inches
Note: use actual body weight if lean body weight is less than actual weight.
Intravenous iron preparations (mg elemental iron/ml)
Iron dextran = 50 mg
Iron sucrose: = 20 mg
Sodium ferric gluconate = 12.5 mg
Ferumoxytol = 30 mg
*The formula was derived from: iron dextran injection calculator by David McAuley, GlobalRPh http://www.globalrph.com/iron-dextran.htm with permission

Table 2. Comparison of intravenous iron preparations available in the USA.

	Iron dextran	Iron sucrose	Sodium ferric gluconate	Ferumoxytol
Infusion dose	100 mg	100 mg	125 mg	510 mg
Test dose required	Yes	No	No	No
Rate of injection*	100 mg given over 2 min (50 mg/min)	100 mg given over 2–5 min (20–50 mg/min)	125 mg given over 10 min (12.5 mg/min)	510 mg given over 17 s (30 mg/s)
Rate of infusion (in 0.9% NaCl)*	Not FDA approved	100 mg/100 ml 0.9% NaCl given over 15 min	125 mg/100 ml 0.9% NaCl over 1 h	Not FDA approved

*Injection/infusion rates are based on studies in hemodialysis dependent-chronic kidney disease patients. FDA, US Food and Drug Administration.

literature in support of intravenous iron *versus* oral iron in the medical management of anemia associated with chronic intestinal bleeding and details of administration (doses, interval, factors to assess when the next dose is needed, etc.) are lacking. Comparative studies of the different intravenous iron preparations have not been carried out in terms of sustaining the hemoglobin levels among those with chronic blood loss and are sorely needed to provide physicians with good practice-based guidelines.

Research questions include the therapeutic doses and frequency of iron infusions indicated, as well as, which indices are best to guide therapy and identify when additional infusions are necessary. Many physicians remain hesitant in implementing intravenous iron therapy in patients with chronic blood loss from the gut. Until we are able to get answers to these questions, many patients with chronic gastrointestinal bleeding will continue to receive substandard therapy for iron deficiency anemia and suffer end-organ damage because of chronic anemia.

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Conflict of interest statement

The authors have no potential conflicts of interest with regard to this work.

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