Management of Iron Deficiency Anemia

Kristine Jimenez, MD, Stefanie Kulnigg-Dabsch, MD, and Christoph Gasche, MD

Dr Jimenez is a fellow in gastroenterology, Dr Kulnigg-Dabsch is a specialist in internal medicine, and Dr Gasche is a specialist in internal medicine, gastroenterology, and hepatology and is an associate professor at the Medical University of Vienna in Vienna, Austria. Dr Gasche is also the founder and head of Loha for Life, Centre of Excellence for Iron Deficiency in Vienna, Austria.

Address correspondence to: Dr Christoph Gasche Division of Gastroenterology and Hepatology Medical University of Vienna Währinger Gürtel 18-20 1090 Vienna Austria Tel: +43-1-40400-47640 Fax: +43-1-40400-47350 E-mail: christoph.gasche@meduniwien.ac.at

Keywords

Anemia of chronic disease, intravenous iron, iron deficiency anemia, iron replacement therapy, oral iron, hemoglobin Abstract: Anemia affects one-fourth of the world's population, and iron deficiency is the predominant cause. Anemia is associated with chronic fatigue, impaired cognitive function, and diminished well-being. Patients with iron deficiency anemia of unknown etiology are frequently referred to a gastroenterologist because in the majority of cases the condition has a gastrointestinal origin. Proper management improves quality of life, alleviates the symptoms of iron deficiency, and reduces the need for blood transfusions. Treatment options include oral and intravenous iron therapy; however, the efficacy of oral iron is limited in certain gastrointestinal conditions, such as inflammatory bowel disease, celiac disease, and autoimmune gastritis. This article provides a critical summary of the diagnosis and treatment of iron deficiency anemia. In addition, it includes a management algorithm that can help the clinician determine which patients are in need of further gastrointestinal evaluation. This facilitates the identification and treatment of the underlying condition and avoids the unnecessary use of invasive methods and their associated risks.

nemia affects one-fourth of the world's population, accounting for 8.8% of the total global burden of disease.^{1,2} Iron deficiency Lis the predominant cause of anemia across countries and in both sexes, with women more commonly afflicted.^{1,2} The prevalence of anemia increases with age³ and in the hospital setting. Anemia decreases the capacity for work and increases health care costs.^{4,5} Iron deficiency is also associated with restless legs syndrome (RLS), diminished quality of life, fatigue, impaired cognitive function, and infertility, all of which may occur in the absence of anemia and may be reversed with iron therapy.⁶⁻²¹ Gastrointestinal conditions, such as celiac disease and inflammatory bowel disease (IBD), as well as chronic kidney disease (CKD), cancer, and chronic heart failure (CHF) increase the risk for anemia and iron deficiency,²²⁻³⁰ and iron deficiency may influence clinical outcome. In CHF, iron deficiency is associated with an increased risk of mortality, regardless of the hemoglobin (Hb) level.^{29,30} Iron deficiency is also associated with reactive thrombocytosis, potentially increasing the risk for thromboembolic events.³¹⁻³⁸



Figure. A proposed algorithm for the management of iron deficiency anemia (IDA).

^a Endurance athletes and pregnant women should be treated without further diagnostic testing.

^b Celiac serology, anti-parietal cell antibody, *Helicobacter pylori* (stool), and fecal occult blood test.

EGD, esophagogastroduodenoscopy; GI, gastrointestinal; Hb, hemoglobin; IV, intravenous; Ob/Gyn, obstetrics/gynecology.

Patients with iron deficiency anemia of uncertain etiology are usually referred to a gastroenterologist because gastrointestinal conditions are the most common causes,³⁹⁻⁴³ with only menstrual blood loss in premenopausal women a more frequent cause. This article concurs with most of the recommendations of the British Society of Gastroenterology⁴⁴; however, we propose an alternative, streamlined management algorithm (Figure).

Pathophysiology

Anemia resulting from iron-restricted erythropoiesis occurs through several mechanisms. In pure iron deficiency, depleted iron stores are due to an imbalance between iron uptake and utilization. Anemia may not be present initially because of iron recycling from erythrocyte turnover. However, iron deficiency alone is associated with fatigue and RLS, so patients may be symptomatic without anemia.¹⁶⁻¹⁸ The persistence of a negative balance leads to microcytic and hypochromic anemia. Adequate iron repletion and management of the cause of iron deficiency (Table 1) lead to resolution.

Functional iron deficiency, in contrast, is due to impaired iron release into the circulation from entero-

cytes, macrophages, or hepatocytes. Erythropoiesis is iron restricted; anemia develops despite adequate iron stores, and erythrocytes may appear normocytic or microcytic.⁴⁵ This is the basis of anemia of chronic disease (ACD), in which inflammation leads to the overexpression of hepcidin, blocking the absorption of iron by enterocytes and its release from macrophages and hepatocytes.^{45,46} Thus, oral iron is ineffective, and intravenous iron is preferred. In certain patients (eg, those with IBD), the combination of iron deficiency and inflammation may result in significant anemia, which must be considered during management and therapy.

Diagnosis

The World Health Organization defines anemia as a level of Hb below 13.0 g/dL in male adults, below 12.0 g/dL in female adults who are not pregnant, and below 11.0 g/dL in pregnant women.⁴⁷ Hb levels may vary across age and race,⁴⁸ so care must be taken, particularly in the interpretation of borderline values. Furthermore, smokers and inhabitants of higher altitudes may have higher baseline Hb levels,^{49,50} and participation in endurance sports may alter Hb levels.⁵¹

Table 1. Causes of Iron Deficiency

Diminished Uptake

Malabsorption

- Celiac disease
- Duodenal resection/gastric bypass surgery
- Inflammatory bowel disease (ileal-jejunal disease and/or anemia of chronic disease)
- *Helicobacter pylori* gastritisAutoimmune gastritis

Dietary causes

- Malnutrition
- High intake of phytates, polyphenols

Increased Demand

- Pregnancy, lactation
- Childhood
- Erythropoiesis-stimulating agents (in chronic kidney disease, chemotherapy-induced anemia)

Enhanced Loss

Gynecologic causes

- Meno(metro)rrhagia (myoma, endometriosis, bleeding disorders)
- Uterine cancer

Gastrointestinal causes

- Malignancy
- Upper gastrointestinal blood loss
- Gastric/duodenal ulcer
- Variceal bleeding
- Esophagitis, erosive gastritis
- Mallory-Weiss syndrome
- Angiodysplasia, vascular ectasia
- Dieulafoy lesions
- Rare: Meckel diverticula, Cameron lesions
- Lower gastrointestinal blood loss
- Diverticulosis/diverticulitis
- Hemorrhoids, anal fissures, rectal ulcers
- Angiodysplasia
- Inflammatory bowel disease
- Infectious colitis

Other causes

- Surgery, trauma, childbirth, blood donation
- Prolonged nonsteroidal anti-inflammatory drug use
- Parasitic infection (eg, hookworm, tapeworm)

Rare Causes

- Idiopathic pulmonary hemosiderosis
- Hereditary hemorrhagic telangiectasia
- Coagulation disorders, platelet dysfunction
- Congenital iron deficiency (iron-refractory iron deficiency anemia)

The mean corpuscular Hb and mean corpuscular volume distinguish macrocytic anemia from iron deficiency anemia, which is hypochromic and typically microcytic. Deficiencies of multiple nutrients (eg, malabsorption) or the use of thiopurine medications (eg, azathioprine in IBD) can lead to a combination of iron deficiency anemia and macrocytosis, with resultant normocytic anemia. In this situation, a wide red cell distribution width aids identification of the iron deficiency component.⁵² The platelet and leukocyte counts help to rule out pancytopenia. Thalassemia traits also present with microcytic, hypochromic anemia and should be considered in populations in which these traits are highly prevalent. Further parameters to diagnose iron deficiency are the transferrin saturation (TfS), which reflects the iron available for erythropoiesis, and the serum level of ferritin, an iron storage protein.53,54 A TfS below 20% and a ferritin level lower than 30 ng/mL are indicative of iron deficiency. However, ferritin is an acute phase protein that increases during inflammation. Inflammatory parameters such as C-reactive protein help identify these situations. Different cutoff values are used in the presence of inflammatory comorbidities-such as IBD (<100 ng/mL),^{53,54} CKD (<500 ng/mL plus TfS <30%),⁵⁵ and CHF (<100 ng/mL or <100-299 ng/mL plus TfS <20%)⁵⁶—to diagnose iron deficiency. If the diagnosis remains unclear, the soluble transferrin receptor (sTfR) and sTfR/log ferritin index (<1) can be used to distinguish between iron deficiency anemia and ACD because the sTfR is elevated only in iron deficiency anemia.⁵⁷⁻⁵⁹

Management of Iron Deficiency Anemia

There is clear evidence to support prompt treatment in all patients with iron deficiency anemia because it is known that treatment improves quality of life and physical condition as well as alleviates fatigue and cognitive deficits.⁸⁻²⁰ Although clear evidence is lacking, iron deficiency without anemia is associated with RLS and chronic fatigue, and treatment alleviates these symptoms.^{7,14-18} In CHF, iron replacement therapy has been shown to be beneficial, even when anemia is not present.^{8,12-14} Thus, the decision to treat iron deficiency in a patient without manifest anemia must be made on an individual basis.^{53,54} The treatment of iron deficiency anemia in patients with CKD, CHF, or cancer should be undertaken in conjunction with the appropriate specialists because different guidelines may apply.

Oral Iron

Intestinal iron absorption is limited. The maximum rate of absorption of 100 mg of oral iron is 20% to 25% and is reached only in the late stage of iron deficiency. Latent iron deficiency and iron deficiency anemia correspond to mean absorption rates of 10% and 13%, respectively, whereas healthy males absorb 5% and healthy females 5.6%.⁶⁰ Iron that remains in the intestinal lumen may cause mucosal injury,^{61,62} and studies in animal models suggest an exacerbation of disease activity and the induction of carcinogene-

sis in IBD.⁶³ Furthermore, dose-dependent gastrointestinal side effects hinder compliance and result in nonadherence in up to 50% of patients.⁶⁴ Thus, it is reasonable to adjust the dosage to improve tolerability. Although doses typically range from 100 to 200 mg of elemental iron per day, successful repletion can be achieved with doses as low as 15 to 30 mg of elemental iron daily.⁶⁵⁻⁶⁷ Several formulations are available over the counter and are typically composed of ferrous iron salts (eg, ferrous sulfate, ferrous gluconate, and ferrous fumarate).

Oral iron supplementation is effective when intestinal uptake is intact. However, its use should be limited to patients with mild anemia (Hb, 11.0-11.9 g/dL in nonpregnant women and 11.0-12.9 g/dL in men) because repletion occurs slowly. When faster repletion is desired, intravenous administration is the preferred route. Nevertheless, oral iron is readily available, inexpensive, and convenient, making it a viable treatment option.

The response to therapy should be carefully monitored. The Hb level should increase by 2 g/dL within 4 to 8 weeks, although some patients may report an improved sense of well-being after a few days. If the Hb level does not respond appropriately within this time frame, treatment should be modified (changed to intravenous iron) and the cause of the lack of response evaluated (Figure). Depending on the severity of the deficiency and underlying cause, normalization of the Hb level may take up to 3 months, and it may take longer to replace iron stores (ferritin >100 µg/L).

Intravenous Iron

Intravenous iron is very effective in the treatment of iron deficiency anemia⁶⁸⁻⁷⁴ and should be considered when oral iron is ineffective.⁶⁹⁻⁷¹ The efficacy of oral iron is diminished when uptake through the gut is impaired (eg, in celiac disease, autoimmune gastritis, ACD, or post–gastric or duodenal resection) or when iron losses are large and/or continuous (eg, with menorrhagia, gastrointestinal bleeding, or postsurgery). Diminished patient compliance due to side effects also limits the efficacy of oral iron. In these situations, intravenous iron therapy is preferred because the gut is bypassed, allowing faster repletion (Table 2). Ferritin expression increases shortly after administration and reaches higher levels than with oral iron,⁷¹⁻⁷³ which can diminish the recurrence of iron deficiency anemia in the long term.^{75,76}

The main disadvantage of intravenous iron is the necessity for administration by a health care professional, with the associated costs. Safety was an issue in the past because of an increase in serious adverse events noted with high-molecular-weight iron dextran (HMWID).⁷⁷ This was generalized to include all intravenous formulations; however, a review of the US Food and Drug

Table 2. Oral Vs Intravenous Iron

Oral Iron				
 Pros Available over the counter Convenient Inexpensive Effective when intestinal absorption is not impaired 	 Cons Limited daily intestinal absorption results in slower iron repletion. Dose-dependent gastrointestinal side effects (nausea, vomiting, abdominal pain, constipation) may limit patient compliance. Uptake is impaired in the setting of disease (eg, celiac disease, anemia of chronic disease, autoimmune gastritis). Mucosal injury and/or potential exacerbation of disease activity may occur in inflammatory bowel disease. Alteration of microbiota and tumorigenic potential have been observed.^a 			
Intravenous Iron				
 Pros Fast repletion of iron stores Safe if formulations with dextran are avoided Effective even when intestinal absorption is impaired 	 Cons Requires administration by a health care professional, with associated increased costs Potential for iron overload and transient increase in oxidative stress Potential for anaphylactic reactions with dextran-containing formulations 			

^a Data from animal models.

Administration database from 1998 to 2000 showed that the cumulative rate of serious adverse events for all intravenous formulations excluding HMWID (ie, lowmolecular-weight iron dextran, iron sucrose, and ferric gluconate) is low (<1:200,000).78 Furthermore, a study of ferric carboxymaltose and HMWID revealed similar efficacy, with fewer hypersensitivity reactions for ferric carboxymaltose.⁷⁹ Few studies have directly compared the intravenous formulations in terms of efficacy to recommend the most effective one, but it is advisable to avoid HMWID because of the potential risk of anaphylactic reactions. In the United States and Europe, HMWID has been taken off the market. A test dose is required for all dextran-containing compounds, and if sensitivity to dextran is known, it is also prudent to include a test dose for iron sucrose and iron gluconate (Table 3).

The required dose of parenteral iron was historically calculated with the Ganzoni formula, in which total iron deficit in mg = [body weight in kg × (target Hb – actual Hb in g/dL) × 0.24] + 500.⁸⁰ However, this formula is inconvenient and inconsistently used, and it underestimates iron requirements.^{74,81} The FERGIcor (FERinject

Iron Formulation	Test Dose	Dose Per Session ^a	
High-molecular-weight iron dextran	25 mg (0.5 mL) over 5 minutes, monitor 1 hour	100 mg of iron intravenously at ≤50 mg/min	
Low-molecular-weight iron dextran	25 mg (0.5 mL) over 30 seconds, monitor 1 hour	100 mg of iron intravenously at ≤50 mg/min	
Ferric carboxymaltose	No	750 mg of iron intravenously at 100 mg/min or infusion over 15 minutes. For patients weighing <50 kg (110 lb), maximum of 15 mg of iron per kilogram of body weight	
Ferumoxytol	No	510 mg of iron intravenously at 30 mg/s or infusion over 15 minutes	
Iron sucrose	No	100-200 mg intravenously over 2-5 minutes or infusion over 15 minutes	
Sodium ferric gluconate complex	No	62.5-125 mg intravenously at 12.5 mg/min or infusion over 1 hour	

Table 3.	Intravenous	Iron	Preparations
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^a Dosing based on US prescription label. See label for details.

in GI Disorders to Correct Iron Deficiency) trial compared a simpler dosing scheme with Ganzoni-calculated dosing and found better efficacy and compliance for the simpler regimen.¹⁰ Although this study was conducted in patients with IBD, it can be used as a reference point for general treatment. Patients with more severe anemia (<7.0 g/dL) may require an additional 500 mg of iron.⁵⁴ The treatment of iron deficiency without anemia can be undertaken with 500 to 1000 mg¹⁵ (Table 4). When large amounts of iron are required, ferric carboxymaltose and low-molecular-weight iron dextran are advantageous because higher doses can be administered per infusion,^{8,69,74,82} whereas other formulations (iron sucrose and ferric gluconate) require multiple infusion schedules with increased associated costs (Table 3).

Iron balance is controlled by modifying intestinal uptake, with no active excretion. Thus, care must be taken not to cause iron overload when this regulation is bypassed. Within the first 8 weeks after infusion, the serum ferritin level is highly elevated and does not correlate well with body iron stores.83 Evaluation of the ferritin level should be considered 8 to 12 weeks after the end of treatment. A TfS exceeding 50% is an indicator of iron overload, and treatment should be modified accordingly.⁸⁴ The Hb level should increase by 2 g/dL within 4 to 8 weeks of iron replacement. Patients not responding to intravenous iron are likely to have ACD and may be considered for treatment with erythropoiesis-stimulating agents in addition to intravenous iron. To minimize adverse events, the Hb should be increased to the lowest level needed to avoid transfusion. When erythropoiesis-stimulating agents are used, the target Hb level should not exceed 12 g/dL.54

Blood Transfusion

Blood transfusion should be highly restricted in chronic iron deficiency anemia. It may be considered for patients with active bleeding who are hemodynamically unstable, or for patients with critical anemia (Hb level <7 g/dL), acute myocardial ischemia, or if all other treatments fail to correct the anemia.⁸⁵⁻⁸⁷ In patients with significant cardiovascular disease, higher cutoff values (Hb <8 g/dL) may apply.⁸⁵ Transfusions are only a temporary solution, and proper management should include the identification and treatment of the underlying condition. In addition, intravenous iron (and erythropoiesis-stimulating agents if necessary) should be administered together to correct and maintain the Hb level and iron stores and prevent the need for subsequent transfusions.

Identifying the Cause of Iron Deficiency

Once iron deficiency anemia has been diagnosed, the cause of the iron deficiency should be identified because the underlying condition may require immediate management (eg, a gastrointestinal malignancy) and predispose the patient to recurrence. To reduce unnecessary testing, we have proposed a diagnostic algorithm to distinguish which patients are in need of extensive gastrointestinal evaluation (Figure).

Iron therapy without further diagnostic evaluation may be initiated in endurance athletes, frequent blood donors, and pregnant women, groups that are predisposed to iron deficiency anemia. If anemia is severe, a gastrointestinal cause of iron deficiency may be considered. Adequate iron supplementation during pregnancy prevents complications associated with severe anemia (eg, fetal and/or maternal mortality, prematurity, and spontaneous abortion).⁸⁸ When oral iron exacerbates pregnancyrelated nausea and vomiting, intravenous iron is a safe and effective alternative.⁷² If there is no adequate response to therapy, further gastrointestinal evaluation may be considered after delivery.

Pertinent points in the patient history include diet (eg, vegetarian), nonsteroidal anti-inflammatory drug use,

Degree of Iron Deficiency	Hemoglobin Level, g/dL	Dose for Body Weight <70 kg, mg	Dose for Body Weight ≥70 kg, mg
No anemia	Normal	500	1000
	10-12 (women)		
Moderate	10-13 (men)	1000	1500
Severe	7-10	1500	2000
Critical	<7	2000	2500

Table 4. Simple Scheme for the Estimation of Total Iron Need

Modified from Evstatiev R, et al, with permission.¹⁰

family history of hematologic disorders (thalassemia and bleeding disorders), and recent potential causes of blood loss (eg, childbirth and surgery), as well as a history of gastrointestinal disease.

Gastrointestinal conditions are, collectively, the primary cause of iron deficiency anemia in men and postmenopausal women and are second only to menstrual blood loss in premenopausal women³⁹⁻⁴³ (Table 1). Menorrhagia affects approximately 30% of women of reproductive age.⁸⁹ Inquiry about the number of pads or tampons used per menstrual cycle (>21), frequency of change (more often than every 3 hours), passage of large clots, or the simultaneous use of pads and tampons helps to identify affected patients.⁹⁰ An obstetrician/gynecologist should be consulted for the management of menorrhagia, as well as a hematologist if a coagulation disorder is suspected. Unless the patient fulfills any of the criteria for concurrent high-risk conditions (age 50 years or older, family history of gastrointestinal malignancy, gastrointestinal symptoms, or Hb level <10.0 g/dL; Figure), management can be restricted to iron replacement. Oral iron is effective, but more severe bleeding may require a switch to intravenous products to achieve a positive iron balance. If iron deficiency anemia persists despite intravenous iron therapy and the adequate management of blood loss, further gastrointestinal investigation (at least noninvasive tests; see below) should be considered because gastrointestinal conditions can coexist with menorrhagia.91,92

Patients in whom iron deficiency anemia is diagnosed who are more than 50 years old, who have a family history of gastrointestinal cancer, or who are at increased risk for gastrointestinal malignancy should undergo an evaluation that includes esophagogastroduodenoscopy (EGD) and colonoscopy⁹³⁻⁹⁵ (Figure). Men whose Hb level is below 13.0 g/dL should likewise be investigated because gastrointestinal pathology is likely, and male sex increases the risk for gastrointestinal malignancy.^{42,93,94,96} Similarly, an Hb level below 10.0 g/dL in women increases the likelihood of gastrointestinal pathology and should be investigated.^{43,97} The risk of a more severe underlying pathology, such as cancer, increases as the Hb level falls.^{94,95} Patients who report accompanying gastrointestinal symptoms should undergo more extensive evaluation. If these criteria are not fulfilled but menstrual blood loss cannot account for iron deficiency anemia (eg, after hysterectomy or after menopause), a gastrointestinal investigation should also be considered.

The initial evaluation should include noninvasive screening for celiac disease, Helicobacter pylori infection, and autoimmune atrophic gastritis. These conditions are common causes of refractory iron deficiency anemia because the patients do not respond well to oral iron replacement, and the diagnosis may initially be missed.^{22,23,98-103} A positive screening result facilitates targeted EGD, with the acquisition of appropriate biopsy specimens to confirm the diagnosis and reduce the likelihood that disease has been overlooked (Figure). This is particularly true for patients who have early autoimmune gastritis without vitamin B₁₂ deficiency. Fecal occult blood testing (FOBT) may be useful in identifying patients with iron deficiency anemia who may have gastrointestinal lesions.^{41,93} Although a positive FOBT result in combination with iron deficiency anemia warrants invasive gastrointestinal evaluation, 104,105 a negative test result does not exclude gastrointestinal bleeding and should not preclude EGD/colonoscopy in patients who have fulfilled prior criteria for evaluation. Furthermore, even if only 1 of 3 FOBT results is positive, endoscopic examination is still recommended.

If no criteria for gastrointestinal investigation are fulfilled, patients should be re-evaluated after 4 to 8 weeks of treatment. A switch to intravenous iron and further gastrointestinal investigation should be considered if there is no adequate response to initial therapy.

Long-Term Considerations in the Management of Iron Deficiency

Iron Deficiency and Thrombosis

Iron deficiency is known to be associated with reactive thrombocytosis³¹; however, the mechanism behind this phenomenon remains unclear. Studies in adult women show a correlation between platelet count and TfS,^{32,33} as well as serum iron,³³ and more severe anemia leads to higher counts.³³ Animal models of iron deficiency recapitulate this observation, which occurs with altera-

tions in megakaryopoiesis^{106,107} and augmented platelet aggregability.¹⁰⁷ Altered platelet function has also been found in patients with iron deficiency and was alleviated by iron therapy.^{108,109}

Studies in pediatric as well as adult populations, particularly women, report an association between stroke and iron deficiency anemia.³⁴⁻³⁸ Patients with pulmonary arteriovenous malformations are at higher risk for ischemic strokes, and a low serum level of iron doubles this risk.¹¹⁰ Anemia is common in both cancer and IBD,^{24,28,53} and both increase the risk for venous thromboembolism.^{84,111-113} Thrombocytosis is not uncommon in either condition,¹¹⁴⁻¹¹⁶ and in cancer, a high platelet count is an independent risk factor for venous thromboembolism.^{111,112}

Interestingly, iron therapy in IBD has been shown to normalize platelet counts as well as platelet function.^{117,118} Iron therapy also lowers the platelet count in CKD.¹¹⁹ In cancer, the concurrent administration of intravenous iron and an erythropoiesis-stimulating agent diminishes the incidence of venous thromboembolism more than an erythropoiesis-stimulating agent alone.¹²⁰ Collectively, this suggests that proper iron management can potentially diminish the incidence of thromboembolic events by reducing both platelet number and activity.

Iron Therapy and Carcinogenesis

Iron homeostasis is tightly regulated to protect against redox damage by free iron yet still provide enough iron for erythropoiesis and cellular function. Fe(II) iron reacts with hydrogen peroxide to form highly reactive hydroxyl radicals (Fenton reaction). Hydroxyl radicals react with all biomolecules, and they can damage nucleotide bases and cause DNA strand breaks.^{46,121} One concern in iron therapy is the potential for tumor promotion or progression.

Several NHANES (National Health and Nutrition Examination Survey) studies¹²²⁻¹²⁴ have found that a high TfS (high level of available iron), in combination with high iron intake, increases cancer risk. In contrast, the Swedish AMORIS (Apolipoprotein Mortality Risk) study¹²⁵ found a positive association between total iron-binding capacity, which increases when the level of available iron is low, and cancer risk. Population studies have found an association between a high level of consumption of red meat and increased colorectal cancer risk,^{126,127} but not when the study population is female.^{128,129} These incongruous results are likely due to a variety of other factors, such as geographic differences in diet, prevalence of disease, and prevalence of iron deficiency.

Clinical and animal studies of oral iron (primarily ferrous sulfate) and intravenous iron (primarily iron sucrose and iron gluconate) show an increase in oxidative stress markers in different organ systems (reviewed by Koskenkorva-Frank and colleagues¹²¹). The propensity to induce oxidative stress depends on the amount of free redox-active iron, which in turn depends on drug pharmacokinetics. Intravenous iron compounds vary in stability, with less stable complexes such as iron sucrose and iron gluconate dissociating in circulation, and more stable iron complexes such as ferric carboxymaltose and low-molecular-weight iron dextran remaining intact until broken down in the endolysosome.¹²¹ Potential alternative oral iron compounds have been studied, in which the purportedly less reactive Fe(III) iron is combined with a complex to increase bioavailability (Fe[III] hydroxidepolymaltose and ferric maltol).

Unfortunately, few studies have directly compared drugs, and the long-term consequences of iron therapy with respect to carcinogenesis are as of yet unclear (reviewed by Beguin and colleagues¹³⁰). Nevertheless, the adequate and appropriate administration of iron should diminish the risk of iron oversupply, especially in the context of iron deficiency anemia.

Conclusion

Anemia is highly prevalent in the general population and in the clinical setting. It is associated with diminished quality of life, worsening of clinical outcome, and increased health care costs. Iron deficiency is the predominant culprit, and iron deficiency alone may cause fatigue, RLS, and impaired cognitive function. Iron deficiency anemia should be treated upon diagnosis, and treatment should be considered for iron deficiency without anemia when it is symptomatic. Gastroenterologists have become the central managers of patients with intestinal bleeding or iron malabsorption. They are experts in endoscopic procedures conducted for diagnostic and therapeutic purposes. They should also become experts in iron replacement therapy and be competent in administering iron intravenously when needed.

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References

^{1.} de Benoist B, McLean E, Egli I, Cogswell M, eds. WHO Global Database on Anaemia. Geneva, Switzerland: World Health Organization; 2008.

^{2.} Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood.* 2014;123(5):615-624.

^{3.} Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood.* 2004;104(8):2263-2268.

^{4.} Nissenson AR, Wade S, Goodnough T, Knight K, Dubois RW. Economic burden of anemia in an insured population. *J Manag Care Pharm*. 2005;11(7):565-574.

5. Haas JD, Brownlie T 4th. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *J Nutr.* 2001;131(2S-2):676S-688S; discussion 688S-690S.

6. Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ. The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. *Am J Hematol.* 2013;88(4):261-264.

7. Wang J, O'Reilly B, Venkataraman R, Mysliwiec V, Mysliwiec A. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: a randomized, double-blind, placebo-controlled study. *Sleep Med.* 2009;10(9):973-975.

8. Anker SD, Comin Colet J, Filippatos G, et al; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med.* 2009;361(25):2436-2448.

9. Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. *Inflamm Bowel Dis.* 2006;12(2):123-130.

10. Evstatiev R, Marteau P, Iqbal T, et al. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology*. 2011;141(3):846-853.e1-2.

11. Seid MH, Dahl NV, Lau G, Bernard K, Strauss W. Effect of ferumoxytol on quality of life in iron deficiency anemia from abnormal uterine bleeding. *Obstet Gynecol.* 2014;123(5):181S-182S.

12. Comin-Colet J, Lainscak M, Dickstein K, et al. The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a subanalysis of the FAIR-HF study. *Eur Heart J*. 2013;34(1):30-38.

13. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J.* 2015;36(11):657-668. 14. Avni T, Leibovici L, Gafter-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. *Eur J Heart Fail.* 2012;14(4):423-429.

15. Favrat B, Balck K, Breymann C, et al. Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women—PREFER a randomized, placebo-controlled study. *PLoS One.* 2014;9(4):e94217.

16. Verdon F, Burnand B, Stubi CL, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. *BMJ*. 2003;326(7399):1124.

17. Krayenbuehl PA, Battegay E, Breymann C, Furrer J, Schulthess G. Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration. *Blood.* 2011;118(12):3222-3227.

18. Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet.* 1996;348(9033):992-996.

19. Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status: a longitudinal analysis of cognitive test scores to age 19 years. *Arch Pediatr Adolesc Med.* 2006;160(11):1108-1113.

20. Falkingham M, Abdelhamid A, Curtis P, Fairweather-Tait S, Dye L, Hooper L. The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. *Nutr J.* 2010;9(1):4.

21. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Iron intake and risk of ovulatory infertility. *Obstet Gynecol.* 2006;108(5):1145-1152.

22. Hershko C, Hoffbrand AV, Keret D, et al. Role of autoimmune gastritis, Helicobacter pylori and celiac disease in refractory or unexplained iron deficiency anemia. *Haematologica*. 2005;90(5):585-595.

 Corazza GR, Valentini RA, Andreani ML, et al. Subclinical coeliac disease is a frequent cause of iron-deficiency anaemia. *Scand J Gastroenterol.* 1995;30(2):153-156.
 Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. *Aliment Pharmacol Ther.* 2006;24(11-12):1507-1523.

25. Gasche C. Anemia in IBD: the overlooked villain. *Inflamm Bowel Dis.* 2000;6(2):142-150.

26. De Nicola L, Minutolo R, Chiodini P, et al; SIN-TABLE CDK Study Group. Prevalence and prognosis of mild anemia in non-dialysis chronic kidney disease: a prospective cohort study in outpatient renal clinics. *Am J Nephrol.* 2010;32(6):533-540.

27. Minutolo R, Locatelli F, Gallieni M, et al; REport of COmorbidities in non-Dialysis Renal Disease Population in Italy (RECORD-IT) Study Group. Anaemia management in non-dialysis chronic kidney disease (CKD) patients: a multicentre prospective study in renal clinics. *Nephrol Dial Transplant*. 2013;28(12):3035-3045.

28. Baribeault D, Auerbach M. Iron replacement therapy in cancer-related anemia. *Am J Health Syst Pharm.* 2011;68(10 suppl 1):S4-S14; quiz S15-S16.

 Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J.* 2010;31(15):1872-1880.
 Klip IT, Comin-Colet J, Voors AA, et al. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J. 2013;165(4):575-582.e3.

31. Dan K. Thrombocytosis in iron deficiency anemia. *Intern Med.* 2005;44(10):1025-1026.

32. Kadikoylu G, Yavasoglu I, Bolaman Z, Senturk T. Platelet parameters in women with iron deficiency anemia. *J Natl Med Assoc.* 2006;98(3):398-402.

33. Park MJ, Park PW, Seo YH, et al. The relationship between iron parameters and platelet parameters in women with iron deficiency anemia and thrombocytosis. *Platelets.* 2013;24(5):348-351.

34. Keung YK, Owen J. Iron deficiency and thrombosis: literature review. *Clin Appl Thromb Hemost.* 2004;10(4):387-391.

35. Chang YL, Hung SH, Ling W, Lin HC, Li HC, Chung SD. Association between ischemic stroke and iron-deficiency anemia: a population-based study. *PLoS One*. 2013;8(12):e82952.

36. Maguire JL, deVeber G, Parkin PC. Association between iron-deficiency anemia and stroke in young children. *Pediatrics*. 2007;120(5):1053-1057.

37. Azab SF, Abdelsalam SM, Saleh SH, et al. Iron deficiency anemia as a risk factor for cerebrovascular events in early childhood: a case-control study. *Ann Hematol.* 2014;93(4):571-576.

38. Gillum RF, Sempos CT, Makuc DM, Looker AC, Chien CY, Ingram DD. Serum transferrin saturation, stroke incidence, and mortality in women and men. The NHANES I Epidemiologic Followup Study. National Health and Nutrition Examination Survey. *Am J Epidemiol.* 1996;144(1):59-68.

39. Cook IJ, Pavli P, Riley JW, Goulston KJ, Dent OF. Gastrointestinal investigation of iron deficiency anaemia. *Br Med J (Clin Res Ed)*. 1986;292(6532):1380-1382.

40. Kepczyk T, Kadakia SC. Prospective evaluation of gastrointestinal tract in patients with iron-deficiency anemia. *Dig Dis Sci.* 1995;40(6):1283-1289.

41. Green BT, Rockey DC. Gastrointestinal endoscopic evaluation of premenopausal women with iron deficiency anemia. *J Clin Gastroenterol.* 2004;38(2):104-109.

42. Carter D, Levi G, Tzur D, Novis B, Avidan B. Prevalence and predictive factors for gastrointestinal pathology in young men evaluated for iron deficiency anemia. *Dig Dis Sci.* 2013;58(5):1299-1305.

43. Carter D, Maor Y, Bar-Meir S, Avidan B. Prevalence and predictive signs for gastrointestinal lesions in premenopausal women with iron deficiency anemia. *Dig Dis Sci.* 2008;53(12):3138-3144.

44. Goddard AF, James MW, McIntyre AS, Scott BB; British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. *Gut.* 2011;60(10):1309-1316.

45. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005;352(10):1011-1023.

Evstatiev R, Gasche C. Iron sensing and signalling. *Gut.* 2012;61(6):933-952.
 Assessing the Iron Status of Populations. 2nd ed. Geneva, Switzerland: World Health Organization; 2007.

 Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood*. 2006;107(5):1747-1750.
 Cook JD, Boy E, Flowers C, Daroca MC. The influence of high-altitude living

on body iron. *Blood.* 2005;106(4):1441-1446. 50. Nordenberg D, Yip R, Binkin NJ. The effect of cigarette smoking on hemoglo-

bin levels and anemia screening. JAMA. 1990;264(12):1556-1559.
 Dickson DN, Wilkinson RL, Noakes TD. Effects of ultra-marathon training

and racing on hematologic parameters and serum ferritin levels in well-trained athletes. *Int J Sports Med.* 1982;3(2):111-117.

52. Oustamanolakis P, Koutroubakis IE, Messaritakis I, Kefalogiannis G, Niniraki M, Kouroumalis EA. Measurement of reticulocyte and red blood cell indices in the evaluation of anemia in inflammatory bowel disease. *J Crohns Colitis.* 2011;5(4):295-300.

53. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis.* 2007;13(12):1545-1553.

54. Dignass AU, Gasche C, Bettenworth D, et al; European Crohn's and Colitis Organisation [ECCO]. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis*. 2015;9(3):211-222.

55. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int.* 2012;2012(suppl 2012):2279-2335.

56. McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012;33(14):1787-1847.

57. Beguin Y. Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. *Clin Chim Acta*. 2003;329(1-2):9-22.

58. Skikne BS, Punnonen K, Caldron PH, et al. Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: a prospective multicenter evaluation of soluble transferrin receptor and the sTfR/log ferritin index. *Am J Hematol.* 2011;86(11):923-927.

59. Infusino I, Braga F, Dolci A, Panteghini M. Soluble transferrin receptor (sTfR) and sTfR/log ferritin index for the diagnosis of iron-deficiency anemia. A metaanalysis. *Am J Clin Pathol.* 2012;138(5):642-649.

Werner E, Kaltwasser JP, Ihm P. Intestinal absorption from therapeutic iron doses (author's transl) [in German]. *Arzneimittelforschung*. 1976;26(11):2093-2100.
 de Silva AD, Tsironi E, Feakins RM, Rampton DS. Efficacy and tolerability of oral iron therapy in inflammatory bowel disease: a prospective, comparative trial. *Aliment Pharmacol Ther*. 2005;22(11-12):1097-1105.

62. Abraham SC, Yardley JH, Wu TT. Erosive injury to the upper gastrointestinal tract in patients receiving iron medication: an underrecognized entity. *Am J Surg Pathol.* 1999;23(10):1241-1247.

63. Seril DN, Liao J, Ho KL, Warsi A, Yang CS, Yang GY. Dietary iron supplementation enhances DSS-induced colitis and associated colorectal carcinoma development in mice. *Dig Dis Sci.* 2002;47(6):1266-1278.

64. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS One.* 2015;10(2):e0117383.

65. Zhou SJ, Gibson RA, Crowther CA, Makrides M. Should we lower the dose of iron when treating anaemia in pregnancy? A randomized dose-response trial. *Eur J Clin Nutr.* 2009;63(2):183-190.

66. Makrides M, Crowther CA, Gibson RA, Gibson RS, Skeaff CM. Efficacy and tolerability of low-dose iron supplements during pregnancy: a randomized controlled trial. *Am J Clin Nutr.* 2003;78(1):145-153.

67. Rimon E, Kagansky N, Kagansky M, et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med.* 2005;118(10):1142-1147.

68. Koutroubakis IE, Oustamanolakis P, Karakoidas C, Mantzaris GJ, Kouroumalis EA. Safety and efficacy of total-dose infusion of low molecular weight iron dextran for iron deficiency anemia in patients with inflammatory bowel disease. *Dig Dis Sci.* 2010;55(8):2327-2331.

69. Onken JE, Bregman DB, Harrington RA, et al. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. *Transfusion*. 2014;54(2):306-315.

70. Rozen-Zvi B, Gafter-Gvili A, Paul M, Leibovici L, Shpilberg O, Gafter U. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: systematic review and meta-analysis. *Am J Kidney Dis.* 2008;52(5):897-906.

71. Lindgren S, Wikman O, Befrits R, et al. Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: a randomized, controlled, evaluator-blind, multicentre study. *Scand J Gastroenterol*, 2009:44(7):838-845.

72. Khalafallah A, Dennis A, Bates J, et al. A prospective randomized, controlled trial of intravenous versus oral iron for moderate iron deficiency anaemia of pregnancy. *J Intern Med.* 2010;268(3):286-295.

73. Schröder O, Mickisch O, Seidler U, et al. Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease—a randomized, controlled, open-label, multicenter study. *Am J Gastroenterol.* 2005;100(11):2503-2509.

74. Kulnigg S, Stoinov S, Simanenkov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol.* 2008;103(5):1182-1192.

75. Khalafallah AA, Dennis AE, Ogden K, et al. Three-year follow-up of a randomised clinical trial of intravenous versus oral iron for anaemia in pregnancy. *BMJ Open.* 2012;2(5):e000998.

76. Evstatiev R, Alexeeva O, Bokemeyer B, et al. Ferric carboxymaltose prevents recurrence of anemia in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2013;11(3):269-277.

77. Auerbach M, Macdougall IC. Safety of intravenous iron formulations: facts and folklore. *Blood Transfus.* 2014;12(3):296-300.

 Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmén J. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant*. 2006;21(2): 378-382.

79. Hussain I, Bhoyroo J, Butcher A, Koch TA, He A, Bregman DB. Direct comparison of the safety and efficacy of ferric carboxymaltose versus iron dextran in patients with iron deficiency anemia. *Anemia*. 2013;2013:169107. 80. Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities [in German]. *Schweiz Med Wochenschr.* 1970;100(7):301-303.

81. Reinisch W, Staun M, Tandon RK, et al. A randomized, open-label, noninferiority study of intravenous iron isomaltoside 1,000 (Monofer) compared with oral iron for treatment of anemia in IBD (PROCEED). *Am J Gastroenterol.* 2013;108(12):1877-1888.

82. Auerbach M, Pappadakis JA, Bahrain H, Auerbach SA, Ballard H, Dahl NV. Safety and efficacy of rapidly administered (one hour) one gram of low molecular weight iron dextran (INFeD) for the treatment of iron deficient anemia. *Am J Hematol.* 2011;86(10):860-862.

83. Ali M, Rigolosi R, Fayemi AO, Braun EV, Frascino J, Singer R. Failure of serum ferritin levels to predict bone-marrow iron content after intravenous iron-dextran therapy. *Lancet.* 1982;1(8273):652-655.

84. Novacek G, Weltermann A, Sobala A, et al. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. *Gastroenterology*. 2010;139(3): 779-787, 787.e1.

85. Carson JL, Grossman BJ, Kleinman S, et al; Clinical Transfusion Medicine Committee of the AABB. Red blood cell transfusion: a clinical practice guideline from the AABB. *Ann Intern Med.* 2012;157(1):49-58.

86. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med.* 2013;368(1):11-21.

87. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med.* 1999;340(6):409-417.

 Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW; Nutrition Impact Model Study Group (anaemia). Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ*. 2013;346:f3443.

Rees MC. Role of menstrual blood loss measurements in management of complaints of excessive menstrual bleeding. *Br J Obstet Gynaecol.* 1991;98(3):327-328.
 Warner PE, Critchley HO, Lumsden MA, Campbell-Brown M, Douglas A, Murray GD. Menorrhagia I: measured blood loss, clinical features, and outcome in women with heavy periods: a survey with follow-up data. *Am J Obstet Gynecol.* 2004;190(5):1216-1223.

91. Vannella L, Aloe Spiriti MA, Cozza G, et al. Benefit of concomitant gastrointestinal and gynaecological evaluation in premenopausal women with iron deficiency anaemia. *Aliment Pharmacol Ther.* 2008;28(4):422-430.

 92. Annibale B, Lahner E, Chistolini A, et al. Endoscopic evaluation of the upper gastrointestinal tract is worthwhile in premenopausal women with iron-deficiency anaemia irrespective of menstrual flow. *Scand J Gastroenterol*. 2003;38(3):239-245.
 93. Capurso G, Baccini F, Osborn J, et al. Can patient characteristics predict the outcome of endoscopic evaluation of iron deficiency anemia: a multiple logistic

regression analysis. *Gastrointest Endosc.* 2004;59(7):766-771. 94. James MW, Chen CM, Goddard WP, Scott BB, Goddard AF. Risk factors for gastrointestinal malignancy in patients with iron-deficiency anaemia. *Eur J*

Gastroenterol Hepatol. 2005;17(11):1197-1203. 95. Hamilton W, Lancashire R, Sharp D, Peters TJ, Cheng KK, Marshall T. The importance of anaemia in diagnosing colorectal cancer: a case-control study using

electronic primary care records. Br J Cancer. 2008;98(2):323-327.
96. Ioannou GN, Rockey DC, Bryson CL, Weiss NS. Iron deficiency and gastrointestinal malignancy: a population-based cohort study. Am J Med. 2002;113(4):276-280.

 Bini EJ, Micale PL, Weinshel EH. Evaluation of the gastrointestinal tract in premenopausal women with iron deficiency anemia. *Am J Med.* 1998;105(4):281-286.
 Annibale B, Capurso G, Chistolini A, et al. Gastrointestinal causes of refractory iron deficiency anemia in patients without gastrointestinal symptoms. *Am J Med.* 2001;111(6):439-445.

99. Srinivas M, Basumani P, Podmore G, Shrimpton A, Bardhan KD. Utility of testing patients, on presentation, for serologic features of celiac disease. *Clin Gastroenterol Hepatol.* 2014;12(6):946-952.

100. Kaye PV, Garsed K, Ragunath K, Jawhari A, Pick B, Atherton JC. The clinical utility and diagnostic yield of routine gastric biopsies in the investigation of iron deficiency anemia: a case-control study. *Am J Gastroenterol.* 2008;103(11):2883-2889.

101. Dickey W, Kenny BD, McMillan SA, Porter KG, McConnell JB. Gastric as well as duodenal biopsies may be useful in the investigation of iron deficiency anaemia. *Scand J Gastroenterol*. 1997;32(5):469-472.

 Barada K, Habib RH, Malli A, et al. Prediction of celiac disease at endoscopy. Endoscopy. 2014;46(2):110-119.

103. Robson K, Alizart M, Martin J, Nagel R. Coeliac patients are undiagnosed at routine upper endoscopy. *PLoS One*. 2014;9(3):e90552.

104. Raju GS, Gerson L, Das A, Lewis B; American Gastroenterological Association. American Gastroenterological Association (AGA) Institute medical position statement on obscure gastrointestinal bleeding. *Gastroenterology*. 2007;133(5):1694-1696.

105. Bull-Henry K, Al-Kawas FH. Evaluation of occult gastrointestinal bleeding. *Am Fam Physician*. 2013;87(6):430-436.

106. Choi SI, Simone JV, Jackson CW. Megakaryocytopoiesis in experimental iron deficiency anemia. *Blood.* 1974;43(1):111-120.

107. Evstatiev R, Bukaty A, Jimenez K, et al. Iron deficiency alters megakaryopoiesis and platelet phenotype independent of thrombopoietin. *Am J Hematol.* 2014;89(5):524-529.

108. Akay OM, Akin E, Mutlu FS, Gulbas Z. Effect of iron therapy on platelet function among iron-deficient women with unexplained menorrhagia. *Pathophysiol Haemost Thromb.* 2008;36(2):80-83.

109. Woods HF, Youdim MB, Boullin D, Callender S. Monoamine metabolism and platelet function in iron-deficiency anaemia. *Ciba Found Symp.* 1976;(51):227-248.

110. Shovlin CL, Chamali B, Santhirapala V, et al. Ischaemic strokes in patients with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia: associations with iron deficiency and platelets. *PLoS One.* 2014;9(2):e88812.

111. Khorana AA, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. *Cancer.* 2005;104(12):2822-2829.

112. Simanek R, Vormittag R, Ay C, et al. High platelet count associated with venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). *J Thromb Haemost.* 2010;8(1):114-120.

113. Danese S, Papa A, Saibeni S, Repici A, Malesci A, Vecchi M. Inflammation and coagulation in inflammatory bowel disease: the clot thickens. *Am J Gastroenterol.* 2007;102(1):174-186.

114. Edwards RL, Rickles FR, Moritz TE, et al. Abnormalities of blood coagulation tests in patients with cancer. *Am J Clin Pathol.* 1987;88(5):596-602.

115. Danese S, de la Motte C, Fiocchi C. Platelets in inflammatory bowel disease: clinical, pathogenic, and therapeutic implications. *Am J Gastroenterol.* 2004;99(5):938-945.

116. Voudoukis E, Karmiris K, Oustamanolakis P, et al. Association between thrombocytosis and iron deficiency anemia in inflammatory bowel disease. *Eur J Gastroenterol Hepatol.* 2013;25(10):1212-1216.

117. Kulnigg-Dabsch S, Evstatiev R, Dejaco C, Gasche C. Effect of iron therapy on platelet counts in patients with inflammatory bowel disease-associated anemia. *PLoS One.* 2012;7(4):e34520.

118. Kulnigg-Dabsch S, Schmid W, Howaldt S, et al. Iron deficiency generates secondary thrombocytosis and platelet activation in IBD: the randomized, controlled thromboVIT trial. *Inflamm Bowel Dis.* 2013;19(8):1609-1616.

119. Yessayan L, Yee J, Zasuwa G, Frinak S, Besarab A. Iron repletion is associated with reduction in platelet counts in non-dialysis chronic kidney disease patients independent of erythropoiesis-stimulating agent use: a retrospective cohort study. *BMC Nephrol.* 2014;15(1):119.

120. Henry DH, Dahl NV, Auerbach MA. Thrombocytosis and venous thromboembolism in cancer patients with chemotherapy induced anemia may be related to ESA induced iron restricted erythropoiesis and reversed by administration of IV iron. *Am J Hematol.* 2012;87(3):308-310.

121. Koskenkorva-Frank TS, Weiss G, Koppenol WH, Burckhardt S. The complex interplay of iron metabolism, reactive oxygen species, and reactive nitrogen species: insights into the potential of various iron therapies to induce oxidative and nitrosa-tive stress. *Free Radic Biol Med.* 2013;65:1174-1194.

122. Stevens RG, Jones DY, Micozzi MS, Taylor PR. Body iron stores and the risk of cancer. *N Engl J Med.* 1988;319(16):1047-1052.

123. Stevens RG, Graubard BI, Micozzi MS, Neriishi K, Blumberg BS. Moderate elevation of body iron level and increased risk of cancer occurrence and death. *Int J Cancer.* 1994;56(3):364-369.

124. Mainous AG III, Gill JM, Everett CJ. Transferrin saturation, dietary iron intake, and risk of cancer. *Ann Fam Med.* 2005;3(2):131-137.

125. Gaur A, Collins H, Wulaningsih W, et al. Iron metabolism and risk of cancer in the Swedish AMORIS study. *Cancer Causes Control.* 2013;24(7):1393-1402.

126. Nelson RL. Iron and colorectal cancer risk: human studies. Nutr Rev. 2001;59(5):140-148.

127. Norat T, Bingham S, Ferrari P, et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst.* 2005;97(12):906-916.

128. Kabat GC, Miller AB, Jain M, Rohan TE. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. *Br J Cancer*. 2007;97(1):118-122.

129. Kato I, Dnistrian AM, Schwartz M, et al. Iron intake, body iron stores and colorectal cancer risk in women: a nested case-control study. *Int J Cancer*. 1999;80(5):693-698.

130. Beguin Y, Aapro M, Ludwig H, Mizzen L, Osterborg A. Epidemiological and nonclinical studies investigating effects of iron in carcinogenesis—a critical review. *Crit Rev Oncol Hematol.* 2014;89(1):1-15.