Management of Iron Deficiency Anemia

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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.

Anemia affects one-fourth of the world’s population, accounting for 8.8% of the total global burden of disease.1,2 Iron deficiency is 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

Keywords
Anemia of chronic disease, intravenous iron, iron deficiency anemia, iron replacement therapy, oral iron, hemoglobin
Patients with iron deficiency anemia of uncertain etiology are usually referred to a gastroenterologist because gastrointestinal conditions are the most common causes, 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 Gastroenterology; 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. 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 enterocytes, macrophages, or hepatocytes. Erythropoiesis is iron restricted; anemia develops despite adequate iron stores, and erythrocytes may appear normocytic or microcytic. 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. 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. Hb levels may vary across age and race, 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, and participation in endurance sports may alter Hb levels.
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. 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. 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), CKD (<500 ng/mL plus TfS <30%), and CHF (<100 ng/mL or <100-299 ng/mL plus TfS <20%)—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.

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. Although clear evidence is lacking, iron deficiency without anemia is associated with RLS and chronic fatigue, and treatment alleviates these symptoms. In CHF, iron replacement therapy has been shown to be beneficial, even when anemia is not present. Thus, the decision to treat iron deficiency in a patient without manifest anemia must be made on an individual basis. 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%. Iron that remains in the intestinal lumen may cause mucosal injury, and studies in animal models suggest an exacerbation of disease activity and the induction of carcinogene-

### Table 1. Causes of Iron Deficiency

<table>
<thead>
<tr>
<th>Diminished Uptake</th>
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<tbody>
<tr>
<td><strong>Malabsorption</strong></td>
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<tr>
<td>• Celiac disease</td>
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<tr>
<td>• Duodenal resection/gastric bypass surgery</td>
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<tr>
<td>• Inflammatory bowel disease (ileal-jejunal disease and/or anemia of chronic disease)</td>
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<tr>
<td>• Helicobacter pylori gastritis</td>
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<tr>
<td>• Autoimmune gastritis</td>
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<tr>
<td><strong>Dietary causes</strong></td>
</tr>
<tr>
<td>• Malnutrition</td>
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<tr>
<td>• High intake of phytates, polyphenols</td>
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<tr>
<td><strong>Increased Demand</strong></td>
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<td>• Pregnancy, lactation</td>
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<td>• Childhood</td>
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<tr>
<td>• Erythropoiesis-stimulating agents (in chronic kidney disease, chemotherapy-induced anemia)</td>
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<tr>
<td><strong>Enhanced Loss</strong></td>
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<tr>
<td><strong>Gynecologic causes</strong></td>
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<tr>
<td>• Menorrhagia (myoma, endometriosis, bleeding disorders)</td>
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<tr>
<td>• Uterine cancer</td>
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<tr>
<td><strong>Gastrointestinal causes</strong></td>
</tr>
<tr>
<td>• Malignancy</td>
</tr>
<tr>
<td>• Upper gastrointestinal blood loss</td>
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<tr>
<td>• Gastric/duodenal ulcer</td>
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<tr>
<td>• Variceal bleeding</td>
</tr>
<tr>
<td>• Esophagitis, erosive gastritis</td>
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<tr>
<td>• Mallory-Weiss syndrome</td>
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<tr>
<td>• Angiodysplasia, vascular ectasia</td>
</tr>
<tr>
<td>• Dieulafoy lesions</td>
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<tr>
<td>• Rare: Meckel diverticula, Cameron lesions</td>
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<tr>
<td>• Lower gastrointestinal blood loss</td>
</tr>
<tr>
<td>• Diverticulosis/diverticulitis</td>
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<tr>
<td>• Hemorrhoids, anal fissures, rectal ulcers</td>
</tr>
<tr>
<td>• Angiodysplasia</td>
</tr>
<tr>
<td>• Inflammatory bowel disease</td>
</tr>
<tr>
<td>• Infectious colitis</td>
</tr>
<tr>
<td><strong>Other causes</strong></td>
</tr>
<tr>
<td>• Surgery, trauma, childbirth, blood donation</td>
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<tr>
<td>• Prolonged nonsteroidal anti-inflammatory drug use</td>
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<tr>
<td>• Parasitic infection (eg, hookworm, tapeworm)</td>
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<tr>
<td><strong>Rare Causes</strong></td>
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<tr>
<td>• Idiopathic pulmonary hemosiderosis</td>
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<tr>
<td>• Hereditary hemorrhagic telangiectasia</td>
</tr>
<tr>
<td>• Coagulation disorders, platelet dysfunction</td>
</tr>
<tr>
<td>• Congenital iron deficiency (iron-refractory iron deficiency anemia)</td>
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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. 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. 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), CKD (<500 ng/mL plus TfS <30%), and CHF (<100 ng/mL or <100-299 ng/mL plus TfS <20%)—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.
sis in IBD. Furthermore, dose-dependent gastrointestinal side effects hinder compliance and result in nonadherence in up to 50% of patients. 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. 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 non-pregnant 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 anemia and should be considered when oral iron is ineffective. The efficacy of oral iron is diminished when uptake through the gut is impaired (eg, in celiac disease, autoimmune gastritis, ACD, 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, reaching higher levels than with oral iron, which may limit patient compliance. In these situations, intravenous iron therapy is preferred because the gut is bypassed, allowing faster repletion (Table 2).

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). This was generalized to include all intravenous formulations; however, a review of the US Food and Drug Administration database from 1998 to 2000 showed that the cumulative rate of serious adverse events for all intravenous formulations excluding HMWID (ie, low-molecular-weight iron dextran, iron sucrose, and ferric gluconate) is low (<1:200,000). Furthermore, a study of ferric carboxymaltose and HMWID revealed similar efficacy, with fewer hypersensitivity reactions for ferric carboxymaltose. 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. However, this formula is inconvenient and inconsistently used, and it underestimates iron requirements. The FERGIcor (FERinject...
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.55 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 pregnancy-related 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,
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 women (Table 1). Menorrhagia affects approximately 30% of women of reproductive age. 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. 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.

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 colonoscopy (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. Similarly, an Hb level below 10.0 g/dL in women increases the likelihood of gastrointestinal pathology and should be investigated. The risk of a more severe underlying pathology, such as cancer, increases as the Hb level falls. 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. 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. Although a positive FOBT result in combination with iron deficiency anemia warrants invasive gastrointestinal evaluation, 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 thrombocytosis; however, the mechanism behind this phenomenon remains unclear. Studies in adult women show a correlation between platelet count and TfS, as well as serum iron, and more severe anemia leads to higher counts. Animal models of iron deficiency recapitulate this observation, which occurs with altera-

<table>
<thead>
<tr>
<th>Degree of Iron Deficiency</th>
<th>Hemoglobin Level, g/dL</th>
<th>Dose for Body Weight &lt;70 kg, mg</th>
<th>Dose for Body Weight ≥70 kg, mg</th>
</tr>
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<tbody>
<tr>
<td>No anemia</td>
<td>Normal</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-12 (women)</td>
<td>1000</td>
<td>1500</td>
</tr>
<tr>
<td></td>
<td>10-13 (men)</td>
<td></td>
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<tr>
<td>Severe</td>
<td>7-10</td>
<td>1500</td>
<td>2000</td>
</tr>
<tr>
<td>Critical</td>
<td>&lt;7</td>
<td>2000</td>
<td>2500</td>
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</tbody>
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Table 4. Simple Scheme for the Estimation of Total Iron Need

Modified from Evstatiev R, et al, with permission.
tions in megakaryopoiesis\textsuperscript{106,107} and augmented platelet aggregability.\textsuperscript{107} Altered platelet function has also been found in patients with iron deficiency and was alleviated by iron therapy.\textsuperscript{108,109}

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

Interestingly, iron therapy in IBD has been shown to normalize platelet counts as well as platelet function.\textsuperscript{117,118} Iron therapy also lowers the platelet count in CKD.\textsuperscript{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.\textsuperscript{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 reoxidation of 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.\textsuperscript{46,121} One concern in iron therapy is the potential for tumor promotion or progression.

Several NHANES (National Health and Nutrition Examination Survey) studies 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) study 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,\textsuperscript{126,127} but not when the study population is female.\textsuperscript{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 colleagues).\textsuperscript{121} 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.\textsuperscript{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) hydroxide-polymaltose 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 colleagues).\textsuperscript{120} 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.

**References**


