

## REVIEW ARTICLE

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## Iron-Deficiency Anemia

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**I**RON DEFICIENCY AND IRON-DEFICIENCY ANEMIA ARE GLOBAL HEALTH problems and common medical conditions seen in everyday clinical practice. Although the prevalence of iron-deficiency anemia has recently declined somewhat, iron deficiency continues to be the top-ranking cause of anemia worldwide, and iron-deficiency anemia has a substantial effect on the lives of young children and premenopausal women in both low-income and developed countries.<sup>1</sup> The diagnosis and treatment of this condition could clearly be improved.

Iron is crucial to biologic functions, including respiration, energy production, DNA synthesis, and cell proliferation.<sup>2</sup> The human body has evolved to conserve iron in several ways, including the recycling of iron after the breakdown of red cells and the retention of iron in the absence of an excretion mechanism. However, since excess levels of iron can be toxic, its absorption is limited to 1 to 2 mg daily, and most of the iron needed daily (about 25 mg per day) is provided through recycling by macrophages that phagocytose senescent erythrocytes. The latter two mechanisms are controlled by the hormone hepcidin, which maintains total-body iron within normal ranges, avoiding both iron deficiency and excess.

Iron deficiency refers to the reduction of iron stores that precedes overt iron-deficiency anemia or persists without progression. Iron-deficiency anemia is a more severe condition in which low levels of iron are associated with anemia and the presence of microcytic hypochromic red cells.

Iron-restricted erythropoiesis indicates that the delivery of iron to erythroid precursors is impaired, no matter how replete the stores.<sup>3,4</sup> Stores may be normal or even increased because of iron sequestration in cases of anemia of chronic inflammation, which is observed in patients with autoimmune disorders, cancer, infections, and chronic kidney diseases.<sup>3,4</sup> The presence of both iron deficiency and anemia of chronic disorders is common and may be seen in elderly patients<sup>5</sup> and patients with chronic kidney disease.<sup>6</sup> However, a substantial fraction of the anemia that is typical in elderly patients occurs in the absence of iron deficiency or elevated hepcidin levels.<sup>7</sup>

Functional iron deficiency is a state of iron-poor erythropoiesis<sup>8</sup> in which there is insufficient mobilization of iron from stores in the presence of increased demands, as is observed after treatment with erythropoiesis-stimulating agents.<sup>9</sup> (See the Glossary for definitions of terms related to iron-deficiency anemia.)

This review reconsiders iron deficiency and its anemia in light of advances in the understanding of systemic iron homeostasis and examines causes, pathophysiological features, and treatment options in adults. Readers are referred elsewhere for information on the presentation, symptoms, and diagnosis of iron-deficiency anemia through laboratory tests and on issues that are specific to children or pregnancy.<sup>10-13</sup>

## Glossary

**Anemia of chronic disorders or anemia of inflammation:** Multifactorial anemia associated with increased cytokine production, up-regulation of hepcidin, and abnormal iron homeostasis.

**Functional iron deficiency:** Insufficient mobilization of erythroid iron in the presence of increased requests, as occurs after treatment with erythropoiesis-stimulating agents.

**Iron deficiency:** Depressed levels of total body iron, especially iron stores, with preservation of levels of erythroid iron.

**Iron-deficiency anemia:** Depressed levels of total body iron in the presence of anemia.

**Iron-restricted erythropoiesis:** A reduced supply of iron for the purpose of erythropoiesis, regardless of the level of iron stores, which are usually replete.

**Iron-refractory iron-deficiency anemia (IRIDA):** Iron-deficiency anemia that is unresponsive to oral iron treatment, in most cases referring to the genetic disease caused by a mutation in *TMPRSS6*, the gene encoding transmembrane protease, serine 6, also known as matriptase-2.

## A GLOBAL HEALTH PROBLEM

Iron deficiency affects more than 2 billion people worldwide,<sup>1</sup> and iron-deficiency anemia remains the top cause of anemia, as confirmed by the analysis of a large number of reports on the burden of disease in 187 countries between 1990 and 2010<sup>14</sup> and by a survey on the burden of anemia in persons at risk, such as preschool children and young women.<sup>15</sup> Prevention programs have decreased rates of iron-deficiency anemia globally; the prevalence is now highest in Central and West Africa and South Asia.<sup>14,15</sup> The estimated prevalence of iron deficiency worldwide is twice as high as that of iron-deficiency anemia.

The reported prevalence of iron deficiency in the absence of dietary fortification is approximately 40% in preschool children, 30% in menstruating girls and women, and 38% in pregnant women.<sup>14-16</sup> These rates reflect the increased physiological need for dietary iron during specific life stages and according to sex. The growth spurt of adolescence is another critical period. For patients in any of these categories, pathologic causes of iron-deficiency anemia are often absent and extensive diagnostic workups are not advised. However, as discussed below, when the response to treatment is unsatisfactory, multiple causes should be considered, even in patients in these high-risk groups.

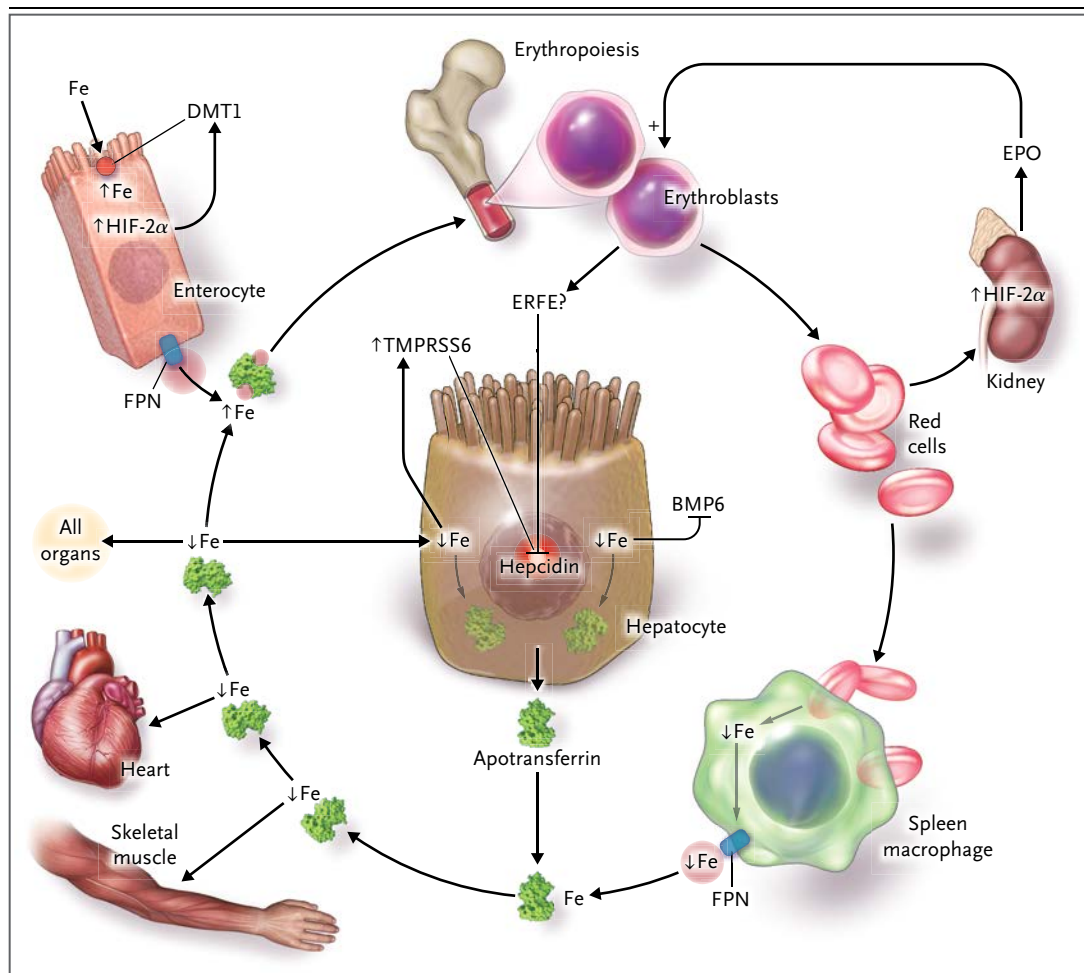
In developing countries, iron deficiency and iron-deficiency anemia typically result from insufficient dietary intake, loss of blood due to intestinal worm colonization, or both. In high-income countries, certain eating habits (e.g., a

vegetarian diet or no intake of red meat) and pathologic conditions (e.g., chronic blood loss or malabsorption) are the most common causes. Paradoxically, it appears to be more difficult to reduce the prevalence of iron-deficiency anemia in high-income countries than in lower-income countries. One reason for this seeming paradox is the high rate of iron deficiency in aging populations.<sup>14</sup>

## MODIFICATIONS OF IRON HOMEOSTASIS IN IRON DEFICIENCY

The mechanisms of iron acquisition are tightly regulated by hepcidin-based homeostatic controls.<sup>2</sup> Hepcidin is a peptide hormone that is synthesized primarily in the liver. It functions as an acute-phase reactant that adjusts fluctuations in plasma iron levels caused by absorptive enterocytes and macrophages in the spleen by binding to and inducing the degradation of ferroportin, which exports iron from cells.<sup>17</sup> Hepcidin expression increases in response to high circulating and tissue levels of iron and in persons with systemic inflammation or infection. Its production is inhibited by the expansion of erythropoiesis, iron deficiency, and tissue hypoxia in response to signals originating in the bone marrow, the liver, and probably muscle tissue and adipocytes.<sup>2,18</sup> Increases in hepcidin levels that are induced by inflammatory cytokines, especially interleukin-6, explain the iron sequestration and reduced supply of erythropoietic iron that occurs in the anemia of chronic disease.

In the general population, hepcidin levels are



**Figure 1. The Iron Cycle — Mechanisms of Adaptation to Iron Deficiency.**

The mechanisms of adaptation to iron deficiency are centered on the suppression of the hepatic hormone hepcidin and the tissue hypoxia that develops consequent to anemia. The production of erythropoietin (EPO) by the kidney increases in response to enhanced levels of hypoxia-inducible factor 2α (HIF-2α). As a consequence of the stimulation of erythropoietin, erythropoiesis is increased and hypochromic microcytic red cells are produced owing to the low availability of iron. Senescent red cells are destroyed by macrophages, and their iron is recycled. The increase in erythropoiesis suppresses the production of hepcidin. In mice, this function is mediated by erythroferrone (ERFE), which is secreted by the erythroblasts<sup>21</sup> to maintain adequate iron absorption and efficiency in erythropoiesis. HIF-2α increases the expression of the duodenal divalent metal transporter 1 (DMT1)<sup>22</sup> on the apical surface of enterocytes to increase the transfer of dietary iron from the lumen to enterocytes. Hepcidin levels are depressed in response to a reduction in the physiologic signals that maintain its production (e.g., increases in levels of iron-bound transferrin and in the iron content of the liver),<sup>2,18</sup> to the increased activity of the inhibitor transmembrane protease, serine 6 (TMPRSS6),<sup>23</sup> to the reduction in levels of the activator bone morphogenetic protein 6 (BMP6), and to increased inhibition from erythropoietin-stimulated erythropoiesis. Ferroportin (FPN), which is no longer being degraded because of the low levels of hepcidin, exports the available iron across the enterocyte basal membrane and from macrophage stores<sup>17</sup> to the circulation. Once stores are exhausted, levels of circulating iron decrease, even if absorption from the lumen is increased. Reduced levels of iron in the liver trigger increases in the synthesis of the iron carrier transferrin (referred to as apotransferrin when not bound to iron), further decreasing levels of iron-bound transferrin, the ligand of the transferrin receptor. Consequently, the uptake of iron from transferrin receptors by all cells and organs (e.g., skeletal muscles and the heart) is reduced.

low in girls and young women and higher — strong direct correlation with serum levels of ferritin.<sup>19,20</sup> In iron deficiency, the transcription of hepcidin is suppressed. This adaptive mechanism is similar to levels in men — in postmenopausal women; fluctuations in hepcidin levels have a

**Table 1. Causes of Iron Deficiency.**

Cause	Example
<b>Physiologic</b>	
Increased demand	Infancy, rapid growth (adolescence), menstrual blood loss, pregnancy (second and third trimesters), blood donation
<b>Environmental</b>	Insufficient intake, resulting from poverty, malnutrition, diet (e.g., vegetarian, vegan, iron-poor)
<b>Pathologic</b>	
Decreased absorption	Gastrectomy, duodenal bypass, bariatric surgery, <i>Helicobacter pylori</i> infection, celiac sprue, atrophic gastritis, inflammatory bowel diseases (e.g., ulcerative colitis, Crohn's disease)*
Chronic blood loss	Gastrointestinal tract, including esophagitis, erosive gastritis, peptic ulcer, diverticulitis, benign tumors, intestinal cancer, inflammatory bowel diseases, angiodysplasia, hemorrhoids, hookworm infestation, obscure source Genitourinary system, including heavy menses, menorrhagia, intravascular hemolysis (e.g., paroxysmal nocturnal hemoglobinuria, autoimmune hemolytic anemia with cold antibodies, march hemoglobinuria, damaged heart valves, microangiopathic hemolysis) Systemic bleeding, including hemorrhagic telangiectasia, chronic schistosomiasis, Munchausen's syndrome (e.g., self-induced hemorrhages)
<b>Drug-related</b>	Glucocorticoids, salicylates, NSAIDs, proton-pump inhibitors
<b>Genetic</b>	Iron-refractory iron-deficiency anemia
<b>Iron-restricted erythropoietic</b>	Treatment with erythropoiesis-stimulating agents, anemia of chronic disease, chronic kidney disease*

\* Inflammatory conditions may be associated with iron deficiency. NSAIDs denotes nonsteroidal antiinflammatory drugs.

nism facilitates the absorption of iron (Fig. 1) and the release of iron from body stores. Intestinal iron uptake from the gut lumen through divalent metal transporter 1 (DMT1) is increased by the activation of hypoxia-inducible factor 2 $\alpha$ .<sup>22</sup> The degree of store repletion determines the rapidity with which iron deficiency develops in cases of blood loss or a drastic reduction in iron absorption. Hepatocytes appear to be a long-term reservoir for iron and release it more slowly than macrophages.

#### CAUSES OF IRON-DEFICIENCY ANEMIA

Poverty, malnutrition, and famine are self-explanatory causes of anemia in the multitude of people living with iron deficiency in developing countries, especially children and pregnant women. In addition, a cereal-based diet decreases iron bioavailability because phytates in grains sequester iron in a poorly absorbable complex. Other common causes in developing countries include hookworm infections and schistosomiasis, which cause chronic blood loss.<sup>14</sup> Strict vegan and vegetarian diets, malabsorption, and chronic blood loss resulting from heavy menstrual

losses are well-known causes of iron-deficiency anemia in developed countries (Table 1). Chronic blood loss from the gastrointestinal tract, including occult blood, especially in male patients and elderly patients, may reveal the presence of benign lesions, angiodysplasia, or cancer. The origin of obscure gastrointestinal blood loss,<sup>24</sup> especially from the small bowel, may be clarified by means of video-capsule endoscopy, which is increasingly used when conventional workups for iron-deficiency anemia return negative results.<sup>25</sup> Persons who donate blood regularly are also at risk for iron deficiency, and their iron levels should be monitored.

In rare forms of intravascular hemolysis, iron is lost in the urine, and iron deficiency then aggravates anemia (e.g., in paroxysmal nocturnal hemoglobinuria). Anemia in endurance athletes may be due to hemolysis, blood loss, and often mild inflammation. Nonsteroidal antiinflammatory drugs and anticoagulants may contribute to blood loss, and proton-pump inhibitors are a frequently overlooked cause of impaired iron absorption (Table 1).<sup>26</sup>

The simultaneous occurrence of multiple causes of iron deficiency is common. In developing countries, low iron intake combined with

intestinal infections with nematodes may result in severe anemia, especially in young children. The severity of iron deficiency is also associated with *Ancylostoma duodenale* (hookworm) load, according to the results of real-time polymerase-chain-reaction assays of fecal samples.<sup>27</sup> In chronic schistosomiasis, blood losses combine with the anemia of inflammation.<sup>28</sup> Patients with hypermenorrhea may also have concomitant malabsorption of iron.<sup>29</sup> In end-stage kidney disease, iron-deficiency anemia results from blood loss during dialysis, reduced hepcidin clearance, inflammation, and certain drugs (e.g., proton-pump inhibitors and anticoagulants). In elderly persons, the prevalence of anemia correlates with advanced age and multiple related conditions, including iron deficiency,<sup>5</sup> inflammatory disorders, decreased levels of erythropoietin, and cancer.<sup>30</sup> Obesity may be associated with mild iron deficiency because of subclinical inflammation, increased hepcidin levels, and decreased iron absorption.<sup>31</sup> Some studies report a high prevalence of iron deficiency (30 to 50%) in patients with congestive heart failure,<sup>32,33</sup> probably because of impaired iron absorption and inflammation: increased serum levels of hepcidin have been reported in the early stages of disease but not during disease progression.<sup>34</sup>

#### IRON-REFRACTORY IRON-DEFICIENCY ANEMIA

Iron-deficiency anemia is usually acquired. However, the elucidation of systemic iron homeostasis has led to the recognition of a rare autosomal recessive disorder, iron-refractory iron-deficiency anemia (IRIDA) (Online Mendelian Inheritance in Man [OMIM] number, 206200).<sup>35</sup> Iron-deficiency anemia is defined as “refractory” when there is an absence of hematologic response (an increase of <1 g of hemoglobin) after 4 to 6 weeks of treatment with oral iron.<sup>29</sup> IRIDA is caused by a mutation in *TMPRSS6*,<sup>36</sup> the gene encoding transmembrane protease, serine 6, also known as matriptase-2, which inhibits the signaling pathway that activates hepcidin (Fig. 1).<sup>37</sup> Loss-of-function mutations in *TMPRSS6* reported in more than 50 families<sup>38,39</sup> have led to constitutively high production of hepcidin, which blocks the intestinal absorption of iron. This type of anemia is variable, more severe in children, and unresponsive to treatment with oral

iron. Typical findings include a striking microcytosis and extremely low transferrin saturation in the presence of normal or borderline-low ferritin levels and high hepcidin levels.<sup>38</sup> The diagnosis ultimately requires sequencing of *TMPRSS6*. IRIDA represents less than 1% of the cases of iron-deficiency anemia seen in medical practice. However, knowledge of this condition is valuable to clinicians, since it clarifies how essential the suppression of hepcidin is (Fig. 1) to the body's response to pharmacologic iron. IRIDA also suggests the existence of genetic susceptibility to iron deficiency. Variants of *TMPRSS6* have been associated with the modulation of serum hepcidin levels in individual persons,<sup>40</sup> the variation in iron levels in population studies,<sup>41,42</sup> and even with iron-deficiency anemia in elderly Chinese women.<sup>43</sup> It is possible that coexisting acquired factors explain the ethnic specificity of the latter association.

In most cases, iron resistance is due to disorders of the gastrointestinal tract<sup>29</sup> (Table 1). Partial or total gastrectomy or any surgical procedure that bypasses the duodenum can cause resistance to oral iron. Bariatric surgery, such as laparoscopic Roux-en-Y gastric bypass, which is performed in selected obese patients to reduce caloric intake and to correct diabetes, is an emerging cause of iron deficiency and anemia because the procedure effectively removes an active iron absorption site from the digestive process and increases gastric pH.<sup>44</sup> The limited follow-up data on patients who have undergone the procedure indicate that iron deficiency develops in up to 45%,<sup>45</sup> particularly in women; lifelong nutritional monitoring and iron supplementation are advised.<sup>46</sup> *Helicobacter pylori* infection decreases iron absorption (Table 1) because the microorganism competes with its human host for available iron, reduces the bioavailability of vitamin C, and may lead to microerosions that cause bleeding.<sup>47</sup> Since it is estimated that half the world's population is infected with *H. pylori*, clinicians should be aware of the possibility of infection and provide treatment in order to eradicate this source of iron-resistant iron-deficiency anemia. The prevalence of celiac disease and its atypical manifestations, which include iron-deficiency anemia, are increasingly recognized worldwide.<sup>48</sup> In one study, screening for the prevalence of gluten sensitivity with the use of anti-transglutaminase antibodies uncovered



negligible incidence among iron-replete participants, whereas 2.5% of participants with iron deficiency had sensitivity to gluten.<sup>49</sup> In another study of a series of patients with iron-refractory iron-deficiency anemia, 5% of participants had gluten sensitivity.<sup>29</sup> These findings suggest that gluten sensitivity may be associated with iron-refractory iron-deficiency anemia. Similarly, autoimmune atrophic gastritis, another rare cause of iron-refractory deficiency anemia, which results from an immune reaction against gastric parietal cells and intrinsic factor, should be considered as a possible albeit unlikely cause of iron-refractory microcytic anemia.<sup>29</sup> In patients with inflammatory bowel disease, anemia may be iron-resistant, but it is multifactorial, often resulting from a combination of deficiencies in iron, folate, and vitamin B<sub>12</sub>, inflammation, and side effects from drug therapy.

#### CLINICAL FINDINGS

Iron-deficiency anemia is chronic and frequently asymptomatic and thus may often go undiagnosed. Weakness, fatigue, difficulty in concentrating, and poor work productivity are nonspecific symptoms ascribed to low delivery of oxygen to body tissues and decreased activity of iron-containing enzymes. The extent to which these nonhematologic effects of iron deficiency are manifested before anemia develops is unclear. Signs of iron deficiency in tissue are subtle and may not respond to iron therapy. Iron deficiency has been reported to decrease cognitive performance and to delay mental and motor development in children.

Severe iron-deficiency anemia in pregnancy is associated with an increased risk of preterm labor, low neonatal weight, and increased newborn and maternal mortality. Iron deficiency may predispose a person to infections, precipitate heart failure, and cause restless leg syndrome. In patients with heart failure, iron deficiency has a negative effect on the quality of life, irrespective of the presence of anemia.<sup>50</sup>

#### DETERMINATION OF IRON STATUS

The traditional laboratory measures and results used to determine iron status and iron deficiency and related conditions (e.g., functional iron deficiency, iron-deficiency anemia, IRIDA,

and anemia of chronic diseases) are well established (Table 2). Serum ferritin level is the most sensitive and specific test used for the identification of iron deficiency (indicated by a level of <30 µg per liter). Levels are lower in patients with iron-deficiency anemia; a transferrin saturation level of less than 16% indicates an iron supply that is insufficient to support normal erythropoiesis. However, in determining iron status, it is important to consider the whole picture rather than relying on single test results. Guidelines for the differential diagnosis of microcytic anemias have recently been reviewed elsewhere.<sup>11,53</sup> The diagnosis of iron-deficiency anemia in the context of inflammation is challenging and cannot be determined on the basis of the results of a single test (Table 2); significantly higher cutoff levels for ferritin are used to define iron-deficiency anemia accompanied by inflammation,<sup>3</sup> with the best predictor being a ferritin level of less than 100 µg per liter. Higher cutoff levels for ferritin are used in the diagnosis of iron deficiency in other conditions (e.g., <300 µg per liter for heart failure<sup>50</sup> and for chronic kidney disease in the presence of a transferrin saturation level of less than 30%<sup>54</sup>). The assessment of iron stores through iron staining of bone marrow specimens obtained by means of biopsy is an option that is not used frequently. At present, no reliable test for hepcidin levels is available.

#### THERAPY

##### CAUTIONS AND GENERAL GUIDELINES

Patients with iron-deficiency anemia should receive iron supplementation. Caution must be used in areas in which malaria is endemic because supplementation may reverse the potentially protective effects of iron deficiency<sup>55</sup> or increase the susceptibility to coinfections.<sup>56</sup> In vitro studies have shown that the malaria parasite *Plasmodium falciparum* is less efficient in infecting iron-deficient erythrocytes than in infecting iron-replete erythrocytes, a protection that is reversed with iron supplementation.<sup>57</sup> Some studies support the view that measurement of hepcidin levels could help to determine the best time (e.g., the end of malaria season) to provide children in these regions with iron supplementation.<sup>58</sup> Emerging data suggest that nonabsorbed iron could be harmful to patients because it

**Table 2. Laboratory Tests for the Measurement of Iron Status in Adults.**

Test	Iron Deficiency	Functional Iron Deficiency	Iron-Deficiency Anemia	IRIDA	Anemia of Chronic Diseases	Iron-Deficiency Anemia and Chronic Diseases	Normal Value
<b>Current</b>							
Iron — $\mu\text{mol/liter}$	Low	Low–normal	Low	Low	Low	Low	10–30
Transferrin saturation — %	$\geq 16$	Low–normal	$< 16^*$	$< 10$	Low–normal	Low–normal	$> 16$ to $< 45$
Ferritin — $\mu\text{g/liter}$	$< 30^\dagger$	Normal	$< 10$	Variable	$> 100^\ddagger$	$< 100^\ddagger$	
Men							40–300
Women							20–200
Hemoglobin — g/dl	Normal	Normal	Low	Low	Low	Low	
Men							$> 13$
Women							$> 12$
Mean corpuscular volume — fl	Normal	Normal	$< 80$	Very low	Low–normal	Low	80–95
Mean corpuscular hemoglobin — pg	Normal	Normal	$< 27$	Very low	Low–normal	Low	27–34
<b>Proposed</b>							
sTfR — mg/liter $\S$	High	High	High	High	Low–normal	Variable	Varies¶
sTfR/log ferritin index	NA	NA	$> 2$	NA	$< 1$	$> 2$	Varies¶
Hepcidin	Low	Low	Very low	Normal–high	High	Normal–high	Varies¶
Zinc protoporphyrin**	Normal	High	High	High	High	High	Varies¶
Reticulocyte hemoglobin content — pg $\dagger\dagger$	$< 25$	$< 29$	Low	Low	Low	Low	$31.2 \pm 1.6$
Perl's staining of bone marrow for iron	Negative	Variable	Negative	Positive	Strongly positive	Positive	Positive

\* The value for transferrin saturation in the diagnosis of iron-deficiency anemia is from Beutler and Waalen.<sup>51</sup>

† The value for ferritin in the diagnosis of iron-deficiency anemia has a sensitivity of 92% and a specificity of 83% according to Goodnough et al.<sup>4</sup>

‡ The value for ferritin in the anemia of chronic disease and the combined value for the anemia of chronic disease and iron deficiency are from Weiss and Goodnough.<sup>3</sup>

§ The value for the soluble transferrin receptor (sTfR), which is shed by the erythroblast membrane in serum, may be useful in the assessment of iron-deficiency anemia, but the methods used to measure sTfR have been not standardized.<sup>3</sup>

¶ Normal values vary according to the method of measurement used.

|| The sTfR/log ferritin index has been proposed to distinguish iron-deficiency anemia in the anemia of chronic disease from the anemia of chronic disease alone.<sup>3</sup>

\*\* The values for zinc protoporphyrin are used only in screening for or monitoring iron-deficiency anemia.<sup>9</sup>

†† Reduction of reticulocyte hemoglobin content is an early sign of functional iron deficiency.<sup>52</sup>

might modify the gut microbiota, increasing the concentration of intestinal pathogens.<sup>59</sup>

The benefit of treating iron deficiency before the development of anemia remains uncertain. A few small studies show that the administration of intravenous iron improves fatigue in women without anemia whose ferritin levels are in the iron-deficient range.<sup>60</sup> Some studies have also suggested that oral iron supplementation benefits physical performance in women of reproductive age,<sup>61</sup> but such studies have included a limited number of participants and are strikingly heterogeneous.

Patients with severe iron-deficiency anemia that causes cardiovascular symptoms, such as heart failure or angina, should receive red-cell transfusions. This approach rapidly corrects not only hypoxia but also iron deficiency, since one unit of packed red cells provides approximately 200 mg of iron.

#### ORAL IRON THERAPY

The administration of oral iron is a convenient, inexpensive, and effective means of treating stable patients. Among the myriad preparations on the market, iron sulfate is the most frequently used; gluconate and fumarate are also effective iron salts. The recommended daily dose for adults with iron deficiency is 100 to 200 mg of elementary iron and that for children is 3 to 6 mg per kilogram of body weight of a liquid preparation; for both groups the supplement should be administered in divided doses without food. The addition of vitamin C may improve absorption. The low hepcidin levels in patients with iron-deficiency anemia ensure effective iron absorption and the rapid recovery of hemoglobin levels; however, 3 to 6 months of treatment are required for the repletion of iron stores and the normalization of serum ferritin levels. Long-term use of oral iron is limited by side effects, including nausea, vomiting, constipation, and metallic taste; these side effects are frequent and, although not severe, are often worrisome to patients. Although oral iron may cause dark stools, it does not produce false positive results on tests for occult blood. If treatment with oral iron fails, the reasons may include premature termination of treatment, lack of compliance with the regimen or discontinuation by the patient, or a truly refractory response to treatment. In the latter case, other, specific treatments,

**Table 3. Indications for Parenteral Iron Therapy.**

#### Established indication

Failure of oral therapy

Iron intolerance or with low iron levels that are refractory to treatment (e.g., after gastrectomy or duodenal bypass, with *Helicobacter pylori* infection, or with celiac disease, atrophic gastritis, inflammatory bowel disease, or genetically induced IRIDA<sup>\*</sup>)

Need for quick recovery (e.g., with severe iron deficiency in the second or third trimester of pregnancy or with chronic bleeding that is not manageable with oral iron, as may occur in patients with congenital coagulation disorders)

Substitution for blood transfusions when not accepted by patient for religious reasons

Use of erythropoiesis-stimulating agents in chronic kidney disease

#### Potential indication

Anemia of chronic kidney disease (without treatment of erythropoiesis-stimulating agents)

Persistent anemia after use of erythropoiesis-stimulating agents in patients with cancer who are receiving chemotherapy

Anemia of chronic disease unresponsive to treatment with erythropoiesis-stimulating agents alone

#### Potential indication with insufficient supporting data

Iron deficiency in heart failure

Transfusion-sparing strategy in surgical patients

<sup>\*</sup> Celiac disease or *H. pylori* infection should be considered if the anemia remains refractory to treatment. IRIDA denotes iron-refractory iron-deficiency anemia.

such as the eradication of infection with *H. pylori* or the introduction of a gluten-free diet in patients with celiac disease, may restore the capacity for iron absorption and eliminate the need for supplementation in some patients.<sup>29</sup> There are no known markers that can be used to predict which patients will or will not have a response to oral iron therapy. The oral iron challenge test (in which 60 mg of oral iron is administered and serum iron levels are measured 1 to 2 hours afterward) is rarely used since it has not been extensively validated. A pilot study showed that measurement of serum hepcidin levels could help to identify patients in whom a response to oral iron is probable (those with low hepcidin levels) and those in whom it is not probable (those with normal or elevated hepcidin levels).<sup>62</sup> However, hepcidin tests are not routinely available for clinical use. Assessment of an early response to oral iron might also be useful in the treatment of iron-deficiency anemia in patients with anemia of chronic disease. One study in patients with rheumatologic dis-



**Table 4. Iron Preparations for Intravenous Use.\***

Formulation	Dose per Infusion	
	Standard	Maximum per Single Infusion
Ferric gluconate (Ferlecit)	125 mg/10–60 min	250 mg/60 min
Iron sucrose (Venofer)	100–400 mg/2–90 min	300 mg/2 hr
Low-molecular-weight iron dextran (INFeD)†	100 mg/2 min	1000 mg/1–4 hr
Ferumoxytol (Feraheme)†	510 mg/>1 min	510–1020 mg/15–60 min
Ferric carboxymaltose (Ferinject)†	750–1000 mg/15–30 min	750–1000 mg/15–30 min
Iron isomaltoside (Monofer)†‡	20 mg/kg of body weight/15 min	20 mg/kg of body weight/15 min

\* Data are adapted from Powers and Buchanan<sup>13</sup> and Auerbach and Ballard<sup>66</sup>

† Drugs that can be administered as a total dose in a single infusion.

‡ Iron isomaltoside is licensed for use only in Europe.

ease and iron-deficiency anemia showed that a change in the hemoglobin content of reticulocytes (and in serum levels of iron and transferrin saturation) may predict the response to the administration of oral iron after 1 week of therapy.<sup>63</sup>

#### PARENTERAL IRON THERAPY

The possibility of hypersensitivity reactions (including anaphylaxis) to high-molecular-weight iron dextran has traditionally limited the indications for the intravenous administration of iron. Newly approved, safer iron formulations are modifying this clinical practice (Table 3). Because the use of intravenous iron circumvents the problem of iron absorption, it is more effective and increases hemoglobin levels more quickly than oral iron.<sup>54,64,65</sup> Another advantage is that in some patients the total dose required (up to 1000 mg) can be provided in a single infusion (Table 4). The dose needed is calculated with this formula: body weight in kilograms  $\times$  2.3  $\times$  hemoglobin deficiency (target hemoglobin level – patient hemoglobin level) + 500 to 1000 mg iron for the repletion of iron stores. The cost of parenteral iron therapy is high, but the number of hospital or clinic visits that are required is significantly decreased.<sup>67</sup>

Patients with malabsorption and genetic IRIDA<sup>38,39</sup> may require intravenous iron. Intravenous administration is also preferred when a rapid increase in hemoglobin level is required or when iron-deficiency anemia caused by chronic blood loss cannot be controlled with the use of oral iron, as is the case in patients with hereditary hemorrhagic telangiectasia. Active inflam-

matory bowel disease is an emerging indication for the use of intravenous iron (Table 3); oral iron is not only ineffective but may also increase local inflammation.<sup>68</sup>

Intravenous iron is essential in the management of anemia in patients with chronic kidney disease who are receiving dialysis and treatment with erythropoiesis-stimulating agents. The addition of iron supplementation may eliminate or delay the need for these agents in some patients with chronic kidney disease who are not receiving dialysis.<sup>6,69</sup> Erythropoiesis-stimulating agents are also used in selected patients with low-risk myelodysplastic syndrome and in patients with cancer who are receiving chemotherapy; in these circumstances, iron supplementation is usually limited to patients with concomitant iron deficiency or to those in whom there is no response to erythropoiesis-stimulating agents; intravenous iron is preferred when high hepcidin levels create a condition that is refractory to supplementation with oral iron.<sup>6</sup> The way in which iron enhances the effect of erythropoiesis-stimulating agents is unclear. One hypothesis suggests that increased iron in macrophages leads to the overexpression of ferroportin by means of the iron-responsive element–iron-regulatory protein system, which enhances the mobilization of iron for use in erythropoiesis.<sup>4</sup> Intravenous iron should be avoided in the first trimester of pregnancy because of the lack of data on safety<sup>70</sup>; it has an acceptable side-effect profile when used later in pregnancy.<sup>71</sup>

Studies of the use of parenteral iron therapy for conditions other than those mentioned are

either limited or not controlled. A multicenter European trial of patients with iron deficiency and chronic heart failure showed that the use of intravenous iron supplementation led to improvements in physical performance, New York Heart Association functional class,<sup>50</sup> and quality of life independently from the correction of anemia<sup>72</sup>; more recently, 1 year of treatment was associated with a reduced risk of hospitalization.<sup>73</sup> However, since these results were based largely on subjective evaluation, larger and longer-term studies are required to assess the real benefit of administering iron to patients with heart failure.

The transient side effects of intravenous iron supplementation include nausea, vomiting, pruritus, headache, and flushing; myalgia, arthralgia, and back and chest pain usually resolve within 48 hours, even after total dose administration.<sup>74</sup> Hypersensitivity reactions are rare,<sup>66,74</sup> as are severe or life-threatening reactions<sup>75</sup>; the pathophysiological features of these reactions are uncertain and might be exacerbated by released free iron,<sup>70,76</sup> a phenomenon that does not occur with currently used formulations. Predisposing conditions are rapid infusions, a history

of atopy, and drug allergy. Practical recommendations for minimizing risk<sup>70</sup> include a slow infusion rate, careful patient observation, and administration by trained health care personnel in an environment with access to resuscitation facilities.<sup>75</sup> The test dose may provide false reassurance; premedication with antihistamine is no longer advised because it may cause hypotension and tachycardia.<sup>70,75,76</sup>

Clinical trials are reassuring with regard to the efficacy and side-effect profile of intravenous iron. Some concern persists with regard to the long-term biologic effects of iron and its effects on the generation of oxygen radicals, patient susceptibility to infections,<sup>54,66</sup> and the potential such treatment would have to worsen conditions such as type 2 diabetes and other chronic metabolic disorders.<sup>77</sup> Well-designed, randomized, controlled trials are needed to verify the long-term effects of intravenous iron supplementation.<sup>78</sup> In the interim, intravenous iron should be used only when the benefits outweigh the risks.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

## REFERENCES

- McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. *Public Health Nutr* 2009;12:444-54.
- Hentze MW, Muckenthaler MU, Galy B, Camaschella C. Two to tango: regulation of mammalian iron metabolism. *Cell* 2010;142:24-38.
- Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;352:1011-23.
- Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood* 2010;116:4754-61.
- Goodnough LT, Schrier SL. Evaluation and management of anemia in the elderly. *Am J Hematol* 2014;89:88-96.
- Macdougall IC. Iron supplementation in nephrology and oncology: what do we have in common? *Oncologist* 2011;16:Suppl 3:25-34.
- Ferrucci L, Semba RD, Guralnik JM, et al. Proinflammatory state, hepcidin, and anemia in older persons. *Blood* 2010;115:3810-6.
- Marković M, Majkić-Singh N, Ignjatović S, Singh S. Reticulocyte haemoglobin content vs. soluble transferrin receptor and ferritin index in iron deficiency anaemia accompanied with inflammation. *Int J Lab Hematol* 2007;29:341-6.
- Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, Cavill I. Guideline for the laboratory diagnosis of functional iron deficiency. *Br J Haematol* 2013;161:639-48.
- Schrier SL. Causes and diagnosis of iron deficiency anemia in the adults. 2014 (<http://www.uptodate.com/contents/causes-and-diagnosis-of-iron-deficiency-anemia-in-the-adult>).
- DeLoughery TG. Microcytic anemia. *N Engl J Med* 2014;371:1324-31.
- Pavord S, Myers B, Robinson S, Allard S, Strong J, Oppenheimer C. UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol* 2012;156:588-600.
- Powers JM, Buchanan GR. Diagnosis and management of iron deficiency anemia. *Hematol Oncol Clin North Am* 2014;28:729-45.
- Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood* 2014;123:615-24.
- Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. *Lancet Glob Health* 2013;1(1):e16-e25.
- Pasricha SR, Drakesmith H, Black J, Hipgrave D, Biggs BA. Control of iron deficiency anemia in low- and middle-income countries. *Blood* 2013;121:2607-17.
- Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science* 2004;306:2090-3.
- Camaschella C. Iron and hepcidin: a story of recycling and balance. *Hematology Am Soc Hematol Educ Program* 2013;2013:1-8.
- Galesloot TE, Vermeulen SH, Geurts-Moespot AJ, et al. Serum hepcidin: reference ranges and biochemical correlates in the general population. *Blood* 2011;117(25):e218-e225.
- Traglia M, Girelli D, Biino G, et al. Association of HFE and TMPRSS6 genetic variants with iron and erythrocyte parameters is only in part dependent on serum hepcidin concentrations. *J Med Genet* 2011;48:629-34.
- Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T. Identification of erythroferrone as an erythroid regulator

- of iron metabolism. *Nat Genet* 2014;46:678-84.
22. Mastrogiannaki MMP, Matak P, Peyssonnaud C. The gut in iron homeostasis: role of HIF-2 under normal and pathological conditions. *Blood* 2013;122:885-92.
  23. Zhang AS, Anderson SA, Wang J, et al. Suppression of hepatic hepcidin expression in response to acute iron deprivation is associated with an increase of matrilysin-2 protein. *Blood* 2011;117:1687-99.
  24. Goenka MK, Majumder S, Goenka U. Capsule endoscopy: present status and future expectation. *World J Gastroenterol* 2014;20:10024-37.
  25. Mustafa BF, Samaan M, Langmead L, Khasraw M. Small bowel video capsule endoscopy: an overview. *Expert Rev Gastroenterol Hepatol* 2013;7:323-9.
  26. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. *Ther Adv Drug Saf* 2013;4:125-33.
  27. Jonker FA, Calis JC, Phiri K, et al. Real-time PCR demonstrates *Ancylostoma duodenale* is a key factor in the etiology of severe anemia and iron deficiency in Malawian pre-school children. *PLoS Negl Trop Dis* 2012;6(3):e1555.
  28. Friedman JF, Kanzaria HK, McGarvey ST. Human schistosomiasis and anemia: the relationship and potential mechanisms. *Trends Parasitol* 2005;21:386-92.
  29. Hershko C, Camaschella C. How I treat unexplained refractory iron deficiency anemia. *Blood* 2014;123:326-33.
  30. Bach V, Schruckmayer G, Sam I, Kemmler G, Stauder R. Prevalence and possible causes of anemia in the elderly: a cross-sectional analysis of a large European university hospital cohort. *Clin Interv Aging* 2014;9:1187-96.
  31. Aigner E, Feldman A, Datz C. Obesity as an emerging risk factor for iron deficiency. *Nutrients* 2014;6:3587-600.
  32. van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. *Nat Rev Cardiol* 2011;8:485-93.
  33. Cohen-Solal A, Damy T, Terbah M, et al. High prevalence of iron deficiency in patients with acute decompensated heart failure. *Eur J Heart Fail* 2014;16:984-91.
  34. Jankowska EA, Malyszko J, Ardehali H, et al. Iron status in patients with chronic heart failure. *Eur Heart J* 2013;34:827-34.
  35. Finberg KE, Heeney MM, Campagna DR, et al. Mutations in TMPRSS6 cause iron-refractory iron deficiency anemia (IRIDA). *Nat Genet* 2008;40:569-71.
  36. Du X, She E, Gelbart T, et al. The serine protease TMPRSS6 is required to sense iron deficiency. *Science* 2008;320:1088-92.
  37. Silvestri L, Pagani A, Nai A, De Domenico I, Kaplan J, Camaschella C. The serine protease matrilysin-2 (TMPRSS6) inhibits hepcidin activation by cleaving membrane hemojuvelin. *Cell Metab* 2008;8:502-11.
  38. De Falco L, Sanchez M, Silvestri L, et al. Iron refractory iron deficiency anemia. *Haematologica* 2013;98:845-53.
  39. Heeney MM, Finberg KE. Iron-refractory iron deficiency anemia (IRIDA). *Hematol Oncol Clin North Am* 2014;28:637-52.
  40. Nai A, Pagani A, Silvestri L, et al. TMPRSS6 rs855791 modulates hepcidin transcription in vitro and serum hepcidin levels in normal individuals. *Blood* 2011;118:4459-62.
  41. Benyamin B, Ferreira MA, Willemsen G, et al. Common variants in TMPRSS6 are associated with iron status and erythrocyte volume. *Nat Genet* 2009;41:1173-5.
  42. Tanaka T, Roy CN, Yao W, et al. A genome-wide association analysis of serum iron concentrations. *Blood* 2010;115:94-6.
  43. An P, Wu Q, Wang H, et al. TMPRSS6, but not TF, TFR2 or BMP2 variants are associated with increased risk of iron-deficiency anemia. *Hum Mol Genet* 2012;21:2124-31.
  44. Warsch S, Byrnes J. Emerging causes of iron deficiency anemia refractory to oral iron supplementation. *World J Gastrointest Pharmacol Ther* 2013;4:49-53.
  45. Stein J, Stier C, Raab H, Weiner R. Review article: the nutritional and pharmacological consequences of obesity surgery. *Aliment Pharmacol Ther* 2014;40:582-609.
  46. Obinwanne KM, Fredrickson KA, Mathiason MA, Kallies KJ, Farnen JP, Kothari SN. Incidence, treatment, and outcomes of iron deficiency after laparoscopic Roux-en-Y gastric bypass: a 10-year analysis. *J Am Coll Surg* 2014;218:246-52.
  47. Franceschi F, Zuccalà G, Roccarina D, Gasbarrini A. Clinical effects of *Helicobacter pylori* outside the stomach. *Nat Rev Gastroenterol Hepatol* 2014;11:234-42.
  48. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 2013;108:656-76.
  49. Murray JA, McLachlan S, Adams PC, et al. Association between celiac disease and iron deficiency in Caucasians, but not non-Caucasians. *Clin Gastroenterol Hepatol* 2013;11:808-14.
  50. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;361:2436-48.
  51. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood* 2006;107:1747-50.
  52. Brugnara C, Mohandas N. Red cell indices in classification and treatment of anemias: from M.M. Wintrobe's original 1934 classification to the third millennium. *Curr Opin Hematol* 2013;20:222-30.
  53. Camaschella C. How I manage patients with atypical microcytic anaemia. *Br J Haematol* 2013;160:12-24.
  54. Macdougall IC, Bock AH, Carrera F, et al. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. *Nephrol Dial Transplant* 2014;29:2075-84.
  55. Sazawal S, Black RE, Ramsan M, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet* 2006;367:133-43.
  56. Drakesmith H, Prentice AM. Hepcidin and the iron-infection axis. *Science* 2012;338:768-72.
  57. Clark MA, Goheen MM, Fulford A, et al. Host iron status and iron supplementation mediate susceptibility to erythrocytic stage *Plasmodium falciparum*. *Nat Commun* 2014;5:4446.
  58. Atkinson SH, Armitage AE, Khandwala S, et al. Combinatorial effects of malaria season, iron deficiency, and inflammation determine plasma hepcidin concentration in African children. *Blood* 2014;123:3221-9.
  59. Kortman GA, Raffatellu M, Swinkels DW, Tjalsma H. Nutritional iron turned inside out: intestinal stress from a gut microbial perspective. *FEMS Microbiol Rev* 2014;38:1202-34.
  60. Krayenbuehl PA, Battegay E, Breyman C, Furrer J, Schulthess G. Intravenous iron for the treatment of fatigue in non-anemic, premenopausal women with low serum ferritin concentration. *Blood* 2011;118:3222-7.
  61. Pasricha SR Sr, Low M, Thompson J, Farrell A, De-Regil LM. Iron supplementation benefits physical performance in women of reproductive age: a systematic review and meta-analysis. *J Nutr* 2014;144:906-14.
  62. Bregman DB, Goodnough LT. Experience with intravenous ferric carboxymaltose in patients with iron deficiency anemia. *Ther Adv Hematol* 2014;5:48-60.
  63. van Santen S, de Mast Q, Oosting JD, van Ede A, Swinkels DW, van der Ven AJ. Hematologic parameters predicting a response to oral iron therapy in chronic inflammation. *Haematologica* 2014;99(9):e171-e173.
  64. 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;54:306-15.
  65. Vadhan-Raj S, Strauss W, Ford D, et al. Efficacy and safety of IV ferumoxytol for adults with iron deficiency anemia previously unresponsive to or unable to tolerate oral iron. *Am J Hematol* 2014;89:7-12.

66. Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. *Hematology Am Soc Hematol Educ Program* 2010;2010:338-47.
67. Bager P, Dahlerup JF. The health care cost of intravenous iron treatment in IBD patients depends on the economic evaluation perspective. *J Crohns Colitis* 2010;4:427-30.
68. Reinisch W, Chowers Y, Danese S, et al. The management of iron deficiency in inflammatory bowel disease — an online tool developed by the RAND/UCLA appropriateness method. *Aliment Pharmacol Ther* 2013;38:1109-18.
69. Bailie GR, Larkina M, Goodkin DA, et al. Variation in intravenous iron use internationally and over time: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2013;28:2570-9.
70. Rampton DFJ, Folkersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. *Haematologica* 2014;99:1671-6.
71. Gupta A, Manaktala U, Rathore AM. A randomised controlled trial to compare intravenous iron sucrose and oral iron in treatment of iron deficiency anemia in pregnancy. *Indian J Hematol Blood Transfus* 2014;30:120-5.
72. 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;34:30-8.
73. 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;36:657-68.
74. Auerbach M, Strauss W, Auerbach S, Rineer S, Bahrain H. Safety and efficacy of total dose infusion of 1,020 mg of ferumoxytol administered over 15 min. *Am J Hematol* 2013;88:944-7.
75. New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines. London: European Medicines Agency, 2013 ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2013/06/WC500144874.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144874.pdf)).
76. Bircher AJAM, Auerbach M. Hypersensitivity from intravenous iron products. *Immunol Allergy Clin North Am* 2014;34:707-23.
77. Fernández-Real JM, Manco M. Effects of iron overload on chronic metabolic diseases. *Lancet Diabetes Endocrinol* 2014;2:513-26.
78. Fishbane S, Hazzan AD. Anaemia: FIND-CKD: intravenous iron in predialysis CKD. *Nat Rev Nephrol* 2014;10:488-9.

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