A Brief Review for Clinicians of Iron Metabolism and the Safety, Efficacy, and Rationale for Use of Intravenous Iron Products

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Abstract: Iron is an abundant element that is essential for multiple biologic processes. Iron metabolism is not entirely understood, but since the discovery of hepcidin, much progress has been made especially in the last five years. This article is intended to enhance clinician understanding of iron metabolism which may inform decisions about parenteral iron use in iron-restricted erythropoiesis (IResE). This article briefly discusses intravenous (IV) iron utilization in iron deficiency, anemia of chronic inflammation (ACI), functional iron deficiency (FID), and anemia associated with chronic kidney disease, heart failure, pregnancy, inflammatory bowel disease and cancer. Oral iron therapy is valuable in mild to moderate pure iron deficiency. Intravenous iron is required when a prompt response is needed in severe pure iron deficiency. ACI is a hypoferremic state resulting from altered iron metabolism. In ACI, IV iron is needed to overcome the blocking effects of hepcidin on intestinal absorption. ESAs stimulate erythropoiesis increasing iron utilization. This surge in iron requirement can result in FID, especially when ESAs are used in patients with ACI. Intravenous iron is required to treat or avoid iron deficiency in FID when inflammation is present. Parenteral iron maximizes ESA response and can make using erythropoiesis-stimulating agents (ESAs) safer by being ESA sparing. The complex and seemingly ubiquitous nature of iron in humans and the inadequate methods of assessment of iron status in inflammatory states means clinical and laboratory monitoring and individualization of care remain essential. The decision to administer intravenous iron is complex as it often lacks robust consensus guidelines; despite this we can expect utilization of these products to increase as they are safe, effective and necessary.

Keywords: Iron, Parenteral Iron, Intravenous Iron, Hepcidin, Ferroportin, Anemia, Metabolism

1. Introduction

Iron is an essential element involved in cellular respiration, energy production, mitochondrial function, cellular proliferation and repair. It is a ubiquitous element that readily donates and accepts electrons. It participates in oxidative-reduction reactions that are essential for many biologic processes and serves as a necessary component of heme (e.g., hemoglobin, myoglobin, cytochrome proteins, myeloperoxidases) and numerous other vital proteins [1]. The regulation of iron uptake, transport, and storage is complex and of great importance considering the potential toxicity of iron. Iron elimination is minimal and essentially non-regulated creating the risk of iron toxicity that can result in multiorgan dysfunction or failure. The aim of this review is to provide clinicians a concise overview of iron metabolism and related disorders, followed by a discussion of select clinical conditions for which intravenous iron may be indicated. The intent is to provide relevant information to aid decision making regarding therapeutic iron, especially intravenous iron.
2. Absorption and Iron Regulation

Dietary iron is normally the sole source of iron in healthy people. The recommended daily allowance of iron in adults is 8 mg in males and 18 mg in females. The average daily iron intake from foods and supplements in the United States is 19.3-20.5 mg/day in men and 17.0-18.9 mg/day in women older than 19 years of age [2]. Iron absorption from the diet is tightly regulated to prevent toxicity at the duodenal enterocyte, where only a small percentage of the dietary iron is absorbed into the bloodstream. The 1-2 mg of iron absorbed daily replaces the expected small amount of intracellular iron lost during epithelial desquamation and normal bleeding. This enterocyte absorption can be increased significantly when needed, but it is not limitless and cannot increase to levels that could rapidly compensate for acute, severe blood loss.

Iron is absorbed from the diet as either inorganic iron, ferritin, or heme. Inorganic iron is more frequently discussed as less is known about ferritin and heme absorption, but their absorption is thought to share several processes with inorganic iron [3]. It is known that heme is catabolized by hemoxygenase-1 in the enterocyte releasing its iron into the common labile iron pool of the cytosol. Dietary iron in the inorganic, oxidized ferric (Fe$^{3+}$) form is largely reduced to the less commonly found ferrous (Fe$^{2+}$) form for absorption. It is thought to be reduced by ferric reductases, such as duodenal cytochrome B (DcytB). This reduction is facilitated by acidic gastric contents and the oxidation-reduction activity of ascorbic acid. Once reduced, Fe$^{2+}$ is transported across the apical enterocyte membrane by divalent metal transporter 1 (DMT1). The presence of the hydrogen ion (H+) gradient generated by the brush border Na+/H+ exchanger in the duodenum facilitates this uptake [1]. Fe$^{2+}$ taken up into enterocytes enters the labile iron pool from which it is obtained for multiple cellular functions including iron-sulfur cluster biosynthesis and heme synthesis by mitochondria, or it is stored in the cell as ferritin. Ferroportin, the major gatekeeper and the only known mammalian exporter of intracellular iron, transports the non-transferrin bound iron from the gastrointestinal enterocytes, macrophages and red blood cells into the bloodstream which is then oxidized to Fe$^{3+}$ and bound to transferrin with the help of a ferroxidase: hephaestin or ceruloplasmin (Figure 1) [4]. Iron trafficking processes help prevent toxicity by minimizing the amount of labile free iron in blood plasma.

At the duodenal enterocyte, Fe$^{3+}$ is reduced by DcytB (brown) to Fe$^{2+}$. Fe$^{2+}$ is transported across the apical membrane by DMT (blue). Fe$^{2+}$ enters the labile iron pool where it is used or stored in the cell. The bulk of labile iron is exported by ferroportin (FPN) (green) to the blood plasma, where it is converted to Fe$^{3+}$ and loaded onto transferrin (purple). Hepcidin (HPN) decreases iron entry into the circulation by binding to FPN.

Humans require 1-2 mg of iron daily to replenish the amount lost through enterocyte shedding or minor bleeding. Systemically, iron absorbed through enterocytes into the bloodstream is converted to the oxidized ferric (Fe$^{3+}$) form with the help of oxidases, hephaestin, or ceruloplasmin. Iron is then loaded onto transferrin, which serves as the main transporter of iron (Figure 1). Each loaded transferrin bound iron is delivered to the bone marrow for red blood cell (RBC) production, and the remaining iron is diverted to storage (Figure 2). The quantity of iron stored as ferritin in the liver is approximately 1000 mg, with an additional 600 mg in the reticuloendothelial macrophages and 300 mg in the bone marrow.

The duodenal enterocyte absorbs iron into the blood plasma where it binds to transferrin (Fe-Tf). Transferrin carries iron mainly to the bone marrow for erythrocyte production. Senescent erythrocytes are destroyed in the spleen, and their iron is released back into plasma to continue the cycle or it is stored in reticuloendothelial macrophages. Ferroportin (FPN) exports iron. Hepcidin (HPN) is produced in the liver. Inflammation, excess iron and other conditions increase hepcidin production resulting in degradation of ferroportin. Erythroferrone (ERFE) from bone marrow inhibits hepcidin production when erythropoietic demand increases.

RBC production requires 20-25 mg of iron daily. Transferrin cycles iron through binding and release multiple times daily to keep up with erythropoietic iron demand.
Transferrin delivers iron into tissue by the ubiquitous Transferrin Receptor 1 (TfR1) [5]. Circulating RBCs contain approximately 2000 mg of iron with an average survival of approximately 120 days. Senescent RBC iron released from macrophages is circulated back into RBC production at the end of the RBC life cycle, or it is captured and stored in reticuloendothelial macrophages. Erythroid cells are often formed around bone marrow nurse macrophages. It is helpful to understand that erythroid cells maintain an intimate relationship with macrophages throughout their lifespan. Ferritin in the blood mainly originates from macrophages, and the level of ferritin in the bloodstream correlates directly with total body iron stores in the absence of inflammation.

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Iron metabolism is extremely complex and not fully understood. Comprehensive reviews have recently been published [3, 5, 6]. At the cellular level, iron regulatory proteins (IRPs) and iron-responsive elements (IREs) affect iron uptake, storage, and exportation out of the mitochondria. Hepcidin, a key hormone secreted by the liver, along with its receptor ferroportin act as the primary mediator of systemic iron homeostasis, controlling iron availability from dietary and storage sources. Interaction between the cellular regulation via the IRP/IRE system and systemic regulation via the hepcidin/ferroportin system is essential. This interaction helps prevent toxicity from excess iron. Hepcidin decreases iron entry into the circulation by binding to ferroportin and inducing ferroportin's internalization, ubiquitination, and degradation in lysosomes. Hepcidin levels are increased by iron overload as a mechanism to prevent iron toxicities. Transferrin Receptor 2 (TfR2) detects the amount of iron stored in the liver and increases hepcidin levels resulting in decreased iron entry into the plasma [3]. Iron deficiency, hypoxia, exogenous erythropoietin, and increased erythropoietic demand from anemia all inhibit hepcidin transcription, resulting in increased ferroportin activity leading to a rise in iron levels in the bloodstream (Figure 2). Insufficient or excess activity of this ferroportin/hepcidin system contributes to many disorders of iron metabolism.

Inflammation is a defense mechanism to injury, toxins, infection, or other insults that involve cytokine or chemokine release. The intensity of inflammation varies with the degree of cytokine release acutely or chronically. Transferrin is decreased by cytokines released during inflammation. Hepcidin acts as an acute phase reactant. Its levels increase with inflammation resulting in limited iron absorption by halting iron export into the bloodstream- the result of which is hypoferrremia. Ferritin also acts as an acute phase reactant. Under the influence of cytokines, it is released in inflammatory states explaining elevated ferritin levels unrelated to total body iron stores. In the presence of inflammation, this explains the low iron, low transferrin iron-binding capacity (TIBC), and elevated ferritin levels often seen on clinical laboratory evaluation (Table 1). Iron handling in this manner is thought to be part of a host defense mechanism to sequester iron away from invading pathogens that require it for replication. This nutritional immunity is an adaptive process involving the hormone hepcidin that itself may be considered a component of the innate immune system [7, 8]. The result is a cycling of iron in a manner that maintains erythropoiesis, avoids iron toxicity, and protects from pathogens that require iron for their metabolism and replication.

### Table 1. Iron Studies.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal</th>
<th>Iron Deficiency Anemia</th>
<th>Anemia of Chronic Inflammation</th>
<th>Iron Overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>60-150 mcg/dL</td>
<td>Low</td>
<td>Low-Normal</td>
<td>High</td>
</tr>
<tr>
<td>TIBC</td>
<td>300-360 mcg/dL</td>
<td>High</td>
<td>Low-Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Tsat</td>
<td>20-50%</td>
<td>Low</td>
<td>Low-Normal</td>
<td>High</td>
</tr>
<tr>
<td>Ferritin</td>
<td>40-200 ng/mL</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

+ Transferrin iron-binding capacity (TIBC); Transferrin saturation (Tsat).

### 3. Iron Deficiency and Iron Overload States

Disordered iron homeostasis is associated with several disease states, most notably iron deficiency (ID). The most widely recognized manifestation of iron deficiency is anemia (IDA). Nearly one-quarter of the world's population is anemic, with half of these cases attributable to IDA [9, 10]. In adults, IDA can reduce physical performance, work productivity, and cognition in the elderly. It can negatively impact a number of outcomes in patients with chronic disease. Iron depletion and deficiency progress through several stages. It takes several days to weeks of deficient iron intake to manifest...
demonstrable changes in the relatively long-lived RBC population. It is important to recognize that iron deficiency in the absence of anemia is much more common than iron deficiency anemia. Symptoms may occur with earlier, milder iron deficiency before the development of anemia. The first stage of mild deficiency is a storage iron depletion with decreased serum ferritin and decreased bone marrow iron levels. This first stage is difficult to detect in the presence of inflammation. Further iron depletion results in marginal deficiency, which is iron-deficient erythropoiesis with depleted iron supply to erythropoietic cells and declining transferrin saturation; however, hemoglobin levels will usually remain normal. In the final stages of deficiency, as iron stores are exhausted, the hemoglobin and hematocrit begin to decline with resulting microcytic RBCs that are hypochromic due to low hemoglobin concentration [11]. Clinically, we are not able to reliably assess iron deficiency in tissue other than in the bone marrow or RBCs. The findings of low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin (MCH) on traditional RBC indices and the hypochromic, microcytic changes on peripheral smear occur later in the clinical course due to the relatively long-lived RBCs. Readily available hematologic indices are not sensitive or specific enough to adequately describe the full spectrum of iron status. This explains why early undetectable iron deficiency may be symptomatic.

Any detected iron deficiency should be thoroughly investigated. Common causes of iron deficiency include insufficient dietary iron, malabsorption of iron, and blood loss. In the absence of continued bleeding, most cases of iron deficiency resolve with oral iron supplementation. The newer approach of administering oral iron twice daily every other day is associated with less frequent adverse gastrointestinal effects and more effective delivery [12, 13]. This approach is thought to avoid the hepcidin elevation and subsequent decrease in percent absorption seen with daily oral iron. More urgently needed iron replacement is addressed with intravenous iron. The parenteral route avoids any concerns about hepcidin impairing absorption, resulting in more rapid correction of anemia and the avoidance of blood transfusions. Clinical conditions with severely impaired iron absorption, such as in post-gastrectomy patients, frequently require IV iron replacement.

The tight regulation of iron absorption and the handling of labile plasma iron (non-transferrin bound iron) avoids life-limiting toxicities. Loss of control over iron regulation occurs in hereditary hemochromatosis, which can be a life-limiting disease. This group of diseases usually involves mutations in hepcidin or the regulatory elements that interact with hepcidin. Disease severity ranges from mild to severe based in part on the specific causative mutation. In severe hemochromatosis, accumulated excess iron is associated with cardiac arrhythmias, restrictive cardiomyopathy, cirrhosis, risk of hepatocellular carcinoma, endocrinopathies, and pancreatic failure. The damage from iron overload also occurs in patients with myelodysplasia, sickle cell anemia, transfusion-dependent thalassemia and others who frequently receive blood transfusions. Serum iron levels, TIBC, and iron saturation (total serum iron level/TIBC) should be monitored in these patients who often require chelation therapy. The iron percent saturation is perhaps the most useful initial clinical iron study. Quantitative assessment of hepatic iron with MRI is frequently indicated when initial iron studies indicate significant overload [14].

4. Anemia of Chronic Inflammation

Anemia of chronic inflammation (ACI) and iron deficiency anemia are the two most common anemias worldwide. Anemia of chronic inflammation (also known as anemia of chronic disease) is the most frequent anemia recognized in hospitalized and chronically ill patients. It is prevalent in chronic infections, autoimmune diseases, cancer, and other diseases with prolonged immune activation. Typically, it is mild to moderately severe anemia (hemoglobin 7-12 g/dL) that develops in the presence of inflammation [15, 16]. ACI, or iron sequestration anemia, is characterized by sequestration of iron in reticuloendothelial macrophages and release from these macrophages of non-labile iron in the form of ferritin. The literature on ACI and iron-related anemias can be unnecessarily complicated, using multiple names that may not be interchangeable, such as anemia of chronic disease, iron-restricted anemia, and functional iron deficiency. Consistent, well-defined terminology will be applied in this article to enhance clarity and accelerate understanding. Perhaps the clearest and most helpful categorization of these iron-related anemias is the use of the term iron-restricted erythropoiesis (IReS) [17]. The four categories of IReS are absolute iron deficiency, iron-sequestration syndromes due to altered iron trafficking driven by inflammation, functional iron deficiency (FID) resulting from an imbalance between surging iron requirement stimulated by erythropoiesis-stimulating agents (ESA) and iron availability, and molecular defects. This report will distinguish true iron deficiency with or without anemia from the iron-sequestration syndromes and FID. Molecular defects are beyond the scope of this article. Evaluating each of these categories' potential contribution may provide some clarity or insight for clinical decision making. The awareness that these categories of Iron Restricted erythropoiesis (IReS) may be seen alone or in any combination is especially useful in anemia of chronic kidney disease where iron deficiency, inflammation, and the use of ESAs are commonly seen together.

Inflammation in healthy individuals is an immune response that constrains and neutralizes infection or other tissue injuries. Inflammation is mediated by cytokines, signaling molecules, that also regulate immunity and hematopoiesis. These cytokines also regulate macrophage recycling of iron and subsequent iron sequestration. Inflammation decreases erythropoietic output and decreases RBC lifespan by enhancing macrophage erythropagocytic activity, resulting in anemia [15, 16]. Inflammatory cytokines, especially interleukin-6 (IL-6), induce hepcidin transcription. Hepcidin degrades ferroportin, thereby decreasing iron export into the
bloodstream from the gastrointestinal tract and macrophages (Figure 2). Hypoferremia develops from decreased iron absorption and increased macrophage retention of iron. The hypoferremia does not necessarily indicate true iron deficiency as the iron stores are typically preserved. Inflammation and increased hepcidin also decrease transferrin production, reflected by a low TIBC (Table 1). Ferritin levels are elevated as macrophages and hepatocytes, in the presence of inflammation, secrete iron-loaded ferritin through nonclassical secretory autophagy and multivesicular body-exosome pathways [18]. The clinical laboratory findings that characterize ACI are low to low-normal iron, low to normal TIBC levels and low to normal transferrin saturation (Tsat) in the presence of normal iron stores and normal to increased ferritin levels. The diagnosis of ACI is made more straightforward in the presence of an elevated erythrocyte sedimentation rate and C-reactive protein. The difficulty arises when ACI coexists with iron deficiency (from mild undetectable to severe) or the ESA-related FID. The use of traditional labs for diagnosis is complicated by the lack of sensitivity and specificity to detect symptomatic mild underlying iron deficiency reliably. Measurement of the serum transferrin receptor (sTfR) can be used to detect absolute iron deficiency, but this marker is less reliable in the presence of inflammation. The sTfR/log Ferritin (TfR-F) index may be more helpful in distinguishing the presence of a coexisting iron deficiency but is not currently widely accepted [9, 19]. Other measures, such as the reticulocyte hemoglobin content or Thomas-plots, can be considered but are also not widely accepted or available at most institutions [20, 21]. The development of more accurate laboratory testing is needed to improve our ability to assess iron deficiency or FID in the presence of ACI.

The development of ACI is a complex pathophysiological process affecting multiple systems. At the level of the bone marrow, circulating cytokines blunt the response to erythropoietin (EPO). This bone marrow hyporesponsiveness to erythropoietin in the presence of inflammation has been linked to both interleukin-1 (IL-1) and IL-6 [22]. The inflammatory response lowers plasma iron available for erythropoiesis, thus favoring host defense over RBC production [17]. One possible explanation of why these changes evolved is that non-transferrin bound iron is a potent stimulus for gram-negative bacteria [23, 24]. The term hepcidin was derived due to its production in the liver (hep) and its antimicrobial properties (cidin) [24, 25]. The body's efforts to sequester essential iron away from pathogens has been termed nutritional immunity, which is an adaptive immunity and may be considered part of the innate immune system [9]. The mechanisms of inflammation and iron handling are not fully understood, but what is known helps us understand iron's tight control, especially during inflammation states.

ACI is the primary or contributing cause of anemia in chronic obstructive pulmonary disease, chronic heart failure, chronic kidney disease, and other conditions. Therapeutic decisions in ACI are usually individualized based upon the disorders present, the degree of inflammation, and the inflammation type. In most cases, ACI is best managed by decreasing the underlying inflammation. Clinical examples of this approach are demonstrated in the management of Castleman's disease with anti-IL-6 therapy and rheumatoid arthritis with anti-TNFα therapy [26, 27]. ACI alone rarely reaches the severity of anemia that pure iron deficiency can frequently reach. The anemia of ACI is less severe than that of advanced iron deficiency in part because retained heme and iron in macrophages cause ferroportin synthesis by macrophages, thereby increasing iron release, preventing the development of more severe anemia. In this situation, the body's erythropoietic need for iron exceeds the immune needs for hypoferremia.

Intravenous iron therapy is often required in ACI as increased hepcidin makes correction with oral therapy difficult due to ferroportin degradation. IV iron may improve this anemia, but it comes with risks of iron overload and possibly infusion-related safety issues. ESAs have been used in ACI to increase erythrocyte production. This raises the demand for iron in the low iron state of ACI and often results in FID. IV iron should be considered when ESA is provided to avoid the development of an FID. Other concerns include decreased responsiveness to erythropoietin (EPO) and ESA in ACI as well as concerns for ESA-related thrombotic complications [16, 28, 29, 30]. Specific consensus guidelines for IV iron and ESA use in ACI are lacking. This lack of guidance means that the therapeutic provision of IV iron with or without ESA in ACI requires an individualized approach beginning with considering the contribution of the patient's anemia to morbidity and the therapy's potential impact on prognosis. Novel agents such as hepcidin antagonists, transferrin receptor blockers, or IRE/IRP targeted agents may become necessary in this disorder.

5. Anemia of Chronic Kidney Disease

Anemia of chronic kidney disease is an expected consequence of both inflammation and reduced EPO synthesis as renal mass declines in chronic kidney disease (CKD). A clinical predictor of the development of anemia in CKD is the declining glomerular filtration rate [31-33]. EPO is synthesized in peritubular interstitial fibroblasts in the renal cortex and outer medulla [34, 35]. Anemia in CKD can be expected from decreased EPO production alone; although, it may be multifactorial in the setting of inflammation, frequent use of ESA, and iron deficiency. Progression of anemia in CKD can lead to debility, lethargy, muscle fatigue, and renal function deterioration. The treatment approach differs depending on the patient's need for dialysis. In non-dialysis dependent patients, treatment is usually not instituted until patients are symptomatic or severely anemic [36]. Iron deficient patients may begin therapy with oral iron agents, but oral therapy can be expected to be suboptimal in the inflammatory state (ACI) of CKD. Intravenous iron products are required for non-responders to oral iron supplementation. Absolute or relative EPO deficiency may also be present in
patients have been suboptimal. In the FIND CKD trial, serious providing IV iron when serum ferritin is < 500 ng/mL and patients with an active infection.

Evidence from large randomized controlled trials in CKD, highlighting ESA administration's adverse health effects, led to advocating for IV iron therapy as an ESA sparing adjunct in CKD [39]. Intravenous iron should always be considered as it can optimize ESA effectiveness, and it is ESA sparing.

ESA use improves the quality of life for end-stage renal disease patients in dialysis-dependent patients when the hemoglobin is less than 10gm/dL [36, 40, 41, 42, 43]. CKD patients on dialysis are prone to developing iron-deficiency anemia from blood loss in the dialyzer circuit and frequent blood sampling. Ongoing blood loss and ESA use lowers iron levels, which can lead to iron deficiency and suboptimal ESA response in these patients creating an FID in the setting of anemia of chronic kidney disease. Virtually all dialysis patients at some point will benefit from an ESA in addition to parenteral iron. Determining the appropriate timing and dosing of IV iron is a clinical challenge, made more difficult by the lack of sensitivity and specificity in iron deficiency routine tests. Monitoring total body iron in these patients with serum iron, transferrin saturation, and TIBC is routine clinical practice but suboptimal, as previously stated [17]. Ferritin levels are also problematic as they reflect hepatosplenic siderosis more than bone marrow iron stores [44, 45].

The safety of IV iron use in CKD patients has been questioned, given the concern of iron overload [46]. Indiscriminate IV iron use results in iron overload and suboptimal response to ESAs. Excess iron in CKD patients can result in liver iron levels equal to untreated hemochromatosis patients [47]. The production of reactive iron species from excess iron leads to organ malfunction [48]. Caution is particularly needed in patients with predisposing conditions such as cirrhosis. Intravenous iron administration in dialysis patients must be monitored as IV iron may also carry an increased risk of infection, oxidative stress, vascular calcification, cardiovascular morbidity and mortality [36, 46, 49]. Clinicians frequently temporarily discontinue IV iron in patients with an active infection.

Clinical studies on the timing and dosing of IV iron in CKD patients have been suboptimal. In the FIND CKD trial, serious adverse events were similar between oral and IV use [50]. This contrasts with the REVOKE trial where statistically significant higher levels of serious adverse cardiovascular events, infections, and hospitalizations were seen with IV iron [49]. The differences between these studies have been discussed in the literature [36, 51-53]. The Kidney Disease: Improving Global Outcomes (KDOQI) guidelines suggest providing IV iron when serum ferritin is < 500 ng/mL and transferrin saturation (TSAT) < 30%. The National Kidney Foundation: Kidney Disease Outcomes Quality Initiative (KDOQI) and Canadian guidelines agree with these iron laboratory cutoffs for initiating IV iron in CKD [46]. Despite some agreement, an evidence-based consensus of IV iron use has yet to be established. The most widely accepted, clinically useful study to date is the PIVOTAL trial published in 2018 [40]. This study's primary endpoint was death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. Giving high-dose IV iron sucrose at 400 mg monthly, unless ferritin >700 ug/L or transferrin saturation >40%, was superior to giving low dose 0-400 mg monthly IV iron sucrose as needed when ferritin <200 ug/L or the transferrin saturation was <20% [40]. High-dose iron therapy patients in this study had fewer blood transfusions and received lower doses of ESAs. The higher dose regimen was non-inferior in terms of cardiovascular events, such as myocardial infarction or heart failure hospitalization rates and was ESA sparing. Current clinical practice is often guided by this landmark study; although, longer follow-up may better address safety concerns. A need for more randomized clinical trials along with new therapeutic agents for anemia of CKD remains.

6. Heart Failure

Heart failure is an inflammatory condition associated with elevated inflammatory cytokines, such as IL-1, IL-6 and tumor necrosis factor-alpha (TNFα) [54, 55]. The anemia that develops in heart failure is poorly understood and considered to be multifactorial with underlying ACI and/or iron deficiency. Anemia is common in heart failure patients and correlates with decreased exercise capacity, increased rehospitalization rates, and predicts poorer outcomes and quality of life [57, 58]. Multiple factors may contribute to anemia in heart failure, including iron deficiency, renal dysfunction, drug effects, bone marrow hyporesponsiveness, cardiac performance, and altered neurohormonal and inflammatory responses [59]. Patients who have heart failure with reduced ejection fraction (HFrEF) and anemia compared to patients with HFpEF without anemia are typically older, more likely to have CKD, more severe heart failure, worse functional statuses, lower exercise capacity, reduced quality of life and higher neurohormonal and pro-inflammatory cytokine activation. Surprisingly, anemic heart failure patients have been found to have better left ventricular ejection fractions (LVEF), presumably due to lower blood viscosity. In patients with HFpEF and CKD, hemoglobin increases have been demonstrated to decrease LVEF and cardiac output [60] proportionally. An increase in hemoglobin over time is associated with decreased LVEF [59-62]. Higher hemoglobin levels in HFpEF may increase blood viscosity, systemic vascular resistance, raise the left ventricular afterload and cause the LVEF to decrease.

Heart cells require iron for energy production and metabolic processes. Elevated cytokines in heart failure could be expected to produce hepcidin and ACI; however, recent studies have demonstrated decreased systemic hepcidin levels in heart failure [63, 64]. The iron regulation, heart failure, and inflammation interactions seem paradoxical and become even
Intravenous iron is recommended to treat iron deficiency, regardless of hemoglobin level for symptomatic patients with HFrEF [721]. A meta-analysis of IV iron, specifically ferric carboxymaltose (FCM) on mortality and hospitalizations using individual patient data extracted from four randomized controlled trials including data from two small previously unreported studies, concluded that IV iron was associated with a reduction in recurrent cardiovascular hospitalizations in HFrEF [64]. The 2016 European Society of Cardiology guidelines gave a Class IIa recommendation for IV FCM to be considered in symptomatic patients to alleviate heart failure symptoms, improve exercise capacity, and quality of life in patients with ferritin <100 ugs/L or ferritin 100-299 ugs/L along with Tsat <20%. The 2017 American College of Cardiology, American Heart Association, and Heart Failure Society of American (ACC/AHA/HFSA) guidelines also gave a Class IIb recommendation for IV iron use to improve functional status and quality of life in patients with New York Heart Association (NYHA) functional class II and III and a serum ferritin <100 ugs/L defined as absolute iron deficiency, or serum ferritin 100-300ug/L in combination with a Tsat of <20%. These recommendations favor IV iron in heart failure patients with iron deficiency but are not strong recommendations. Consensus on whether IV iron should be given to all iron-deficient patients regardless of anemia status has not been established. The clinical benefits of IV iron therapy in patients with heart failure result from increases in hemoglobin concentration in iron-deficient, anemic patients and perhaps from replenition of iron for other iron-requiring metabolic processes. Clinically, patients often report symptomatic improvement within twenty-four hours of iron infusion, which is far too soon to be attributed to improved anemia. This early symptomatic improvement may be a result of iron replenition in cellular energy-producing processes other than erythropoiesis. The benefits of IV iron use in heart failure patients have been demonstrated, but further studies are needed to investigate whether there is an impact on overall mortality.

The use of ESA in heart failure patients has also been previously investigated. ESA’s improved exercise duration and 6-minute walk distance in heart disease, but all-cause mortality improvement was borderline [72]. The large RED-HF trial of ESA found no effect on hospitalization or deaths and had higher thromboembolic events [73]. This trial suggests that anemia by itself is probably not a mediator of poor outcomes, but rather a marker of heart failure severity. It showed no improvement in outcomes but an increase in thromboembolic events. The overall consequences of correcting anemia in heart failure with ESAs are a tradeoff between the favorable effects of improving oxygen delivery and the putative cardioprotective effects of ESAs and the unfavorable effects of higher hemoglobin with increasing viscosity, vascular resistance, blood pressure and of ESA hypercoagulability. ESA use is known to increase strokes and thromboembolic events. These agents did not improve outcomes but were associated with a higher risk of adverse events. They are considered to have no benefit with heart failure (HF) and anemia and should not be used to improve morbidity and mortality [74].

The pathophysiologic changes in anemia of heart failure are not entirely understood. The familiar problem of inability to reliably determine iron status with usual clinical lab studies makes it difficult to determine if undetected iron deficiency might explain symptoms, such as fatigue in CHF patients. It is known that improvement in non-hematopoietic tissue function can be seen with IV iron [69]. The presence of iron deficiency without anemia explains symptomatic improvement with IV iron. The use of infrequent IV iron dosing based on clinical and laboratory evaluation, including post-therapy reassessment, appears at present to be our most prudent
strategy in select heart failure patients with iron deficiency with or without anemia.

7. Anemia in Cancer

Anemia is commonly seen in cancer patients, with a wide-ranging prevalence (29-60%) across different malignancies [75]. Anemia in cancer patients has been identified as an independent adverse prognostic factor for survival [76]. Symptom severity is widely variable, with quality of life frequently being negatively affected. Malignancy-related anemia may be caused by bleeding, hemolysis, chemotherapy-induced myelosuppression, nutritional deficiencies, bone marrow infiltration or destruction and many other causes. Cancer, especially advanced cancer, is a chronic disease that has an inflammatory component. As in other inflammatory anemias, serum iron, TIBC, Tsat, and ferritin are not always as helpful in discerning iron deficiency in the presence of ACI.

Prior to the 1990s, the only therapeutic options for anemia in cancer were oral iron and blood transfusion. Oral iron may be sufficient in pure iron deficiency, but treatment often fails to improve iron stores adequately and is often intolerable due to gastrointestinal disturbance. Blood transfusion is very effective but carries infectious, immunologic, and other significant risks [77-79]. In the 1990s, ESAs were introduced for use in chemotherapy-induced anemia. ESAs were initially used in anemic cancer patients who were not iron deficient to improve quality of life. These agents were widely used until it was shown that they increase the risk of thromboembolic events and mortality. A large meta-analysis from 53 randomized controlled trials demonstrated a 17% higher risk of mortality in cancer patients who received ESAs than controls [80, 81].

Concern over increased risk of cancer progression has been raised but was not proven in clinical trials. The risk associated with ESAs prompted enrollment of these agents in the Risk Evaluation and Mitigation Strategies (REMS) program. Guideline recommendations and Federal Drug Administration (FDA) approval for ESAs in cancer became more restrictive. They are only indicated for incurable disease patients receiving palliative chemotherapy with a hemoglobin below 10 g/dL who would not benefit from blood transfusions. Several cancer society guidelines (i.e., European Society of Medical Oncology, American Society of Hematology, American Society of Clinical Oncology, National Comprehensive Cancer Network) vary with regards to Tsat and ferritin cutoffs. However, they are similar in regards to sparing ESA use in cancer. More restrictive use led to the addition of iron supplementation to ESAs in an effort to be ESA sparing. In a meta-analysis of cancer patients on chemotherapy, the benefit of IV iron with ESA was demonstrated [82]. Intravenous iron supplementation improves hemoglobin response to ESA, decreases blood transfusion rates in patients receiving ESA, and decreases the dose of ESA required [70]. The difficulties in providing ESAs safely to anemic cancer patients has shifted the focus to use IV iron alone. IV iron has demonstrated benefit in terms of improved anemia without significant safety concerns in systematic reviews [83, 84].

Cancer is a heterogeneous disease often with a dynamic, widely variable clinical course involving multiple primary sites and hundreds of histologic cell types. The usual diagnostic laboratory studies of serum iron, TIBC, Tsat and ferritin do not provide enough information in many patients to understand their iron status with confidence. Consequently, it is unlikely that guidelines can be robust enough with these limitations to develop specific and comprehensive guidelines for anemia in cancer. Oral iron should be reserved for patients with true iron deficiency anemia and the ability to tolerate the treatment. Intravenous iron should remain first-line for those with severe iron deficiency requiring a more prompt correction. In the presence of anemia in cancer patients, IV iron should be used early and before ESAs. The use of ESA in cancer should follow its restricted indication, and in most cases, should be preceded or accompanied by IV iron. This approach is similar to that used in CKD patients with anemia [40, 85]. The use of IV iron in most cancer patients will remain an individual decision as guidelines exist, but cannot be expected to address the heterogeneity presented in these diseases and their clinical circumstances. Blood transfusion remains the last line of therapy that likely will be needed less due to more prevalent IV iron utilization.

8. Inflammatory Bowel Disease

We have previously discussed the impact of hepcidin elevation and inflammation on iron handling and RBC levels. Cytokines and chemokines produced in inflammatory bowel disease (IBD) negatively affect erythropoietin activity by inhibiting proliferation and differentiation of erythroid progenitor cells and decreasing RBC half-life as seen in other inflammatory disorders. Iron deficiency anemia is the most common IBD systemic complication due to decreased absorption and bleeding from gastrointestinal involvement. Quality of life and morbidity of IBD are negatively impacted by anemia and iron deficiency. As a result, screening for iron deficiency anemia in IBD has been recommended [86]. Oral iron is recommended as initial therapy for mild iron deficiency in IBD. However, effectiveness may be inadequate due to impaired absorption from mucosal disruption, inflammation, or drug therapy's direct effects. Gastrointestinal side effects from oral iron may also be more prominent in IBD patients. Intravenous iron is initiated with severe anemia and is recommended when oral iron is ineffective or produces intolerable side effects. European Crohn's and Colitis Organization (ECCO) guidelines suggest that IV iron should be used as a first-line for these patients [87]. IV iron provides advantages over oral iron in anemic patients during flares of IBD or IBD patients with severe iron deficiency anemia. ESAs are not commonly used in IBD, but the ECCO guidelines suggest that IV iron should be continued to avoid FID development when an ESA is utilized. The use of IV iron will continue to be important in IBD patients with iron deficiency.
Anemia is a frequent complication seen during pregnancy, with iron deficiency being the most common cause. Antepartum iron deficiency can occur due to increased iron demands from the developing fetus, while postpartum deficiency often results from blood loss during delivery. According to the World Health Organization, the estimated prevalence of anemia in pregnancy is 30-50% and is particularly highest in developing countries [88]. Clinicians need to distinguish between physiologic anemia due to increased plasma volume and true anemia from an underlying pathological cause. The impact of iron deficiency in gravidas has been linked to increased reports of fatigue and depression [88, 89]. Anemia during pregnancy and the postpartum period is associated with increased maternal and fetal morbidity and mortality. Antepartum anemia interferes with the normal intrauterine growth, which can lead to preterm labor and even fetal loss. Neonates who are born iron deficient demonstrate cognitive and behavioral abnormalities along with developmental delays. Despite the considerable adverse effects associated with antepartum iron deficiency, prophylactic treatment with oral iron supplementation in addition to prenatal vitamins is currently not recommended in countries with adequate nutritional resources [88].

Oral iron is frontline therapy for iron deficiency in pregnancy, although many women report medication adherence issues. The most common reasons for limited medication adherence include gastrointestinal side effects such as constipation, dyspepsia, and metallic taste. Constipation is common during pregnancy due to increased progesterone slowing gastric transit and rectal compression by an enlarging gravid uterus, which may further limit oral iron tolerance [88]. Transfusion rates have previously been reported to be higher in women receiving oral iron versus intravenous [90]. Transfusion should remain a last resort both in the antepartum and postpartum periods unless necessary. The appropriate treatment of iron deficiency prevents both the associated complications previously described and the potential necessity for transfusions. In severe iron deficiency cases due to intolerance or lack of response, intravenous iron has been safely used in multiple studies after the first trimester [88].

The use of intravenous iron should be guided by the severity of the iron deficiency and concerns surrounding oral therapy's potential tolerance. The use of intravenous iron has been shown to achieve a more rapid correction of iron deficiency than oral therapy [90]. Several studies have shown higher hemoglobin levels in patients receiving IV iron versus oral therapy, 1.3-2.5 g/dL, compared to 0.6-1.3 g/dL, respectively [88]. Concerns about teratogenicity have limited intravenous iron use in the past, and still no first-trimester safety data exist. Parenteral iron has been extensively studied after the first trimester and is considered a safe alternative to oral iron therapy. The most feared adverse reaction to IV therapy is anaphylaxis, which is extremely rare and associated with no longer available high molecular-weight iron dextran formulations. Safe and effective preparations in pregnancy have substituted these former preparations without any reported serious adverse events. In a recent meta-analysis involving over 10,000 patients, intravenous iron was not associated with an increased risk of serious adverse events or infections than placebo or other oral iron therapies [91]. More commonly seen adverse effects to parenteral therapy are minor infusion reactions such as flushing, dizziness, and flu-like symptoms, occurring at a rate of 1-5%. Currently, iron sucrose 200-300 mg/day IV is the mainstay of therapy in pregnancy. One observational study suggested ferric carboxymaltose to be a safe substitute with potentially fewer side effects as it was shown not to cross the placental barrier [92]. Intravenous iron will likely be used more frequently in these patients as it is effective and safe in pregnant women, with no serious adverse effects reported in numerous published studies.

9. Iron Products

Therapy for mild to moderate iron-deficiency anemia is usually an oral iron preparation. The optimal response to oral iron therapy is a 2 g/mL increase in hemoglobin after three weeks. Therapy should be continued until ferritin's repletion to >100 ng/mL, which usually requires three months or more of therapy [93]. A hemoglobin increase of less than 1 g/dL after three weeks should prompt evaluation for underlying celiac disease, bleeding, autoimmune gastritis, or other causes of malabsorption [94, 95]. The use of oral iron frequently causes gastrointestinal side effects such as nausea, vomiting, constipation, and heartburn. It is thought that because only 10-20% of an oral iron dosage is absorbed, the excess in gastrointestinal iron directly causes adverse effects. Some of the adverse gastrointestinal effects may be due to changes in the gut microbiome from excess iron [96].

The alternate day (i.e., every other day) oral dosing strategy has been utilized to decrease the amount of iron given to minimize gastrointestinal symptoms. This approach maximizes absorption by allowing hepcidin levels to normalize on the days iron is not given. A pilot study by Moretti et al. on non-anemic iron deficiency premenopausal women suggested alternate-day administration of oral iron might be as effective as the daily schedule [12]. Two prospective randomized trials have confirmed this approach in non-anemic women [12, 13]. The alternate-day regimen is now the preferred schedule for oral iron replacement. In circumstances where more rapid correction of severe iron deficiency with a hemoglobin less than 8 g/dL, or for patients with inadequate oral iron absorption, IV iron is administered. The use of IV iron is often needed to comply with conservative RBC transfusion policies. Blood transfusion for iron deficiency anemia is only indicated for the uncommon cases with hemodynamic instability or signs of myocardial ischemia.

Initially, parenteral iron was given as an intramuscular injection of ferric hydroxide. These early products produced local side effects, including pain and discoloration. More importantly, they were associated with hemodynamic toxicity due to labile free iron [93, 97, 98]. This toxicity led to iron
preparations with carbohydrate shells around the iron to decrease labile free iron. Iron saccharide was the first product developed in 1947. It was replaced by a more effective product, high-molecular-weight dextran iron (HMWD), in 1954. The first HMWD product, iron dextran (Imferon), was removed from the market in 1992 by the manufacturer after a recall and reports of rare hypersensitivity cases, some of which were fatal. Other HMWD products are also no longer available. Low-molecular-weight dextran iron (LMWD), INFeD entered the US market in 1992. All currently available parenteral iron products are composed of a colloidal solution of polynuclear cores of Fe$^{3+}$ hydroxide surrounded by carbohydrate shells [95, 100] (Figure 3). The available products in the United States are low-molecular-weight iron dextran (LMWD) INFeD, iron sucrose (IS) Venofer, ferric gluconate (FG) Ferrlecit, ferumoxytol (FXT) Feraheme, ferric carboxymaltose (FCM) Injectafer, and iron isomaltoside (ISM) Monfer. The generic name, trade name, maximal infusion rate, maximal dose, and presence of any black box warnings are listed in Table 2. All of these products are nanoparticle formulations [99]. Infusion of the particles results in iron uptake by macrophages. The products with more stable nanoparticles are less likely to cause infusion reactions and can generally be given more rapidly or at higher doses. Less stable products must be given over one hour.

### Compostion of IV Iron Products

![Figure 3. Colloidal iron core with a carbohydrate shell.](image)

### Table 2. Intravenous Iron Products.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Approved</th>
<th>Max Dose</th>
<th>Max Infusion Rate</th>
<th>Black Box Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe-dextran (LMWD)</td>
<td>INFeD</td>
<td>1991</td>
<td>1000 mg</td>
<td>4-6 hr</td>
<td>Yes</td>
</tr>
<tr>
<td>Fe-glucosate (FG)</td>
<td>Ferrlecit</td>
<td>1999</td>
<td>125 mg</td>
<td>10 min</td>
<td>No</td>
</tr>
<tr>
<td>Fe-sucrose (IS)</td>
<td>Venofer</td>
<td>2000</td>
<td>200mg IV push</td>
<td>2-5 min</td>
<td>No</td>
</tr>
<tr>
<td>Ferumoxytol (FXT)</td>
<td>Feraheme</td>
<td>2009</td>
<td>510 mg</td>
<td>15 min, repeat in 3-8 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Fe-carboxymaltose (FCM)</td>
<td>Injectafer</td>
<td>2013</td>
<td>750 mg</td>
<td>15 min, repeat in 7 days</td>
<td>No</td>
</tr>
<tr>
<td>Fe-isomaltoside (ISM)</td>
<td>Monfer</td>
<td>2020</td>
<td>1000 mg</td>
<td>20 min</td>
<td>No</td>
</tr>
</tbody>
</table>

The reputation parenteral iron had for producing hemodynamic toxicity led to prolonged caution with IV iron products in the medical community. This began to change recently when it was realized that potentially lethal reactions were almost exclusively from the no longer available HMWD products [92, 94, 100]. In one report, absolute rates of life-threatening adverse events were 0.6, 0.9, and 11.8 per million with iron sucrose, ferric gluconate and high molecular weight dextran iron, respectively [101]. The serious adverse events with current IV iron products are rare, with estimates of less than 1 in 200,000 doses [91]. These rates are comparable to IV contrast dye, considered among the safest intravenously administered agents [102]. One of the currently available products, FXT, was first developed and is still sometimes utilized as an IV contrast [103]. Intravenous iron appears to be much safer than blood transfusion, with its estimated adverse effect rate of 1:20,000 [104]. When they occur, the infusion reactions are mild and resolve quickly by discontinuing the infusion and slowing the infusion rate.

Other therapies to treat these mild reactions are usually unnecessary. Patients with an allergic diathesis or with inflammatory arthritis can be premedicated with corticosteroids. The use of diphenhydramine and other antihistamines should be avoided as pretreatment may be responsible for most perceived reactions to iron dextran. The potential adverse reactions produced by current IV iron agents are not IgE mediated, but rather complement-mediated activation-related pseudoallergy [105-107].

Intravenous iron is safe, effective, and convenient as a slow IV push or short infusion. The safety of these products does not mean that adverse reactions will not develop, but they are relatively rare. Intravenous iron should only be administered where resuscitation facilities are immediately available by staff trained for anaphylactoid and anaphylactic reactions. An excellent guide for the management of and minimization and management has been published [104]. Concerns about the safety of available products and the potential harm from long-term repeated administration have not been fully addressed. However, the risk of long-term use appears to be minimal [98]. Specific formulations, such as FCM and possibly IS, can cause hypophosphatemia, which delayed FCM’s FDA approval in 2008. The hypophosphatemia from FCM develops due to increased concentration of intact fibroblast growth factor 23 (FGF-23), a hormone derived from osteocytes, resulting in altered renal phosphate handling [107, 108]. This hypophosphatemia should be monitored, but it appears to be rarely of clinical significance.

### 10. Discussion

The categories of iron-restricted erythropoiesis published by Goodnough et al. are useful in clarifying these anemias [17]. Pure iron deficiency or mild iron deficiency anemia with no inflammatory component (low serum iron, low Tsat, high
In anemia of pregnancy, concerns about teratogenicity have limited intravenous iron use due to a lack of first-trimester safety data. The use of intravenous iron has been extensively studied after the first trimester and is considered a safe alternative to oral iron therapy. The use of IV iron should be guided by both the severity of the iron deficiency and concerns surrounding potential intolerance of oral therapy. The most feared adverse reaction to IV therapy is anaphylaxis, which is extremely rare now that high molecular-weight iron dextran formulations are unavailable.

Quality of life and morbidity of IBD are negatively impacted by anemia and iron deficiency. Therefore, screening for iron deficiency anemia in IBD is recommended [87]. Initial therapy for mild iron deficiency in IBD may be oral iron, but the response may be inadequate due to impaired absorption from mucosal disruption or drug therapy. Additionally, the gastrointestinal side effects of oral iron may be more prominent in IBD patients. ECCO guidelines suggest IV iron as first-line therapy in aggravated anemia and when oral therapy is insufficient or causes intolerable side effects. The ECCO guidelines also suggest that IV iron should be continued to avoid FID development when ESA is utilized. The use of IV iron will continue to be important in IBD patients.

Iron metabolism involves multiple systemic and cellular components and is not fully understood. The ability to confidently determine iron status in ACI with readily available studies does not exist. Serum hepcidin or serum transferrin receptor assays have not changed this uncertainty. Therapeutic decisions will become easier when newer methods of evaluating iron status in ACI become available. Care for ACI should be individualized utilizing clinical judgment, monitoring, and routinely available laboratory iron studies. Fortunately, safety concerns with IV iron have dramatically decreased after HMWD was discontinued in 1992. Novel agents such as hepcidin antagonists, transferrin receptor blockers, or IRE and IRP targeted agents may become important in this disorder. Today, IV iron is frequently the workhorse for ACI therapy.

References


