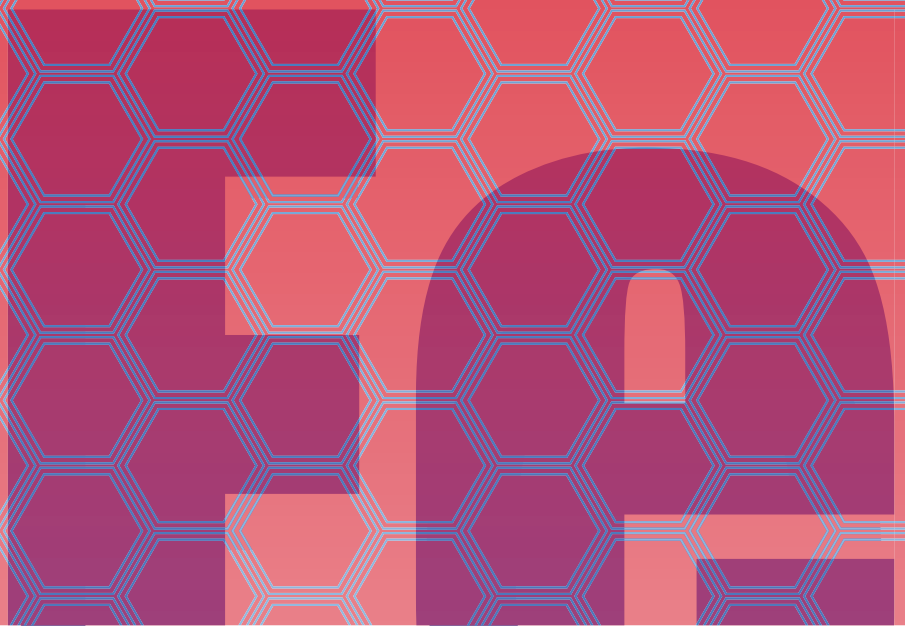
Clinical Update

Issues in Iron Management

in the Hemodialysis Patient



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Introduction

CKD related anemia is a common comorbidity of patients on hemodialysis. Objectives for treating anemia include improving iron stores and providing erythropoiesis-stimulating agent (ESA) to maintain acceptable levels of hemoglobin (Hb) concentration. The treatment of choice for repleting iron stores in hemodialysis patients is intravenous (IV) iron therapy. Although research shows IV iron is more efficacious for restoring iron status compared to oral iron supplements, it should be used judiciously due to risk of adverse events.

Iron Deficiency in Hemodialysis Patients

Iron deficiency is a commonly encountered reversible cause of CKD related anemia and ESA hyporesponsiveness. In addition to the usual causes of iron deficiency, patients on hemodialysis experience routine iron loss due to the dialysis treatment (retention of blood in dialyzer and blood lines), frequent blood draws for laboratory testing, surgical procedures, accidental blood loss (vascular access), and gastrointestinal blood loss. As a consequence, patients on hemodialysis lose approximately 1000 mg of iron per year.[1]

Correction of iron deficiency with iron supplementation can reduce the severity of anemia in patients on hemodialysis. Iron status is assessed using transferrin saturation (TSAT) and ferritin, and guides the indication for iron replacement therapy; however, both indices have caveats that limit their utility in assessing available and stored iron. Clinical practice guidelines suggest the use of IV iron if TSAT is <30% and Ferritin is <500ng/ml, but also suggest exercising caution to balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia related symptoms against the risks of harm in individual patients.[2,3]

IV Iron Use and Serum Ferritin Levels

The use of IV iron in hemodialysis is on the rise. The percentage of patients in the U.S. receiving IV iron has increased from 55% in August 2010 to 69% in April 2014, and prescribed IV dosing of iron has gone from an average of 802 milligrams/month in August 2010 to 914 milligrams/month in April 2014 (reflects 90th percentile of prescribed doses).[4,5] Recent escalation of IV iron use is likely related to an effort to lower ESA dosing requirements based on recent events such as a black box warning added to ESA labeling and initiation of the prospective payment system reimbursement policy.

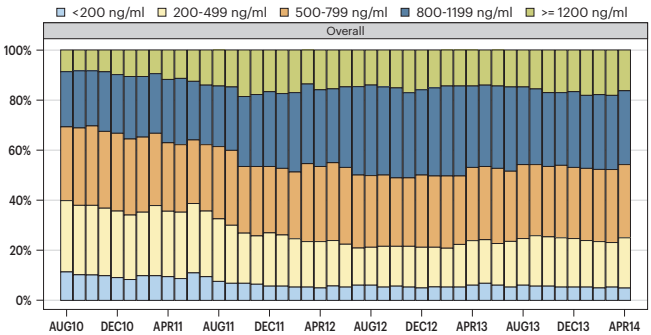
The usual dose of IV iron for dialysis patients is a bolus injection of 100 to 1000 mg, which may exceed transferrin binding sites leading to the presence of free or labile iron concentrations. It is not well appreciated that IV iron formulations exhibit zero-order or capacity limited metabolism by the reticuloendothelial system. This results in longer residence time in plasma with higher administered doses, especially with larger molecular weight formulations.[6] Therefore, IV iron therapy provides a much larger amount of iron compared to the iron losses associated with dialysis and exceeds intestinal iron absorption of 1 to 2 mg/day, over the course of 3 to 4 meals.[7] IV iron also circumvents the carefully regulated iron absorption process in the gastrointestinal tract. This raises concerns of risk for iron toxicity.

Serum ferritin levels have also increased. Serum ferritin levels in U.S. dialysis patients have significantly increased from 2010 to 2012 and remain high. In April 2014, mean ferritin was 799 ng/ml and >75% of patients had ferritin above 500 ng/ml (figure 1).[4] Moreover, mean ferritin levels in the U.S. are the highest when compared to levels in Europe and Japan. High serum ferritin levels are associated with risk of infection, as well as higher mortality risk.[8]

Figure 1 U.S. Trends in Serum Ferritin[4]

Serum ferritin (3 month average), categories

National sample

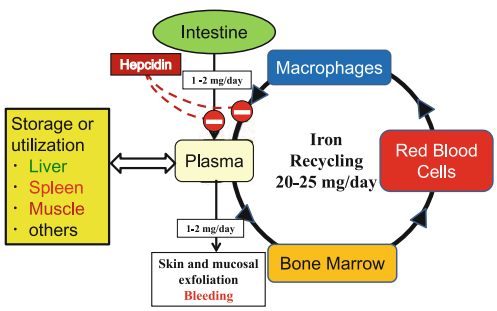


Values at each month are based on the average of at least one measurement obtained within the prior 3 months
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").
Source: US-DOPPS Practice Monitor, August 2014; http://www.dopps.org/DPM

Iron Toxicity and Iron Overload

Hepcidin regulates iron recycling and absorption (Figure 2).[9] Since IV iron is injected directly into the bloodstream, it bypasses hepcidin-regulated intestinal absorption mechanism and is transported into the reticuloendothelial system (RES) where it is stored.[10,11] The inflammatory state associated with CKD may upregulate hepcidin which binds to ferroportin (FPN), resulting in the internalization and degradation of FPN, which sequesters iron by inhibiting iron release by macrophages.[12] As a consequence, despite a normal or elevated serum ferritin, transferrin-bound iron (iron pool available for erythropoiesis) remains low. This leads to functional iron deficiency defined as TSAT <20% and Ferritin >200-500 ng/ml. This raises concerns regarding potential risk of iron toxicity and iron overload. Also, iron accumulation has been reported in hemodialysis patients receiving IV iron. In a magnetic resonance imaging (MRI) study of liver iron stores in a cohort of 119 hemodialysis patients, investigators found that 84% of patients had mild to severe hepatic iron overload, and 30% had severe iron overload.[13] As this is not liver toxicity the clinical significance is unclear, but still concerning.

Figure 2. Hepcidin regulates iron metabolism



Nakanishi, Clin Exp Nephrol 2012

Potential Risks of IV Iron

The prevalent use of IV iron and biological plausibly of iron toxicity in hemodialysis patients raises concerns over risks of anaphylaxis, infection, oxidative stress and cardiovascular disease, and vascular calcification.

Anaphylaxis

Iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic reactions and, should, therefore, be used with vigilance. Although the occurrence of anaphylaxis may be less common with the advent of lower molecular weight dextran IV iron and non-dextran IV iron preparations, precautions are still warranted. The European Medicines Agency recommends administering all IV iron complexes only when staff is trained to evaluate and manage anaphylactic reactions and resuscitation facilities are immediately available. Patients should also be closely monitored for signs of hypersensitivity during and for at least 30 minutes after each administration of an IV iron product.[14]

Infection

Excessive use of IV iron may compromise immune function and increase risk of infection.[7,10] Excess IV iron has been shown to deplete helper T-cells, impair phagocytic ability of polymorphonuclear leukocytes, and limit antibody production.[15] Since iron is essential for bacterial growth and virulence, availability of labile or loosely bound iron could potentiate microbial infection. A study of hemodialysis patients showed that use of IV iron sucrose caused transferrin oversaturation, resulting in free iron in circulation. The appearance of free iron was associated with increased bacterial growth of *Staphylococcus epidermidis* in the serum of these patients *in vitro*.[16] In a recent meta-analysis, Litton et al. found a significant increased risk of all cause infections after IV iron therapy.[17] In a large epidemiologic analysis a significant association between bolus dosing of IV iron preparations and the incidence of infection-related mortality and hospitalization was observed.[18]

Oxidative Stress and Cardiovascular Disease

Administration of IV iron products results in the appearance of free iron, associated with a rise in biomarkers of oxidative stress and inflammation. Free ferric iron from IV iron compounds can be reduced to ferrous iron by endogenous reducing agents (e.g. ascorbate) which then reacts with hydrogen peroxide (Fenton reaction), leading to the generation of highly reactive hydroxyl radical. Fe^{3+} is then converted back to Fe^{2+} by superoxide via the Haber-Weiss reaction. These reactions result in continuous production of iron-catalyzed hydroxyl radical and perpetuate oxidative stress.[15]

Oxidative stress induced by IV iron may contribute to the pathogenesis of cardiovascular disease. Pharmacologically relevant concentration of IV iron products cause endothelial injury and dysfunction and induce monocyte adhesion.[19] Progression of atherosclerosis is also associated with the cumulative annual dose of IV iron in hemodialysis patients.[20]

Vascular Calcification

Iron may have a role in the pathogenesis of calcific uremic arteriolopathy (CUA), previously known as calciphylaxis, which is associated with significant morbidity and mortality. Although CUA is a rare disease, a recent study shows the incidence per 10,000 hemodialysis patients rose significantly from 3.7 in 2007 to 5.7 in 2011.[21] CUA is characterized by microvascular calcification and thrombosis, resulting in tissue necrosis. Early reports in humans suggest an association between iron exposure and development of calciphylaxis.[22,23] A recent observational study of CKD and dialysis patients shows an association between iron exposure and iron deposition in affected vessels and tissue as evidenced by diagnostic CUA skin biopsies.[24] The authors hypothesize that while iron deposition alone may not be responsible for the induction of CUA, its presence is important in creating a favorable milieu for its development. Therefore, the combination of IV iron and dysfunctional iron metabolism in patients on dialysis may lead to free iron deposition in sensitized mircrovasculature and mediate vascular calcification.[24]

Emerging Anemia Management Therapies

There are a few emerging anemia management therapies for patients on dialysis that offer new strategies to improve anemia management in dialysis patients (Table 1).[25]

Soluble ferric pyrophosphate (SFP) is a novel investigational drug for the treatment of iron deficiency in hemodialysis patients. SFP delivers iron via dialysate slowly during dialysis treatment and replaces 5-7 mg of iron lost during each treatment to maintain iron balance.[26,27] SFP enters the blood and immediately binds to apo-transferrin, then goes directly to the bone marrow.[28] Unpublished studies show that SFP delivers iron and maintains Hb concentration without increasing serum ferritin and reduces ESA usage by 35%.[29,30] There have also been no reported cases of anaphylaxis.[31]

A novel class of drug is under investigation that selectively inhibits hypoxia inducible factor prolyl hydroxylases (HIF-PH) and stabilizes HIF. HIF is a key regulatory protein which stimulates endogenous erythropoietin (EPO) production, increases transferrin production, and decreases hepcidin. Increasing HIF activity through inhibition of HIF-PH may provide an alternative treatment for anemia and may protect against damage related to ischemia-reperfusion.[32]

Table 1. Emerging Non-Intravenous Therapies for Anemia Management[25]

Class of Agent	Mechanism of Action	Route of Delivery	Advantages
Soluble ferric pyrophosphate	Diffusion from dialysate to blood, bypassing the RES	Dialysate	Bio-available iron delivered to transferrin in a physiological manner
Hypoxia inducible factor prolyl hydroxylase inhibitors	Stabilizes HIF; promotes non-renal erythropoietin production	Oral	Does not cause ESA-induced hypertension

ESA: erythropoiesis-stimulating agent; RES: reticuloendothelial system. Adapted from: Besarab A. Neph News Issues 2014.

Conclusion

The current treatment of choice for correcting iron deficiency in dialysis patients is IV iron therapy. There is growing concern over upward trends in IV iron use, IV iron dosing, and elevated serum ferritin levels. IV iron therapy exceeds dialysis associated iron losses and bypasses the biological safeguards for iron handling and transport. The resulting free circulating iron is associated with risk of iron toxicity, iron overload, and adverse events. The advent of new emerging anemia therapies for patients on dialysis may augment iron delivery, and thereby reduce the risk of adverse events associated with IV iron.

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