Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

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Before the introduction of erythropoiesis-stimulating agents (ESAs) in 1989, repeated transfusions given to patients with end-stage renal disease caused iron overload, and the need for supplemental iron was rare. However, with the widespread introduction of ESAs, it was recognized that supplemental iron was necessary to optimize hemoglobin response and allow reduction of the ESA dose for economic reasons and recent concerns about ESA safety. Iron supplementation was also found to be more efficacious via intravenous compared to oral administration, and the use of intravenous iron has escalated in recent years. The safety of various iron compounds has been of theoretical concern due to their potential to induce iron overload, oxidative stress, hypersensitivity reactions, and a permissive environment for infectious processes. Therefore, an expert group was convened to assess the benefits and risks of parenteral iron, and to provide strategies for its optimal use while mitigating the risk for acute reactions and other adverse effects.

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Iron is a vital element for numerous bodily functions, most notably as an ingredient of hemoglobin (Hb). Most healthy people can achieve a stable iron balance, managing to ingest the required amount of iron in the diet to compensate for the small amount of daily iron losses from the gut. However, many patients with advanced chronic kidney disease (CKD) are in negative iron balance as a result of reduced dietary intake, impaired absorption from the gut, and increased iron losses. This is particularly true in hemodialysis (HD) patients, for whom supplemental iron is often essential to keep pace with blood loss and the requirements for erythropoiesis.

Intravenous iron is a highly effective means of replacing iron deficits and can enhance erythropoiesis, allowing lower requirements for ESA therapy. This is particularly important since the realization that ESA therapy may result in a number of adverse clinical outcomes, most notably stroke, venous thromboembolic disease, and vascular access thrombosis. However, aside from changes in laboratory parameters, the evidence base evaluating outcomes related to the use of i.v. iron is sparse, and the effect of i.v. iron on hard clinical outcomes including death and major health events is uncertain. Moreover, there is evidence from laboratory, animal, and observational studies that i.v. iron may exacerbate oxidative stress, potentiate atherogenesis and cardiovascular (CV) toxicity, and increase the propensity for infections, as well as occasionally induce hypersensitivity reactions.

This conference was convened to critically examine the evidence base and to identify gaps in knowledge so as to inform future clinical research. The four main themes discussed were: iron overload, oxidative stress, infections, and hypersensitivity reactions.

ACHIEVING THE RIGHT BALANCE: IRON DEFICIENCY VERSUS IRON OVERLOAD

Causes, definition, and diagnosis of iron deficiency

Patients with CKD are prone to iron deficiency, and its etiology is multifactorial. The definition of iron deficiency can be considered under 2 main categories: *absolute*, when there is a deficiency of total body iron stores (Table 1); and *functional*, when there are ample or increased total body iron stores, but with sequestration of iron in the reticuloendothelial system (RES), with inadequate iron supply for erythropoiesis.

With respect to functional iron deficiency, sequestration of iron within the RES is primarily due to inflammation. Since transferrin is a negative acute phase protein, serum transferrin tends to be reduced in CKD patients.[1] As a result, total iron binding capacity is decreased. At a given transferrin saturation, the absolute amount of iron bound to transferrin in the circulation and available for erythropoiesis is lower in CKD patients than in healthy people with normal or near-normal kidney function. Stimulation of erythropoiesis with ESAs creates an increased demand for iron and can unmask and/or aggravate decreased iron availability.

Iron loss is largely due to blood loss. The relation between blood loss and iron loss depends on the Hb level (e.g., Hb 12 g/dl: 0.40 mg iron per ml blood; Hb 10 g/dl: 0.36 mg iron per ml blood). In non-dialysis CKD patients, the average gastrointestinal blood loss can be elevated (estimated blood loss of 3.2 ml/d, approximately 1.2 L/yr, corresponding to about 0.4 g iron/yr) as compared to that of healthy people (0.83 ml/d, corresponding to about 0.1 g iron/yr).[2] In HD patients, some evidence indicates an even larger increase of gastrointestinal blood loss (mean 5.0 ml/d).[3] Procedure- and laboratory test–related blood loss of patients on HD is of the order of 2–5 l/yr,[4] but may vary considerably over time and among patients; blood loss is also influenced, for example, by anticoagulant and antiplatelet agent prescription.[5–7] In aggregate, iron losses in HD patients are considered to be of the order of 1–2 g/yr, but may be highly variable, and in some patients may be as high as 4–5 g/yr.

Both ferritin and transferrin saturation have their shortcomings in assessing iron status and guiding iron therapy in patients with CKD.[8–11] The diagnosis of absolute iron deficiency is usually based on low serum ferritin concentrations (<20–30 μg/l) that reflect low body iron stores. In CKD patients, because of the presence of inflammation, threshold values indicating iron deficiency are generally considered to be higher than in those without kidney disease. Serum ferritin levels of 100 or 200 μg/l are frequently cited as a cutoff value in non-dialysis CKD and dialysis patients, respectively.[12] Although the evidence is rather limited, it is generally felt that a transferrin saturation <20% is indicative of absolute iron deficiency, although transferrin saturations above this do not exclude this condition.[12]

Even when iron stores and circulating iron are sufficient, iron supply for erythropoiesis can be inadequate, as in instances during intense stimulation of erythropoiesis with ESAs, or under conditions of blocked iron release from macrophages by inflammation.

Percentage of hypochromic red cells and reticulocyte Hb content have been utilized as indicators of inadequate iron supply,[11,13] but problems of analyzer availability and the need for the analysis to be performed soon after blood sampling preclude their widespread adoption into routine clinical practice.

Measuring serum hepcidin has been proposed as a means of identifying patients who might benefit from increasing either ESA or i.v. iron dosing,[14] but to date, such an approach has not been shown to be clinically useful.[13,15–17] Furthermore, hepcidin assays are not harmonized or standardized.[18–20]

Table 1 | Causes of absolute iron deficiency

- Blood loss for laboratory tests, aggravated by hospitalizations
- Gastrointestinal losses (may be exacerbated by systemic anticoagulation during dialysis, and/or the use of maintenance oral anticoagulants or antiplatelet drugs used for the treatment or prevention of cardiovascular disease)
- Blood losses associated with the hemodialysis procedure, including dialyzer blood loss and blood loss from the arteriovenous fistula or graft puncture site and from catheters
- Reduced intestinal iron absorption, at least in part due to increased hepcidin levels, and medications (e.g., proton pump inhibitors and calcium-containing phosphate binders)[113–115]
- Reduced intake due to poor appetite, malnutrition, and dietary advice (e.g., protein restriction)

Doses of iron required to correct iron deficiency

Since the true amount of iron loss in individual patients and patient groups is uncertain, the precise doses required to compensate for this loss inevitably remain uncertain. Applying doses of i.v. iron in excess of ongoing losses will result in positive iron balance, the consequences of which are unknown.

In general, i.v. iron doses in excess of 3 g/yr are likely to be associated with an increased risk of exceeding the ongoing iron loss and inducing positive iron balance. In patients who routinely receive i.v. iron, higher requirements for i.v. iron to maintain Hb within a target range, or within the patient's usual range, should prompt the search for increased losses, particularly from the gastrointestinal tract.

Iron overload and its impact on organ function and patient outcomes

There is no feasible method available to determine total body iron content. Thus, the present definitions of iron deficiency and overload remain imperfect, and one has to rely on presumed functional consequences of decreased or increased iron stores and surrogate markers.

Iron overload represents a condition of increased total body iron content that is possibly associated with a time-dependent risk of organ dysfunction. Pathologic iron overload represents a condition of increased body iron content associated with signs of organ dysfunction that are presumably caused by excess iron.

The consequences of increased body iron content depend on a variety of factors, including the distribution of iron among parenchymal cells and cells of the RES, the duration of iron excess in relation to the life expectancy of the patient, comorbidities, and others. The circumstances under which increased iron content is associated with clinically relevant adverse consequences and the nature of these consequences are insufficiently defined. Observations in patients with inherited hemochromatosis suggest that parenchymal iron excess and labile iron can be harmful, whereas iron stored within cells of the RES may be of less concern,[21,22] although intrahepatic iron might induce hepatic damage through iron-induced mesenchymal activation.[23]

Serum ferritin, when elevated, does not always correlate with elevations in liver iron content.[24–26] Hyperferritinemia is thus not synonymous with iron overload, and the level of serum ferritin does not indicate whether iron is stored in parenchymal cells or cells of the RES.[27] Since high transferrin saturation facilitates parenchymal iron deposition, of particular concern appears to be a combination of high transferrin saturation and high serum ferritin, based on experience in patients with hereditary hemochromatosis[28] and transfusion-induced iron overload.[29]

Magnetic resonance imaging scans have been shown to provide a reliable estimate of tissue iron content in non-CKD populations,[30,31] and measurements in unselected HD patients suggest that liver iron content is increased compared to reference values in the majority of patients.[32] However, the clinical relevance of increased liver iron content in the absence of elevated liver enzymes is unclear. At present, there is insufficient evidence to support the use of hepatic magnetic resonance imaging in guiding iron therapy in clinical practice.

Organ toxicity associated with iron overload in hematologic diseases depends on various factors, including the magnitude and speed of iron accumulation. The main target organs are liver, myocardium, endocrine glands, and joints.[28,33] However, the magnitude, distribution, and duration of iron accumulation in CKD patients may be insufficient to produce toxicity similar to that observed in hemochromatosis. Given that i.v. iron use has increased markedly in HD patients over the past few years,[34,35] the exposure to higher amounts may not have accrued long enough to detect such toxicity. Although end-organ damage from i.v. iron administration in patients with kidney disease has not been unequivocally established, at present one cannot exclude the toxicity potential of iron induced by repeated high-dose i.v. iron administration in CKD.

OXIDATIVE STRESS IN UREMIA

Oxidative stress or oxidant-derived tissue injury results from an overproduction of reactive oxygen/nitrogen species or impairment in the cellular antioxidant enzymatic activities, leading to oxidation of macromolecules such as proteins, carbohydrates, lipids, and DNA. Increased levels of oxidative stress markers are present in uremic plasma and are thought to be fingerprints of increased oxidative stress (Figure 1). Oxidative stress occurs early in the evolution of impaired kidney function and is believed to herald a poor prognosis,[36] and often associates with persistent inflammation.[37] Although numerous markers are now available for estimating oxidative stress,[37] practical concerns, such as absence of established reference ranges, variable analytical techniques, and the lack of understanding regarding the relations between markers and impaired kidney function and associated comorbidities,[38] preclude their widespread adoption in the clinical setting. Thus, at the present time there is no gold standard for measuring or monitoring oxidative stress to guide clinical risk assessment or prognosis.

Clinical studies in CKD patients have shown that i.v. iron administration promotes oxidative damage to peripheral blood lymphocyte DNA,[39] protein oxidation,[40] and lipid peroxidation.[41] In addition to direct pro-oxidative effects, studies have shown that administration of i.v. iron compounds promotes cellular apoptosis,[42] endothelial dysfunction,[43,44] and monocyte adhesion.[42,43]

Iron-mediated oxidative stress and CV risk

Despite numerous basic and clinical studies, the question of whether or not iron administration promotes atherosclerosis and arterial remodeling remains unresolved. Moreover, although iron has been detected in human atherosclerotic plaques,[45] it is not yet proven that this accumulation is deleterious and promotes CV disease. A recent study in ApoE knockout mice and ApoE/ffe mice fed with a high-fat diet demonstrated that the atherosclerotic plaque size was not increased in mice with elevated macrophage iron.[46] In contrast, a recent study in the mouse remnant kidney model showed that iron sucrose aggravated early atherosclerosis by increasing monocyte-endothelial adhesion and increased superoxide production.[47] In a cohort of 58,058 HD patients, i.v. iron doses greater than 400 mg/mo were associated with higher CV death rates.[48] Although clinical studies have also demonstrated significant correlations among cumulative iron dose, intimal media thickness,[49,50] and CV events,[51] these findings are difficult to interpret because of their observational nature and confounding by indication. A recent retrospective study of 117,050 HD patients showed no association between large doses of iron and short-term CV morbidity and mortality.[52]

Increased hepcidin: important mediator of CV risk?

Hepcidin is the key iron regulatory protein synthesized in the liver that is sensitive not only to iron deficiency but is also upregulated in response to increased circulating and stored iron levels,[53] inflammation,[54] and infections,[55] and is down-regulated by hepcidin inhibitors, including testosterone,[56] estrogen,[57] and erythroferrone.[58] Some studies suggest that increased hepcidin may increase CV risk by preventing mobilization of iron from macrophages (Figure 2). Hepcidin and macrophage iron correlate with monocyte chemoattractant protein-1 release and vascular damage in patients with metabolic disease.[59] Moreover, in a clinical study of 766

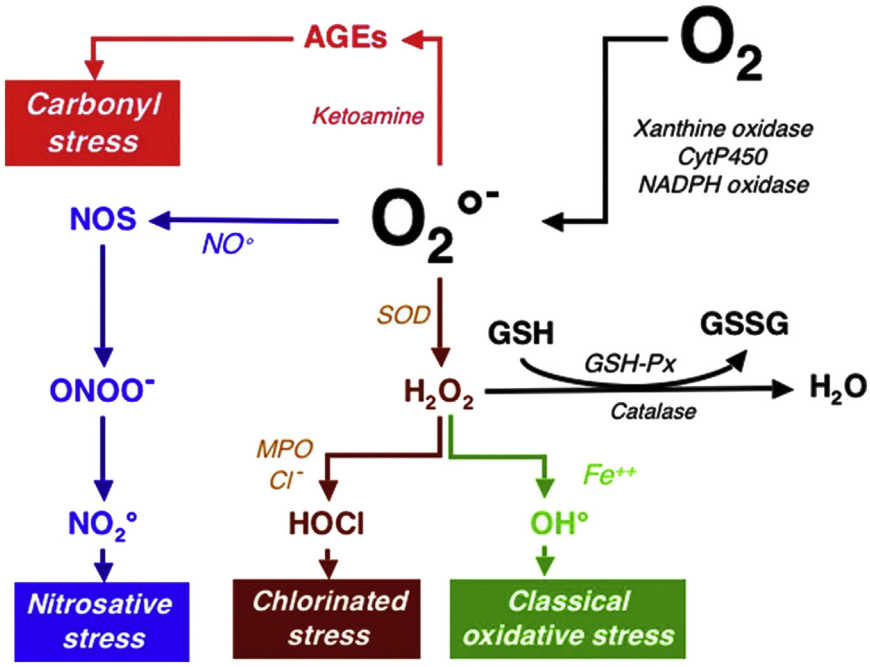

Figure 1 | Schematic representation of oxidation and antioxidant pathways in chronic kidney disease. AGEs, advanced glycation end products; CytP450, cytochrome P450; GSH, reduced glutathione; GSH-Px, glutathione peroxidase; GSSG, oxidized glutathione; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; NOS, nitric oxide synthase; ONOO-, peroxynitrite; SOD, superoxide dismutase. Reproduced with permission from Stenvinkel *et al.*[110]

women without kidney disease, serum hepcidin was associated with the presence of atherosclerotic plaques.[60] Indirect evidence for a proatherogenic role of hepcidin comes from a study that shows that pharmacological suppression of hepcidin increases macrophage reverse cholesterol transport and limits atherosclerosis.[61] In the context of CKD, the evidence that links increased hepcidin to CV disease is limited. However, one study showed an association between increased

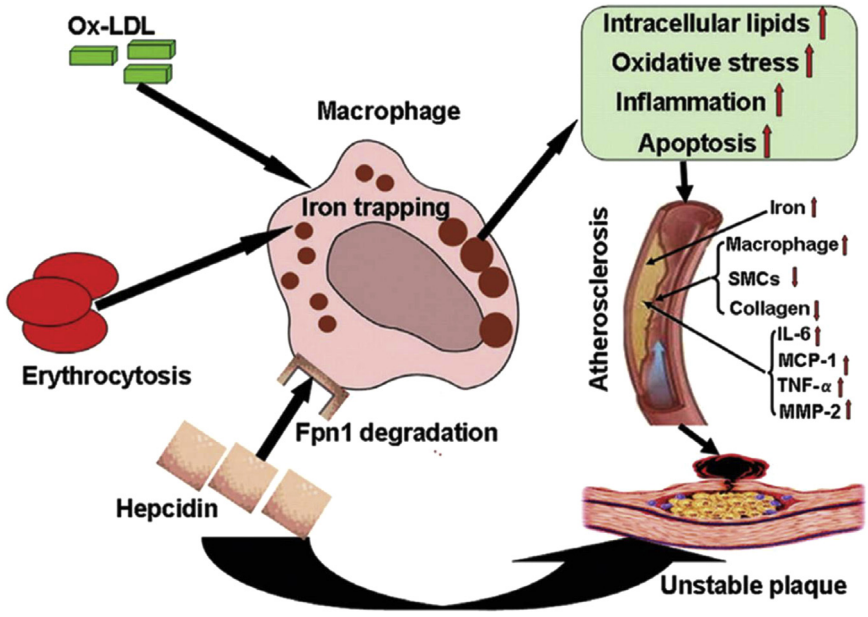

Figure 2 | Proposed mechanisms underlying the hepcidin-induced plaque instability. In the setting of erythrophagocytosis, hepcidin suppresses iron release from macrophages via downregulation of iron-exporting protein Fpn1 and increases iron storage. Iron trapping results in accumulated intracellular lipids and enhanced oxidative stress, inflammatory responses, and macrophage apoptosis. Thus, hepcidin is essential for Ox-LDL–mediated phenotypic switching of iron-loaded macrophages leading to atherosclerotic plaque destabilization. Fpn1, ferroportin 1; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; MMP-2, matrix metalloproteinase-2; Ox-LDL, oxidized low-density lipoprotein; SMCs, smooth muscle cells; TNF-α, tumor necrosis factor-α. Caption text and figure reproduced with permission from Li *et al.*[111]

hepcidin and arterial stiffness,[62] and in the Convective Transport Study (CONTRAST) of 405 HD patients, serum hepcidin-25 was related to CV events even after correction for the presence of inflammation.[63]

Increased ferritin: a surrogate marker or a real risk factor?

Increased circulating concentrations of ferritin are frequently observed in patients with CKD.[32,64] However, like hepcidin, ferritin is also significantly upregulated in the acute phase response and particularly in the presence of low serum iron, transferrin, and transferrin saturation, and is just as likely to reflect an inflammatory as an iron-replete state. In the general population, high serum ferritin is associated with an increased risk of myocardial infarction[65] and carotid plaques.[66] In patients with CKD, the associations between iron parameters and outcomes are confounded by multiple factors. One study reported that low serum iron is a predictor of poor outcome[67] even after adjustment for ferritin and the inflammatory marker C-reactive protein. In contrast, another observational study of 58,058 HD patients showed an association between high ferritin (>800 ng/ml) and mortality, which was markedly attenuated following the correction for markers of malnutrition and inflammation.[48] Since correction for markers of inflammation markedly attenuated the risk associated with hyperferritinemia, prospective controlled studies are needed to assess whether hyperferritinemia-associated CV risk merely represents a risk *marker* or is in fact a risk *factor*.

Can antioxidants blunt potential pro-oxidative effects of iron supplementation?

Although some studies have shown beneficial effects of a single dose of vitamin E[68] or short treatment with *N*-acetylcysteine[69] on surrogate markers of lipid peroxidation, it would be premature to recommend a single antioxidative therapy prior to iron supplementation. Indeed, a study in 13 HD patients showed that the combination of i.v. iron and vitamin C was actually associated with an *increased* production of reactive oxygen species.[70] It can be speculated that in the presence of poorly liganded iron, molecules that are normally antioxidants can actually act as pro-oxidants by reducing ferric iron to catalytically active ferrous iron. A recent randomized controlled trial (RCT) in 353 HD patients examining the effects of 6 months of antioxidative therapy (tocopherols and α-lipoic acid) failed to influence biomarkers of inflammation and oxidative stress.[71] Thus, we currently do not know whether increased oxidative stress in the uremic milieu responds to antioxidative treatment strategies.

IRON ADMINISTRATION AND RISK OF INFECTIONS

Iron is of central importance in host-pathogen interaction because of its key role in biological processes including mitochondrial respiration and DNA synthesis.[72,73] Accordingly, the proliferation and pathogenicity of many microorganisms, such as bacteria, viruses, parasites, helminths, and fungi, are dependent on the availability of iron.[74,75] Iron also exerts subtle effects on host immune function by modulating immune cell proliferation and differentiation and by directly regulating cytokine formation and antimicrobial immune effector mechanisms. Thus, imbalances of iron homeostasis can affect the risk for, and the outcome of, infections.[74,76,77]

Clinical epidemiologic evidence

Data from patients on HD. Ishida and Johansen[78] critically reviewed the association between iron and infection in patients receiving HD. These authors identified studies that evaluated the association between serum ferritin (13 studies) and iron usage (24 studies) and the risk of infection.

Among the 13 studies that examined the risk of infection according to serum ferritin, 9 reported an association and 4 did not. Studies showing associations generally reported a 1.5- to 3.1-fold higher incidence of bacterial infection or infection-related mortality, which translates into an excess of 16–50 bacterial infections per 100 patient-years among patients with higher serum ferritin.

Among the 24 studies that evaluated iron usage and infection, the results were equivocal, as 12 observational studies reported an association while 10 did not. Two RCTs also did not uncover an association though they were not primarily designed to assess the risk of infection.[79–81] Among the 12 studies showing an association between iron usage and infection, data from the United States Renal Data System reported a 14%–45% higher risk of infection-related mortality with higher frequency and higher dose of i.v. iron,[78] and Dialysis Clinics Inc. found that higher mean i.v. iron dose per dialysis treatment was independently associated with a higher risk of infection-related mortality at 6 months compared to a lower mean i.v. iron dose or no iron.[78]

Only 2 studies have examined the risk of infection with different i.v. iron formulations. In one study of 63 HD patients, the adjusted relative risks for bacteremic episodes with iron sucrose versus ferric gluconate were 2.92 (95% confidence interval 1.01–8.50) and 2.84 (95% confidence interval 1.32–6.09), respectively.[82] In another study of 559 patients, mean i.v. iron sucrose dose was significantly higher in patients with catheter-related sepsis than in patients without; similar findings were reported in patients who received i.v. iron dextran.[83]

In one study of 117,050 patients comparing mortality with different dosing patterns of i.v. iron,[84] the authors reported that bolus dosing, when compared to maintenance dosing, was associated with a higher risk of infection-related hospitalization, the risk being highest among patients with a catheter or history of recent infection. An association between bolus dosing and infection-related mortality was also observed. In contrast, maintenance or low-dose iron dosing was not associated with a higher risk of infection-related hospitalization or mortality outcomes when compared with no iron.

More recent data. A multicenter study from Japan prospectively evaluated the association between serum ferritin

and i.v. iron usage and adverse outcomes and mortality among 1086 HD patients. The authors reported a significantly higher risk of infection with higher serum ferritin compared to lower ferritin, and with high and even low doses of i.v. iron compared with no i.v. iron.[85] In contrast to the Japanese study, the outcomes of 32,435 patients receiving i.v. iron in 12 countries were analyzed,[86] and, when compared to patients receiving 100–199 mg/mo, those receiving an average of 300–399 mg/mo or ≥400 mg/mo had a higher risk of all-cause mortality, but no significant increase in mortality due to infection. In another incident cohort of 9544 US dialysis patients, a higher cumulative dose of i.v. iron was not associated with infection-related hospitalizations,[87] while another prospective, observational study of 235 incident dialysis patients reported that those who received i.v. iron had a significantly lower all-cause mortality, including marginally lower sepsis-related mortality.[88]

Lastly, a meta-analysis that evaluated the safety and efficacy of i.v. iron therapy for functional iron deficiency reported no association of i.v. iron with risk of infection, but only limited conclusions could be drawn as it only included 2 studies comprising 359 analyzable patients.[89] In contrast, a recent systematic review and meta-analysis of RCTs evaluating the safety and efficacy of i.v. iron therapy, which included HD and non-dialysis CKD patients, reported that i.v. iron was associated with a significantly higher risk of infection compared with either oral iron or no iron supplementation.[90] However, these findings were tempered by the fact that infection was not a predefined end point in many of the pooled studies and thus the introduction of unmeasured bias cannot be excluded.[91]

Data from peritoneal dialysis and nondialysis CKD patients. Scant data are available regarding the effect of i.v. iron therapy and the risk of infection in peritoneal dialysis or non-dialysis CKD patients. In a study of 379 peritoneal dialysis patients, there were more peritonitis episodes during the 6 months after i.v. iron infusion, especially with iron dextran, compared to the peritonitis episodes during the 6 months before iron infusions (15 episodes vs. 8 episodes, respectively, in 6 months), but the difference was not statistically significant.[92] A recent RCT by Agarwal *et al.*[93] comparing oral versus i.v. iron in non-dialysis CKD patients showed a higher rate of serious adverse events in the i.v. iron treatment group, with increased CV events and infections requiring hospital admission. However, this study examined a single center, with a single investigator adjudicating all serious adverse events and only 99 subjects completing the trial. It is also of concern why the findings of Agarwal *et al.*[93] are so discrepant with those reported in the much larger FIND-CKD study,[94] a multicenter study conducted in 626 non-dialysis CKD patients worldwide and with considerably greater patient-years of follow-up. Even though patients were treated with much higher doses of i.v. ferric carboxymaltose (FCM) in FIND-CKD, no safety signals were evident, and indeed the incidences of infections (adverse events: 33.1% vs. 34.0% vs. 30.4%; serious adverse events: 3.9% vs. 3.3% vs. 3.8%) and cardiac events (6.5% vs. 4.7% vs. 4.5%) were identical across all 3 groups (high-ferritin FCM, low-ferritin FCM, and oral iron, respectively).

In summary, the evidence base for iron administration and risk of infection derives mostly from observational studies conducted in HD patients, which are prone to confounding. The few RCTs conducted in this area included a small number of patients with a short follow-up and were not specifically designed to assess the risk of infection with i.v. iron, while several systematic reviews and meta-analyses performed to date are inconclusive. Despite the conflicting evidence concerning i.v. iron use and the risk of infections, we concluded that the current KDIGO recommendations, which call for balancing potential benefits versus risks of i.v. iron therapy, as well as advising against i.v. iron use in patients with an active systemic infection, are still prudent.

HYPERSENSITIVITY

The safety of administration of i.v. iron compounds has been of concern given the well-recognized risk of life-threatening adverse reactions to high–molecular weight iron dextran and other older formulations. Although it is accepted that the dextran component of the formulation is likely to be the cause of these reactions, the general risk of parenteral iron administration needs to be clarified now that newer formulations are available that allow complete replacement doses in 15–60 minutes, and novel methods of iron delivery such as iron supplementation in the dialysate and iron-containing

Table 2 | General classifications of drug hypersensitivity reactions

Anaphylactic reactions
- Characterized by 2 or more organ systems involved (skin, gut, respiratory, cardiovascular)
- Objective evidence of bronchoconstriction, stridor, hypotension, severe generalized urticaria, nausea, abdominal pain

Minor infusion reaction
- Often described as pressure in the chest or lumbar region, associated with flushing, with or without minor urticaria, but no hypotension or other organ involvement

Flare in pre-existing immune and/or inflammatory conditions, particularly rheumatoid arthritis
- Manifesting as arthralgia

It is generally not possible to predict those at risk for a hypersensitivity reaction, but the following patient characteristics may indicate a higher risk:
- Prior reaction to any i.v. iron formulation
- Moderate to severe asthma
- Multiple pre-existing drug hypersensitivities or allergies[116]
- Pre-existing immune-mediated disease (e.g., autoimmune disorders)
- Mast cell–associated disorders
- High transferrin saturation or low plasma transferrin levels, which may increase the likelihood of circulating labile iron during infusion[117,118]

Local skin reactions to extravasated iron can occur. Infusion-specific risk factors such as use of higher doses and rapid rate of infusion[118] should also be considered when evaluating for any potential reactions. Whether generic formulations have a greater propensity for increased labile iron reactions is as yet unclear.

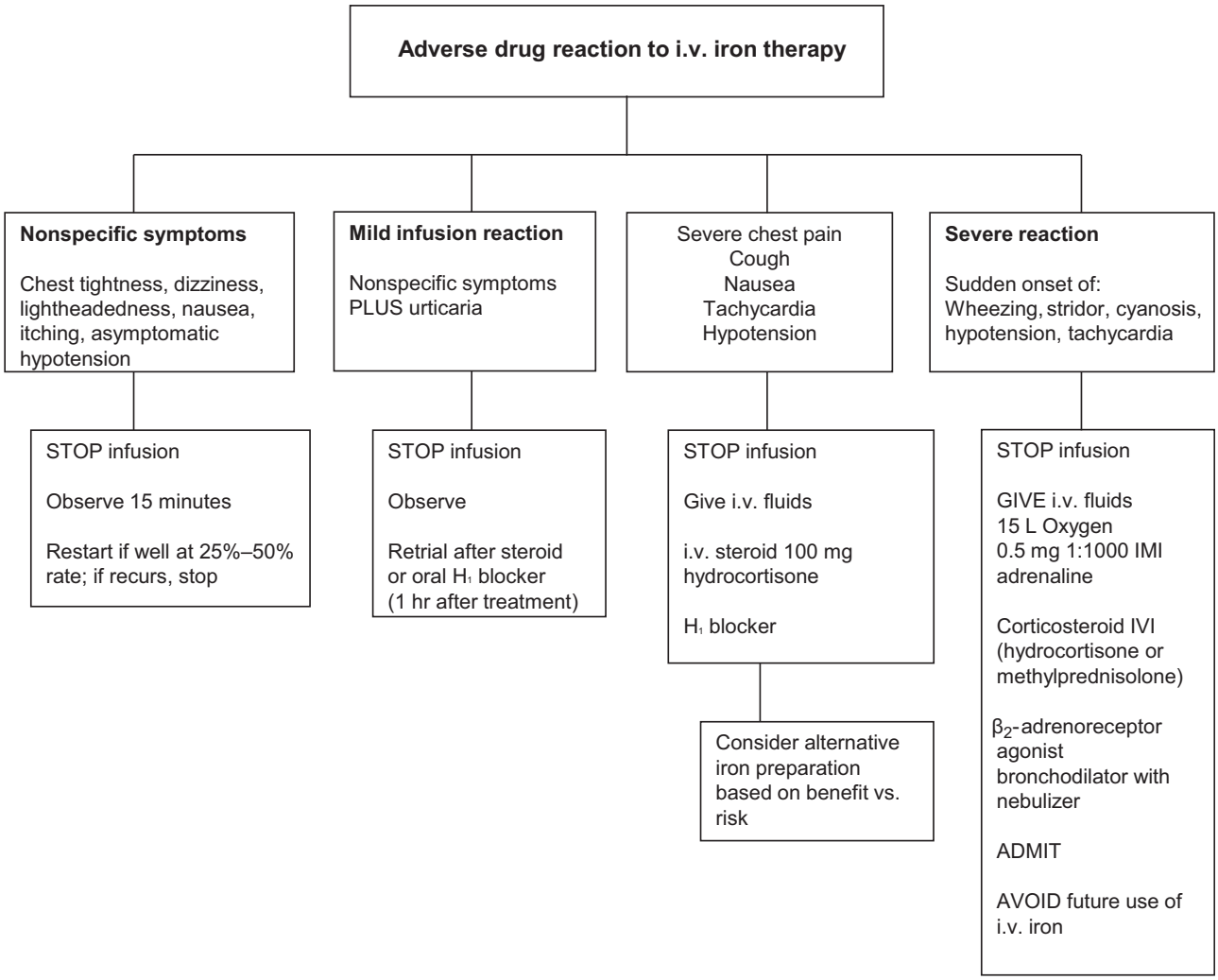

Figure 3 | Suggested management of reactions to i.v. iron. Optimal clinical treatment of severe anaphylaxis includes adrenaline as an essential anti-anaphylactic drug given by intramuscular injection of 0.5 mg in 1:1000 solution. This should be repeated after 5–10 minutes if needed. Additional supportive oxygen should be given at a high rate (>15 liters/min) by face mask. Volume loading should be given using 1 liter of crystalloid solution in addition to an antihistamine (H_1 blocker) and corticosteroids to prevent a protracted or biphasic course of anaphylaxis.[112] For nonspecific reactions, stopping the infusion for at least 15 minutes and monitoring the response (i.e., pulse, blood pressure, respiratory rate, and oxygen saturation) may be sufficient. If the patient improves, then the iron infusion can be resumed at 25%–50% of the initial infusion rate with monitoring. For mild reactions, if treatment is restarted, i.v. H_1 blockers and corticosteroids should be considered and monitoring after therapy should be continued for 1 hour. If the infusion is discontinued and the reaction subsides, then rechallenge with the same or a different iron preparation may be undertaken in an environment where monitoring is available. A much lower dose of the iron preparation or slower infusion rate should be considered to gain reassurance that this reaction is likely to be dose-related and possibly due to labile iron release. IMI, intramuscular injection; IVI, intravenous infusion.

phosphate binders have been developed. Despite the rarity of these reactions, the conference attendees deemed it a high priority to assess the characteristics of reactions to i.v. iron as well as to provide advice on how these reactions should be managed.

Reactions to i.v. iron

Side effects of oral iron are common, occurring in up to 60% of patients,[95] and these predominantly include constipation and nausea, which could result in reduced adherence to oral iron intake. Anaphylaxis to oral iron supplementation has been reported but is extremely rare.[96]

Intravenous iron was initially administered as iron oxide and was found to have an unacceptably high rate of toxic reactions.[97] Toxicity was largely thought to be attributable to labile iron, and subsequent iron preparations have been formulated with the iron salt encased in a carbohydrate shell, commonly a dextran polymer, sucrose, or gluconate. The resultant size of the complex determines the degradation kinetics, with iron dextran releasing iron more slowly than the lower–molecular weight formulations. Hence, lower doses of iron sucrose and iron gluconate are recommended when given as a single infusion to minimize the risk of higher levels of labile iron and of potential reactions. With the exception of

Table 3 | Practical tips for management of hypersensitivity reactions to i.v. iron

- The first dose (either in a CKD or dialysis setting) should be administered in a clinical facility.
- Although total-dose iron infusions have not been demonstrated to have significant risk,[119] i.v. doses of iron gluconate or iron sucrose should not exceed 125 or 200 mg/dialysis, respectively, because of the potential risk for iron not binding immediately to transferrin and resulting in a reaction due to labile iron.
- There is no physiological basis to recommend that patients should be observed for 30 minutes after an infusion of iron is completed, since i.v. iron delivery should not be associated with a severe delayed reaction (as is observed with subcutaneous antigen presentation in vaccination or allergen immune therapy).
- There is no evidence that pretreatment with corticosteroids or antihistamines (H_1 channel blockers) reduces the risk of severe reactions to i.v. iron. Paradoxically, i.v. antihistamines may be associated with unwanted side effects, particularly drowsiness or flushing upon rapid infusion.[120] Hence no pretreatment with corticosteroids or antihistamines is recommended in patients identified as being at potential risk of a hypersensitivity reaction. Desensitization protocols to limit hypersensitivity reactions are not established and, therefore, not recommended.
- Jurisdictional requirements regarding the use of i.v. iron vary and thus, should be followed closely. For example, in 2013 the EMA made recommendations following reports of several hypersensitivity reactions in 3 pregnant women receiving low–molecular weight iron dextran compounds,[121] all of whom made a complete recovery. The recommendations were extrapolated to all patient groups receiving any i.v. iron compounds. This conference agreed with the current position of the EMA that all i.v. iron preparations can rarely cause hypersensitivity reactions, though the total number of life-threatening reports is low. Although the data show a clear association of iron medications and hypersensitivity reactions, the data cannot be used to detect differences in the safety profiles of different formulations. The attendees concurred that i.v. iron should not be administered in the first trimester of pregnancy. It was also agreed that a test dose was not useful in any circumstance to predict the risk of hypersensitivity to i.v. iron.

CKD, chronic kidney disease; EMA, European Medicines Agency.

Table 4 | Research recommendations

- The roles of low-protein diets and the effects of concomitant drugs on iron deficiency are still poorly understood. A better understanding of the mechanisms and determinants of oral iron absorption will facilitate identification of predictors of iron absorption that could stratify patients for future trials with oral iron.
- Estimates of iron loss are generally limited to procedure-related and lab test–related losses only, but not GI loss. More precise estimates of iron loss in the gut should be performed in larger and unselected HD and non-HD patient and CKD populations.
- The development of a methodology to objectively determine body iron stores and tissue distribution in CKD and ESRD patients would be highly valuable. The role of MRI in detecting clinically relevant changes in tissue iron content (i.e., iron uptake in the Kupffer cells of the RES vs. in hepatocytes of the liver parenchyma) should be further ascertained. Can iron accumulation potentially aggravate other comorbidities in CKD patients (e.g., viral hepatitis, non-alcoholic steatohepatitis)?
- Studies should evaluate whether thresholds for increased risk of organ damage in patients with HFE hereditary hemochromatosis (i.e., TSAT >45%, ferritin >1000 μg/l) are applicable to patients with CKD and whether less strikingly abnormal values are also markers for harm.
- Studies should be conducted to determine whether treatment with iron has clinically relevant beneficial effects beyond stimulation of erythropoiesis in patients with CKD. This concept has been reported in patients with CHF,[122] as well as in patients with pulmonary arterial hypertension,[123] restless leg syndrome,[124,125] and premenopausal women with low ferritin levels.[126,127]
- The role of hepcidin as a predictor for progression of anemia and CV events in CKD nondialysis patients should be further clarified.[34,35,128] Further research should also clarify whether hepcidin has independent proatherogenic effects in the uremic milieu and whether its modulation may mitigate arterial remodeling and atherosclerosis.
- Studies are needed to determine whether decreased antioxidative defense mechanisms in the uremic milieu may prolong and/or increase the magnitude of oxidative stress following iron injections.[129] Since the available i.v. iron formulations are structurally heterogeneous with different stability and pharmacokinetic profiles,[130] further research should be conducted to dissect the specific effects of various i.v. iron compounds on the magnitude and time response of both established and novel oxidative stress biomarkers.
- Prospective controlled studies are needed to examine whether iron promotes atherosclerosis and arterial remodeling and accelerates CV mortality, especially in vulnerable subgroups such as CKD patients with diabetes mellitus and/or persistent inflammation.
- There is an urgent need for RCTs to assess the relative safety and efficacy of i.v. iron in the management of CKD-related anemia, particularly in relation to hard clinical end points, as well as infection risk and other patient-related outcomes. Improved methodologic aspects of RCT design to consider include (i) random allocation of patients to high-dose vs. low-dose i.v. iron, high vs. low serum ferritin target, bolus vs. maintenance dosing, and different i.v. iron formulations vs. placebo; (ii) use of cluster RCTs (i.e., randomized to facility practice); (iii) use of rescue therapy for patients who develop iron deficiency to maintain the Hb level above 9 g/dl (10–12 g/dl); (iv) use of a fixed dose of ESA; (v) inclusion of outcomes such as ESA dose, blood transfusions, infection, mortality, CV events (e.g., stroke and myocardial infarction), quality of life, and other patient-related outcomes.
- Observational studies should be conducted in predialysis CKD patients, kidney transplant recipients, and peritoneal dialysis patients to determine infection and CV risks, and possible benefits with i.v. iron in these populations.
- Experimental studies using uremic animal models should be performed to test the effects of i.v. iron on active infection and the risk of developing new-onset infections with pathogens most commonly encountered in the CKD population (e.g., *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and gram-negative bacteria). Do iron perturbations result in exacerbation of latent or chronic infections such as tuberculosis, subacute bacterial endocarditis, or hepatitis C?
- A standardized questionnaire should be used to report *any* adverse reaction from an i.v. iron preparation using an adapted version of Ring and Messmer's classification of adverse drug reactions.[131] If implemented, this questionnaire could be used across jurisdictions and help identify patients at risk for i.v. iron preparations that carry a higher risk of adverse drug reactions.
- Future research should ideally address the value of tryptase measurements in acute hypersensitivity reactions. Importantly, measurements should not be taken immediately after a reaction, but at least 1 hour after the onset of symptoms and supplemented by a baseline tryptase measurement a few days later. Additional measurement of complement factors C3a/C5a and C4 could provide information on the presence of immune-mediated reactions.

CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; GI, gastrointestinal; Hb, hemoglobin; HD, hemodialysis; MRI, magnetic resonance imaging; RCT, randomized controlled trial; RES, reticuloendothelial system; TSAT, transferrin saturation.

higher–molecular weight iron dextran, the statistical differences in adverse reactions among different formulations cannot be quantified and are unlikely to be significant given the low incidence of reactions. However, a strong consensus is that higher–molecular weight iron dextran should not be used, given that alternative formulations are now available with lower absolute risks of reactions.

In non-dialysis CKD and dialysis patients, with or without concomitant ESA use, the advent of formulations available for more rapid infusion (e.g., lower–molecular weight iron dextran, FCM, iron isomaltoside 1000, and ferumoxytol) could provide considerable benefit. These formulations may be viable alternatives to oral iron supplementation and, despite their higher drug acquisition costs, may be cost-effective in certain health-care settings.[98–101]

Given the lack of clarity on the cause of systemic reactions to i.v. iron, we suggest a classification according to the severity of reaction, which can then be used to recommend the subsequent approach to both acute and longer-term therapy (Table 2).

Anaphylactic (severe to life-threatening) reactions. It has been shown that higher–molecular weight iron dextran had 3–4 times the rate of life-threatening adverse reactions at 11.3 per million patients compared with 3.3 per million patients for lower–molecular weight iron dextran, and 0.9 and 0.6 per million population for ferric gluconate and iron sucrose, respectively.[102] Excluding higher–molecular weight iron dextran, which is no longer commercially available, anaphylactic reactions are extremely rare, with an incidence of <1:200,000. The US Food and Drug Administration recently posted a regulatory update regarding severe hypersensitivity reactions with ferumoxytol, along with advice to slow down the rate of administration.[103]

To date, pharmaceutical filing and published trials have not demonstrated anaphylactic reactions with intradialytic administration of soluble ferric pyrophosphate[104] or oral ferric citrate[105] or with another iron compound currently under development, heme iron polypeptide.[106] However, given the rarity of reactions with any form of iron administration, it cannot be concluded that oral or intradialytic administration of iron is without risk.

So far there is no established and validated allergological work-up such as skin testing or *in vitro* tests available to predict or confirm hypersensitivity. Improved clinical documentation of hypersensitivity reactions to iron in the future should also include an allergological work-up to identify possible, but as-yet unproven, risk factors such as asthma, mastocytosis, concurrent use of drugs (e.g., beta blockers and angiotensin-converting enzyme inhibitors), and atopic status.

Minor infusion reactions. Minor infusion reactions are not uncommon and may be characterized by symptoms such as flushing, mild chest discomfort, dizziness, light-headedness, nausea, or itching. In practice, asymptomatic hypotension is sometimes observed, but this is considered a nonspecific reaction unless iron is a known allergen for the patient from prior administration. Some patients may develop myalgia or arthralgia (the so-called Fishbane reaction), which is usually self-limiting and does not require treatment with adrenaline or antihistamines. These mild infusion reactions may be diagnosed via their ability to resolve when the infusion is stopped or given at a slower rate[107] and should generally not preclude the ongoing use of i.v. iron preparations.

Management of hypersensitivity reactions to i.v. iron. Patients who have had a life-threatening reaction to i.v. iron should not receive further i.v. iron compounds. However, if patients experienced more minor features of hypersensitivity, then an alternative formulation could be tried at a later date with appropriate monitoring.[108] A consensus algorithm for the management of reactions to i.v. iron is shown in Figure 3. Practical management tips are also provided in Table 3.

CONCLUSION

Present available data do not allow any firm statement to be made on the potential dangers of high-dose iron administration and high ferritin levels. However, this conference has identified gaps in knowledge to inform future research agendas (Table 4) and concluded that RCTs are urgently required to address the shortfall in the evidence base. An ongoing trial, PIVOTAL,[109] is recruiting 2080 HD patients across 55 sites in the UK who are being randomized to a high-dose versus a low-dose i.v. iron regimen with a planned follow-up of between 2 and 4 years. Hard end points such as death, myocardial infarction, stroke, heart failure, and infections are being assessed. In the meantime, nephrologists would do well to recognize broadly the benefits and the limitations of i.v. iron therapy, pending further robust scientific data.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Complete Conference Report

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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APPENDIX

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