Is there material hazard to treatment with intravenous iron?

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We have been invited to write this article, exploring the question of whether we expose our patients to material hazard when we treat them with intravenous iron. It is a reasonable question to ask with any therapeutic agent, especially after a period in which the use of the agent has increased significantly. The answer to the question, to a degree, is dependent on the intended definition of the word material. We shall seek to utilize a working definition, in which material hazard is that which would outweigh any anticipated benefits that the treatment might confer. As such, we believe that there is not material hazard in the use of intravenous iron. Before exploring the risks of iron therapy, we will begin with a brief consideration of the benefits of intravenous iron for improving the anaemia of haemodialysis patients.

Anaemia is one of the major causes of morbidity, mortality and diminished quality of life for dialysis patients [1–3]. Churchill and Collins have each performed analyses that associated lower haemoglobin levels with increased subsequent hospital days [1,4]. In another analysis by Collins, a haematocrit value lower than 33% was associated with an increased risk of death [3]. The EPIBACDIAL multicentre study, found low haemoglobin concentrations to be a major predictor of the development of bacteraemia [5]. A synthesis of a broad literature regarding anaemia in dialysis patients led the American NKF-DOQI anaemia guideline development team to recommend that haematocrit be maintained in the 33–36% range [6]. If this level is achieved, then the patient should live longer, and with a better quality of life.

The recommended haematocrit range stands in disturbing contrast to the results actually achieved in haemodialysis patients. As recently as 1993, the USRDS Wave 1 Morbidity and Mortality Study found that 48% of American haemodialysis patients had haematocrit values of < 30% [7]. It is clear that if we seek to improve patient outcomes by raising haematocrits into the NKF-DOQI recommended range of 33–36%, then we still have a long way to go. The 1998 ESRD Core Indicators Report documents that 44% of American haemodialysis patients had haematocrit values below this range in 1997 [8].

While there are several factors that contribute to suboptimal haematocrit values, the USRDS study noted above demonstrates the important role of iron deficiency. In fact, this study found that in 1993, 54% of America haemodialysis patients were iron deficient as measured by transferrin saturation (TSAT) < 20%. Remarkably, fully 25% of patients had absolute iron starvation, with TSAT < 10% [7]. This is a level of iron deficiency at which the body’s ability to produce energy is markedly compromised.

An interesting 10-year historical perspective on iron treatment in haemodialysis patients is emerging. In 1989, recombinant human erythropoietin (rHuEpo) became clinically available in the US. This was a time in which iron overload was more the concern of nephrologists than iron deficiency. Yet only 5 years later the aforementioned USRDS study demonstrated the emergence of an epidemic of iron deficiency. Now, 5 years later still, 10 years after the introduction of rHuEpo, the pendulum has swung back and iron overload is again becoming a concern. The Core Indicators Report noted a mean serum ferritin of 505 ng/ml in the US in 1997 [8]. It is therefore a very reasonable time to reconsider the weighing of risk and reward in iron treatment.

When haemodialysis patients are treated with rHuEpo, iron deficiency usually develops. The choices to supplement iron include several types of orally administered iron, or intravenous iron. Oral iron has limited efficacy, and frequently causes gastrointestinal side effects. In contrast, the efficacy of intravenous iron for improving anaemia therapy tends to be outstanding. A large series of studies have documented that intravenous iron treatment leads to a significant improvement in rHuEpo responsiveness [9–17]. There are several safety issues, however, that may lead to a degree of risk to patients. I will now discuss these issues, and consider how safety may affect treatment.

In the US, iron dextran has been the only form of intravenous iron available until recently. This agent is associated with occasional severe anaphylactoid type reactions. Hamstra et al. in a study of nonuraemic subjects, found the rate of these reactions to be 0.6% of patients treated [18]. Our group studied haemodialysis patients, and found the reactions to occur in 0.7% of patients treated [19]. Because these types of reac-
tions are well studied, it is easy to factor the impact into risk-reward considerations. Two intravenous agents used in Europe, iron saccharate and ferric gluconate, are likely to cause less anaphylactoid reactions. There is little published data to help quantitate the risk with these drugs.

As intravenous iron use has increased in haemodialysis patients, questions have been raised as to the safety of ongoing exposure to these agents. Particularly, there has been concern about iron’s oxidative properties, the risk for infection or cardiovascular disease, and the possibility of iron overload itself.

Iron is a reactive substance, with oxidative properties that are highly valuable to the body in the production of energy. Living organisms devote much effort to sequestering iron so that the oxidative nature of free iron does not damage normal tissues. As such, the human body typically contains approximately 4000 mg of iron, yet concentrations of free iron that are so low as to be nearly unmeasurable [20]. With certain diseases that cause severe overload of iron, such as haemochromatosis, iron can no longer be safely sequestered, and tissue damage may result from free iron exposure. In haemochromatosis, oxidative injury to the heart, liver, pancreas and other organs may cause profound morbidity [21]. This occurs over decades of organ exposure to very high ambient iron levels. There is nothing about end-stage renal disease itself that predisposes to iron accumulation [in fact, haemodialysis leads to ongoing negative iron balance]. It is possible, however, that with long-term indiscriminate use of intravenous iron that iron overload might occur. In this case oxidative damage to tissue and organs due to free iron could result. Measures such as the serum ferritin are not very accurate for the detection of iron overload [22]. As such, relatively low levels must be chosen to avoid the risk of excess iron accumulation. In the US, the NKF-DOQI panel chose a serum ferritin of 800 ng/ml as an upper limit to intravenous iron treatment [6]. This level should effectively rule out the possibility of iron overload and the risk of oxidative tissue damage.

Other than via chronic iron overload, another hypothetical means of oxidative tissue injury could occur as endothelial damage due to free iron release from intravenous iron compounds. Generally these agents bind iron quite tightly, with iron dextran having a remarkably high dissociation constant. Other agents such as ferric gluconate and iron saccharate bind iron with less avidity [23], yet there is little evidence to suggest that clinically significant free iron release occurs with these, or any intravenous iron products.

The issue of increased risk of cardiovascular disease with the use of intravenous iron is of interest. The plausibility of this relationship hinges on the fact that free iron, via the Haber–Weiss reaction, can induce the production of reactive oxygen species [24]. The resulting lipid peroxidation might accelerate systemic atherosclerotic disease [25]. The clinical significance of this is unclear. Population studies have yielded mixed results, some demonstrating increased risk for cardiac events with increased iron storage [26,27], while others demonstrate no relationship [28–30]. A recent review summarized the existing literature, with a conclusion that 'iron overload states do not appear to be strongly associated with increased risk of atherosclerotic disease' [31]. Nonetheless, because of the great burden of cardiovascular disease in end-stage renal disease, further study in this area is warranted.

The risk of infection in patients treated with intravenous iron has been of some interest. Iron is an important growth factor for microorganisms, and as such it is biologically plausible that iron could increase infection risk. In the laboratory, it has been shown that excess free iron can enhance the infectivity of certain bacteria [32]. In animal studies, excess iron has been demonstrated to convert mild into severe infections [33]. In humans, the role that iron might play in the risk for infections is not known. The genetic disease, haemochromatosis, causes profound long-term exposure to severe iron overload, and as such it is a reasonable first place to look for such a relationship. It is not clear that these patients have any increase in risk for infection, although certain highly iron-sensitive bacteria, such as Y. enterocolitica, do cause clinically relevant infections in these patients [34]. In addition, after treatment with desferoxamine (DFO), haemochromatosis patients have rarely developed infections probably due to increased iron exposure (dialysis patients have also occasionally been infected during DFO therapy) [35].

While iron seems to be a growth factor for microorganisms, iron excess may also predispose to infection by hindering host defenses. A recent study reported by Patruta et al. found that bacterial killing in haemodialysis patients is diminished when the serum ferritin was greater than 650 ng/ml (although the transferrin saturation was <20%). In addition, neutrophils from a group of patients with iron overload due to haematologic disease also exhibited altered phagocytic function. Taken together these results suggest that excess iron may indeed tend to inhibit an important component of host defense. It is difficult, however, to translate this laboratory finding into an understanding of potential clinical impact. The authors simply recommended avoiding overtreatment with intravenous iron [36].

As we move from laboratory studies of iron and infection risk to trying to understand the implications for patients, we may begin by considering anecdotal clinical experience. The genetic disease haemochromatosis, as mentioned above, does not appear to be associated with a noticeably increased risk of infection. Another disease state in which iron overload was common was end-stage renal disease, prior to the introduction of rHuEpo. Anecdotally, it does not appear that infection risk was greater in that time period, although good data is not available. These clinical observations are helpful, and serve as prima facie evidence that suggests that iron overload probably does not increase infection risk to any great degree. To critically establish such a relationship, a randomized clinical trial would be needed. There would be several
ways to design such a study to provide a ‘pure’ answer to the question. To the best of my knowledge, no such studies have been reported in the English-language literature. Those studies that have been published suffer from suboptimal methodologies that make it difficult to link cause and effect. Most studies in dialysis patients were performed prior to the introduction of rHuEpo, when transfusion of blood was the primary treatment for anaemia. This confounds analyses, in that blood transfusion causes iron loading, but also causes immunosuppression which directly impacts the risk for infection. In addition, the use of serum ferritin as the marker of iron load is problematic in that infection itself raises the serum ferritin independent of iron status.

Tielmanns et al. in a retrospective review, found that when the serum ferritin was > 500 ng/ml in haemodialysis patients the risk for infection was increased by approximately five-fold [37]. Seifert et al. found progressively higher rates of bacterial infections at serum ferritin levels > 330 ng/ml [38]. Similarly, Hoen et al. found risk for bacteraemia to be increased when the serum ferritin was > 500 ng/ml [39]. The Hoen study was performed in an era when rHuEpo use was not commonplace. Given the profound effect of rHuEpo treatment on iron status, the investigators performed a similar study that was reported in 1998. This prospective study included 988 haemodialysis patients from 19 French haemodialysis centres. Four independent risks for bacteraemia were identified by multivariate analysis: (i) catheter as vascular access, (ii) a prior history of bacteraemia, (iii) use of immunosuppressive therapy, and (iv) lower haemoglobin concentration. Regarding iron, neither the serum ferritin concentration nor treatment with iron itself were related to risk for infection [40]. This study is probably the best study to date of this subject, in that it was prospective, multicentre, and rich in clinical data.

In contrast to the Hoen study, studies presented at the 1997 and 1998 ASN conference by Collins’ group found a positive association between intravenous iron dextran treatment and risk of infection. These were claims-based analyses from Medicare data. In the 1997 analysis of 33 120 haemodialysis patients, a 35% increase in the risk of infectious death was noted with the use of frequent but low doses of intravenous iron compared to other treatment strategies [41]. In the 1998 study, the use of >17 vials of intravenous iron dextran over a 5–6 month period was associated with a 20% increase infectious mortality [42]. Taken together, the studies demonstrate an interesting association between patterns of iron treatment and risk for infections and death. The source of data, claims information, burdened the studies with important missing clinical information such as dose of intravenous iron, serum ferritin concentrations, and other vitally important clinical parameters. Because of this, we are left wondering whether certain patterns of i.v. iron dosing are harmful, or in contrast, if i.v. iron dosing was simply a marker for patients who were sicker, and at increased risk. It is important to note that the second study controlled better for covariates, and found substantially less risk.

The current state of the literature relating to iron and infection risk in dialysis patients does not allow for firm conclusions as to whether iron plays a role in infection risk. In developing risk-reward considerations, it is difficult to factor this issue in a meaningful way. The following statements may summarize our current understanding of this issue: (i) it is biologically plausible that iron may play a role in infection, (ii) a rigorous quantification of risk in dialysis patients is not possible at the present time, (iii) the 1998 Hoen study makes clear that factors other than iron are the primary predictors of infection risk in dialysis patients. The role of iron, if any, would therefore be minimal in comparison.

The risks of iron therapy, both known and hypothetical, must be weighed against the well-recognized benefits of therapy. Intravenous iron is highly efficacious for improving the response of haemodialysis patients to rHuEPO. This is supported by a broad literature of clinical studies [9–17]. The use of intravenous iron is vital to allow haemodialysis patients to reach the NKF-DOQI target haematocrit of 33–36%. The panel stated, in guideline 8, ‘To achieve and maintain a hematocrit of 33–36%, most haemodialysis patients will require intravenous iron on a regular basis’ [6]. Since haematocrit levels below 33% have been associated with an increased risk of hospitalization and death, intravenous iron is clearly a necessity to improve patient outcomes.

In conclusion, it is not likely that intravenous iron treatment exposes the dialysis patient to material risk. Much of our understanding about the risk of iron treatment, however, is incomplete. Given current knowledge, the NKF-DOQI recommendation not to exceed a serum ferritin of 800 ng/ml should greatly reduce the risk of therapy. Because of the importance of iron management to optimal anaemia therapy, intravenous iron treatment remains a standard of care for many patients on haemodialysis.

References
