

# Intravenous Iron Exposure and Outcomes in Patients on Hemodialysis

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Iron is an essential trace element that is important for normal body function. However, excess iron in animal studies has been shown to be toxic, because it can enhance radical oxygen generation, impair neutrophil and T-cell function, and also promote bacterial growth (1,2). This dichotomy requires the body to meticulously regulate iron homeostasis, perhaps more than any other substance. Iron content of the body is controlled by hepcidin, ferroportin, ferritin, transferrin, and other molecules and processes designed to strictly limit iron availability and carefully sequester iron, protecting cells and tissues from oxidative damage (3).

Iron stores are tightly regulated by the body. In the normal physiologic state, about 1 mg iron is slowly absorbed from the diet over 24 hours (4) under tight regulation by intestinal, hepatic, and other systems. In contrast, when a patient is injected with a typical dose of intravenous iron, 100 mg directly enters the bloodstream in minutes, bypassing many regulatory processes. By superficial observation, it seems remarkable that intravenous injection of iron seems to be well tolerated. However, the safety and efficacy of intravenous iron remain largely unknown. There have been no clinical trials of adequate sample size and duration to provide us sufficient understanding of the safety of intravenous iron. This does not mean that intravenous iron is unsafe but rather, that safety has not been adequately evaluated.

Before the introduction of recombinant human erythropoietin (EPO), iron overload in patients on dialysis was a common problem as a result of multiple blood transfusions (5). With the introduction of EPO, increasing hemoglobin concentrations led to a massive shift of iron from storage tissues to the erythron, and iron deficiency became a frequent problem (6). Subsequently, primarily as a result of increased intravenous iron treatment, mean serum ferritin doubled from 300 to 600 ng/ml from 1993 to 2001 and remained stable at approximately 600 ng/ml from 2000 to 2010 (7). With the advent of bundled ESRD reimbursement for intravenous drugs in 2011, intravenous iron treatment increased again, and the mean serum ferritin concentration surged, recently stabilizing at 799 ng/ml (Figure 1). As of April of 2014, 75% of United States patients on hemodialysis had serum ferritin >500 ng/ml (8), and approximately 70% of patients are treated with intravenous iron each month. Are such a high rate of intravenous iron treatment and the resulting high

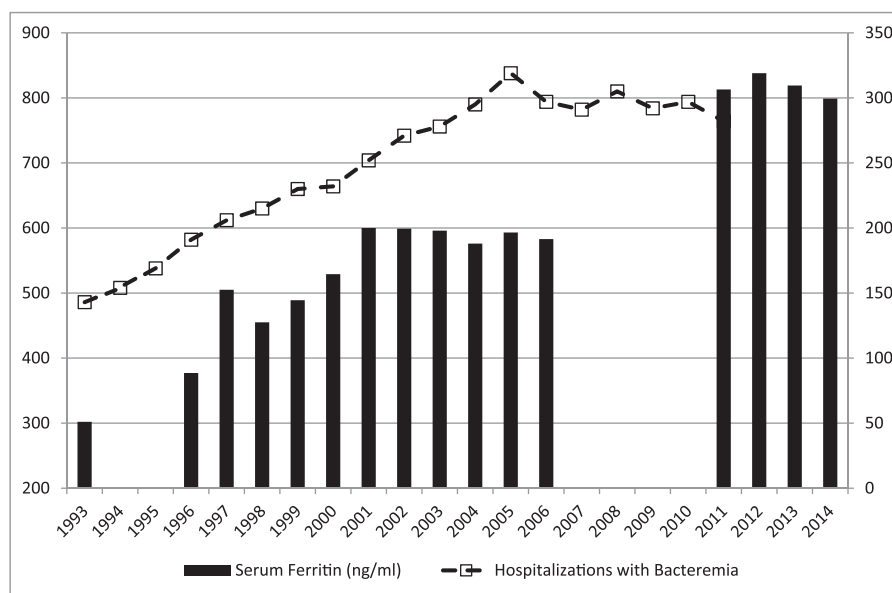
serum ferritin concentrations harmful for patients? A substantial body of clinical trial evidence would be required to answer this question. At present, we know that intravenous iron treatment, even with high levels of serum ferritin, results in increased hemoglobin levels and reduced EPO dose requirements (9,10). This reduces cost of care, but it is unclear if this benefits the patient. No safety end points in the use of intravenous iron have been adequately studied. Therefore, it is not currently possible to carry out a basic aspect of any treatment decision balancing benefit and risk.

Although causality cannot be gauged, observational studies help us understand the association of intravenous iron treatment with beneficial or harmful outcomes. For example, Feldman *et al.* (11) found no relationship between the amount of intravenous iron dosing and risk for mortality after adjusting for various characteristics, including time-varying measures of iron administration. Kalantar-Zadeh *et al.* (12) studied patients from Davita Inc. (United States dialysis clinics). Compared with patients receiving no intravenous iron, those who received up to 400 mg per month had improved survival. In contrast, patients receiving >400 mg per month had a significantly greater risk for mortality (12). A relatively underpowered study of Taiwanese patients on dialysis found that intravenous iron doses >800 mg over 6 months were associated with a higher risk of mortality compared with lower doses (13). In this issue of *CJASN*, Miskulin *et al.* (14) report on patients on hemodialysis treated at Dialysis Clinic Inc. facilities. The study used robust statistical methods to account for time-varying confounding (14). The large number of subjects lost to follow-up or excluded might somewhat bias the results (14). In addition, the time period used for study (2003–2008) was one where the use of intravenous iron was somewhat lower, with mean serum ferritin in this study approximately 30% lower than current United States mean values. Overall, however, the methodology was strong, making this one of the most important observational studies on the subject. The main result was that there was no clear association between any level of intravenous iron dosing and risk for all-cause or cardiovascular-related mortality. Taken together, with respect to the relationship of intravenous iron and mortality, the results of the published observational studies are mixed. This uncertainty emphasizes the need for a well powered clinical trial to study the issue.

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**Figure 1.** | Mean serum ferritin from 1993 to 2014 among United States patients on hemodialysis. Annual rate of hospitalizations with bacteremia/sepsis coded as principal or secondary diagnosis per 1000 patient-years (US Renal Data System 2013 Annual Data Report).

The study by Miskulin *et al.* (14) also raises concern with respect to intravenous iron and infection. Iron is a key nutrient for microorganisms. Bacteria have evolved powerful mechanisms for obtaining iron (15), and the human body works to sequester iron in storage tissues when infection is present. The battle over this key resource may be disrupted by intravenous injection of iron. This has been studied in different ways. Zager *et al.* (2) studied intravenous iron sucrose injection in mice and found that it exacerbated the septic state. Teehan *et al.* (16) evaluated iron storage levels in patients on hemodialysis receiving intravenous iron and found that patients with replete iron indices were at increased risk for bacteremia compared with patients with deficient iron stores. Brookhart *et al.* (17) retrospectively studied 117,050 patients on dialysis treated at Davita Inc. dialysis facilities and found that patients receiving >200 mg intravenous iron per month had an increased risk for hospitalization or death because of infection. Brookhart *et al.* (17) also found that bolus dosing of intravenous iron (100 mg in at least two consecutive treatments) was associated with greater infection risk than maintenance dosing. Miskulin *et al.* (14) found a trend of increased risk for infection-related mortality when cumulative iron dose exceeded 1050 mg over 3 months or 2100 mg over 6 months. Although these results did not reach statistical significance, they must be weighed together with the existing body of evidence on the safety of intravenous iron. A meta-analysis conducted by Litton *et al.* (18) reviewed 24 published studies and found increased risk of infection with intravenous iron compared with oral or no iron treatment (hazard ratio, 1.33; 95% confidence interval, 1.10 to 1.64). In contrast, a prospective observational study by Hoen *et al.* (19) found no relationship between infection and serum ferritin or intravenous iron dosing.

The US Renal Data System publishes data in its annual data report on infections in general and provides a breakdown on different types of infections (7). Because injected

iron is present in circulation, any relationship to infection risk might be more apparent with bacteremia and sepsis than deep-seated tissue infections. The USRDS data for bacteremia and sepsis show an interesting pattern (Figure 1). As the mean serum ferritin of United States patients on dialysis approximately doubled from 1993 to 2001, the rate of bacteremia/sepsis increased approximately 40%. From 2001 to 2010, mean serum ferritin stabilized, and after a few years lag, the bacteremia/sepsis rate also stabilized (7). In 2011, the mean serum ferritin increased sharply again, but data for bacteremia and sepsis are not yet available for that time period. Gross inspection of the temporal relationship between mean ferritin and the rate of bacteremia/sepsis suggests an association between them. However, great caution is advised, because the rate of catheters also increased during some of this time period, the age of the population increased, and the number of patients with diabetes increased as well. Additional analysis is required to better understand this relationship. Taken together, the current literature is mixed but suggests that intravenous iron treatment may be related to subsequent infection risk. Of note, the most recent Kidney Disease Improving Global Outcomes guidelines recommend withholding iron infusions in patients with evidence of systemic infections (20).

In conclusion, neither the risks nor benefits of intravenous iron treatment are understood sufficiently. This lack of knowledge may not have been an important problem in the early 1990s, when iron deficiency was ubiquitous in this population and benefits of treatment probably far outweighed risks. However, today, with most patients receiving intravenous iron treatment and having a mean serum ferritin of 799 ng/ml, we require a better understanding of treatment use and safety. In a sense, this state of knowledge on the safety profile of intravenous iron is akin to erythropoiesis-stimulating agents before the key clinical trials that exposed the risks of overly aggressive treatment. Satanyana's famous quotation, "those who cannot remember the past, are condemned to repeat it,"

was amended by George Will, who added at the end of the quote “and those who do remember the past are also condemned to repeat it.” For the nephrology community to reduce harm to patients and improve their outcomes, we must ensure that well powered clinical studies of intravenous iron are developed and conducted, assessing both use and safety.

#### Disclosures

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See related article, “Intravenous Iron Exposure and Mortality in Patients on Hemodialysis,” on pages 1930–1939.