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Iron and Infection in Hemodialysis Patients

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Abstract

Intravenous iron is an important component of the treatment of anemia of end-stage renal disease (ESRD), but it is biologically plausible that iron could increase the risk of infection through impairment of neutrophil and T cell function and promotion of microbial growth. Any such increase in risk would be particularly important because infection is a significant cause of mortality and morbidity in dialysis patients. The overall evidence favors an association between iron and infection in hemodialysis patients, but the optimal iron management strategy to minimize infection risk has yet to be identified. There is a need for further research on this topic, particularly in light of increased utilization of intravenous iron following implementation of the bundled ESRD reimbursement system.

Several reviews on the possible association between iron and infection among patients with end-stage renal disease (ESRD) published in 1999 concluded that the available evidence could not definitively link iron with infection (1–3). However, despite the subsequent publication of studies that both support and oppose an association between iron and infection, more recently published reviews have tended to favor the possibility of an association and even advocated the withholding of intravenous iron in the setting of active infection (4–6). Reexamination of this topic is warranted because there have been additional studies (7–15) and new guidelines (16–18) since these more recent reviews.

Kidney Disease Outcomes Quality Initiative (KDOQI) addressed the topic of iron and infection risk in their 2000 anemia guidelines and concluded that maintaining a serum ferritin within the recommended range was unlikely to pose a risk for bacterial infection in patients with chronic kidney disease (CKD) (19). However, subsequent international CKD anemia guidelines advised caution with using intravenous iron in the setting of infection

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(16,17), and some recommended avoiding or withholding intravenous iron in patients with systemic infection (18,20).

The most recent of these guidelines was published by Kidney Disease Improving Global Outcomes (KDIGO) in 2012 and advised avoiding intravenous iron in patients with active systemic infections (18). However, this recommendation was not graded and was based on the biologic plausibility that iron may increase the risk of infection (21–25) as well as limited data from observational studies in hemodialysis patients (26–28). Despite the lack of a “clear answer” as to whether intravenous iron increases infection risk in CKD patients, the Work Group erred on the side of caution and considered iron administration to be harmful in the setting of infection. However, it did not discuss the possibility that withholding iron out of concern for infection may lead to iron deficiency, which may in itself pose a risk for infection (1,29–31).

Reexamination of the safety of intravenous iron is especially timely in light of the recent introduction of the bundled ESRD reimbursement system in 2011, which appears to have prompted increased utilization of intravenous iron (32). This review will discuss the biologic plausibility of increased infection risk with iron use and critically evaluate the current body of literature pertaining to the influence of iron on the risk for infection in hemodialysis patients.

Iron and Infection: Biologic Plausibility

Iron participates in important oxidation-reduction reactions that are essential for life (33). “Free” (i.e., unbound) iron (Fe^{2+} and Fe^{3+}) contributes to the formation of reactive oxygen species (34,35), which are important for phagocyte function (1,36). Iron is required for proper host defense against infection, and iron deficiency has been associated with impaired neutrophil function (1,29–31). However, an excess of iron has also been linked to impaired neutrophil and T cell function and promotion of microbial growth in *in vitro* and *in vivo* studies involving animals and humans, although the duration of this effect has not been well-established as the longest follow-up times were 2–3 days (37,38).

In neutrophils from healthy volunteers incubated with ferric compounds (39–41) and non-dialysis patients with iron overload (42), impairments in polymorphonuclear (PMN) cell migration, phagocytosis, and survival have been observed. There is also evidence of impaired function in neutrophils obtained from dialysis patients with iron overload (43–45) or treated with intravenous iron (38,46). While much of the literature on the biologic basis for increased infection risk due to iron has focused on neutrophil function, there is also evidence of an influence of iron on T cell function. In mice that had been iron overloaded with intraperitoneal injections of iron dextran, failure to mount a Th1-mediated protective immune response to *Candida albicans* infection has been observed (24). Treatment with deferoxamine (iron chelator) restored the Th1 response and ability of iron overloaded mice to survive *Candida albicans* infection.

In addition to its effects on PMN and T cell function, iron may promote bacterial growth directly. Several *in vitro* and *in vivo* studies in animals and humans have shown iron to be a growth factor for numerous bacteria and other pathogens (47). For example, the risk of death

in mice inoculated intraperitoneally with *Pasturella septica* increased by 9–10 fold when lysed red blood cells or purified hemoglobin were first mixed with the bacteria as a source of iron prior to injection (48). Humans have developed mechanisms for withholding iron from microorganisms as part of their host defense against infection (49). The iron-binding proteins transferrin (found in highest concentrations in plasma and lymphatic fluids) and lactoferrin (found predominantly in mucosal secretions and phagocytic granules) (49) are thought to sequester iron away from microorganisms and provide a form of nonspecific immunity against infection (33,36,49). However, some bacteria can still compete for iron by producing siderophores (iron chelators), while others can directly acquire iron from transferrin via a membrane-bound transferrin receptor (1).

Intravenous iron may result in over-saturation of host iron-binding proteins, increasing free iron availability and promoting bacterial growth (37,50–52). In a study of twelve hemodialysis patients injected with 100 mg of iron saccharate, mean transferrin saturation and catalytically active iron concentration increased from baseline by 5 minutes, remained elevated for at least 210 minutes, and returned to baseline by 2–3 days (37). After inoculation with *Staphylococcus epidermidis*, bacterial growth at 9 to 24 hours was higher in serum obtained 210 minutes after iron saccharate injection compared to serum obtained before iron saccharate injection. The higher bacterial growth found in the 210 minutes sample was abolished by addition of iron-free apotransferrin to the serum, indicating that *Staphylococcus epidermidis* growth was dependent on the presence of non-transferrin-bound serum iron.

Ferritin and Infection in Hemodialysis Patients

Thirteen studies with sample sizes ranging from 61 to 2,662 have examined the link between serum ferritin and infection in hemodialysis patients (Table 1). Nine of these studies found that high serum ferritin (typically defined as >500 or 1,000 ng/mL or, equivalently, µg/L) was associated with higher incidence of bacterial infection or infection-related mortality (11,13,28,53–58). The incidence of bacterial infection ranged from 0.34 to 0.59 infections per patient-year (in studies evaluating the rate of infection) and 0.93% to 61.9% (in studies evaluating the proportion with infection) in the higher serum ferritin groups and 0.09 to 0.18 infections per patient-year and 0% to 37% in the lower serum ferritin groups (13,28,53–56,58). In absolute terms, these studies suggest an excess of 16 to 50 infections per 100 patient-years in the higher compared with the lower serum ferritin groups. In studies that expressed the association between serum ferritin and bacterial infection as ratios, higher serum ferritin was independently associated with a 1.5 to 3.1-fold higher incidence of bacterial infection or infection-related mortality (11,28,57,58).

However, four studies did not observe an association between higher serum ferritin and infection. There was no significant difference in bacteremia-free tunneled catheter survival comparing patients with serum ferritin >500 and ≤500 ng/mL (59), the proportion with infection, pneumonia, or cellulitis/carbuncle comparing patients with serum ferritin >600 and <600 ng/mL (12), or a significant association between serum ferritin and infection-related mortality (60). In addition, a team of French investigators (Hoen *et al.*) found that serum ferritin was not a significant risk factor for bacteremia (26), a result that is in contrast

to their prior finding that higher serum ferritin was an independent risk factor for bacterial infection (57). The authors attribute these discrepant results to the lower prevalence of iron overload (defined as a serum ferritin >1,000 ng/mL) in the more recent study (5%) compared to the older study (over 10%).

It is also worth noting that the prevalence of erythropoietin use was much lower in the earlier (16.1%) than later (51.5%) Hoen *et al.* study. In hemodialysis patients with transfusional iron overload, erythropoietin treatment lowers serum ferritin and transferrin saturation and improves phagocytosis and killing of *Yersinia enterocolitica* (61). Thus, it is possible that the increased prevalence of erythropoietin use may have contributed to the lack of association between ferritin and bacterial infection observed in the later Hoen *et al.* study. Additionally, the earlier study (57) measured serum ferritin at the time of first bacterial infection (or at the end of the study period if no bacterial infection was present) whereas the later study (26) assessed the association of *baseline* ferritin with subsequent infection. Inferences from studies evaluating the association between serum ferritin and infection, such as the Hoen *et al.* studies, are confounded by the fact that ferritin is an acute phase reactant that may be elevated in the setting of infection (62). Thus, it is possible that the results from the earlier study were biased in favor of finding an association between serum ferritin and infection given the timing of ferritin measurement.

Aside from the limitations of serum ferritin as a predictor variable, studies involving ferritin also had limitations in the definition of their outcome variable. Some of these studies focused solely on the outcome of sepsis/bacteremia (26,28,54,56,59) or excluded certain types of bacterial infections (55) and may have underestimated the association between serum ferritin and bacterial infection. Many of these studies were descriptive and either did not control for confounding (12,13,53–55,59) or made very limited attempts to do so (56). Some of these studies were conducted before erythropoiesis-stimulating agents and intravenous iron were widely used and during a time when blood transfusions were the mainstay of treatment for anemia of ESRD (53–57). In this setting, it would be expected that iron overload was mainly due to repeated blood transfusion, which typically provides a larger iron load than intravenous iron administered according to international guidelines (6) and may have a different impact on immune function and infection risk than iron overload caused by intravenous iron (63,64). Thus, the relevance of these studies to the current practice environment, in which widespread erythropoiesis-stimulating agent use has reduced the need for repeated blood transfusions and prevalence of iron overload (3,65), is unclear. Finally, all but four studies involved patients from countries other than the U.S. (11,13,26,53–57,59), limiting generalizability to U.S. hemodialysis patients. The percentage of studies finding an association between serum ferritin and infection risk was higher in studies conducted outside than inside of the U.S. (78% vs. 50%).

Iron Usage and Infection in Hemodialysis Patients

Twenty-four studies have evaluated the association between iron usage and infection in hemodialysis patients (Table 2). While not the primary aim of the analyses, two randomized-controlled studies have addressed the association between any iron usage or more “aggressive” iron repletion and infection in hemodialysis patients. In the Dialysis Patients’

Response to IV Iron with Elevated Ferritin (DRIVE) study, anemic (hemoglobin < 11 g/dL) hemodialysis patients with serum ferritin 500–1,200 ng/mL and transferrin saturation $< 25\%$ were randomized to ferric gluconate (125 mg intravenously for eight consecutive dialysis sessions) or no iron (7). The number of infections over the 6-week study was not substantially different between the two groups. Another trial randomized hemodialysis patients with hemoglobin < 9.5 g/dL, serum ferritin 150–600 ng/mL and transferrin saturation 19–30% to iron dextran to achieve and maintain a transferrin saturation of 30–50% or to maintain a transferrin saturation of 20–30% over a 6 month period (66). There was one death due to infection in the former group in a patient with multiple risk factors for infection. Each group had one admission for an infectious etiology.

However, the majority of studies (twenty-two) evaluating the association between iron usage and infection in hemodialysis patients are observational and have yielded conflicting results. The sample sizes ranged from 21 to 309,219, and the iron exposure and infectious outcome variables were heterogeneously defined. Twelve of these studies found an association between any iron usage or higher dose or frequency of iron usage and infection or infection-related mortality (9,11,15,59,60,67–73).

While a few studies evaluated the infection risk of any iron usage (11,60,72), most of these studies incorporated iron dose or frequency into their iron exposure variables. In two large studies, higher frequency and higher dose of intravenous iron were independently associated with 14 to 35% higher risk of infection-related mortality (67,68). In another large study, compared with a reference mean dose of 25–34 mg of intravenous iron per dialysis treatment, high dose (> 34 mg per dialysis treatment) and no iron were independently associated with higher hazard of infection-related mortality whereas low dose (1–13 mg per dialysis treatment) was independently associated with lower hazard of infection-related mortality (70). Other studies observed a significantly higher iron dosage (at study conclusion) in patients who had developed catheter-related bacteremia compared to those who had not (59) and a significantly higher mean number of intravenous iron vials per month among those with a higher number of hospitalizations for vascular access infections (71). A relatively small study ($n=111$) observed a significantly higher rate of bacterial infection with higher iron sucrose dose but not higher frequency dosing (69). In contrast, a much larger study ($n=117,050$) found a relatively modest but higher independent hazard of infection-related hospitalization or mortality (HR 1.08, 95% CI 1.05–1.11) and an excess of 26 of these events per 1,000 patient-years with bolus compared to maintenance intravenous iron (15). They also found a higher independent hazard of infection-related hospitalization or mortality (HR 1.05, 95% CI 1.02–1.08) and an excess of 13 of these events per 1,000 patient-years with high (> 200 mg/month) compared with low (1–200 mg/month) dose intravenous iron. However, compared with no intravenous iron, receipt of maintenance (HR 0.99, 95% CI 0.97–1.02) and low dose (HR 0.99, 95% CI 0.97–1.02) intravenous iron were not significantly associated with infection-related hospitalization or mortality.

Only a couple of studies have examined differences among formulations of iron. In one study, there was a significantly higher rate of bacteremia with iron sucrose compared to ferric gluconate, although the association between iron dose and bacteremia was uncertain (73). Another study observed a significant association between iron sucrose and catheter-

related sepsis; iron dextran did not have a significant association with catheter-related sepsis (9).

The remaining ten studies did not find an association between iron and infection (8,10,12,14,26–28,58,74,75). Iron (intravenous or oral) usage within the last 6 months was not significantly associated with hazard of bacteremia (26), and in a follow-up study by the same team of investigators analyzing a subset of the original cohort, intravenous iron and weekly intravenous iron dose were not significantly associated with hazard of bacteremia (27). Two studies observed that 3-month cumulative intravenous iron dose was not significantly associated with incidence of bacterial infection or bacteremia (28,58). Within the year after implementation of more “aggressive” iron repletion protocols, two studies did not report a substantial increase in the incidence of infectious complications compared to the year prior to protocol implementation (14,74). In a six-week observational extension of the DRIVE study (DRIVE-II), the ferric gluconate group had a lower number of infections classified as serious than the control group during the 12-week period encompassed by DRIVE and DRIVE-II (10). In a phase IV study of hemodialysis patients receiving replacement or maintenance iron sucrose, the rate of mortality from infection or sepsis was not significantly different from that observed in the United States Renal Data System (USRDS), and the rate of hospitalization from infection was significantly lower than that of the USRDS (75). Among hemodialysis patients with serum ferritin >800 ng/mL and transferrin saturation <25%, there was no significant difference in incident infection or infectious hospitalization over a 4 month follow-up period between groups suspected and not suspected of having functional iron deficiency; the former group had a higher 3-month mean cumulative intravenous ferric gluconate dose than the latter group (8). Finally, there was no significant difference in the proportion with infection, pneumonia, or cellulitis/carbuncle comparing patients with intravenous iron dose >455 and ≤455 mg/month (12).

Observational studies evaluating the association between iron use and infection have primarily had a cohort design in which confounding between subjects may not have been adequately controlled. Some studies were primarily descriptive with respect to the association between iron and infection and did not include multivariate analysis (8,10,12,14,59,69,71,72,74,75). Even in studies in which several comorbidities were included in the multivariate models, the possibility of residual confounding remains (15,26,27,67,68). In the studies that did not find a substantial increase in infectious complications after implementation of an aggressive iron repletion protocol, it is possible that other temporal trends prevented detection of an increased incidence of infectious complications (14,74). As noted by the study authors, comparison of the rates of hospitalization and death from infection between the likely healthier patients in the phase IV study and the general dialysis population is limited by selection bias, although all of the study patients were exposed to intravenous iron compared to only 55–60% during the course of a year in the general dialysis population (75).

Considering the studies of the association between iron usage and infection as a group, some may deserve more emphasis than others. The sample size was relatively small (<150) in many studies (7,8,10,14,28,58,59,66,69,72–74), and the duration of follow-up time was brief in some studies (7,10,72), which may have limited detection of an effect of iron on

infectious outcomes. Of note, most of the large studies did show an association between iron and infection, which may reflect a real effect or residual confounding. Nearly two-thirds (fifteen of twenty-four) of the studies involved hemodialysis patients from countries other than the U.S. (11,26,27,59,69,74) with different anemia management practices (76) or older cohorts (i.e., 2002 or older) of U.S. patients (28,58,60,66–68,70,71,73), limiting generalizability of the results within the setting of current intravenous iron prescription practices for U.S. hemodialysis patients. However, the percentage of studies that found an association between iron and infection risk was the same (50%) in studies conducted inside and outside of the U.S. It is possible that iron sucrose, the most widely used preparation in the U.S. (77), may exert a different effect on infection risk than ferric gluconate or iron dextran based on *in vitro* data (39,78) and clinical studies (9,73).

Conclusions

The majority of studies focusing on serum ferritin showed an association with infection, but the results from studies evaluating iron usage were more mixed. Overall, the current body of literature appears to favor an association between iron and infection in hemodialysis patients, though several limitations must be acknowledged and publication bias cannot be ruled out. There is a suggestion of possible increased infection risk with iron sucrose compared to ferric gluconate and iron dextran (9,73), though this must be investigated further in larger studies. Only one study compared the infection risk between bolus and maintenance dosing using multivariate analysis (15), and the finding of higher risk with bolus dosing must be confirmed in future studies before definitive conclusions can be made about which dosing strategy minimizes infection risk. Although there are no clinical data specifically supporting the recommendation by KDIGO and other international CKD anemia guidelines to avoid or withhold intravenous iron among patients with systemic infection (18,20), it may be prudent to do so among most hemodialysis patients with signs or symptoms of infection given that the overall evidence supports an association between iron and *incident* infectious outcomes. However, it is unclear when iron therapy should be restarted. It is biologically plausible that intravenous iron could exert a relatively acute immunosuppressive effect (37,38), but no clinical studies have specifically evaluated the duration of infection risk posed by iron in hemodialysis patients.

Intravenous iron is important in the treatment of anemia of ESRD, but the optimal strategy to prevent iron deficiency and minimize risk of infection has yet to be identified. It will be important to focus on conducting large studies that compare current dosing strategies and newer agents, consider novel designs to address confounding given that large randomized controlled trials are unlikely, and examine more recent data in the post-bundle era.

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References

1. Fishbane S. Review of issues relating to iron and infection. *Am J Kidney Dis.* 1999; 34(4 Suppl 2):S47–52. [PubMed: 10516376]
2. Besarab A, Frinak S, Yee J. An indistinct balance: the safety and efficacy of parenteral iron therapy. *J Am Soc Nephrol.* 1999; 10(9):2029–2043. [PubMed: 10477157]
3. Eschbach JW, Adamson JW. Iron overload in renal failure patients: changes since the introduction of erythropoietin therapy. *Kidney Int Suppl.* 1999; 69:S35–43. [PubMed: 10084284]
4. Brewster UC, Perazella MA. Intravenous iron and the risk of infection in end-stage renal disease patients. *Semin Dial.* 2004; 17(1):57–60. [PubMed: 14717813]
5. Brewster UC. Intravenous iron therapy in end-stage renal disease. *Semin Dial.* 2006; 19(4):285–290. [PubMed: 16893405]
6. Horl WH. Iron therapy for renal anemia: how much needed, how much harmful? *Pediatr Nephrol.* 2007; 22(4):480–489. [PubMed: 17206511]
7. Coyne DW, Kapoian T, Suki W, Singh AK, Moran JE, Dahl NV, Rizkala AR. DRIVE Study Group. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. *J Am Soc Nephrol.* 2007; 18(3):975–984. [PubMed: 17267740]
8. Kopelman RC, Smith L, Peoples L, Biesecker R, Rizkala AR. Functional iron deficiency in hemodialysis patients with high ferritin. *Hemodial Int.* 2007; 11(2):238–246. [PubMed: 17403177]
9. Diskin CJ, Stokes TJ, Dansby LM, Radcliff L, Carter TB. Is systemic heparin a risk factor for catheter-related sepsis in dialysis patients? An evaluation of various biofilm and traditional risk factors. *Nephron Clin Pract.* 2007; 107(4):c128–32. [PubMed: 17957123]
10. Kapoian T, O'Mara NB, Singh AK, Moran J, Rizkala AR, Geronemus R, Kopelman RC, Dahl NV, Coyne DW. Ferric gluconate reduces epoetin requirements in hemodialysis patients with elevated ferritin. *J Am Soc Nephrol.* 2008; 19(2):372–379. [PubMed: 18216316]
11. Jenq CC, Hsu CW, Huang WH, Chen KH, Lin JL, Lin-Tan DT. Serum ferritin levels predict all-cause and infection-cause 1-year mortality in diabetic patients on maintenance hemodialysis. *Am J Med Sci.* 2009; 337(3):188–194. [PubMed: 19282675]
12. Pollak VE, Lorch JA, Shukla R, Satwah S. The importance of iron in long-term survival of maintenance hemodialysis patients treated with epoetin-alfa and intravenous iron: analysis of 9.5 years of prospectively collected data. *BMC Nephrol.* 2009; 10 6-2369-10-6.
13. Galic G, Tomic M, Galesic K, Kvesic A, Soljic M, Londar Z, Valencic M, Martinovic Z, Vuckov S. The etiological relation between serum iron level and infection incidence in hemodialysis uremic patients. *Coll Antropol.* 2011; 35(1):93–101. [PubMed: 21667534]
14. Bansal A, Sandhu G, Gupta I, Kalahalli S, Nayak R, Zouain E, Chitale RA, Meisels I, Chan G. Effect of Aggressively Driven Intravenous Iron Therapy on Infectious Complications in End-Stage Renal Disease Patients on Maintenance Hemodialysis. *Am J Ther.* 2012 Jul 23. [Epub ahead of print].
15. Brookhart MA, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Kshirsagar AV. Infection Risk with Bolus versus Maintenance Iron Supplementation in Hemodialysis Patients. *J Am Soc Nephrol.* 2013; 24(7):1151–1158. [PubMed: 23787911]
16. Madore F, White CT, Foley RN, Barrett BJ, Moist LM, Klarenbach SW, Culleton BF, Tonelli M, Manns BJ. Canadian Society of Nephrology. Clinical practice guidelines for assessment and management of iron deficiency. *Kidney Int Suppl.* 2008; (110):S7–S11. [PubMed: 18668119]
17. Tsubakihara Y, Nishi S, Akiba T, Hirakata H, Iseki K, Kubota M, Kuriyama S, Komatsu Y, Suzuki M, Nakai S, Hattori M, Babazono T, Hiramatsu M, Yamamoto H, Bessho M, Akizawa T. 2008 Japanese Society for Dialysis Therapy: guidelines for renal anemia in chronic kidney disease. *Ther Apher Dial.* 2010; 14(3):240–275. [PubMed: 20609178]
18. Kidney Disease Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney international Supplement.* 2012; 2:279–335.
19. IV. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease. Update 2000. *Am J Kidney Dis.* 2001; 37(1 Suppl 1):S182–238. [PubMed: 11229970]

20. Locatelli F, Aljama P, Barany P, Canaud B, Carrera F, Eckardt KU, Horl WH, Macdougall IC, Macleod A, Wiecek A, Cameron S. European Best Practice Guidelines Working Group. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant*. 2004; 19(Suppl 2):ii1–47. [PubMed: 15206425]
21. Wessling-Resnick M. Iron homeostasis and the inflammatory response. *Annu Rev Nutr*. 2010; 30:105–122. [PubMed: 20420524]
22. Appelberg R. Macrophage nutritive antimicrobial mechanisms. *J Leukoc Biol*. 2006; 79(6):1117–1128. [PubMed: 16603587]
23. Byrd TF, Horwitz MA. Interferon gamma-activated human monocytes downregulate transferrin receptors and inhibit the intracellular multiplication of *Legionella pneumophila* by limiting the availability of iron. *J Clin Invest*. 1989; 83(5):1457–1465. [PubMed: 2496141]
24. Mencacci A, Cenci E, Boelaert JR, Bucci P, Mosci P, Fe d'Ostiani C, Bistoni F, Romani L. Iron overload alters innate and T helper cell responses to *Candida albicans* in mice. *J Infect Dis*. 1997; 175(6):1467–1476. [PubMed: 9180188]
25. Nairz M, Theurl I, Ludwiczek S, Theurl M, Mair SM, Fritsche G, Weiss G. The co-ordinated regulation of iron homeostasis in murine macrophages limits the availability of iron for intracellular *Salmonella typhimurium*. *Cell Microbiol*. 2007; 9(9):2126–2140. [PubMed: 17466014]
26. Hoen B, Paul-Dauphin A, Hestin D, Kessler M. EPIBACDIAL: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol*. 1998; 9(5):869–876. [PubMed: 9596085]
27. Hoen B, Paul-Dauphin A, Kessler M. Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients. *Clin Nephrol*. 2002; 57(6):457–461. [PubMed: 12078950]
28. Teehan GS, Bahdouch D, Ruthazer R, Balakrishnan VS, Snyderman DR, Jaber BL. Iron storage indices: novel predictors of bacteremia in hemodialysis patients initiating intravenous iron therapy. *Clin Infect Dis*. 2004; 38(8):1090–1094. [PubMed: 15095212]
29. Yetgin S, Altay C, Ciliv G, Laleli Y. Myeloperoxidase activity and bactericidal function of PMN in iron deficiency. *Acta Haematol*. 1979; 61(1):10–14. [PubMed: 217216]
30. Moore LL, Humbert JR. Neutrophil bactericidal dysfunction towards oxidant radical-sensitive microorganisms during experimental iron deficiency. *Pediatr Res*. 1984; 18(8):789–794. [PubMed: 6089085]
31. Cu Y, Zhang ZN, Li RS. Influence of latent iron deficiency on generation of oxygen species in polymorphonuclear leucocytes. *Chin Med J (Engl)*. 1990; 103(8):642–646. [PubMed: 2122944]
32. Fuller DS, Pisoni RL, Bieber BA, Gillespie BW, Robinson BM. The DOPPS Practice Monitor for US dialysis care: trends through December 2011. *Am J Kidney Dis*. 2013; 61(2):342–346. [PubMed: 23127619]
33. Bullen JJ, Ward CG, Rogers HJ. The critical role of iron in some clinical infections. *Eur J Clin Microbiol Infect Dis*. 1991; 10(8):613–617. [PubMed: 1748112]
34. Braugher JM, Duncan LA, Chase RL. The involvement of iron in lipid peroxidation. Importance of ferric to ferrous ratios in initiation. *J Biol Chem*. 1986; 261(22):10282–10289. [PubMed: 3015924]
35. Keyer K, Imlay JA. Superoxide accelerates DNA damage by elevating free-iron levels. *Proc Natl Acad Sci U S A*. 1996; 93(24):13635–13640. [PubMed: 8942986]
36. Sunder-Plassmann G, Patruta SI, Horl WH. Pathobiology of the role of iron in infection. *Am J Kidney Dis*. 1999; 34(4 Suppl 2):S25–9. [PubMed: 10516372]
37. Parkkinen J, von Bonsdorff L, Peltonen S, Gronhagen-Riska C, Rosenlof K. Catalytically active iron and bacterial growth in serum of haemodialysis patients after i.v. iron-saccharate administration. *Nephrol Dial Transplant*. 2000; 15(11):1827–1834. [PubMed: 11071973]
38. Deicher R, Ziai F, Cohen G, Mullner M, Horl WH. High-dose parenteral iron sucrose depresses neutrophil intracellular killing capacity. *Kidney Int*. 2003; 64(2):728–736. [PubMed: 12846772]
39. Sengoelge G, Kletzmayer J, Ferrara I, Perschl A, Horl WH, Sunder-Plassmann G. Impairment of transendothelial leukocyte migration by iron complexes. *J Am Soc Nephrol*. 2003; 14(10):2639–2644. [PubMed: 14514743]

40. Ichii H, Masuda Y, Hassanzadeh T, Saffarian M, Gollapudi S, Vaziri ND. Iron sucrose impairs phagocytic function and promotes apoptosis in polymorphonuclear leukocytes. *Am J Nephrol*. 2012; 36(1):50–57. [PubMed: 22722756]
41. van Asbeck BS, Marx JJ, Struyvenberg A, van Kats JH, Verhoef J. Effect of iron (III) in the presence of various ligands on the phagocytic and metabolic activity of human polymorphonuclear leukocytes. *J Immunol*. 1984; 132(2):851–856. [PubMed: 6690620]
42. van Asbeck BS, Marx JJ, Struyvenberg A, Verhoef J. Functional defects in phagocytic cells from patients with iron overload. *J Infect*. 1984; 8(3):232–240. [PubMed: 6736664]
43. Cantinieaux B, Boelaert J, Hariga C, Fondu P. Impaired neutrophil defense against *Yersinia enterocolitica* in patients with iron overload who are undergoing dialysis. *J Lab Clin Med*. 1988; 111(5):524–528. [PubMed: 3361231]
44. Waterlot Y, Cantinieaux B, Hariga-Muller C, De Maertelaere-Laurent E, Vanherweghem JL, Fondu P. Impaired phagocytic activity of neutrophils in patients receiving haemodialysis: the critical role of iron overload. *Br Med J (Clin Res Ed)*. 1985; 291(6494):501–504.
45. Flament J, Goldman M, Waterlot Y, Dupont E, Wybran J, Vanherweghem JL. Impairment of phagocyte oxidative metabolism in hemodialyzed patients with iron overload. *Clin Nephrol*. 1986; 25(5):227–230. [PubMed: 3013477]
46. Patruta SI, Edlinger R, Sunder-Plassmann G, Horl WH. Neutrophil impairment associated with iron therapy in hemodialysis patients with functional iron deficiency. *J Am Soc Nephrol*. 1998; 9(4):655–663. [PubMed: 9555668]
47. Khan FA, Fisher MA, Khakoo RA. Association of hemochromatosis with infectious diseases: expanding spectrum. *Int J Infect Dis*. 2007; 11(6):482–487. [PubMed: 17600748]
48. Bullen JJ, Rogers HJ. Effect of haemoglobin on experimental infections with *Pasteurella septia* and *Escherichia coli*. *Nature*. 1968; 217(5123):86. [PubMed: 4865592]
49. Mietzner TA, Morse SA. The role of iron-binding proteins in the survival of pathogenic bacteria. *Annu Rev Nutr*. 1994; 14:471–493. [PubMed: 7946530]
50. Ward CG, Hammond JS, Bullen JJ. Effect of iron compounds on antibacterial function of human polymorphs and plasma. *Infect Immun*. 1986; 51(3):723–730. [PubMed: 3512430]
51. Ward CG, Bullen JJ, Rogers HJ. Iron and infection: new developments and their implications. *J Trauma*. 1996; 41(2):356–364. [PubMed: 8760553]
52. Bullen JJ, Armstrong JA. The role of lactoferrin in the bactericidal function of polymorphonuclear leucocytes. *Immunology*. 1979; 36(4):781–791. [PubMed: 108208]
53. Seifert A, von Herrath D, Schaefer K. Iron overload, but not treatment with desferrioxamine favours the development of septicemia in patients on maintenance hemodialysis. *Q J Med*. 1987; 65(248):1015–1024. [PubMed: 3455553]
54. Boelaert JR, van Landuyt HW, Valcke YJ, Cantinieaux B, Lornoy WF, Vanherweghem JL, Moreillon P, Vandepitte JM. The role of iron overload in *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* bacteremia in hemodialysis patients. *J Infect Dis*. 1987; 156(2):384–387. [PubMed: 3598237]
55. Tielemans CL, Lenclud CM, Wens R, Collart FE, Dratwa M. Critical role of iron overload in the increased susceptibility of haemodialysis patients to bacterial infections. Beneficial effects of desferrioxamine. *Nephrol Dial Transplant*. 1989; 4(10):883–887. [PubMed: 2515493]
56. Boelaert JR, Daneels RF, Schurgers ML, Matthys EG, Gordts BZ, Van Landuyt HW. Iron overload in haemodialysis patients increases the risk of bacteraemia: a prospective study. *Nephrol Dial Transplant*. 1990; 5(2):130–134. [PubMed: 2113211]
57. Hoen B, Kessler M, Hestin D, Mayeux D. Risk factors for bacterial infections in chronic haemodialysis adult patients: a multicentre prospective survey. *Nephrol Dial Transplant*. 1995; 10(3):377–381. [PubMed: 7792034]
58. Teehan GS, Ruthazer R, Balakrishnan VS, Snyderman D, Jaber BL. Iron storage indices and risk of bacterial infections in hemodialysis patients. *Hemodial Int*. 2004; 8(3):226–232. [PubMed: 19379422]
59. Jean G, Charra B, Chazot C, Vanel T, Terrat JC, Huot JM, Laurent G. Risk factor analysis for long-term tunneled dialysis catheter-related bacteremias. *Nephron*. 2002; 91(3):399–405. [PubMed: 12119469]

60. Nurko S, Young EE, Port FK. Parenteral Iron and Infection Mortality Risk in Hemodialysis Patients, (abstract). *J Am Soc Nephrol*. 1999; 10:252A.
61. Boelaert JR, Cantinieux BF, Hariga CF, Fondu PG. Recombinant erythropoietin reverses polymorphonuclear granulocyte dysfunction in iron-overloaded dialysis patients. *Nephrol Dial Transplant*. 1990; 5(7):504–517. [PubMed: 2130296]
62. Kalantar-Zadeh K, Kalantar-Zadeh K, Lee GH. The fascinating but deceptive ferritin: to measure it or not to measure it in chronic kidney disease? *Clin J Am Soc Nephrol*. 2006; 1 (Suppl 1):S9–18. [PubMed: 17699375]
63. Bordin JO, Heddle NM, Blajchman MA. Biologic effects of leukocytes present in transfused cellular blood products. *Blood*. 1994; 84(6):1703–1721. [PubMed: 8080981]
64. Klein HG. Immunologic aspects of blood transfusion. *Semin Oncol*. 1994; 21(2 Suppl 3):16–20. [PubMed: 8202721]
65. U.S. Renal Data System. Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: 1994. USRDS 1994 Annual Data Report.
66. Besarab A, Amin N, Ahsan M, Vogel SE, Zazuwa G, Frinak S, Zazra JJ, Anandan JV, Gupta A. Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. *J Am Soc Nephrol*. 2000; 11(3):530–538. [PubMed: 10703677]
67. Collins A, Ebben J, Ma J. Frequent IV iron dosing is associated with higher infectious deaths, (abstract). *J Am Soc Nephrol*. 1997; 8:190A.
68. Collins A, Ebben J, Ma J, Xia H IV. Iron dosing patterns and mortality, (abstract). *J Am Soc Nephrol*. 1998; 9:205A.
69. Canziani ME, Yumiya ST, Rangel EB, Manfredi SR, Neto MC, Draibe SA. Risk of bacterial infection in patients under intravenous iron therapy: dose versus length of treatment. *Artif Organs*. 2001; 25(11):866–869. [PubMed: 11903138]
70. Sun Y, Stidley CA, Harford AM, Brown RH, Zager PG. Increased Cardiovascular & Infectious Deaths in Hemodialysis (HD) Patients Treated with High Dose Intravenous Iron Therapy (IV Fe), (abstract). *J Am Soc Nephrol*. 2002; 13:434A.
71. Roberts TL, Obrador GT, St Peter WL, Pereira BJ, Collins AJ. Relationship among catheter insertions, vascular access infections, and anemia management in hemodialysis patients. *Kidney Int*. 2004; 66(6):2429–2436. [PubMed: 15569336]
72. Brewster UC, Coca SG, Reilly RF, Perazella MA. Effect of intravenous iron on haemodialysis catheter microbial colonization and blood-borne infection. *Nephrology (Carlton)*. 2005; 10(2): 124–128. [PubMed: 15877670]
73. Sirken G, Raja R, Rizkala AR. Association of different intravenous iron preparations with risk of bacteremia in maintenance hemodialysis patients. *Clin Nephrol*. 2006; 66(5):348–356. [PubMed: 17140164]
74. Macdougall IC, Chandler G, Elston O, Harchowal J. Beneficial effects of adopting an aggressive intravenous iron policy in a hemodialysis unit. *Am J Kidney Dis*. 1999; 34(4 Suppl 2):S40–6. [PubMed: 10516375]
75. Aronoff GR, Bennett WM, Blumenthal S, Charytan C, Pennell JP, Reed J, Rothstein M, Strom J, Wolfe A, Van Wyck D, Yee J. United States Iron Sucrose (Venofer) Clinical Trials Group. Iron sucrose in hemodialysis patients: safety of replacement and maintenance regimens. *Kidney Int*. 2004; 66(3):1193–1198. [PubMed: 15327417]
76. Pisoni RL, Bragg-Gresham JL, Young EW, Akizawa T, Asano Y, Locatelli F, Bommer J, Cruz JM, Kerr PG, Mendelssohn DC, Held PJ, Port FK. Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2004; 44(1):94–111. [PubMed: 15211443]
77. Hirth RA, Turenne MN, Wheeler JR, Nahra TA, Sleeman KK, Zhang W, Messana JA. The Initial Impact of Medicare's New Prospective Payment System for Kidney Dialysis. *Am J Kidney Dis*. 2013; 62(4):662–669. [PubMed: 23769138]
78. Pai AB, Boyd AV, McQuade CR, Harford A, Norenberg JP, Zager PG. Comparison of oxidative stress markers after intravenous administration of iron dextran, sodium ferric gluconate, and iron

sucrose in patients undergoing hemodialysis. *Pharmacotherapy*. 2007; 27(3):343–350. [PubMed: 17316146]

Table 1
Association between Serum Ferritin and Infection-Related Mortality in Hemodialysis Patients

Author/Year	Country/# of centers	N ^a	Predictor(s)	Outcome(s)	Results ^b	Summary
<i>Association Between Serum Ferritin and Infection or Infection-Related Mortality</i>						
Seifert 1987 (53)	Germany 2 centers	184	Mean SF during study period: 10–330, 331–1,000 or 1,001–2,000 ng/mL	Bacterial infections (BIs)/patient-year (PY) where BI includes septicemia and other BIs	0.34 BIs/PY (SF 331–1,000 ng/mL) vs. 0.18 BIs/PY (SF 10–330 ng/mL), $p<0.05$; 0.59 BIs/PY (SF 1,001–2,000 ng/mL) vs. 0.18 BIs/PY (SF 10–330 ng/mL), $p<0.01$.	Higher rates of BI were observed in the higher SF groups.
Boelaert 1987 (54)	Belgium 36 centers	1,421	SF at time of questionnaire: <500 or >500 ng/mL	Proportion with <i>Yersinia enterocolitica</i> bacteremia (YEB) in the previous 5 years	0.93% YEB (SF >500 ng/mL) vs. 0% YEB (SF <500 ng/mL), $p<0.05$.	A higher proportion of previous YEB was observed in the higher SF group.
Tielemans 1989 (55)	Belgium 1 center	61	Mean SF during study period: 500 or >500 ng/mL	Bacterial infections (BIs)/patient-year (PY) where BI includes septicemia and other BIs; time to first BI	0.48 BIs/PY (SF >500 ng/mL) vs. 0.09 BIs/PY (SF 500 ng/mL), $p<0.001$. Shorter time to first BI with higher ferritin, $p<0.005$ (logrank).	A higher rate of BI and shorter time to BI were observed in the higher SF group.
Boelaert 1990 (56)	Belgium 1 center	158	SF classified every 3 months: <500 , 500–1,000, or $>1,000$ ng/mL (<500 and 500–1,000 ng/mL combined for analysis)	Bacteremic episodes (BEs)/patient-year (PY)	0.34 BEs/PY (SF $>1,000$ ng/mL) vs. 0.12 BEs/PY (SF 1,000 ng/mL), $p<0.005$.	A higher rate of BEs was observed in the higher SF group.
Hoen 1995 (57)	France 13 centers	607	SF at first bacterial infection (BI) or end of study period if no BI: <500 or 500 ng/mL	Bacterial infection (BI) over 6 month period	OR for BI (SF 500 vs. <500 ng/mL): 1.79 (95% CI 1.06–3.00).	Higher SF was independently associated with higher odds of BI.
Teehan 2004 (58)	U.S. 1 center	87	Iron deficiency (TSAT $<20\%$ and SF <100 ng/mL), functional iron deficiency (TSAT $<20\%$ and SF >100 ng/mL), iron replete (TSAT $>20\%$ and SF >100 ng/mL). Measured at baseline prior to initiation of IV iron. (Iron deficiency and functional iron deficiency combined for analysis.)	Proportion with bacterial infection (BI), which included bacteremia or bacterial pneumonia, and time to BI over 2 years	Higher proportion of BI in iron replete (56%) than functionally iron deficient (27%) or iron deficient (37%) groups. HR for BI (iron replete vs. non-iron replete): 3.1 (95% CI 1.4–6.8).	Iron repletion was independently associated with higher hazard of BI.
Teehan 2004 (28)	U.S. 2 centers	132	Iron deficiency (TSAT $<20\%$ and SF <100 ng/mL), functional iron deficiency (TSAT $<20\%$ and SF 100 ng/mL), iron replete (TSAT $>20\%$ and SF 100 ng/mL). Based on mean values within 3 months of starting IV iron. (Iron deficiency and functional iron	Proportion with bacteremia and time to first bacteremic episode over 1 year	Proportion with bacteremia in iron replete (35%) vs. non-iron replete (18%), $p=0.06$. HR for bacteremia (iron replete vs. non-iron replete): 2.5 (95% CI 1.1–5.7).	Iron repletion was independently associated with higher hazard of bacteremia.

Author/Year	Country/# of centers	N ^a	Predictor(s)	Outcome(s)	Results ^b	Summary
Jenq 2009 (11)	Taiwan 3 centers	187	deficiency combined for analysis.) deficiency combined for analysis.) Baseline SF (measured during first week of study, ng/mL)	Infection-related mortality (IRM) at 1 year	HR for IRM: 1.001 per 1 ng/mL (95% CI 1.000–1.002) or 1.5 per 500 ng/mL.	Higher SF was independently associated with higher hazard of IRM.
Galic 2011 (13)	Bosnia & Herzegovina 1 center	120	SF (time of ascertainment not specified): 500 or >500 ng/mL	Proportion with sepsis and vascular access infection (VAI) at 18 months	61.9% with sepsis (SF >500 ng/mL) vs. 27.3% with sepsis (SF 500 ng/mL), p 0.005. 45.5% with VAI (SF >500 ng/mL) vs. 5.1% with VAI (SF 500 ng/mL), p<0.001.	Higher proportions with sepsis and VAI were observed in the higher SF group.
No Association Between Serum Ferritin and Infection or Infection-Related Mortality						
Hoen 1998 (26)	France 19 centers	985	Baseline SF (ng/mL)	Bacteremia over 6 month period	p>0.2 for association of SF with bacteremia.	SF was not significantly associated with hazard of bacteremia.
Nurko 1999 (60)	U.S. Medicare database	2,662	SF (time of ascertainment not specified)	Infection-related mortality (IRM) at 2 years	No numerical data provided.	SF was not significantly associated with hazard of IRM.
Jean 2002 (59)	France 1 center	89 (129 TCs)	Mean SF within 2 months prior to study initiation: 500 or >500 ng/mL	Bacteremia-free TC survival	p 0.2 (logrank) for comparison of bacteremia-free TC survival curves for SF >500 and 500 ng/mL.	Higher SF was not significantly associated with TC bacteremia (i.e., failed bacteremia-free TC survival).
Pollak 2009 (12)	U.S. 3 centers	1,418	SF <600 vs. >600 ng/mL	Proportion with infection, pneumonia, or cellulitis/carbuncle	SF >600 vs. <600 ng/mL: % with infection (48.1% vs. 46.1%, p 0.8), pneumonia (17.6% vs. 20.2%, p 0.2), cellulitis/carbuncle (13.5% vs. 12.3%, p 0.6).	Higher SF was not significantly associated with proportion of infection, pneumonia or cellulitis/carbuncle.

SF = serum ferritin (ng/mL equivalent to µg/L), TSAT = transferrin saturation, IV = intravenous, OR = odds ratio, HR = hazard ratio, CI = confidence interval, TC = tunneled catheter.

^aIncludes sample size with serum ferritin available or included in risk factor analysis if this information was provided.

^bIn some cases, rates and percentages were derived from the results reported in studies in order to standardize units and for ease of interpretation.

Table 2
Association between Iron and Infection and Infection-Related Mortality in Hemodialysis Patients

Author/Year	Country/# of centers	N ^a	Predictor(s)	Outcome(s)	Results ^b	Summary
<i>Association Between Iron and Infection or Infection-Related Mortality</i>						
Collins 1997 (67)	U.S. Medicare database	33,120	IV iron use frequency (1–3 or 4–6 months) in 6-month entry period	Infection-related mortality (IRM) at 6 months	RR for IRM (4–6 months vs. 1–3 months): 1.35, p 0.001.	Higher frequency IV iron use was independently associated with higher risk of IRM.
Collins 1998 (68)	U.S. Medicare database	309,219	IV iron use frequency (1–2, 3–4 or 5–6 months) and dose (1–6, 7–11, 12–17, >17 vials) in 6-month entry period	Infection-related mortality (IRM) at 1 year	RR for IRM (>17 vials of IV iron for 3–4 months vs. no IV iron): 1.14, p<0.01. RR for IRM (>17 vials of IV iron for 5–6 months vs. no IV iron): 1.20, p<0.01.	Higher frequency and higher dose IV iron use were independently associated with higher risk of IRM.
Nurko 1999 (60)	U.S. Medicare database	2,662	IV iron use	Infection-related mortality (IRM) at 2 years	HR for IRM (IV iron use vs. no IV iron use): 1.99 (95% CI 1.26–3.15).	IV iron use was independently associated with higher hazard of IRM.
Canziani 2001 (69)	Brazil 1 center	111	IV IS (100 mg/dose): 10 doses over 28 treatment days, 20 doses over 70 treatment days, or 10 doses over 70 treatment days	Bacterial infections (BIs)/patient per month	0.13 vs. 0.06 BIs/patient per month in 2g vs. 1g IV IS over 70 days, respectively, p 0.04. 0.08 vs. 0.06 BIs/patient per month in 1 g IV IS over 28 vs. 70 days, respectively, p 0.2.	A higher rate of BI with higher IV iron dose rather than higher dosing frequency was observed.
Jean 2002 (59)	France 1 center	89 (129 TCs)	Mean total IV iron dose (mg), ascertained at end of study	Mean total IV iron dose (mg) in bacteremic vs. bacteremia-free TC groups	Mean total IV iron dose 2,012 ± 1900 mg in bacteremic vs. 1,116 ± 949 mg in bacteremia-free TC group, p<0.001.	Higher IV iron use was observed in the bacteremic TC group than in the bacteremia-free TC group.
Sun 2002 (70)	U.S. Dialysis Clinic, Inc. database	14,886	Mean IV iron dose per dialysis treatment: no iron, low (1–13 mg), medium (14–23 mg), reference (25–34 mg) or high (>34 mg)	Infection-related mortality (IRM)	HR for IRM (vs. reference dose) and 95% CI: No iron 2.09 (1.57–2.78), low dose 0.66 (0.44–0.98), moderate dose 0.97 (0.67–1.41), high dose 1.74 (1.23–2.48).	High dose and no IV iron were independently associated with a higher hazard of IRM. Low dose iron was independently associated with a lower hazard of IRM.

Author/Year	Country/# of centers	N ^a	Predictor(s)	Outcome(s)	Results ^b	Summary
Roberts 2004 (71)	U.S. Medicare database	186,348 (prevalent cohort)	Mean IV iron vials (primarily 100 mg vials of ID) per month	Mean IV iron vials per month by number of hospitalizations for vascular access infection (HVAI) during 2000: 0, 1, 2	Mean IV iron vials per month in 2 vs. 0 HVAI (1.87 vs. 1.63, $p < 0.001$) and 1 vs. 0 HVAI (1.82 vs. 1.63, $p < 0.001$).	A higher number of IV iron vials was observed in groups with more frequent HVAI.
Brewster 2005 (72)	U.S. 1 center	21 (15 IV iron-treated)	Receipt of IV FG (125 mg x 5 consecutive HD sessions) vs. no IV iron	New-onset TC colonization during IV FG treatment or subsequent 3 HD sessions and incidence of clinical blood-borne infection within 30 days after study period.	New-onset TC colonization during or after IV FG (50%) vs. no IV iron (0%), $p = 0.1$. Incidence of clinical blood-borne infection after IV FG vs. no IV iron (7% vs. 0%).	A trend towards increased new-onset TC colonization following IV FG was observed.
Sirken 2006 (73)	U.S. 1 center, changed from using only FG (period 1, P1: 4/01-1/02) to only IS (period 2, P2: 2/02-11/02)	Group A: 63 on HD in P1 and P2 Group B: 41 on HD in P1 or P2	Use of IV IS (vs. IV FG) and use of >2,000 mg (vs. 2,000 mg) IV iron (any type) over a 10-month period	Bacteremic episodes (BEs)	IRR for BEs (IV IS vs. IV FG): 2.92 (95% CI 1.01–8.50) and 2.84 (95% CI 1.32–6.09) in groups A and B, respectively. IRR for BEs (>2,000 vs. 2,000 mg IV iron): 2.42 (95% CI 1.03–5.63) and 1.54 (95% CI 0.42–5.64) in groups A and B, respectively.	IV IS was independently associated with a higher rate of bacteremia than IV FG. The association between IV iron dose and bacteremia was uncertain.
Diskin 2007 (9)	U.S. 1 center	559 (796 dialysis catheters)	Mean IV IS dose (mg) and mean IV ID dose (mg) from 2000 to 2006	Mean IV IS and IV ID dose in catheter-related sepsis (CRS) and non-CRS groups and sepsis-free catheter survival	Mean IV IS in CRS ($940.7 \pm 1,131.2$ mg) vs. non-CRS ($553.7 \pm 1,131.2$ mg), $p = 0.001$. Mean IV ID in CRS ($483.6 \pm 1,255.3$ mg) vs. non-CRS (191.5 ± 734.2 mg), $p < 0.001$. $p < 0.001$ for association between IV IS and lower sepsis-free catheter survival. $p = 0.1$ for association between IV ID and lower sepsis-free catheter survival.	Higher IV IS and IV ID doses were observed in the CRS than non-CRS group. IV IS was independently associated with CRS, but there was no significant association between IV ID and CRS.
Jenq 2009 (11)	Taiwan 3 centers	187	Absence of IV iron treatment during 1 year study period	Infection-related mortality (IRM) at 1 year	HR for IRM (absence vs. presence of IV iron treatment): 0.30 (95% CI 0.10–0.93).	Lack of IV iron treatment was independently associated with lower hazard of IRM.
Brookhart 2013 (15)	U.S. Medicare and LDO database	117,050	Bolus ^c vs. maintenance and high (>200 mg) vs. low	Infection-related hospitalization (IRH) or mortality (IRM) over subsequent 3 month period. IRH was defined as hospitalization for sepsis,	HR for IRH or IRM (bolus vs. maintenance dosing): 1.08 (95% CI 1.05–1.11).	Bolus and high dose IV iron were independently associated with

Author/Year	Country/# of centers	N ^a	Predictor(s)	Outcome(s)	Results ^b	Summary
No Association Between Iron and Infection or Infection-Related Mortality						
Hoen 1998 (26)	France 19 centers	985	Iron (IV or oral) supplementation within the last 6 months	Bacteremia over 6 month period	HR for IRH or IRM (high vs. low dose): 1.05 (95% CI 1.02–1.08).	higher hazard of IRH or IRM.
Macdougall 1999 (74)	U.K. 3 centers, modified ^d IV iron protocol in 11/97	116	1 year prior (11/96 to 11/97) and after (11/97 to 11/98) iron protocol introduced	Bacteremic episodes (BEs)/patient-month (PM)	p>0.2 for association between iron within the last 6 months and bacteremia.	Iron within the last 6 months was not significantly associated with hazard of bacteremia.
Besarab 2000 (66)	U.S. 1 center	44 for AE analysis (23 in study group)	IV ID to achieve/maintain TSAT 30–50% (study) vs. maintain TSAT 20–30% (control)	Infection-related death (IRD) and infection-related hospitalization (IRH) over 6 month period	0.040 BEs/PM 11/96 to 11/97 vs. 0.044 BEs/PM 11/97 to 11/98.	There was no substantial increase in the rate of bacteremia after the introduction of an “aggressive” IV iron protocol.
Hoen 2002 (27)	France 19 centers	969 (397 IV iron-treated)	IV iron within the last 6 months (overall cohort) and weekly iron dose (subgroup with IV iron use)	Bacteremia over 6 month period	1 IRD and 1 IRH in study group, 0 IRD and 1 IRH in control group.	The number of IRHs was equal in the study and control groups. There was one IRD in the study group.
Teehan 2004 (58)	U.S. 1 center	87	3-month cumulative IV iron dose	Time to bacterial infection (BI), which included bacteremia or bacterial pneumonia, over 2 years	p>0.05 (logrank) for association between IV iron dose and BI.	IV iron dose was not significantly associated with risk of BI.
Teehan 2004 (28)	U.S. 2 centers	132	3-month cumulative IV iron dose	Time to first bacteremic episode over 1 year	p 0.3 for association between IV iron dose and bacteremia.	IV iron dose was not significantly associated with hazard of bacteremia.
Aronoff 2004 (75)	U.S. multi-center	665	IV IS repletion (100 mg for 10 consecutive HD sessions) or IV IS maintenance (100 mg weekly for 10 weeks)	Infection-related hospitalizations (IRH)/patient-year (PY) and infection-related deaths (IRD)/patient-year (PY) compared to USRDS rates	0.227 IRHs/PY (study) vs. 0.422 IRHs/PY (USRDS 1995 to 1997), p<0.001. 0.021 IRDs/PY (study) vs. 0.034 IRDs/PY (USRDS 2000), p 0.08.	The study population had a lower rate of IRH and no significant difference in rate of IRD compared to the

Author/Year	Country/# of centers	N ^a	Predictor(s)	Outcome(s)	Results ^b	Summary
Kopelman 2007 (8)	U.S. 1 center	39	Suspected FID (n=14; mean IV FG over 3 months 1,065 ± 555 mg) vs. no FID (n=25; mean IV FG over 3 months 23 ± 51 mg)	Incident infection and infection as cause of hospitalization over 4 month period	No IRHs or IRDs were detected in the IV FG group. FID vs. non-FID: % with incident infection (28.6% vs. 20%, p 0.7), infection as cause of hospitalization (0% vs. 12%, p 0.5).	There was no significant difference in incident infection or infection as the cause of hospitalization between the suspected FID and no FID groups.
Coyne 2007 (7) (DRIVE)	U.S. 37 centers	132 for AE analysis (66 in IV FG group)	IV FG (125 mg for 8 consecutive HD sessions) vs. no iron (control)	Number of infection episodes over 6 weeks	12 episodes in 8 patients (IV FG), 13 episodes in 10 patients (control).	The number of infections was not substantially different between the IV FG and control groups.
Kaplan 2008 (10) (DRIVE-II)	U.S. 37 centers	132 for AE analysis (66 in IV FG group)	IV FG (125 mg for 8 consecutive HD sessions) vs. no iron (control) from DRIVE	Number of serious infection episodes over 12 weeks	4 episodes in 4 patients (IV FG), 12 episodes in 10 patients (control).	The number of infections was lower in the IV FG than control group.
Pollak 2009 (12)	U.S. 3 centers	1,128 with IV iron data	IV iron: 455 vs. >455 mg/month	Proportion with infection, pneumonia, or cellulitis/carbuncle	IV iron >455 vs. 455 mg/month: % with infection (45.0% vs. 49.1%, p 0.2), pneumonia (15.1% vs. 22.6%, p 0.9), cellulitis/carbuncle (12.6% vs. 16.9%, p 0.08).	Higher IV iron dose was not significantly associated with higher proportion of infection, pneumonia or cellulitis/carbuncle.
Bansal 2012 (14)	U.S. 1 center, modified ^e IV iron protocol in 6/10	140	1 year prior (6/09 to 5/10) and after (6/10 to 5/11) iron protocol modified	Infectious complications (hospitalizations for infectious complications, pneumonias, culture positive bacteremias, soft tissue infections, osteomyelitis)	Before vs. after protocol modified: number with hospitalizations for infectious complications (39 vs. 32, p 0.4), pneumonias (13 vs. 6, p 0.2), culture positive bacteremias (6 vs. 11, p 0.7), soft tissue infections (5 vs. 11, p 0.2), osteomyelitis (7 vs. 9, p 0.7).	There was no significant increase in the incidence of infectious complications after modification of the IV iron protocol to target higher TSAT.

IV = intravenous, IS = iron sucrose, ID = iron dextran, FG = ferric gluconate, TC = tunneled catheter, HD = hemodialysis, LDO = large dialysis organization, TSAT = transferrin saturation, USRDS = United States Renal Data System, FID = functional iron deficiency, DRIVE = Dialysis Patients' Response to IV Iron with Elevated Ferritin study, AE = adverse events, RR = risk ratio, HR = hazard ratio, IRR = incidence rate ratio, CI = confidence interval.

^a Includes sample size used in analysis if this information was provided.

^b In some cases, rates were derived from the results in reported in studies in order to standardize units and for ease of interpretation.

^c Bolus dosing was defined as administrations of at least 100 mg iron during at least two consecutive dialysis sessions within a month or 2 administrations of >100 mg iron that had the potential to exceed 600 mg within 30 days based on spacing between the doses in the sequence.

^d Adopted “aggressive” IV iron protocol: Iron sucrose 100 mg IV weekly if serum ferritin 150–1,000 ng/mL. Withhold iron sucrose if serum ferritin >1,000 ng/mL. If serum ferritin <150 ng/mL, more aggressive protocol was used, though not described, until serum ferritin was within range for weekly iron sucrose.

^e Target transferrin saturation increased from 20% to 30%.