Infection Risk with Bolus versus Maintenance Iron Supplementation in Hemodialysis Patients

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ABSTRACT
Intravenous iron may promote bacterial growth and impair host defense, but the risk of infection associated with iron supplementation is not well defined. We conducted a retrospective cohort study of hemodialysis patients to compare the safety of bolus dosing, which provides a large amount of iron over a short period of time on an as-needed basis, with maintenance dosing, which provides smaller amounts of iron on a regular schedule to maintain iron repletion. Using clinical data from 117,050 patients of a large US dialysis provider merged with data from Medicare’s ESRD program, we estimated the effects of iron dosing patterns during repeated 1-month exposure periods on risks of mortality and infection-related hospitalizations during the subsequent 3 months. Of 776,203 exposure/follow-up pairs, 13% involved bolus dosing, 49% involved maintenance dosing, and 38% did not include exposure to iron. Multivariable additive risk models found that patients receiving bolus versus maintenance iron were at increased risk of infection-related hospitalization (risk difference [RD], 25 additional events/1000 patient-years; 95% confidence interval [CI], 16 to 33) during follow-up. Risks were largest among patients with a catheter (RD, 73 events/1000 patient-years; 95% CI, 48 to 99) and a recent infection (RD, 57 events/1000 patient-years; 95% CI, 19 to 99). We also observed an association between bolus dosing and infection-related mortality. Compared with no iron, maintenance dosing did not associate with increased risks for adverse outcomes. These results suggest that maintenance iron supplementation may result in fewer infections than bolus dosing, particularly among patients with a catheter.


Anemia is common among patients with ESRD and associated with increased morbidity, mortality, and risk of hospitalization.1 The anemia of ESRD is managed primarily with erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron supplements.2 Recent safety concerns about ESAs3-4 as well as changes in reimbursement policies in Medicare’s ESRD program have led to increased reliance on IV iron for the management of anemia.5,6 The trend to greater use of iron is reinforced by evidence suggesting that more frequent iron use decreases ESA requirements in patients with treatment-refractory anemia.7

Despite the prevalence of anemia in ESRD and potential risks associated with ESAs, considerable uncertainty exists about the optimal use of ESAs and IV iron in this population.8,9 Iron treatment strategies have been reported to vary substantially among clinicians.8,10 Some physicians administer large repletion doses of iron (hereafter termed bolus dosing) over consecutive dialysis sessions on an
intermittent, as-needed basis. Others physicians instead provide low-dose administrations of iron (hereafter termed maintenance dosing) every 1–2 weeks to maintain iron stores. Currently, there is little evidence regarding the safety and effectiveness of these different approaches to iron supplementation.

Infection risk has been a persistent concern associated with IV iron use in hemodialysis patients. Frequent administration of IV iron may lead to oversaturation of transferrin and the release of free, catalytically active iron into circulation. Because iron is essential for bacterial growth, free iron may plausibly cause infection or worsen an existing infection. Iron is also believed to impair host immune response by decreasing function of polymorphonuclear leukocytes. However, despite these concerns, to date, there have been few large epidemiologic studies of the infection risk of IV iron use in ESRD.

To help identify the safest approach to IV iron use, we conducted a large-scale, nonexperimental study comparing the short-term infection risks associated with different IV iron dosing practices in a contemporary cohort of patients undergoing chronic hemodialysis.

RESULTS

We identified 117,050 patients who met study entry requirements and contributed data on 776,203 iron exposure/follow-up periods (Figure 1). Table 1 presents patient characteristics of the primary cohort stratified by dosing pattern: 24% of the sample received high-dose iron, 38% received low-dose iron, and 38% received no iron. Maintenance dosing was more common than bolus dosing (49% versus 13%).

There were differences in demographic and clinical characteristics by dosing pattern. Bolus dosing was more common in the South and among individuals with a catheter. Infections and comorbidities (e.g., diabetes, stroke, or myocardial infarction [MI]) were more common in the bolus and high-dose groups. Differences in anemia management variables by dosing group were generally as expected. For example, a greater percentage of individuals who received a transfusion or had a gastrointestinal (GI) bleed during the baseline period received high-dose iron or bolus dosing. Median monthly iron exposure for the high-dose group was 400 versus 125 mg for the low-dose group (Table 1). Median monthly iron exposures for the bolus and maintenance groups were 700 and 200 mg, respectively.

In Table 2, we present unadjusted and adjusted results for the high versus low dose and bolus versus maintenance dosing comparisons. In the adjusted models for the primary cohort, both high-dose iron and bolus dosing were associated with increased risks of hospitalization for infection and infection-related hospitalization or death. In relative terms, the increased risk of infection for the high- versus low-dose comparison was small (hazard ratio [HR], 1.05; 95% confidence interval [CI], 1.02 to 1.08). Owing to the high incidence of infections among dialysis patients, this result translates into 12 additional infection-related hospitalizations/1000 person-yr. The risk of infection was higher in patients receiving bolus versus maintenance iron dosing, with HRs of 1.08 (95% CI, 1.05 to 1.11) for infection-related hospitalization and infection-related hospitalization or death. These results translate into larger absolute risk differences of 25 infection-related hospitalizations/1000 person-yr and 26 infection-related hospitalizations or deaths/1000 person-yr. These results were robust to variations in the length of the exposure and follow-up periods (Supplemental Tables 4 and 5).

Figures 2, 3, 4 present forest plots of the risk differences (RDs) for the bolus versus maintenance comparisons in various subgroups for infection-related hospitalization, mortality, and composite outcome. The absolute risks for an infection-related hospitalization associated with bolus dosing were largest among patients with a catheter (RD, 73 events/1000 patient-yr; 95% CI, 48 to 99) and a recent infection (RD, 57 events/1000 patient-yr; 95% CI, 19 to 99) (Figure 2). Individuals with low transferrin saturation (TSAT) and low ferritin or high TSAT and high ferritin at baseline had the highest risks of infection-related hospitalization relative to the other TSAT by ferritin combinations, with RDs of 32.4 events/1000 patient-yr (95% CI, 19.1 to 47.5) and 34.0 events/1000 patient-yr (95% CI, 1.4 to 79.2), respectively. Individuals with lower albumin levels at baseline were also generally at higher risk of an infection-related hospitalization along with individuals with hemoglobin levels above 10 g/dl. Bolus dosing was also associated with a slight increased risk of infection-related death among individuals with baseline ferritin<200 mcg/L (Figure 3). Risk differences among the subgroups for the composite outcome of infection-related hospitalization or death were similar to RDs for infection-related hospitalization (Figure 4).

The HRs and RDs for the high versus low dose and bolus versus maintenance comparisons by subgroup are presented in Supplemental Tables 9 and 10.

Our results were robust to the addition of covariates beyond our a priori specified full model and similar when a variety of propensity score methods were used (Supplemental Material and Supplemental Tables 11 and 12).
DISCUSSION

We conducted a large comparative study of the infection risk associated with different IV iron dosing practices in typical patients undergoing chronic hemodialysis in the United States. We found evidence that the practice of bolus dosing (giving a large amount of iron over consecutive dialysis sessions) was associated with an increased risk of infection requiring hospitalization. Although the relative risk is small, the absolute risk is large, suggesting that, compared with maintenance dosing, bolus dosing may cause an additional 25 hospitalized infections per year per 1000 patients treated. We also observed a slightly increased risk of infection associated with total monthly iron doses greater than 200 mg. There was no evidence of risk of infection or any other adverse outcomes among patients receiving maintenance dosing. Our results were robust to variations in the study design and multivariable adjustment.

The observed associations between iron dose and infection are not unexpected. Although the role of iron in bacterial growth and infection risk is biologically plausible and has been shown in animal models, data from large CKD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High (24.0%)</th>
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<th>Maintenance (49.2%)</th>
<th>Nonuser (38.2%)</th>
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<tr>
<td>Mean (SD) age (yr)</td>
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<td>60.6 (15.1)</td>
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<td>51.6</td>
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<td>0.5 (1.7)</td>
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<td>10.6</td>
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<td>Vascular access (%)</td>
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<td>13.1</td>
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<td>MI (%)</td>
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<td>COPD and asthma (%)</td>
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<td>16.0</td>
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<td>Cancer (%)</td>
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<td>9.8</td>
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<tr>
<td>GI bleeding (%)</td>
<td>6.4</td>
<td>3.9</td>
<td>7.7</td>
<td>4.2</td>
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Laboratory values and medications median (interquartile range)

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<tr>
<td>Index TSAT (%)</td>
<td>23.0 (18.0–29.0)</td>
<td>28.0 (23.0–36.0)</td>
<td>20.0 (16.0–26.0)</td>
<td>28.0 (22.0–35.0)</td>
<td>31.0 (24.0–41.0)</td>
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<td>Ferritin (mcg/L)</td>
<td>457 (280–641)</td>
<td>514 (351–678)</td>
<td>433 (240–642)</td>
<td>505 (344–669)</td>
<td>743 (473–977)</td>
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<td>Hemoglobin (g/dl)</td>
<td>12.1 (11.3–13.0)</td>
<td>12.2 (11.5–13.0)</td>
<td>11.9 (11.0–12.8)</td>
<td>12.3 (11.5–13.0)</td>
<td>12.2 (11.4–13.0)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.90 (3.60–4.10)</td>
<td>3.90 (3.70–4.10)</td>
<td>3.80 (3.50–4.10)</td>
<td>3.90 (3.70–4.10)</td>
<td>3.90 (3.70–4.10)</td>
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<tr>
<td>Baseline EPO (1000 u/mo)</td>
<td>81.1 (41.5–148)</td>
<td>52.1 (26.0–99.5)</td>
<td>93.6 (48.4–172)</td>
<td>56.1 (27.5–105)</td>
<td>44.0 (19.8–88.0)</td>
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<td>EPO during exposure (1000 u/mo)</td>
<td>75.0 (36.3–142)</td>
<td>50.7 (24.2–97.5)</td>
<td>89.1 (44.0–167)</td>
<td>53.0 (26.0–101)</td>
<td>47.5 (22.0–94.6)</td>
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<td>Iron during baseline period (mg)</td>
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<td>125 (100–250)</td>
<td>225 (0–550)</td>
<td>200 (100–250)</td>
<td>0 (0–50.0)</td>
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<tr>
<td>Iron during exposure period (mg)</td>
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<td>125 (100–200)</td>
<td>700 (400–1000)</td>
<td>200 (100–250)</td>
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COPD, chronic obstructive pulmonary disease; u/mo, units/month.

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We also observed an association between dosing practices and risk of infection-related mortality. The existing epidemiologic evidence linking iron exposure and mortality is inconclusive, with some studies finding evidence of harm,30,31 one study finding no association,32 and one study finding benefits in patients with severe anemia but risks in patients with mild anemia.33 These studies are difficult to compare because of differences in patients, available data, study designs, statistical methods, and exposure definitions. Of the existing studies, our study is the only one to focus on the short-term effects of iron exposure.

The potential risks of bolus dosing of iron supplements must be viewed in light of its reported benefits. The Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) I and II studies found that, in patients with high ferritin and low TSAT (a subgroup likely to be hyporesponsive to ESA therapy), bolus administration of iron reduced ESA requirements and improved iron status and hemoglobin levels relative to no iron treatment.7,34 In both DRIVE I and II, there were no increases in the risks of infection in the iron-treated groups, but the studies were small (n=134 and n=129, respectively); also, patients were followed for only 6 or 12 weeks. The DRIVE I trial did not include a maintenance dosing arm; it is possible that a maintenance dosing approach in such patients could provide a similar clinical benefit without possible risk of infection. The risk–benefit tradeoff may also vary across patient subgroups. For example, the benefits of bolus dosing may outweigh the risks in the subgroup of populations on iron and infections are lacking. An abstract reported that frequency of iron administration was associated with increased risk of infection-related mortality in ESRD.23 A small clinical study found that cumulative iron exposure was associated with increased risk of bacteremia.24 Whether clinicians should administer iron in the presence of infection remains controversial. Although some recommend withholding iron during acute infection,25–28 others argue that the evidence supporting this recommendation is weak.21,29

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We also observed an association between dosing practices and risk of infection-related mortality. The existing epidemiologic evidence linking iron exposure and mortality is inconclusive, with some studies finding evidence of harm,30,31 one study finding no association,32 and one study finding benefits in patients with severe anemia but risks in patients with mild anemia.33 These studies are difficult to compare because of differences in patients, available data, study designs, statistical methods, and exposure definitions. Of the existing studies, our study is the only one to focus on the short-term effects of iron exposure.

The potential risks of bolus dosing of iron supplements must be viewed in light of its reported benefits. The Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) I and II studies found that, in patients with high ferritin and low TSAT (a subgroup likely to be hyporesponsive to ESA therapy), bolus administration of iron reduced ESA requirements and improved iron status and hemoglobin levels relative to no iron treatment.7,34 In both DRIVE I and II, there were no increases in the risks of infection in the iron-treated groups, but the studies were small (n=134 and n=129, respectively); also, patients were followed for only 6 or 12 weeks. The DRIVE I trial did not include a maintenance dosing arm; it is possible that a maintenance dosing approach in such patients could provide a similar clinical benefit without possible risk of infection. The risk–benefit tradeoff may also vary across patient subgroups. For example, the benefits of bolus dosing may outweigh the risks in the subgroup of
patients eligible for the DRIVE study, but in other subgroups, such as patients with a history of recent infections, the risks of bolus dosing may outweigh its benefits. Additional research comparing the relative benefits and risks of iron dosing practices across a variety of clinically relevant subgroups is needed.

Our study possessed several limitations. First, our study focused on short-term effects. Estimation of the long-term risks of iron exposure effects requires careful statistical adjustment for time-varying confounding factors. Although our study cannot make statements about long-term safety of iron, the infection-related outcomes that we have studied would likely be short-term consequences. Second, our study had a nonexperimental design. Our results could have been confounded by unobserved differences among the patient groups. However, our statistical models contained the important determinants of iron treatment decisions, including TSAT, ferritin, hemoglobin, and history of recent infections. We also found that our results were not affected by additional adjustment for various comorbid conditions beyond our a priori selected covariates, suggesting an absence of residual confounding. Third, our comorbidity and outcome measures were based on International Classification of Diseases, 9th Revision, Clinical Modification codes and cause of death reporting. We may have missed comorbidities that did not require a health care encounter in the 6-month baseline period. Our outcomes may also have been misclassified to some degree. However, we observed similar associations when more sensitive but less specific definitions were considered. Fourth, our study design required survival until 9 months after the start of dialysis, and therefore, our results may not generalize to all incident patients.

The limitations of our study are counterbalanced by two important strengths. First, by focusing on the short-term effects of a well-defined exposure with covariates defined before exposure and outcomes ascertained after the exposure assessment period ends, we eliminated or minimized many sources of bias common to nonexperimental studies of longitudinal exposures, including immortal person-time bias, selection bias, and time-varying confounding. Second, the detailed and rich clinical and administrative data used by our study allowed us to control for important clinical and laboratory variables while also capturing important events that occurred outside of the clinic, such as hospitalization and death.

In summary, our results suggest that bolus or repletion dosing of iron, a common contemporary dosing strategy, may increase the short-term risk of infections that require hospitalization. This risk seems to be particularly elevated in patients with a catheter and those patients with a history of a recent infection. The potential infection risk associated with more aggressive iron use must be balanced with its known benefits, such as diminished ESA requirements and improved anemia management, particularly in patients with high ferritin and low TSAT. Additional research examining the effectiveness of different iron dosing practices across various patient subgroups could lead to a more individualized approach to iron therapy that maximizes hemoglobin control while minimizing infection risk.
CONCISE METHODS

We examined 5 years of data (2004–2008) from the clinical research database of a large dialysis provider merged with data from the US Renal Data System (USRDS). The clinical database was used to obtain detailed information on iron dosing and other anemia management and clinical parameters. The USRDS data were used to obtain information on hospitalizations and demographic and clinical characteristics (e.g., comorbidities).

We used a retrospective cohort design with a 6-month baseline period, a 1-month iron exposure period, and a 3-month follow-up period (Figure 1). The index date of the exposure period was anchored on the day of a laboratory assessment of TSAT, because this information is used to guide subsequent iron administration. Eligible subjects could contribute multiple exposure/follow-up periods.

We identified center-based, outpatient hemodialysis patients covered by Medicare Parts A and B who had at least one TSAT measurement between January 30, 2004 and November 30, 2008 (the November 30th date was chosen to allow for the 1-month exposure period and at least 1 day of follow-up). These patients constituted our population of interest. We had several exclusion criteria that are outlined in Supplemental Material.

We examined two outcomes related to infection: hospitalization for infection and death attributed to infection. These outcomes were determined by examining the Medicare inpatient and outpatient claims and death notification data. We also created a composite outcome of infection-related hospitalization or death. Because our definition of hospitalization for infection was specific to sepsis, vascular access infection, or pneumonia, we conducted sensitivity analyses with broader, more sensitive infection definitions: hospitalization for infection of any major organ system, use of IV antibiotics, and a composite of hospitalization and antibiotic use. All of the outcomes are defined in Supplemental Material (Supplemental Table 1).

The primary exposures of interest were high-versus low-dose iron administration and bolus versus maintenance dosing. We defined high dose as >200 mg IV iron in the 1-month exposure period. Low dose was defined as 1–200 mg IV iron. A month was classified as a bolus month if it contained administrations of at least 100 mg iron during at least two consecutive dialysis sessions. We also classified a month as a bolus month if it contained two or more 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. For example, two consecutive iron doses of 200 mg each within 10 days would qualify as a bolus dose according to our definition. Months that had no bolus dosing patterns were classified as maintenance months. We also included a no iron category for the high versus low and bolus versus maintenance comparisons.

To minimize the effects of total dose in our comparison of bolus versus maintenance dosing practices, we conducted a subgroup analysis among individuals who received 400–500 mg iron per month and classified the months as bolus or maintenance as defined above.

Covariates in our analyses included demographic characteristics (e.g., age, sex, race, Medicaid eligibility, census region, and year), clinical characteristics (e.g., cause of ESRD, vintage, body mass index [BMI], type of vascular access, and number of hospital days), laboratory and anemia management variables (baseline hemoglobin, ferritin, TSAT, iron dose, epoetin alfa [EPO] dose, and albumin; receipt of a blood transfusion; and EPO dose during exposure period), and several

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Figure 3. Infection-related mortality risk was generally increased among patients receiving bolus dosing. Risk differences of infection-related mortality for bolus versus maintenance dosing across patient subgroups.
comorbidity measures. Because of the potential relation between iron use and infections, we created four history of infection variables: history of pneumonia, sepsis, or vascular access infection during the baseline period and history of any infection in the last month. Covariates are defined in Supplemental Material (Supplemental Table 2).

To assess the relation between iron dosing practices and adverse outcomes, we used Cox proportional hazards regression analyses to estimate HRs and semiparametric additive risks models to estimate RDs. Individuals were censored by death (for the hospitalization outcomes), loss to follow-up, or receipt of a kidney transplant or administratively by the end of available data. We first estimated an unadjusted HR (e.g., high versus low dose) for each outcome and then estimated a multivariable-adjusted HR. We conducted several sensitivity analyses varying the length of the exposure and follow-up periods, adding additional covariates, and using three different propensity score methods. These sensitivity analyses are described more completely in Supplemental Material.

We also conducted the analyses on several demographic and clinical subgroups, defined in Supplemental Table 3. Individuals were categorized based on race, vintage, catheter use, history of infection in the last month of baseline, TSAT levels at baseline, ferritin levels at baseline, TSAT × ferritin combinations (e.g., low TSAT and high ferritin) at baseline, hyporesponsiveness to ESAs at baseline, albumin levels at baseline, and hemoglobin levels at baseline.

The study design, analytic methods, outcome, and covariate definitions were all selected in consultation with a panel of scientific experts and stakeholders and specified in a protocol submitted to the Agency for the Healthcare Research and Quality.

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The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by AHRQ or DHHS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US Government or the USRDS. DaVita Clinical Research had no role in the design or implementation of this study or the decision to publish. M.A.B. had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DISCLOSURES

M.A.B. has received investigator-initiated grant support from Amgen and served as a scientific advisor for Pfizer, Amgen, and Rockwell Medical but has not accepted personal compensation for this service (honoraria declined,

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**Figure 4.** The infection-related hospitalization or infection-related mortality risk associated with bolus dosing was particularly large among patients with a central venous dialysis catheter and also among patients with a history of a recent infection. Risk differences of the composite outcome of infection-related hospitalization or infection-related mortality for bolus versus maintenance dosing across patient subgroups.
REFERENCES


This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2012121164/-/DCSupplemental.