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CME Article

A retrospective, real-world study of IV iron use to treat iron deficiency anemia during acute infection

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KEY POINTS

- **Administration of IV iron therapy during acute infections was associated with improved 14- and 90-day survival.**
- **IV iron therapy in patients with acute infection was associated with better hemoglobin recovery, no increase in length of stay, and fewer days with transfusion than no IV iron.**

The administration of IV iron to treat anemia during acute infection remains controversial owing to concerns of exacerbating the infection. We conducted a retrospective cohort study using the TriNetX Research Network (2000 to June 2025) to evaluate the safety and efficacy of IV iron administration in adults with iron deficiency anemia and infection (methicillin-resistant *Staphylococcus aureus* [MRSA] bacteremia, pneumonia, urinary tract infection [UTI], colitis, or cellulitis). Patients must have received antibiotic agents within 2 days of infection for inclusion and were stratified by IV iron exposure. Propensity matching (1:1) was performed within each cohort. Survival was significantly higher ($P < .001$ for each infection type) at both 14 and 90 days in patients who received IV iron (MRSA bacteremia, 97.6% vs 95.0% and 88.6% vs 83.8%; pneumonia, 95.7% vs 91.5% and 84.7% vs 78.1%; UTI, 97.6% vs 95.7% and 89.1% vs 85.6%; colitis, 97.6% vs 95.5% and 89.7% vs 83.8%; and cellulitis, 98.5% vs 97.4% and 92.2% vs 89.2%). Hemoglobin recovery 60 to 90 days after infection was significantly greater (all $P < .001$) when IV iron was administered across all subgroups (MRSA bacteremia, +1.3 vs +1.0 g/dL; pneumonia, +1.3 vs +1.0 g/dL; UTI, +1.4 vs +1.0 g/dL; colitis, +1.5 vs +0.7 g/dL; and cellulitis, +1.4 vs +0.9 g/dL). The findings observed for each infection type studied suggest that IV iron administration during acute infection does not exacerbate infection and is associated with improved survival and enhanced recovery from anemia in hospitalized patients. Prospective studies are needed to confirm these findings and expand their applicability.

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Disclosures

CME questions author Laurie Barclay, freelance writer and reviewer, Medscape Education, declares no competing financial interests.

Learning objectives

Upon completion of this activity, participants will:

1. Describe survival and hospital utilization metrics associated with IV iron administration in hospitalized adults with iron deficiency anemia (IDA) and infection, based on findings of a retrospective cohort study
2. Describe hematological outcomes associated with IV iron administration in hospitalized adults with IDA and infection, based on findings of a retrospective cohort study
3. Describe clinical implications of the safety and efficacy of IV iron administration in hospitalized adults with IDA and infection, based on findings of a retrospective cohort study

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Introduction

Anemia affects nearly one-quarter of the world's population, with iron deficiency anemia (IDA) as the most common anemia type worldwide.[1] The prevalence of anemia is even higher among hospitalized patients, driven by chronic disease, inflammation, malnutrition, and blood loss, with iron deficiency again among the most common etiologies and reported in up to 40% of hospitalized patients.[2-6] Anemia itself has been independently associated with increased morbidity and mortality in patients with pneumonia and sepsis,[7,8] suggesting that untreated iron deficiency may worsen outcomes in infectious states. In a prospective study of intensive care unit patients, the prevalence of iron deficiency was low (8%) initially but increased to 25% to 35% in the months after discharge, highlighting the ongoing risk in this population.[9]

Given the high prevalence and clinical impact of IDA, particularly in hospitalized patients, IV iron has increasingly been used for iron repletion. IV iron is preferred over oral therapy because it avoids gastrointestinal side effects and achieves faster, more robust hemoglobin correction. This is particularly important in patients with chronic kidney disease (CKD), heart failure, inflammatory bowel disease, and pregnancy.[10-14] However, the use of IV iron in patients with acute infections remains controversial owing to concerns of exacerbating the infection.[15-19] Although iron deficiency impairs host defense, thereby predisposing patients to infection,[20] many pathogens depend on iron for growth and virulence, creating direct competition between host and microbe.

Clinical studies of IV iron use during acute infection have yielded conflicting data, with some studies identifying an increased risk of infection with IV iron therapy and others finding that IV iron administration is associated with improved hemoglobin recovery without increased mortality or rehospitalization.[17,21-23] However, most studies have been restricted to disease-specific cohorts, and evidence in general hospitalized populations remains sparse. Given the absence of robust, real-world data and lingering concerns about theoretical harm, many clinicians remain reluctant to use IV iron in this setting. To address this gap, we conducted a retrospective analysis to evaluate the impact of IV iron administration in hospitalized patients with acute infections by examining overall mortality, length of stay (LOS), and hemoglobin levels.

Methods

Data source

Data were obtained from the TriNetX Research Network, a federated platform of deidentified electronic health records (EHRs) from 111 health care organizations. Patients were included if they met the eligibility criteria and received IV iron between 1 January 2000 and 30 June 2025. This study was reviewed by the Charleston Area Medical Center Institute for Academic Medicine Institutional Review Board (IRB). The IRB determined that the research did not involve human subjects, given that it used deidentified data from the TriNetX national database, and was determined to be exempt from further IRB oversight.

Study design and propensity matching

Patients studied were restricted to adults (≥18 years of age) with a diagnosis of one of the following acute infection types: methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, pneumonia, urinary tract infection (UTI), colitis, or cellulitis, as defined by International Classification of Diseases (ICD) coding (supplemental Table 1, available on the *Blood* website). IDA was identified using ICD-10 code D50.x rather than ferritin thresholds, given that ferritin fluctuates during acute infection and may not reliably distinguish true iron deficiency from anemia of inflammation. In addition, laboratory values were not consistently available for a substantial proportion of patients in the database, with ferritin values captured in only 31% to 53% of records. As a result, patients were required to have a provider-documented diagnosis of IDA, identified using ICD-10 code D50.x, recorded in the medical record within 2 days of the infection diagnosis. To ensure a cohort of patients with acute infection, patients also had to receive antibiotic agents within 2 days of infection diagnosis.

Patients were stratified into those who received IV iron within 7 days after the combined IDA/infection diagnosis and those who did not receive IV iron from 1 month before the IDA/infection diagnosis to 3 months after diagnosis. IV iron administration was identified using procedure and medication codes for any of the recognized IV iron formulations (ferumoxytol, ferric carboxymaltose, sodium ferric gluconate, ferric derisomaltose, iron sucrose, or iron dextran), as detailed in supplemental Table 1. Because dosing information was not consistently captured across contributing institutions, exposure was analyzed as a binary variable (≥1 administration).

The index date was defined as the later of the IDA diagnosis or the infection diagnosis. Baseline characteristics were assessed using the most recent values from the 6 months before the index date to the index date. This window was selected to allow capture of comorbidities and laboratory data that might not be remeasured during the hospitalization with infection, while still reflecting the patient's contemporary clinical status. Laboratory variables represent the most recent patient-level results within this period, which for most hospitalized patients correspond to laboratory findings obtained during the same hospital admission as the infection. When specified, the proportion of patients falling into prespecified ranges was reported. Because the TriNetX platform only provides aggregate data, all central tendencies were reported as means; medians and interquartile ranges were not available.

Propensity score matching (1:1) was performed within the TriNetX platform for each infection type, balancing demographics, comorbidities, and laboratory values. Variables with standardized differences (Std. Diff.) of >0.1 were prioritized for matching. Matching variables included mean corpuscular volume (<70, 70-100, and ≥100 fL), hemoglobin (0-1.99, 2-3.99, 4-5.99, 6-7.99, 8-9.99, 10-11.99, 12-13.99, 14-15.99, and ≥16 g/dL), ferritin (<30, 30-99.9, 100-299.9, 300-799.9, and ≥800 ng/mL), and albumin (<2.5, 2.5-2.9, 3-3.49, and ≥3.5 g/dL). Demographics used in matching included age at index, Asian race, and Hispanic/Latino ethnicity, where available. Sex was not used in matching because, when sex was evaluated for imbalance, it was found to be already well balanced between groups across all cohorts (maximum Std. Diff., 0.07 before matching and 0.04 after matching). Comorbidities evaluated for matching were CKD, heart failure, chronic obstructive pulmonary disease, and other anemias.

Outcomes and statistical analysis

The primary outcome examined was survival at 14 and 90 days after the index date. Kaplan-Meier survival analyses were performed within the TriNetX platform, excluding patients who died before the index event. Log-rank tests were used to assess differences, with hazard ratios (HRs) and 95% confidence intervals (CIs) reported. Patients were censored at their last recorded event. Secondary outcomes assessed included the mean number of inpatient days (LOS), antibiotic exposure days, days with respirator use, and the number of days with transfusion of blood or blood products. A full list of outcome codes is presented in supplemental Table 1. Transfusion days were defined as the number of calendar days within 14 days after the index date on which a red blood cell transfusion code was recorded. Transfusion exposure was identified using only inpatient procedure and billing codes denoting red blood cell transfusions and did not include transfusion of platelets or plasma (supplemental Table 1). Because unit-level quantities were unavailable, we used days with a transfusion event as a metric rather than the number of units transfused. Similarly, unit-level quantities were not available for antibiotic use, and days with antibiotic administration were used as a proxy metric. Comparisons were performed within TriNetX using *t* tests.

Hemoglobin recovery was evaluated by examining hemoglobin laboratory values 0 to 1 day after the index date, up to 14 days after the index date, and 60 to 90 days after the index event. Mean (± standard deviation) hemoglobin values were extracted from TriNetX, and the change between groups (IV iron vs no IV iron) was compared using Welch's *t* tests performed outside the TriNetX platform using Python.

Results

Baseline characteristics

The TriNetX database contained 339 145 patients with concurrent IDA and acute infection meeting our inclusion criteria: 56 901 with MRSA bacteremia, 108 559 with pneumonia, 100 253 with UTI, 20 956 with colitis, and 52 476 with cellulitis. A summary of baseline patient demographics is presented in Table 1, with full details in supplemental Tables 2-6. Across cohorts, Asian patients were consistently underrepresented in the IV-iron group compared with the no-IV-iron group. Before matching, patients receiving IV iron generally had lower hemoglobin and ferritin levels, lower mean corpuscular volume, and a higher prevalence of comorbid conditions such as CKD, heart failure, and other anemias. After matching, all Std. Diffs. were reduced to <0.1 in every cohort, except for small residual imbalances in mean hemoglobin in the UTI and colitis cohorts. Before matching, there were 4473 to 19 289 patients who received IV iron and 16 483 to 89 270 patients with no IV iron in each infection-type cohort, depending on the infection present. After propensity matching, there were 4432 to 19 281 patients per treatment group (IV iron and no IV iron) in each cohort (Table 1).

Primary outcome: survival

The administration of IV iron was associated with significantly better survival, the primary outcome studied, in all infection-type cohorts both 14 days and 90 days after diagnosis of infection and IDA ($P < .001$ for all cohorts) (Table 2). Analysis of Kaplan-Meier curves revealed survival differences early in the clinical course, with the curves beginning to separate within 10 days of the index event for all groups except for the cellulitis cohort, which separated closer to day 10 (Figure 1). Once separated, survival probabilities remain distinct throughout the 90-day period. The greatest survival benefit occurred in patients with colitis (HR, 0.60; 95% CI, 0.53-0.68), followed by patients with pneumonia (HR, 0.66; 95% CI, 0.63-0.69) (Figure 1).

Hospital utilization metrics

Hospital utilization metrics were consistently different between patients who received IV iron and patients who did not receive IV iron (Table 3; supplemental Figure 1). LOS was slightly longer among IV iron recipients with MRSA bacteremia (4.39 vs 4.08 days; $P = .0024$) and UTI (4.06 vs 3.86 days; $P = .0007$), whereas no significant difference in LOS was seen in patients with pneumonia, colitis, or cellulitis. In most cohorts, the patients who received IV iron also had a significantly longer course of antibiotic agents (Table 3). Days spent on a respirator were not significantly different with and without IV iron administration except for those in the pneumonia cohort, where the IV-iron group required more respiratory-support days than the no-IV-iron group (1.12 vs 1.09 days; $P = .0084$). The IV-iron group had significantly fewer days with a transfusion than the no-IV-iron group in all infection-type cohorts except the cellulitis cohort (Table 3).

Table 1. Summary of baseline characteristics by infection type and IV iron exposure after propensity matching

MRSA bacteremia			
Characteristic	**IV iron (n = 8433)**	**No IV iron (n = 8433)**	**Standard difference**
Age at index, y	60.1 ± 17.7	60.8 ± 17.6	0.039
Male	3 943 (47)	4 071 (48)	0.0304
White	5 292 (63)	5 256 (62)	0.0088
Black	1 883 (22)	1 986 (24)	0.0291
Hispanic or Latino	432 (5)	623 (7)	0.0936
CKD	3 654 (43)	3 553 (42)	0.0242
Heart failure	3 385 (40)	3 350 (40)	0.0085
Hemoglobin, g/dL	9.1 ± 1.92	9.29 ± 1.99	0.0964
Albumin, g/dL	3.07 ± 0.69	3.05 ± 0.695	0.0346
Pneumonia			
Characteristic	**IV iron (n = 19 281)**	**No IV iron (n = 19 281)**	**Standard difference**
Age at index, y	66 ± 16.7	66.2 ± 17	0.0146
Male	8 435 (44)	8 561 (44)	0.0132
White	12 298 (64)	12 062 (63)	0.0254
Black	4 259 (22)	4 594 (24)	0.0413
Hispanic or Latino	1 087 (6)	1 290 (7)	0.0438
CKD	8 695 (45)	8 563 (44)	< 0.0001
Heart failure	10 105 (52)	10 139 (53)	0.0035
Hemoglobin, g/dL	9.19 ± 2.07	9.42 ± 2.1	0.1096
Albumin, g/dL	3.23 ± 0.658	3.21 ± 0.665	0.0294
UTI			
Characteristic	**IV iron (n = 18 613)**	**No IV iron (n = 18 613)**	**Standard difference**
Age at index, y	65.2 ± 18.4	65.6 ± 18.6	0.0222
Male	5 947 (32)	6 075 (33)	0.0147
White	11 607 (62)	11 315 (61)	0.0324
Black	4 409 (24)	4 714 (25)	0.0381
Hispanic or Latino	1 291 (7)	1 688 (9)	0.0787
CKD	7 871 (42)	7 867 (42)	0.0004
Heart failure	6 901 (37)	6 925 (37)	0.0027
Hemoglobin, g/dL	9.07 ± 2.08	9.29 ± 2.1	0.1055
Albumin, g/dL	3.27 ± 0.665	3.26 ± 0.678	0.01

Values represent n (%) or mean and standard deviation and are taken from the most recent results from 6-months before up to and including the index date (IDA + infection).

Table 1 (continued)

Colitis			
Characteristic	**IV iron (n = 5340)**	**No IV iron (n = 5340)**	**Standard difference**
Age at index, y	58.9 ± 20	59.3 ± 19.6	0.0179
Male	2 110 (40)	2 104 (39)	0.0023
White	3 360 (63)	3 279 (61)	0.0313
Black	1 072 (20)	1 214 (23)	0.0649
Hispanic or Latino	371 (7)	453 (9)	0.0576
CKD	2 012 (38)	1 965 (37)	0.0182
Heart failure	1 706 (32)	1 630 (31)	0.0307
Hemoglobin, g/dL	9.4 ± 2.12	9.63 ± 2.15	0.1106
Albumin, g/dL	3.17 ± 0.724	3.11 ± 0.745	0.086
Cellulitis			
Characteristic	**IV iron (n = 8404)**	**No IV iron (n = 8404)**	**Standard difference**
Age at index, y	59.2 ± 17.3	59.6 ± 17.3	0.022
Male	3 855 (46)	3 977 (47)	0.0291
White	5 412 (64)	5 353 (64)	0.0149
Black	1 796 (21)	1 958 (23)	0.0463
Hispanic or Latino	526 (6)	503 (6)	0.0114
CKD	3 270 (39)	3 287 (39)	0.0041
Heart failure	3 191 (38)	3 194 (38)	0.0007
Hemoglobin, g/dL	9.28 ± 1.97	9.47 ± 1.98	0.0971
Albumin, g/dL	3.17 ± 0.671	3.12 ± 0.698	0.0686

Values represent n (%) or mean and standard deviation and are taken from the most recent results from 6-months before up to and including the index date (IDA + infection).

Hemoglobin changes over time

Across all infection-type cohorts, patients receiving IV iron demonstrated significantly greater improvements in hemoglobin levels from the time of IDA/infection diagnosis to 60 to 90 days after the index date (Table 4; supplemental Figure 2). The largest relative improvement was observed in patients with colitis; a 1.45 g/dL increase in hemoglobin in the IV-iron group vs a 0.74 g/dL increase in the control group without IV iron ($P < .0001$). Patients who received IV iron also had larger early increases in hemoglobin (0.19-0.30 g/dL per infection group from the time of IDA/infection diagnosis to 14 days after the index date) than patients with no IV iron across all infection-type cohorts (supplemental Table 7).

Discussion

In this large, propensity-matched, real-world analysis of hospitalized patients with acute infections, IV iron administration was consistently associated with decreased mortality and improved hemoglobin recovery across diverse infection types, including MRSA bacteremia, pneumonia, UTIs, colitis, and cellulitis. Taken together, these findings indicate that administering IV iron during acute infections confers both survival and hematologic benefits across a broad spectrum of clinical contexts.

The role of IV iron during infection has long been debated. Early mechanistic studies and immunologic models suggested that supplemental iron could exacerbate infection by serving as a nutrient source for pathogens.[18,24] This concern was reinforced by a meta-analysis by Shah et al[17] of randomized controlled trials published from 1966 to 2020, performed primarily in obstetrics patients, surgery patients, and patients with CKD, that compared IV iron with oral iron or no iron and reported an increased risk of infection with iron therapy. However, more recent clinical data have consistently challenged this paradigm, including a single-center retrospective review of ~200 patients given IV iron while hospitalized and treated for a bacterial infection, a 35-patient prospective trial of erythropoiesis after IV iron administration in patients with sepsis, and 2 large studies of patients on hemodialysis.[21-23,25] These studies suggested that administration of IV iron in patients with bacterial infections does not increase mortality

Table 2. Survival outcomes by infection type

Outcome	IV iron, %	No IV iron, %	*P* value	HR (95% CI)
MRSA bacteremia				
14-day survival	97.6	95.0	<.0001	0.48 (0.41-0.57)
90-day survival	88.6	83.8	<.0001	0.67 (0.62-0.73)
Pneumonia				
14-day survival	95.7	91.5	<.0001	0.50 (0.46-0.54)
90-day survival	84.7	78.1	<.0001	0.66 (0.63-0.69)
UTI				
14-day survival	97.6	95.7	<.0001	0.56 (0.49-0.63)
90-day survival	89.1	85.6	<.0001	0.73 (0.69-0.78)
Colitis				
14-day survival	97.6	95.5	<.0001	0.56 (0.45-0.7)
90-day survival	89.7	83.8	<.0001	0.60 (0.53-0.68)
Cellulitis				
14-day survival	98.5	97.4	<.0001	0.58 (0.47-0.72)
90-day survival	92.2	89.2	<.0001	0.70 (0.63-0.78)

Survival was measured by the Kaplan-Meier curve, with significance determined by log-rank test.

and increases erythropoiesis. In addition, when administration of high-dose IV iron monthly vs low-dose IV iron as needed was examined in patients requiring maintenance dialysis, there was no difference in the infection rate between the 2 study groups.[25] Our findings align with these recent studies demonstrating that IV iron can be administered to hospitalized patients with acute infection, with associated improvements in anemia correction and reduced transfusion requirements, which were also noted in Shah's meta-analysis.[17]

Iron homeostasis during acute infections reflects a complex interplay between the host's immune system and pathogen traits that promote survival (Figure 2). Hepcidin is a central regulator of iron homeostasis during acute infections through downregulation of ferroportin, which leads to iron sequestration. In concert with the secretion of high-affinity iron-binding proteins, such as lactoferrin and siderocalin, this decreases the pathogen's access to iron.[26] Lactoferrin, which is abundant in mucosal secretions and neutrophil granules, limits extracellular iron availability, whereas siderocalin neutralizes bacterial siderophores, such as enterobactin, thereby disrupting critical iron acquisition pathways of pathogens such as *Escherichia coli* and *Klebsiella*.[27-29] This hepcidin-induced hypoferremia is a critical host defense mechanism against bacteria, particularly siderophilic bacteria.[30]

In contrast, iron deficiency itself increases the risk of infection. An association between iron deficiency and susceptibility to infection was observed in a meta-analysis published in 2013 that included 2 studies of adults in the intensive care unit, 2 studies of adults after their surgery, and 1 study of postpartum women.[31] A study, published in 2018, using a prospective, population-based registry in Norway found that iron deficiency was associated with an increased risk of bloodstream infections.[32] In a Danish study, women with iron deficiency were found to be at a higher risk of pneumonia, UTIs, and bloodstream infections.[33] Another retrospective analysis found that oral iron supplementation was associated with a decreased risk of pneumonia and cellulitis in hospitalized patients, again demonstrating the potential impact of iron supplementation on immunity.[34] Results similar to ours were seen in a large cohort of adult Medicare recipients who required in-center hemodialysis for end-stage renal disease and received IV iron during hospitalizations for acute infection. These patients did not have worse outcomes, including short-term mortality, LOS, or rehospitalization, than patients who did not receive IV iron.[23] Although this cohort differed from ours (<5% of our cohort had hemodialysis within 1 month of their acute infection), these data highlight that withholding iron may be more detrimental than providing it, reinforcing the clinical rationale for iron repletion even during acute infectious episodes.

To the best of our knowledge, this is the first study to evaluate the impact of IV iron therapy in patients with IDA across the most common types of infections requiring hospitalization.[35] Our findings consistently demonstrated a beneficial effect of IV iron on both 14- and 90-day mortality, particularly among patients with pneumonia, MRSA bacteremia, or colitis, supporting previous observations of improved outcomes in these populations. The beneficial effects of IV iron supplementation are especially notable in patients with pneumonia, in whom anemia has been shown to independently worsen mortality.[7,8]

Beyond correction of anemia, IV iron supplementation may enhance host immune function by improving macrophage activity, oxidative burst, neutrophil production and function, and overall immune responsiveness to infection.[20,36] This may be particularly important when treating MRSA infections, which place a significant burden on global health care.[37] Neutrophils

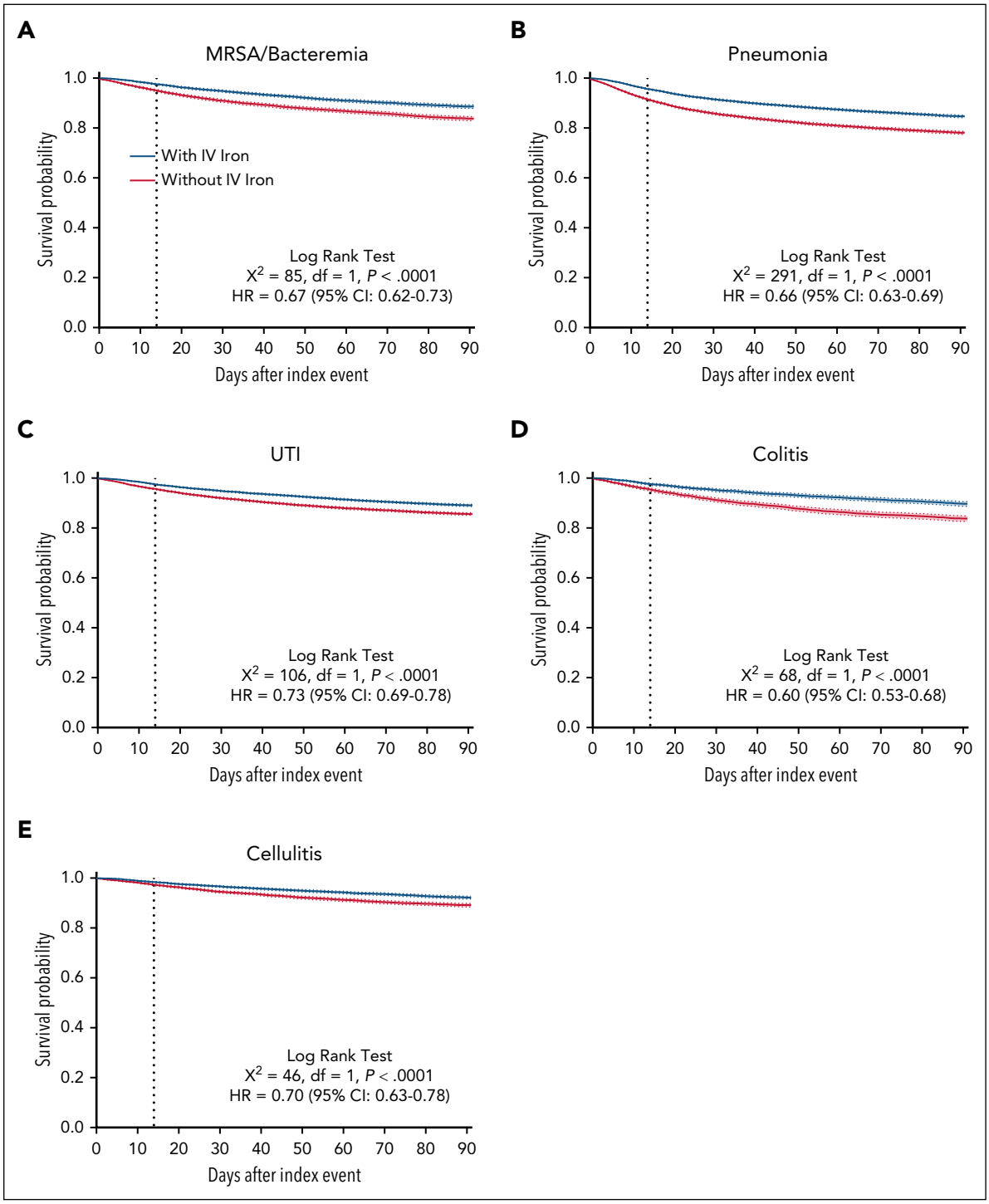

Figure 1. Kaplan-Meier survival curves up to 90 days by infection type, stratified by IV iron exposure. Survival probabilities are shown for patients with MRSA bacteremia (A), pneumonia (B), UTI (C), colitis (D), and cellulitis (E). Blue lines represent patients treated with IV iron, and red lines represent those without IV iron. The dotted horizontal line indicates 14-day survival. HRs and 95% CIs were determined by log-rank test.

are the most important component of innate immunity against MRSA infection, and iron deficiency has a significant effect on neutrophil production and function.[36,38] Iron-deficient neutrophils exhibit decreased phagocytic activity and impaired oxidative burst, which are critical for microbial killing.[39,40] *S aureus* has low affinity for transferrin-bound iron compared with non–transferrin-bound iron.[18] The newer IV iron formulations cause only transient increases in non–transferrin-bound iron and are likely to have a minimal impact on worsening infections.[41] Instead, as per our analysis, replacing iron in iron-deficient patients using newer IV iron formulations seems to be highly beneficial.

Table 3. Secondary outcomes by infection type and IV iron exposure

Outcome	IV iron	No IV iron	*P* value
MRSA bacteremia			
LOS, d	4.4 ± 6.1 (n = 7 764)	4.1 ± 6.3 (n = 7 548)	.0024
Days on antibiotic agents	5.3 ± 4.3 (n = 7 600)	5.2 ± 4.4 (n = 7 482)	.0133
Days on respirator	1.1 ± 0.3 (n = 550)	1.1 ± 0.3 (n = 715)	.8334
Days with transfusion*	1.6 ± 1.1 (n = 2 535)	1.7 ± 1.3 (n = 2 497)	.0002
Pneumonia			
LOS, d	4.5 ± 6.2 (n = 17 987)	4.5 ± 6.7 (n = 17 226)	.3611
Days on antibiotic agents	4.4 ± 3.6 (n = 17 467)	4.2 ± 3.8 (n = 16 921)	<.0001
Days on respirator	1.1 ± 0.4 (n = 2 157)	1.1 ± 0.3 (n = 2 793)	.0084
Days with transfusion*	1.5 ± 1.0 (n = 5 666)	1.6 ± 1.2 (n = 5 373)	<.0001
UTI			
LOS, d	4.1 ± 5.2 (n = 16 856)	3.9 ± 5.5 (n = 15 801)	.0007
Days on antibiotic agents	3.8 ± 3.3 (n = 16 534)	3.5 ± 3.4 (n = 15 838)	<.0001
Days on respirator	1.1 ± 0.3 (n = 867)	1.1 ± 0.3 (n = 1 218)	.3100
Days with transfusion*	1.5 ± 0.9 (n = 5 660)	1.6 ± 1.1 (n = 5 149)	<.0001
Colitis			
LOS, d	4.2 ± 5.6 (n = 3 877)	4.0 ± 6.0 (n = 3 928)	.0599
Days on antibiotic agents	4.9 ± 4.2 (n = 3 945)	5.5 ± 4.2 (n = 4 316)	<.0001
Days on respirator	1.1 ± 0.3 (n = 257)	1.1 ± 0.3 (n = 438)	.3873
Days with transfusion*	1.5 ± 1.0 (n = 1 276)	1.7 ± 1.3 (n = 1 283)	.0010
Cellulitis			
LOS, d	4.1 ± 5.5 (n = 7 558)	4.1 ± 6.0 (n = 7 177)	.4610
Days on antibiotic agents	4.6 ± 4.1 (n = 7 349)	4.3 ± 4.1 (n = 7 088)	<.0001
Days on respirator	1.0 ± 0.2 (n = 301)	1.1 ± 0.3 (n = 423)	.2590
Days with transfusion*	1.6 ± 1.1 (n = 2 207)	1.6 ± 1.2 (n = 2 197)	.2617

*Transfusion of blood or blood products.

Our analyses of the effects of IV iron in patients with colitis, cellulitis, or UTI begin to fill knowledge gaps where data were previously lacking. Cellulitis and UTIs are 2 of the most common infections requiring hospitalization,[42,43] and observational studies previously suggested that iron deficiency was associated with an increased risk of recurrent UTIs and skin and soft tissue infections.[33,34] Our study adds to the findings that IV iron supplementation is associated with improved hemoglobin recovery and lower mortality in patients hospitalized with UTI or cellulitis. Colitis is frequently associated with chronic blood loss, malabsorption, iron deficiency, and anemia.[44] Our analysis showed a survival benefit and improved hemoglobin levels 2 to 3 months after treatment in patients with colitis given IV iron, highlighting the long-term impact of infection on gastrointestinal physiology and malabsorption. In fact, the consistent benefit to hemoglobin levels 2 to 3 months after IV iron supplementation that we observed across all subgroups was greatest in colitis groups. Early hemoglobin levels were also affected, with significantly greater improvements at 14 days with IV iron. Although some increase may be caused by recovery from infection, the consistently higher hemoglobin levels after IV iron supplementation suggest an effect beyond spontaneous recovery. Our findings[42,43] suggest that IV iron provides meaningful hematologic and clinical benefits in hospitalized patients with colitis, cellulitis, or UTI, further supporting its use across diverse infection types.

Limitations

This study has several limitations that warrant consideration. Adverse events, such as hypophosphatemia, hypersensitivity reactions, or infusion-related reactions, are not reliably captured in the TriNetX network. As such, event-level safety data could not be included in this analysis. Instead, the study focused on major clinical outcomes (mortality, hemoglobin recovery, transfusion requirements, and hospital utilization) as indicators of safety and effectiveness. The study's retrospective, observational design precludes definitive conclusions regarding causality. Detailed microbiologic information—including pathogen load, antimicrobial resistance profiles, and infection severity—was not consistently available, limiting the granularity of the subgroup analyses. Furthermore, variability in the timing and dosing of IV iron relative to infection onset may have affected the observed outcomes. Because antibiotic exposure was measured only during the 14 days after the index date and the index date was defined as the later of infection or

Table 4. Changes in hemoglobin by infection type and IV iron exposure

Group	Within 1 d of IDA + infection		60-90 day after IDA + infection			
	Mean ± SD (g/dL)	n	Mean ± SD (g/dL)	n	Change (g/dL)	*P* value
MRSA bacteremia						
IV iron	8.64 ± 1.63	7 788	9.96 ± 1.86	3199	+1.32	<.0001
No IV iron	8.92 ± 1.73	7 759	9.91 ± 1.83	2599	+1.00	
Pneumonia						
IV iron	8.88 ± 1.72	17 932	10.12 ± 1.93	5751	+1.25	<.0001
No IV iron	9.06 ± 1.8	17 494	10.03 ± 1.87	4645	+0.97	
UTI						
IV iron	8.66 ± 1.67	17 054	10.05 ± 1.90	5625	+1.39	<.0001
No IV iron	8.95 ± 1.78	16 550	9.97 ± 1.81	4572	+1.02	
Colitis						
IV iron	8.84 ± 1.709	3 984	10.29 ± 2.01	1763	+1.45	<.0001
No IV iron	9.17 ± 1.81	4 048	9.91 ± 1.88	1427	+0.74	
Cellulitis						
IV iron	8.71 ± 1.67	7 642	10.11 ± 1.93	2611	+1.41	<.0001
No IV iron	9.07 ± 1.76	7 500	9.98 ± 1.87	2248	+0.92	

SD, standard deviation.

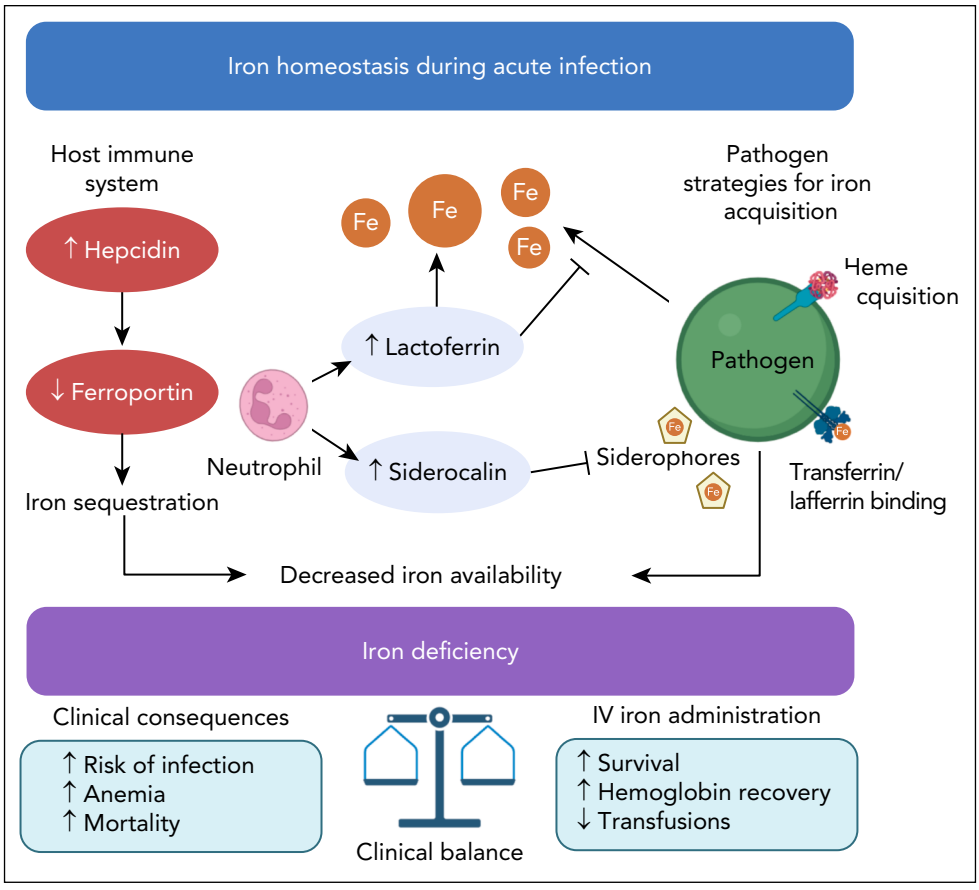

Figure 2. During acute infection, inflammatory signaling increases hepcidin production, leading to downregulation of ferroportin activity and intracellular iron sequestration. This reduces extracellular iron availability to invading pathogens. Neutrophils release lactoferrin, which binds free iron, and siderocalin, which binds bacterial siderophores, further limiting microbial iron acquisition. Pathogens counter with iron-scavenging strategies such as siderophore production, heme acquisition, and transferrin/lactoferrin binding proteins. The resulting competition for iron contributes to iron deficiency, which influences infection outcomes, anemia severity, and the clinical effects of IV iron administration. Figure created with BioRender.com. Collins J. (2026) https://biorender.com/5bda5y0.

IDA diagnosis, some patients had already begun antibiotic agents before the index date and did not have their earlier antibiotic days reflected in this outcome. In addition, clinical factors driving the decision to administer or withhold IV iron—particularly those documented only in narrative physician notes and not captured in structured EHR fields—could not be assessed. The generalizability of our findings to pediatric populations, immunocompromised patients, or critically ill patients requiring intensive care may also be limited, depending on cohort composition. IV iron exposure was analyzed as a binary variable, given that detailed dosing information was not consistently available. We could not assess whether complete iron repletion was accomplished. Oral iron use could not be assessed because over-the-counter formulations are not reliably documented in structured EHR data; therefore, some patients may have received additional iron therapy beyond IV iron, either as supplementation or continuation therapy after incomplete repletion. Because hemoglobin was assessed over 60 to 90 days, longer-term hemoglobin recovery may reflect the combined effects of IV iron and any additional iron therapy. However, in a supplemental analysis, hemoglobin improvement at 14 days was greater in the IV-iron group, a time point at which oral iron would be unlikely to produce a clinically meaningful hematologic response,[45] supporting a direct, early effect of IV iron. Finally, although short-term (14- and 90-day) mortality was assessed, longer-term outcomes, such as recurrent infections, persistent anemia, and functional recovery, were not evaluated.

This study also has analytical limitations. First, most analyses were performed within the TriNetX platform, which provides only aggregate mean values. Median values were not available, which may have better suited non-normal data distributions. Therefore, reliance on means may have introduced greater variance owing to outliers. Second, LOS could only be measured after the diagnosis of IDA and infection. Any hospitalization time before the index event was not captured, which may have underestimated the total hospital stay for some patients. Third, as with all retrospective, observational studies, residual confounding is possible despite propensity score matching. Unmeasured variables, such as illness severity scores, transfusion thresholds, nutritional status, or precise timing of infection onset, may have influenced outcomes. Fourth, TriNetX data are limited to structured EHR fields and have only limited inclusion of granular clinical details such as dosing and whether IV iron was given as a single treatment or a repeated course. Thus, although IV iron administration was required to occur within 7 days after the combined diagnosis of IDA and infection, the deidentified EHR timestamps in TriNetX do not allow verification of the precise sequence of events, so minor misclassification of event timing cannot be fully excluded. In addition, outpatient antibiotic use may not have been recorded. Finally, given the missingness of laboratory hemoglobin data, a detailed exploration of the intermediate impact of IV iron on hemoglobin could not be performed, and the hemoglobin recovery observed at 60 to 90 days likely reflects a combination of recovery from acute illness, resolution of inflammation-associated anemia, and repletion of iron stores. Despite these limitations, this study provides important real-world evidence supporting the safety and potential clinical benefits of IV iron administration in hospitalized patients with acute infections.

Conclusion

This study leveraged a large, real-world cohort of hospitalized patients with acute infections, providing broad generalizability across diverse infection types including pneumonia, MRSA bacteremia, UTIs, cellulitis, and colitis. The findings support IV iron administration during acute infection given that the treatment was associated with improved survival and enhanced recovery from anemia in a large cohort of hospitalized patients. By evaluating mortality, LOS, and hematologic responses, the study offers a balanced assessment of the efficacy and potential clinical benefits of IV iron. Notably, this is one of the first analyses to specifically address IV iron use during acute infections, a population typically excluded from previous studies, thereby filling an important knowledge gap and providing a foundation for future prospective investigations.

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Authorship

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Footnotes

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All data underlying this study were obtained from the TriNetX Research Network, a federated database of deidentified patient records. TriNetX is available through institutional or commercial subscription. No additional data beyond those provided by the platform can be shared by the authors.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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