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## Review Article

# Iron Therapy for Anemia in Diverse Populations: An Umbrella Review of Systematic Reviews

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## ABSTRACT

Iron deficiency anemia is a common condition seen in several demographics, including the general population, those with chronic kidney disease (CKD), those with acute kidney injury (AKI), patients dependent on dialysis, and kidney transplant recipients. This umbrella review synthesizes data only from published systematic reviews and meta-analyses to evaluate the efficacy and safety of iron therapy for chronic and acute anemia in these populations. The evaluation compared intravenous (IV) and oral iron supplementation, concentrating on hemoglobin response, cardiovascular outcomes, and related comorbidities. Data from 45 systematic reviews and meta-analyses demonstrate that in the general population, alternate-day oral iron has equivalent efficacy to daily dosing, while resulting in fewer adverse effects. The evidence for iron therapy in AKI is limited and suggests potential negative consequences from supplementation, while chelation may provide therapeutic benefits. Still, high-quality data on AKI are lacking. IV iron is often more efficacious than oral iron in elevating Hb levels, particularly in patients with CKD and those receiving dialysis, with risk ratios for achieving target Hb levels ranging from 1.23 to 1.71. Iron supplementation after transplantation enhances anemia; nonetheless, appropriate procedures remain undetermined. In terms of safety, IV presents a risk of hypersensitive reactions (relative risk [RR], 3.56 [95% CI, 1.88–6.74]) in contrast to oral iron. However, the absolute risk with modern formulations is low (0.1%–0.5%). Conversely, oral iron is linked to gastrointestinal side effects; IV iron reduces gastrointestinal events by 53% compared to oral iron (RR, 0.47 [95% CI, 0.33–0.66]). IV iron decreases hospitalizations for heart failure (RR, 0.77) in CKD, while it may increase the risk of serious adverse events under certain conditions. Therefore, it can be concluded that there is a need for personalized iron therapy to improve both efficacy and safety. Future research should prioritize high-quality trials in AKI and standardized protocols in transplantation.

**Key words:** Iron therapy, intravenous iron, oral iron, anemia, dialysis, iron deficiency anemia, CKD, AKI, kidney transplantation

## INTRODUCTION

Anemia is especially prevalent in low- and middle-income countries, where it affects up to 40% of the population due to factors such as nutritional deficiencies, infections, and chronic diseases. [1, 2] Common causes in the general population include iron deficiency, which accounts for approximately 50% of cases, as well as deficiencies in vitamin B12 or folate, chronic inflammation, parasitic infections, and genetic abnormalities such as thalassemia. [1] The prevalence of anemia in patients with chronic kidney disease (CKD)

increases with disease progression, ranging from 8.4% in stage 1 to over 53% in stage 5. [3] Anemia in CKD contributes to a substantial global burden that has risen from 1990 to 2021. [4, 5]

The primary causes of CKD include erythropoietin (EPO) deficiency due to decreased renal synthesis, iron dysregulation marked by functional deficiency, chronic inflammation that increases hepcidin levels, bone marrow dysfunction, shortened red blood cell lifespan, and nutritional deficiencies, such as vitamins. [4, 6] Anemia occurs frequently in acute kidney injury (AKI), affecting 50% to 70% of patients, particularly in critical care environments that necessitate continuous renal replacement therapy. [7] It is well documented that anemia in kidney diseases is linked to heightened mortality and cardiovascular risks. [8, 9]

Prevalent etiologies of AKI include acute hemorrhage due to surgical interventions or trauma, hemodilution, inflammation-induced EPO resistance, oxidative stress, and increased levels of catalytic iron, a free, unbound form of iron that facilitates the generation of reactive oxygen species, resulting in ferroptosis (iron-dependent cellular demise) and ensuing tissue damage. [8]

The prevalence of anemia in dialysis-dependent patients, typically those with end-stage kidney disease, surpasses 90%. This condition is influenced by mechanisms akin to those in CKD but is further intensified by blood loss and inflammation associated with dialysis. [7, 10]

Anemia increases kidney graft loss and patient death rates. [10–12] The etiologies of anemia in this category include iron deficiency (predominantly in the initial phases), graft dysfunction, immunosuppressive therapies (such as mycophenolate or calcineurin inhibitors that diminish erythropoiesis), infections, inflammation, surgical blood loss, and nutritional deficiencies. [11–13]

Iron therapy, administered either orally or intravenously, is crucial for the treatment of iron deficiency anemia (IDA); however, its effectiveness differs among populations and methods of delivery. Chronic anemia typically arises from ongoing iron deficiency or malabsorption, whereas acute anemia may result from hemorrhage or inflammatory processes. This umbrella systematic review assesses the effect of oral and intravenous (IV) iron therapy across various contexts, utilizing systematic searches of meta-analyses and systematic reviews. The main outcomes include improvements in Hb levels, cardiovascular events, renal function, and adverse effects. A comparative analysis of IV and oral iron indicates trade-offs in efficacy, tolerance, and complications. While multiple meta-analyses exist for individual populations, no comprehensive synthesis comparing iron therapy across all these groups has been published, highlighting a critical knowledge gap that this review aims to address.

## METHODS (SEARCH STRATEGY)

We conducted an umbrella review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. [14] Databases (PubMed, Embase, Cochrane, Web of Science) were searched until December 2025 using terms including “iron therapy,” “anemia,” “CKD,”

“AKI,” “dialysis,” “kidney transplantation,” “intravenous iron,” “oral iron,” and “meta-analysis.” Inclusion criteria were limited to systematic reviews or meta-analyses reporting Hb changes or clinical outcomes in the specified populations. Exclusion criteria included non-English articles, primary studies (randomized controlled trials [RCTs], observational), case reports, animal data, or non-systematic reviews. This umbrella review was not recorded in PROSPERO, constituting a restriction. The technique rigorously followed the PRISMA 2020 criteria [14] to guarantee meticulous reporting.

In instances where many reviews pertained to the same population or result, the most current, thorough, and highest-quality review (as assessed by AMSTAR-2) was chosen. We used a citation matrix technique to evaluate and quantify any overlap in the main research across the included systematic reviews. We compared reference lists for each pair of reviews with comparable populations to find duplicated main research. When overlapping over 30% of the smaller reviews' included studies, we maintained the review with a greater scope, more comprehensive subgroup analysis, or superior AMSTAR-2 score to minimize double-counting of evidence. This methodology was used qualitatively, since formal statistical adjustments for overlapping main studies were impractical due to the umbrella review design.

Two independent reviewers performed screening, full-text assessment, and data extraction. Quality was appraised with AMSTAR-2; evidence was certainly with GRADE. No new meta-analyses were performed; results were synthesized narratively. The English-language restriction may introduce language bias, which is acknowledged as a limitation. The PRISMA 2020 flow diagram is presented in **Figure 1**. **Table 1** summarizes characteristics of included studies; **Table 2** provides the GRADE summary of evidence.

**Table 1** summarizes the included studies' characteristics, and **Table 2** summarizes the GRADE summary of evidence.

## RESULTS

### Iron Therapy in the General Population

Both daily and alternate-day oral iron supplementation are effective for the general population with IDA, since meta-analyses show comparable increases in Hb levels (mean difference [MD] = 0.28 g/dL [95% CI, -0.01 to 0.56]). [15] Constipation and other gastrointestinal adverse effects are reduced by an alternate-day dosage. [11] Daily iron supplementation raises Hb levels somewhat more (MD = 0.364 g/dL), but at the expense of a higher risk of adverse events, according to a meta-analysis of RCTs. [15] Oral iron produces Hb correction rates in mild to severe anemia that are equivalent to those of daily and non-daily regimens, with the latter exhibiting superior tolerability. [15] Transfusion needs are decreased when severe cases are corrected more quickly with IV iron (relative risk [RR], 0.86 [95% CI, 0.55–1.34]). [16] Alternating-day oral iron is well tolerated in moderate chronic anemia and not inferior to oral daily iron. [17]

### Iron Therapy in CKD

Iron treatment has been linked to lower cardiovascular mortality (RR, 0.81 [95% CI, 0.65–1.02]) and heart failure hospitalization (RR, 0.77 [95% CI, 0.61–0.96]) in CKD. [18]

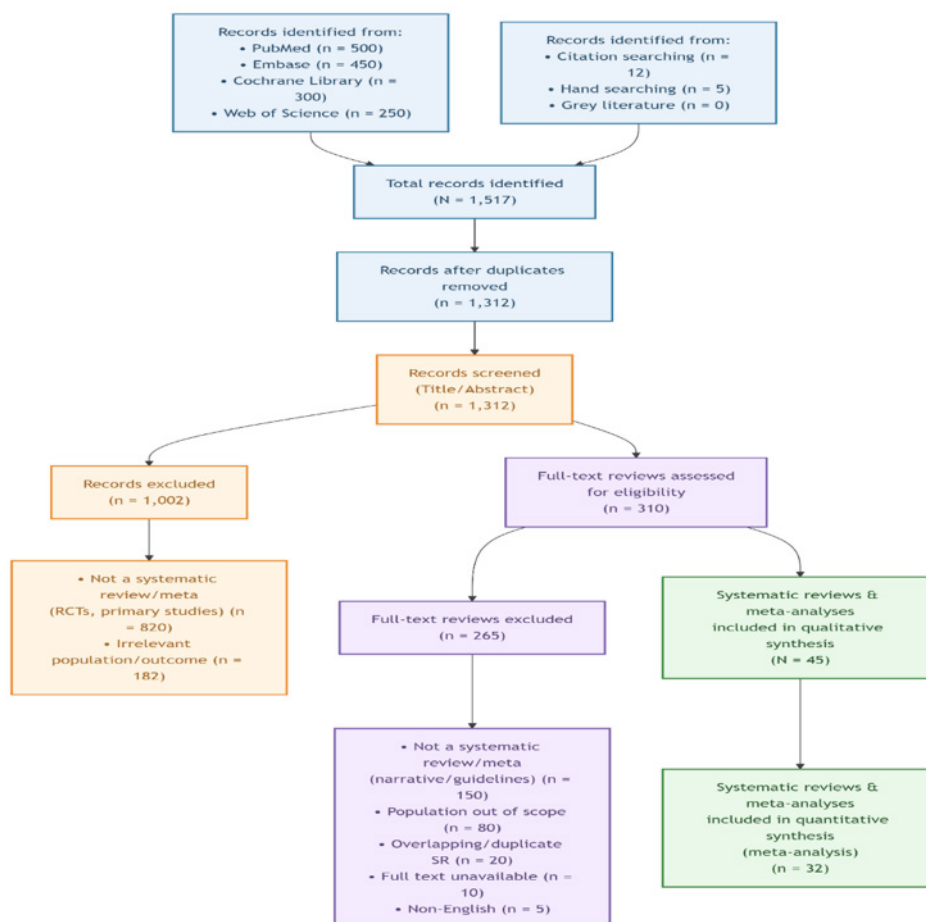


Figure 1: PRISMA 2020 flow diagram.

Table 1: Characteristics of included studies.

Study type	Population	Number of studies	Key interventions	Key outcomes	Quality (AMSTAR-2/RoB)
Meta-analyses/reviews	General population	5	Oral daily vs. alternate-day; IV vs. oral	Hb increase, gastrointestinal AEs, and transfusion rates	Moderate
Meta-analyses/reviews	CKD	10	IV vs. oral iron	Hb targets, cardiovascular mortality, HF hospitalization	Low risk
Meta-analyses/reviews	AKI	4	Iron chelation; IV iron in sepsis	Oxidative stress, mortality, recovery	Low
Meta-analyses/reviews	Dialysis	8	High-dose IV; oral in HF comorbidity	Erythropoiesis-stimulating agent reduction; composite endpoints	High
Meta-analyses/reviews	Post-transplant	6	IV iron; erythropoiesis-stimulating agent + iron	Hb levels; graft outcomes	Moderate
Meta-analyses/reviews	Complications	12	IV vs. oral	Hypersensitivity, gastrointestinal events, SAEs	Moderate to high

Table 2: GRADE summary of evidence.

Outcome	Population	Certainty of evidence	Reason for rating
Hb increase	CKD/dialysis	High	Consistent RCTs, low heterogeneity
Cardiovascular mortality reduction	CKD	Moderate	Downgraded for imprecision
Harm from supplementation	AKI	Low	Limited RCTs, high bias risk
Hypersensitivity reactions	All (IV)	Moderate	Consistent but rare events
gastrointestinal adverse events	All (oral)	High	Strong association in meta-analyses
Graft outcomes	Post-transplant	Low	Observational data, inconsistency

When it comes to increasing Hb (MD, 0.72 g/dL [95% CI, 0.39–1.05]) and reaching goal levels (RR, 1.71 [95% CI, 1.43–2.04]), IV iron is more effective than oral iron. [19] With an RR of 0.85 for composite outcomes, the effects are consistent in chronic renal illness that does not need dialysis. [18] For moderate anemias, oral iron shows improved safety but decreased efficiency, with no discernible change in mortality. [19] Erythropoiesis-stimulating agent dosage is reduced by 23% when high-dose IV iron is administered to patients with severe CKD. [20]

### Iron Therapy in AKI Pathophysiology

The role of iron therapy in AKI is complex and remains poorly defined due to low-quality evidence. The pathophysiology is unique: catalytic (free) iron exacerbates AKI via oxidative stress and ferroptosis, and elevated iron levels are linked to negative outcomes, including higher mortality and complications such as increased pneumonia risk. [21–23]

Regarding safety, IV iron is linked with a significant increase in infection risk compared to oral or no iron, with an RR of 1.16 to 1.17. [24] This increased risk is attributed to iron acting as a nutrient for bacteria and impairing immune function. [24] Furthermore, growing evidence reports that catalytic iron increases are associated with mortality [24] and that aberrant iron metabolism predicts AKI in critically ill patients (log-rank  $P < 0.0001$ ). [25]

Concerning therapeutic interventions, iron chelating therapy may offer theoretical advantages in established AKI by preventing damage and reducing oxidative stress, but this is based on preclinical and limited clinical data. [25] Conversely, iron supplementation in active AKI is not supported by current evidence and may be harmful. Some RCTs suggest it may exacerbate inflammation, although in specific subsets, such as sepsis, IV iron has shown no negative influence on AKI recovery. [22]

Overall, the data regarding AKI are limited and of low quality according to GRADE assessments (Table 2). This results in an evidence base that is insufficient to guide clinical practice. Therefore, current evidence does not support routine iron supplementation in AKI, and chelation remains experimental. High-quality RCTs are urgently needed to elucidate their role.

### Iron Therapy in Dialysis-Dependent Patients

The proactive high-dose IV iron treatment is linked to lower composite endpoints (hazard ratio, 0.85 [95% CI, 0.73–1.00]) and a lower need for erythropoiesis-stimulating drugs in

dialysis patients. [20] Compared to peritoneal dialysis (1.6%–49%), IV iron therapy is more common (11.7%–84.4%) and comes at larger amounts (108–750 mg/month). [26] With a weighted mean difference of 1.17 g/dL, meta-analyses show that IV administration is preferable for Hb response. [19] While oral iron supplementation may reduce the risk of hospitalization in individuals with concurrent heart failure (RR, 0.36), this finding is derived from heart failure populations, and its generalizability to dialysis patients is limited. [27]

### Iron Therapy in Post-Kidney Transplant Patients

Post-transplant anemia impacts up to 40% of kidney recipients, often associated with ID. [28] Hb levels increase with iron treatment; however, IV iron remains underutilized, despite established guidelines. [29] Iron and erythropoiesis-stimulating agents (ESAs) work together to address elevated Hb levels 12 safely. Enhanced graft results correlate with IV iron administration to elevate serum iron levels. [12] Furthermore, IV iron therapy enhances mitochondrial activity before transplantation. [13] (Table 3) represents the five steps that include population identification (Hb level, iron stores, symptoms), severity assessment (hypersensitivity history, active infection), contraindications, chosen route, and response and safety monitoring.

### DISCUSSION

This umbrella review synthesizes evidence from all sections, discusses mechanisms, and clearly outlines knowledge gaps (e.g., AKI, post-transplant protocols). IV iron therapy demonstrates a more rapid correction of Hb levels (MD = 2.05 g/dL compared to 1.65 g/dL for oral administration), though it carries risks of hypersensitivity (RR, 3.56 [95% CI, 1.88–6.74]). However, the absolute risk remains low with modern formulations—severe hypersensitivity reactions occur in approximately 0.1% to 0.5% of patients receiving newer IV iron preparations (ferric carboxymaltose, ferric derisomaltose, ferumoxytol, and iron isomaltoside), compared to higher rates with older high-molecular-weight iron dextran formulations that are now rarely used 20. To address potential inconsistencies in safety reporting across studies, note that RR estimates are derived from pooled meta-analyses with moderate heterogeneity ( $I^2$ , 40%–60%), and absolute risks vary by patient comorbidities (e.g., lower in non-CKD populations). [20]

Oral iron is associated with a higher incidence of gastrointestinal events (RR, 0.47 reduction with IV administration [95% CI, 0.33–0.66]), resulting in increased

**Table 3:** Iron therapy recommendations across populations.

Population	Step 1: Identify population	Step 2: Assess severity (Hb, ferritin, symptoms)	Step 3: Check contraindications	Step 4: Choose a route	Step 5: Monitor response and safety
General (mild IDA)	General population	Hb <12/13 g/dL, ferritin <30 ng/mL	Active infection, etc.	Oral (alternate-day)	Hb at 4 weeks, gastrointestinal tolerance
CKD/dialysis	CKD stages 3–5, dialysis	Hb <10 g/dL, TSAT <20%	Hypersensitivity history	IV (high-dose)	Ferritin-TSAT, infection risk
AKI	Acute setting	Hb <8 g/dL or symptomatic	Sepsis (relative)	Consider chelation	Renal recovery, oxidative markers
Post-transplant	Early (<6 months)	Hb <10 g/dL	None specific	IV preferred	Graft function, Hb trend

discontinuation rates (RR, 3.27 for lower IV rates). [6, 25] IV iron therapy during pregnancy decreases maternal complications by 21%, although it incurs higher costs. [21] Serious adverse events occur more frequently with IV (RR, 4.57), although they are often unrelated. [25]

### Justification for IV Iron Therapy

Superior in malabsorption conditions (e.g., CKD, inflammatory bowel disease) with reduced gastrointestinal complications; in opposition: Logistical challenges and less frequent severe adverse reactions. Oral treatments are suitable for mild cases due to cost-effectiveness; however, they exhibit low compliance attributed to side effects. In cardiac failure, IV iron enhances quality of life without mortality improvement. [30] Optimal use is essential, highlighting IV administration in severe or chronic conditions. Disparities arise mechanistically from factors such as increased hepcidin levels in CKD and dialysis, which hinder oral iron absorption, while IV iron bypasses gastrointestinal first-pass metabolism.

Cost-effectiveness factors, including nursing time and clinic visits for IV iron, are essential for policy, with IV administration preferred in resource-constrained environments only for difficult situations if advantages surpass logistical challenges.

Meta-analyses included in this review suggest that IV iron can reduce overall healthcare expenditures by 15% to 25% in CKD patients due to decreased ESA doses and hospitalizations, translating to savings of \$500 to 2000 per patient-year in affluent regions. [18, 20] Conversely, in low-resource settings, oral iron is more cost-effective, costing \$10 to 50 per course compared to \$200 to 500 for IV iron, underscoring the necessity for context-specific economic assessments.

IV iron achieves faster Hb correction (MD, 2.05 vs. 1.65 g/dL for oral) with fewer gastrointestinal events but higher hypersensitivity risk (absolute incidence 0.1%–0.5% with modern formulations). Oral iron is suitable for mild cases due to cost-effectiveness, while IV iron is preferred in malabsorption states (CKD, dialysis). In resource-limited settings, oral iron remains first-line for most patients. [1, 2] Access to IV iron is constrained by infrastructural deficiencies, such as insufficient infusion facilities, cold chain requirements for some formulations, and financial barriers, which may intensify discrepancies; for example, about 20% to 30% of CKD patients in sub-Saharan Africa get iron treatment, in contrast to 70% to 80% in high-income areas. [6] Additional barriers include a limited number of trained healthcare workers to give IV therapy and monitor for early anaphylactic reactions. Strategies to enhance fairness include advocating for affordable oral formulations, educating community health workers for oversight, and financing IV treatments for high-risk populations. Future studies need to include health equality frameworks to evaluate obstacles such as geographic accessibility and socioeconomic determinants.

### Iron Overload Considerations

Chronic IV iron therapy, especially in dialysis patients undergoing frequent high-dose treatment, raises apprehensions about iron overload and organ deposition. Excessive iron may deposit in the heart, liver, and endocrine organs (pancreas), possibly leading to oxidative stress and

tissue damage over time. [21, 26] Monitoring iron reserves using serum ferritin and transferrin saturation is crucial. However, appropriate criteria are still contested. [19] Current recommendations often advise withholding IV iron when ferritin levels are above 800 ng/mL or transferrin saturation reaches 50%, while the research substantiating these thresholds is limited. [19] Extended investigations are required to evaluate whether cumulative iron dosage is associated with organ malfunction or death.

### Limitations

First, the absence of a PROSPERO registration may result in reporting bias. Second, the omission of non-English systematic review and meta-analysis articles may result in linguistic bias. Third, while the search is current as of December 2025, it may still overlook the most recent articles. Fourth, while our citation matrix method evaluates overlap, the possibility of double-counting primary research among the included meta-analyses cannot be entirely eradicated. The considerable variability in iron formulations, dosage schedules, and patient demographics across the source evaluations constrains the accuracy of our results. The underlying literature did not undergo rigorous assessment for publication bias. The data concerning crucial populations, such as AKI, is notably of worse quality, underscoring a significant study need.

### CONCLUSIONS

Iron treatment is necessary for managing anemia. For mild instances in the general population, taking iron by mouth every other day is enough. For those with CKD and those on dialysis, IV iron is better. Be careful if you have AKI. Personalized, context-specific strategies enhance results. Future multicenter RCTs need to focus on AKI chelation and post-transplant regimens.

### AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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None.

### CONFLICT OF INTEREST

None.

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