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CONCISE DEFINITIVE REVIEW

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Anemia of Critical Illness: A Concise Definitive Review in Critical Care

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OBJECTIVES: Concise definitive review of anemia of critical illness.

DATA SOURCES: Available literature on PubMed and MEDLINE databases.

STUDY SELECTION: Available preclinical studies, clinical trials, observational studies addressing the diagnosis, pathophysiology, and treatment of anemia of critical illness were included.

DATA EXTRACTION: Eligible studies were identified, and recommendations were summarized.

DATA SYNTHESIS: Anemia of critical illness is highly prevalent, persists after ICU discharge and is associated with adverse outcomes. Most ICU patients have anemia of inflammation (high hepcidin, low erythropoietin, low erythroferrone, iron-restricted erythropoiesis) or iron deficiency anemia (low hepcidin). Dysregulation of iron homeostasis can also lead to the release of nontransferrin bound iron (catalytic iron), which catalyzes reactive oxygen species and is associated with organ failure in ICU patients. With significant advances in the understanding of the pathophysiology of anemia in the critically ill, new approaches to anemia management have emerged. Patient blood management, involving an evidence-based multidisciplinary approach with early diagnosis and diagnosis-specific treatment of anemia, optimizing hemostasis, and blood conservation including phlebotomy reduction, has become an increasingly important approach to patient care and represents a strategy that can result in improved patient outcomes in the critically ill.

CONCLUSIONS: The high prevalence of anemia in ICU patients warrants a decisive shift from RBC transfusion as treatment to early proactive pathophysiology-based personalized treatment of anemia.

KEYWORDS: anemia; critical illness; erythropoietin; hepcidin; iron; transfusion

Anemia is very common in the critically ill. Two thirds of patients on ICU admission are anemic, with almost 95% anemic by day 3 (1–3). Hemoglobin concentration declines throughout the ICU/hospital stay with over 80% of ICU patients anemic at hospital discharge (3–5). Anemia can be observed in 45% of ICU patients 12 months following ICU/hospital discharge (4, 5). In the critically ill, anemia is associated with higher morbidity/mortality and longer ICU/hospital length of stay (2, 4, 5).

Historically, treatment of anemia in the critically ill was associated with high rates of RBC transfusions (1, 2, 6). In 1999, the landmark Transfusion Requirements in Critical Care (TRICC) trial demonstrated that a restrictive transfusion strategy was comparable, and in some cases superior, to a liberal transfusion strategy (7). Following the TRICC trial, transfusion research has focused on comparing outcomes between liberal/restrictive transfusion strategies across a variety of clinical settings. More restrictive transfusion practice

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KEY POINTS

Question: What are the epidemiology, pathophysiology and treatments for anemia of critical illness?

Findings: Anemia is very common in the ICU and persists post-discharge. It is important to differentiate the etiology of anemia in ICU patients to facilitate appropriate treatment based on the pathophysiology (anemia of inflammation vs. iron deficiency anemia).

Meaning: With significant advances in the understanding of the pathophysiology of anemia in the critically ill, new approaches to anemia management have emerged.

over the last 2 decades has reduced RBC transfusion in the ICU, although 25% of ICU patients still receive RBC transfusions (8, 9).

The goal of identifying the appropriate transfusion threshold, or "trigger," has led to a perception that there is an acceptable degree of anemia, at least as an alternative to RBC transfusion (10). However, anemia is a clinical condition whose management, independent of transfusion, may lead to improved clinical outcomes (11). This suggests that the focus should shift from transfusion reduction to anemia treatment, with RBC transfusion reduction as a secondary benefit (10, 11). Understanding the pathophysiology of anemia in the critically ill is important in determining the optimal treatment of anemia. Implementation of patient blood management (PBM) in the ICU as a multimodal program to detect and treat anemia, reduce blood loss, correct coagulopathy, and use evidence-based blood transfusion guidelines will result in optimal ICU patient outcomes.

PATHOPHYSIOLOGY OF ANEMIA IN CRITICAL ILLNESS

Most ICU patients have anemia of inflammation (AI). The host inflammatory response results in dysregulation of iron homeostasis (iron-restricted erythropoiesis) and inhibition of erythropoietin production and activity (**Fig. 1**). This inflammatory response, combined with reduced RBC survival and blood loss, commonly from phlebotomy, is responsible for the high prevalence of anemia observed in ICU patients (12, 13).

The main mechanism controlling iron homeostasis centers on the interaction between hepcidin (produced by hepatocytes), the key regulator of iron homeostasis and ferroportin (located in duodenal cells, macrophages, and hepatocytes), the main cellular iron exporter through which iron is absorbed in the duodenum and released from macrophages into the plasma. Hepcidin binding to ferroportin results in ferroportin degradation (14). Therefore, increased hepcidin limits iron availability due to both decreased iron uptake from the gut and decreased iron release from macrophages/hepatocytes (12–15). In contrast, decreased hepcidin leads to increased iron absorption and iron release from macrophages/hepatocytes resulting in iron availability for erythropoiesis.

Under normal circumstances, high iron levels increase hepcidin while iron deficiency decreases hepcidin. However, there are substantial changes in iron homeostasis with inflammation (Fig. 1) (16). Inflammatory cytokines (particularly interleukin-6) and any inflammatory stimulus (infection/trauma) up-regulate hepcidin. Serum hepcidin levels are high in ICU patients with AI (17) and are low in ICU patients with iron deficiency. High hepcidin levels and the resulting hypoferremia inhibit erythroblast proliferation resulting in a functional iron deficiency or iron-restricted erythropoiesis (12). This anemia is usually a normochromic, normocytic anemia with low circulating iron but high serum ferritin (from macrophages/hepatocytes) and high hepcidin levels (12).

Erythropoiesis is also tightly regulated by erythropoietin, which is normally increased in response to anemia (Fig. 1). However, during critical illness, circulating erythropoietin concentrations fall quickly and remain inappropriately low for the degree of anemia observed, due to proinflammatory cytokine inhibition of erythropoietin production and reduced erythropoietin-mediated signaling (12). Decreased renal function also reduces endogenous erythropoietin.

Erythropoietin also influences hepcidin production by stimulating erythroblasts to increase the production of erythroferrone, an erythroid regulator of hepcidin (18). Erythropoietin increases both the number of erythroblasts and the synthesis of erythroferrone by each erythroblast. During normal erythropoiesis, erythropoietin increases circulating erythroferrone,

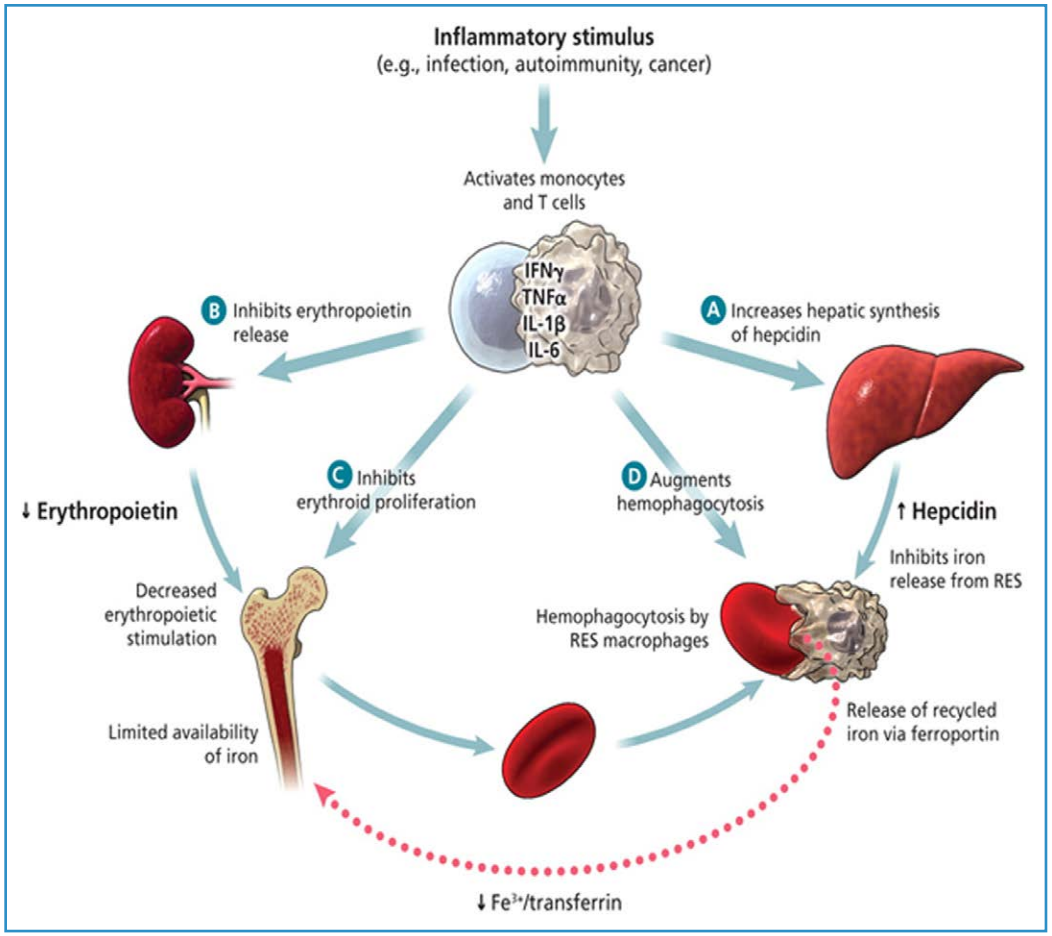

Figure 1. Anemia of inflammation in the ICU. Any inflammatory stimulus, including infection, sepsis, critical illness and trauma, increases hepcidin and decreases erythropoietin, resulting in functional iron deficiency, anemia, and reduced endogenous erythropoiesis. It has been confirmed that serum hepcidin levels are high in ICU patients with anemia of inflammation and hepcidin levels are low in iron deficiency anemia ICU patients. Fe^{3+} = ferric ion, IFNγ = interferon gamma, IL-1β = interleukin-1 beta, IL-6 = interleukin-6, RES = reticuloendothelial system, TNFα = tumor necrosis factor-alpha. From Zarychanski R, Houston DS: Anemia of chronic disease. A harmful disorder or an adaptive, beneficial response? *CMAJ* 2008; 179:333–337. doi: https://doi.org/10.1503/cmaj.071131.

which inhibits hepcidin production by hepatocytes, thus increasing iron availability for erythropoiesis (**Fig. 2**). In ICU patients, erythroferrone concentrations rapidly decrease, resulting in high hepcidin, further contributing to iron-restricted erythropoiesis (19).

In summary, over 90% of ICU patients have low serum iron, total iron binding capacity, and transferrin saturation (TSAT), but increased serum ferritin (3). Concurrently, serum erythropoietin levels are low, with little evidence of appropriate reticulocyte response to endogenous erythropoietin. Hepcidin levels are consistently found to be increased, while erythroferrone levels are decreased (12, 13, 15, 19). The anemia of critical illness, therefore, is a distinct clinical entity characterized by blunted erythropoietin production and response with abnormalities in iron homeostasis consistent with iron-restricted erythropoiesis (12).

Anemia in the critically ill often develops too early to result solely from decreased erythropoiesis. Shortened RBC survival has been consistently observed in inflammatory states and contributes to ICU-acquired anemia. This is a result of increased erythrophagocytosis by hepatic/splenic macrophages resulting from RBC membrane damage from inflammation/critical illness (12).

Also important to the development of anemia is iatrogenic blood loss (20). As many as 70% of hospitalized patients develop hospital-acquired anemia (HAA). A major contributor to HAA is phlebotomy, particularly in the ICU. The Small-volume Tubes to Reduce Anemia and Transfusion (STRATUS) pragmatic multicenter stepped-wedge cluster RCT (n = 27,411, 25 adult medical-surgical ICUs) compared standard blood collection vs. low-volume tubes with the use of needleless closed blood sampling systems. RBC units per patient per ICU stay significantly decreased (relative risk [RR], 0.88 [95% CI, 0.77–1.00]; p = 0.04; absolute reduction of 9.84 RBC units/100 patients per ICU stay [95% CI, 0.24–20.76]) with no negative impact on laboratory analysis. These strategies should be used in all ICU patients to prevent anemia.

Over the last decade, studies of catalytic iron (non-transferrin bound iron [NTBI]) in the critically ill have added to the complexity of the role of iron in ICU

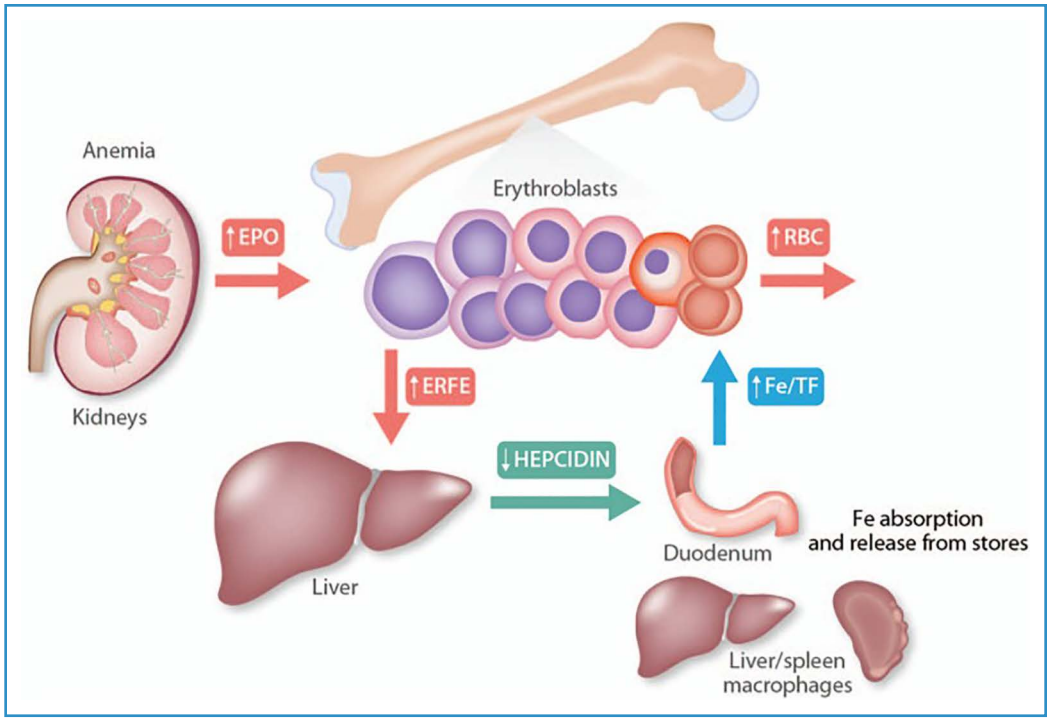

Figure 2. Erythroferrone (ERFE) and erythropoiesis. ERFE plays a significant role in the pathophysiology of anemia of inflammation, which is characterized by high levels of interleukin-6, hepcidin, ferritin, low levels of iron (Fe), transferrin, and ERFE. ERFE, which is important to down-regulate hepcidin, showed a rapid decrease in anemia of inflammation ICU patients, resulting in high hepcidin levels and Fe-restricted erythropoiesis. In response to anemia, increased erythropoietin (EPO) production by the kidney stimulates erythroblasts to increase the production of ERFE, both because EPO increases the number of erythroblasts and because EPO increases the synthesis of ERFE by each erythroblast. Circulating ERFE then acts directly on hepatocytes to suppress hepcidin production, leading to reduced plasma concentration of hepcidin. Low levels of circulating hepcidin allow the efflux of stored Fe, primarily from macrophages and hepatocytes, as well as increased dietary Fe absorption of Fe, so that more Fe is loaded onto transferrin. Increased flows of plasma holotransferrin then deliver Fe to erythroblasts for augmented heme and hemoglobin synthesis. TF = transferrin. From Coffey R, Ganz T: Erythroferrone: An erythroid regulator of hepcidin and iron metabolism. *Hemasphere* 2018; 2:e35.

patients (21, 22). Catalytic iron, or NTBI, is iron not bound to transferrin or other iron binding proteins. Catalytic iron is associated with iron-dependent production of reactive oxygen species and lipid peroxidation resulting in a nonapoptotic form of cell death termed ferroptosis (23). In the critically ill, increased catalytic iron and lipid peroxidation has been shown to be associated with severity of multiple organ dysfunction (24) and increased risk of acute kidney injury (AKI) and mortality in ICU patients (25, 26) (**Fig. 3**).

Generally, ICU patients with AI have low serum iron, low or normal transferrin, and low TSAT. Elevated catalytic iron is observed in clinical settings in which iron scavenging is saturated, that is, high TSAT (21). In the critically ill, a major source of iron release is free hemoglobin, which can saturate iron scavenging systems (21). Catalytic iron has been shown to correlate with free hemoglobin in ICU patients with AKI (26). High TSAT, and elevated catalytic iron, are associated with worse clinical outcomes in several clinical conditions (21). On the other hand, critically ill patients with lower iron levels and a low TSAT were more likely to survive (27).

IRON DEFICIENCY IN CRITICALLY ILL PATIENTS

It is important to differentiate the etiology of anemia in ICU patients to facilitate appropriate treatment based on the pathophysiology (AI vs. iron deficiency anemia [IDA]). Iron deficiency is also associated with increased infection risk via multiple mechanisms and early appropriate treatment of iron deficiency may enhance immune function and reduce infection risk.

IDA has been generally thought to be uncommon in the critically ill. This is in part due to the difficulty in using iron parameters (also acute-phase reactants) for the diagnosis of IDA in the setting of inflammation. Serum ferritin and TSAT levels are low in IDA. But serum ferritin levels increase with inflammation, so cannot be used to reliably diagnosis IDA in ICU patients. Soluble transferrin receptor (sTfR) levels increase in IDA. Since sTfR levels do not increase during inflammation or iron-restricted erythropoiesis as in the critically ill, sTfR measurements can aid in differentiating IDA and AI. Quantitative reticulocyte parameters (reticulocyte hemoglobin content and Delta-hemoglobin equivalent) can directly assess the current iron supply for erythropoiesis and are more specific and sensitive for the diagnosis of IDA in the ICU.

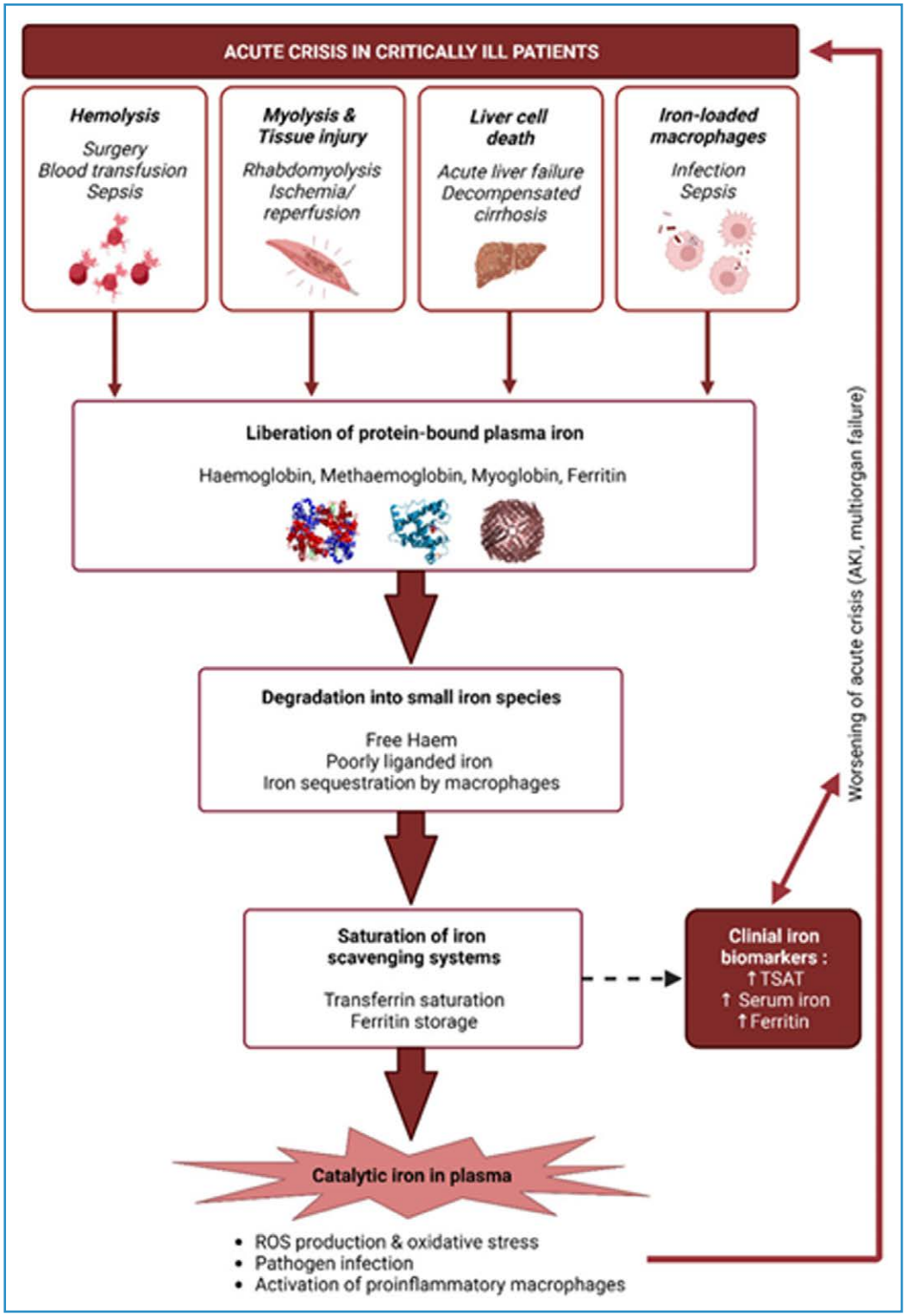

Figure 3. Catalytic iron release in the plasma of critically ill patients. Several acute crises (hemolysis, myolysis/tissue injury, liver cell death, and infection) induce the release of iron-binding proteins and small iron species. This iron release is characterized by increased transferrin saturation and serum iron and ferritin levels, and it correlates with worsening clinical conditions, as catalytic iron can increase oxidative stress, promote pathogen infection, and activate proinflammatory macrophages. AKI = acute kidney injury, ROS = reactive oxygen species, TSAT = transferrin saturation. From Grange et al (21).

Serum hepcidin may present a more reliable way to identify iron deficiency in the critically ill. In patients discharged from the ICU, a low hepcidin level identified iron deficiency in 37% of patients in contrast to 8% identified by iron studies alone (28). A low hepcidin level may also identify patients more likely to respond to iron therapy. Iron deficiency at ICU discharge, diagnosed using hepcidin level, was associated with higher 1-year mortality and decreased physical quality of life (28). In summary, IDA is difficult to diagnose in the ICU and optimal biomarkers are still not fully validated in ICU patients.

TREATMENT OF ANEMIA IN THE CRITICALLY ILL

RBC Transfusion

The most common treatment for anemia in the critically ill is RBC transfusion. Over the last 2 decades, it has become clear that RBC transfusion is not risk free. For the nonbleeding patient in many clinical situations RBC transfusion is of limited benefit (29, 30). RBC transfusion strategies for the

critically ill have recently been reviewed (31–34). Current national guidelines recommend a restrictive transfusion strategy (transfuse when hemoglobin < 7 g/dL) for most hemodynamically stable adult/PICU patients. Higher thresholds are recommended for specific subgroups, including cardiac surgery 7.5 g/dL, orthopedic surgery, or preexisting cardiovascular disease (8 g/dL) (31).

Newer data has emerged from RCTs in patients with acute myocardial infarction and anemia. A recent individual patient-level meta-analysis reported that all-cause mortality and recurrent MI at 30 days was higher in the restrictive group (15.4% restrictive vs. 13.8% liberal; relative risk, 1.13; 95% CI, 0.97–1.30). All-cause 6-month mortality was also increased (20.5% restrictive vs. 19.1% liberal; hazard ratio, 1.08; 95% CI, 1.05–1.11). Secondary analyses of the Myocardial Ischemia and Transfusion (MINT) trial reported no difference in quality of life outcomes, and variable results in chronic kidney disease (CKD), heart failure, and revascularization. Ultimately, individualized transfusion decisions are recommended to optimize outcomes in these patients.

Newer data is also available from RCTs in neurocritical care patients, suggesting different effects across different neurologic pathologies. The Hemoglobin Transfusion Threshold in Traumatic Brain Injury Optimization (HEMOTION) and Transfusion Strategies in Acute Brain Injured Patients (TRAIN) trials reported that liberal strategies (hemoglobin 9–10 g/dL) may improve neurologic recovery in traumatic brain injury (TBI). A systematic review and meta-analysis of transfusion strategy (restrictive vs. liberal) in TBI reported no difference in mortality, infection, or venous thromboembolism (VTE), but improved functional outcomes (Glasgow Outcomes Scale scores: RR, 1.24; 95% CI, 1.06–1.45) with liberal transfusion, associated with increased prevalence of acute respiratory distress syndrome (RR, 1.78; 95% CI, 1.06–2.98). In contrast, the Subarachnoid Hemorrhage Red Cell Transfusion Strategies and Outcome (SAHARA) trial in aneurysmal subarachnoid hemorrhage found no significant difference between liberal (≤ 10 g/dL) and restrictive (≤ 8 g/dL) strategies regarding unfavorable neurologic outcomes.

Iron Therapy

The abnormalities in iron homeostasis observed in the critically ill have generated interest in using iron to treat anemia in ICU patients, although there are limited data. In clinical trials of iron therapy in the ICU, a significant limitation is that anemic patients are often treated regardless of iron status, related to the difficulty in diagnosing IDA in ICU patients.

In a study of 200 critically ill anemic surgical patients, oral iron supplementation resulted in fewer RBC transfusions but no difference in hematocrit or infection risk (35). Similarly, in a randomized controlled trial of parenteral iron in 150 trauma patients with AI, iron supplementation did not result in significant differences in either hemoglobin, RBC transfusion, or infection risk (36). In the Intravenous Iron or Placebo for Anemia in Intensive Care (IRONMAN) trial, treatment with IV iron did not reduce RBC transfusion; however, hemoglobin concentration at hospital discharge was significantly higher (37). A meta-analysis of six RCTs in ICU patients (n = 805) found that iron therapy (oral or IV) resulted in an increase in mean hemoglobin concentration but did not impact RBC transfusion (38). In an updated meta-analysis (n = 1198) that included three additional RCTs, IV iron resulted in an increase in hemoglobin concentration but no difference in either mortality or infections (39). The heterogeneity in study design and clinical outcomes and questions about adequacy/variability of iron dosing limits the meta-analysis conclusions.

A multicenter feasibility RCT (INtravenous iron to treat anaemia following CriTical care [INTACT]) compared single dose ferric carboxymaltose 1000 mg IV vs. usual care in patients on ICU discharge with moderate/severe anemia (hemoglobin < 10 g/dL). IV iron resulted in higher hemoglobin at 28 and 90 days, no difference in infections and significantly reduced hospital readmissions at 90 days (40). In a recent RCT, ICU patients identified as iron responsive were treated with a "Practical Anemia Bundle" that included: 1) 1000 mg IV iron dextran, 2) decreased phlebotomy, and 3) clinical decision support. Hemoglobin concentrations at 1 and 3 months after hospital discharge were significantly greater in the "Practical Anemia Bundle" patients vs. standard care (41, 42). Serum hepcidin level may provide a more reliable means to diagnose iron-restricted erythropoiesis in critically ill patients with anemia (43, 44). It has now been recognized that serum concentration of hepcidin decrease in response to iron deficiency, even in the presence of inflammation (44). Low serum hepcidin concentration may identify a subset of critically ill patients with anemia in whom IV iron therapy is the optimal anemia treatment strategy and may be effective in reducing RBC transfusion requirements (45).

In a prospective observational study, nested within the IRONMAN trial, hepcidin concentration was measured within 48 hours of ICU admission (37). Low hepcidin levels identified patients in whom IV iron therapy was associated with a significant reduction in RBC transfusions (46). A recent RCT (Hepcidin and Iron Deficiency in Critically Ill Patients [Hepcidane] study [47]) used hepcidin levels to identify either absolute or functional iron deficiency at the time ICU discharge (45). Patients with absolute iron deficiency (hepcidin < 20 μg/L) were treated with parenteral iron while patients with functional iron deficiency were treated with parenteral iron and erythropoietin. Despite no difference in the post-ICU length of stay (primary endpoint), 90-day mortality was significantly lower and 1-year survival was increased with treatment for either absolute/functional iron deficiency vs. standard care.

In the past, concern for hypersensitivity reactions associated with high-molecular-weight dextran limited use of parenteral iron. However, with newer formulations of parenteral iron, severe reactions to IV iron are rare (48–50). Recent evidence-based expert consensus recommendation support the use of IV iron over oral iron for treatment of iron deficiency in individuals who require rapid correction, have insufficient response, or side effects related to oral iron.

There have also been concerns about the potential for an increased risk of infection with iron therapy. Fifty years ago, Weinberg (51) described the concept of nutritional immunity, related to hypoferremia, as a host defense to infection. The acute phase response increases sequestration of iron, in part mediated by hepcidin, limiting catalytic iron available for microorganisms (20, 45, 52). On the other hand, increased iron availability could overwhelm iron-scavenging mechanisms leading to an increase in catalytic iron and infection risk. Whether iron therapy in fact increases the infection, risk is unclear. To date, there have been two meta-analyses of IV iron across a range of clinical conditions that suggest an increase in infection risk with IV iron therapy (45, 53). In contrast, studies in ICU patients and surgical populations have not shown an increase in infections with parenteral iron administration (35–37).

Erythropoietic Stimulating Agents

A major feature of the anemia of critical illness is reduced erythropoietin production and activity (54). These observations have suggested that erythropoietic stimulating agent (ESA) treatment could increase hemoglobin and decrease RBC transfusion. This rationale led to a series of RCTs of ESAs in the critically ill (55, 56), which enrolled close to 3000 ICU patients, including 1500 trauma patients. ESAs significantly increased hemoglobin, but no RBC transfusion reduction was noted if transfusion practice was restrictive (55, 56). Of importance, these studies did suggest a mortality benefit for ESAs in trauma patients. This effect was independent of transfusion reduction and is likely a result of nonhematopoietic ESA action (57). Of note, ESA use was associated with an increase in thrombotic complications in patient not receiving therapeutic or prophylactic anticoagulation.

Multiple meta-analyses (58–63) confirm increased hemoglobin and transfusion reduction with ESA use in ICU patients. Most recently, a systematic review and network meta-analysis of pharmacotherapy for reducing RBC transfusion in ICU patients (75 RCTs, n = 15,091) reported that combination iron/ESA therapy reduced transfusions without increase in VTE or infection (63). There are two recent pilot studies suggesting the feasibility of an RCT studying ESA in the critically ill (64, 65). The INtravenous iron to treat anaemia following CriTical care-2 (INTACT-2) multicenter RCT initiated enrollment in U.K. ICUs (2024–2027) and will examine the efficacy and cost-effectiveness of IV iron/erythropoietin for anemia (hemoglobin = 10 g/dL) treatment in ICU patients (n = 1016) at the time of ICU discharge, with the primary outcome measure of physical function of the 36-Item Short Form Survey at 90 days post-randomization (66).

The meta-analysis of the effect of ESAs in critically ill trauma patients (nine studies, n = 2607) found a substantial reduction in mortality (RR, 0.63; 95% CI, 0.49–0.79; p = 0.0001) without increased deep venous thrombosis (62). Unfortunately, in the almost 20 years since the initial ESA RCTs, there had been no studies following up on the possible mortality benefit of ESAs in trauma patients, which remains a missed opportunity (57). Currently, there is an ongoing multicenter RCT (ErythroPOietin in Trauma [EPO-TRAUMA]) to evaluate the impact of ESA on 6-month mortality and severe disability in critically ill mechanically ventilated trauma patients (67).

The 2020 Clinical Practice Guidelines from the French Société Française d'Anesthésie et de

Réanimation and Société de Réanimation de Langue Française critical care groups recommend the ESA use in anemic critically ill and trauma patients in the absence of contraindications (68). In contrast, the clinical practice guideline from the European Society of Intensive Care Medicine recommended against the routine use of a combination of erythropoietin/iron in ICU patients with anemia (31). There are ongoing discussions on optimal use of ESAs in critically ill patients (69, 70). Given the potential increase in thrombotic complications with ESA therapy, VTE prophylaxis should also be considered if ESAs are given.

Modulation of Hepcidin

New emerging AI treatments are directed toward modulating the hepcidin-ferroportin pathway with the goal to reverse hypoferremia and thus treat anemia. Several general approaches have been studied: antagonists that inhibit hepcidin expression or hepcidin-ferroportin interaction; antagonists of hepcidin regulatory pathways; and stabilizers of ferroportin (54, 71). Several compounds directed at the hepcidin-ferroportin axis are in early phase clinical trials (54, 71).

Attempts to modulate hepcidin to treat anemia in the critically ill need to be undertaken with some caution. The elevated hepcidin and the associated hypoferremia observed in the critically ill may in fact provide benefit by decreasing catalytic iron availability (20). It has been demonstrated that hepcidin and hepcidin agonists increase resistance to infection by clearing catalytic iron (72). In contrast, low hepcidin levels and increased catalytic iron are associated with higher mortality in patients with AKI (25).

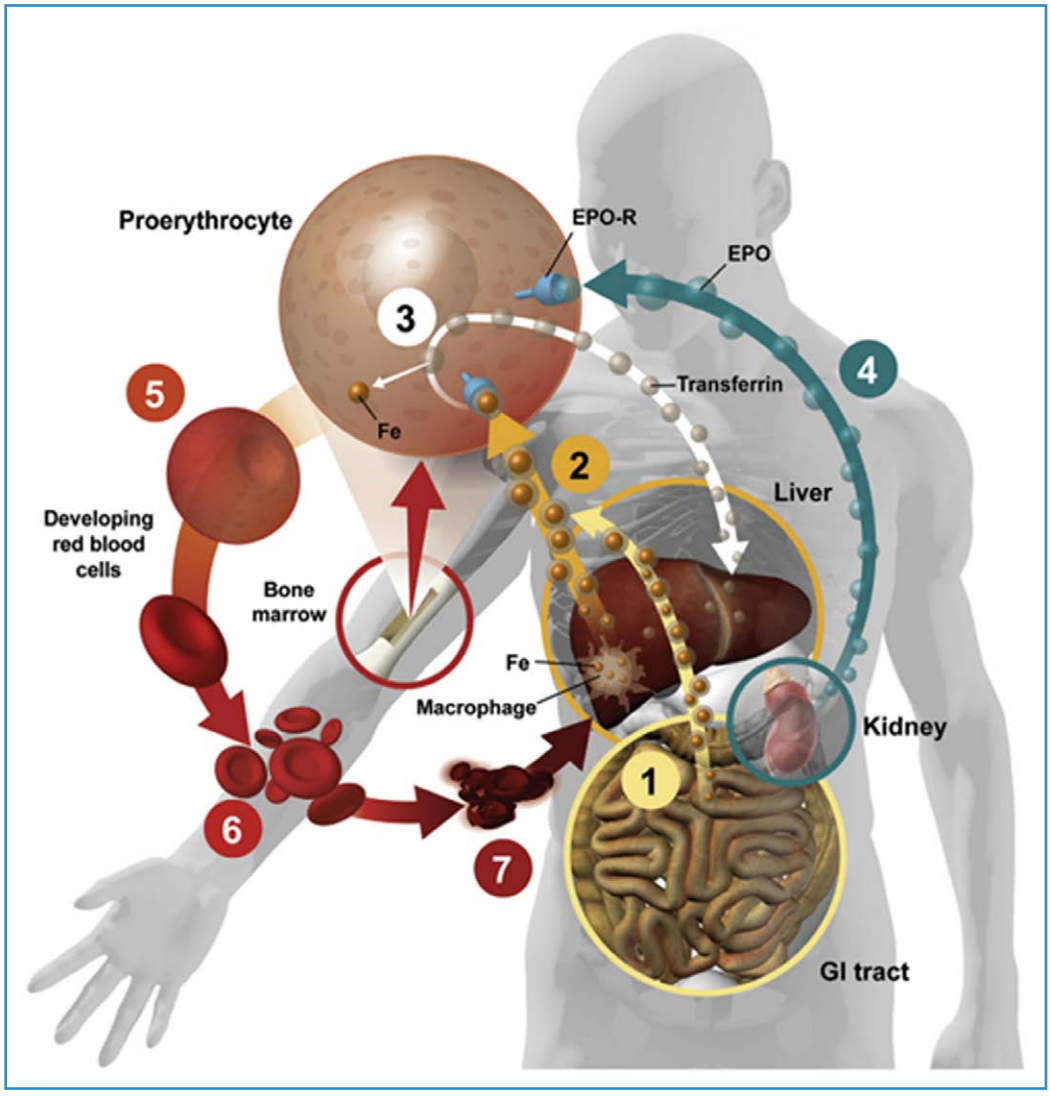

Figure 4. Erythropoietic effects of hypoxia-inducible factor (HIF). (1), HIF upregulates divalent metal transporter 1 and duodenal cytochrome B to increase intestinal iron (Fe) absorption; (2) transferrin transports Fe to transferrin receptors in the bone marrow; (3) Fe is released from transferrin into the developing erythrocyte; (4) HIF upregulates the erythropoietin (EPO) receptor (EPO-R) and endogenous EPO production; (5) HIF upregulates transferrin receptor, increasing Fe uptake by proerythrocytes; (6) HIF promotes the formation of fully functional mature erythrocytes replete with hemoglobin; (7) after a lifespan averaging approximately 120 d, exhausted erythrocytes are scavenged in the liver and the Fe is returned for reuse. GI = gastrointestinal. From Gupta N, Wish JB: Hypoxia-inducible factor prolyl hydroxylase inhibitors: A potential new treatment for anemia in patients with CKD. *Am J Kid Dis* 2017; 69:815–826.

Modulation of Hypoxia-Inducible Factor

Hypoxia-inducible factor (HIF) is a transcription factor that is an important regulator of erythropoiesis (**Fig. 4**). Stabilization of HIF is of paramount importance for optimal erythropoiesis. HIF is degraded under normoxic conditions by HIF-prolyl hydroxylase (HIF-PHD). Inhibition of HIF-PHD by HIF-prolyl hydroxylase inhibitors (HIF-PHIs) leads to HIF activation, increased endogenous erythropoietin production, increased iron uptake from the gut, and iron mobilization from hepatocytes and macrophages, promoting increased erythropoiesis. Serum levels of hepcidin are also reduced indirectly through increased erythropoietic activity and erythroferrone production (73, 74). HIF-PHIs are a new class of oral agents that promote erythropoiesis primarily through increased endogenous erythropoietin production and decrease hepcidin levels. In clinical trials, in patients with CKD, HIF-PHIs have been shown to be noninferior to ESAs (75). Several HIF-PHIs are approved worldwide for CKD patients but the role of these agents for anemia treatment in non-CKD patients awaits more data.

CONCLUSIONS AND FUTURE DIRECTIONS

The high prevalence of anemia in ICU patients both in-hospital and persistent after ICU discharge warrants a decisive shift from RBC transfusion to early proactive pathophysiology-based diagnosis/treatment of anemia. Over the last 2 decades, there has been significant advances in the understanding of the pathophysiology of anemia in the critically ill. This has resulted in new approaches to anemia management. PBM, involving an evidence-based multimodal/multifaceted approach with early diagnosis and diagnosis-specific anemia treatment, optimizing hemostasis, and blood conservation including phlebotomy reduction (76), has become an increasingly important strategy that can result in improved patient outcomes in the ICU (77–79).

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REFERENCES

1. Corwin HL, Gettinger A, Pearl RG, et al: The CRIT study: Anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med* 2004; 32:39–52
2. Vincent JL, Baron JF, Reinhart K, et al; ABC (Anemia and Blood Transfusion in Critical Care) Investigators: Anemia and blood transfusion in critically ill patients. *JAMA* 2002; 288:1499–1507
3. Rodriguez RM, Corwin HL, Pearl RG, et al: Anemia in the critically ill: Role of nutritional deficiency and erythropoietin response. *J Crit Care* 2001; 16:36–41
4. Warner MA, Hanson AC, Frank RD, et al: Prevalence of and recovery from anemia following hospitalization for critical illness among adults. *JAMA Netw Open* 2020; 3:e2017843
5. Warner MA, Hanson AC, Schulte PJ, et al: Early post-hospitalization hemoglobin recovery and clinical outcomes in survivors of critical illness: A population-based cohort study. *J Intensive Care Med* 2022; 37:1067–1074
6. Corwin HL, Parsonnet KC, Gettinger A: RBC transfusion in the intensive care unit: Is there a reason? *Chest* 1995; 108:767–771
7. Hébert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; 340:409–417
8. Vincent JL, Jaschinski U, Wittebole X, et al; ICON Investigators: Worldwide audit of blood transfusion practice in critically ill patients. *Crit Care* 2018; 22:102–110
9. Raasveld SJ, de Bruin S, Reuland MC, et al; InPUT Study Group: Red blood cell transfusion in the intensive care unit. *JAMA* 2023; 330:1852–1861
10. Shander A, Kim T-Y, Goodnough LT: Thresholds, triggers, or requirements—time to look beyond the transfusion trials. *J Thorac Dis* 2018; 10:1152–1157
11. Shander A, Goodnough LT: From tolerating anemia to treating anemia. *Ann Intern Med* 2019; 170:125–126
12. Weiss G, Ganz T, Goodnough LT: Anemia of inflammation. *Blood* 2019; 133:40–50
13. Sihler KC, Napolitano LM: Anemia of inflammation in critically ill patients. *J Intensive Care Med* 2008; 23:295–302
14. Langer AL, Ginzburg YZ: Role of hepcidin-ferroportin axis in the pathophysiology, diagnosis, and treatment of anemia of chronic inflammation. *Hemodial Int* 2017; 21:S37–S46
15. Young B, Zaritsky J: Hepcidin for clinicians. *Clin J Am Soc Nephrol* 2009; 4:1384–1387
16. Napolitano LM: Understanding anemia in the ICU to develop future treatment strategies. *Am J Respir Crit Care Med* 2018; 198:554–555
17. Cherry-Bukowiec JR, Engoren M, Wiktor A, et al: Hepcidin and anemia in surgical critical care: A prospective cohort study. *Crit Care Med* 2018; 46:e567–e574
18. Srole DN, Ganz T: Erythroferrone structure, function, and physiology: Iron homeostasis and beyond. *J Cell Physiol* 2021; 236:4888–4901

19. Boshuizen M, Binnekade JM, Nota B, et al; Molecular Diagnosis and Risk Stratification of Sepsis (MARS) Consortium: Iron metabolism in critically ill patients developing anemia of inflammation: A case control study. *Ann Intensive Care* 2018; 8:56
20. Shander A, Corwin HL: A narrative review of hospital acquired anemia: Keeping blood where it belongs. *Transfus Med Rev* 2020; 34:195–199
21. Grange C, Lux F, Brichart T, et al: Iron as an emerging therapeutic target in critically ill patients. *Crit Care* 2023; 27:475
22. Leaf DE, Swinkels DW: Catalytic iron and acute kidney injury. *Am J Physiol Renal Physiol* 2016; 311:F871–F876
23. Dixon SJ, Lemberg KM, Lamprecht MR, et al: Ferroptosis: An iron-dependent form of nonapoptotic cell death. *Cell* 2012; 149:1060–1072
24. Van Coillie S, Van San E, Goetschalckx I, et al: Targeting ferroptosis protects against experimental (multi)organ dysfunction and death. *Nat Commun* 2022; 13:1046
25. Leaf DE, Rajapurkar M, Lele SS, et al: Plasma catalytic iron, AKI, and death among critically ill patients. *Clin J Am Soc Nephrol* 2014; 9:1849–1856
26. Leaf DE, Rajapurkar M, Lele SS, et al: Iron, hepcidin, and death in human AKI. *J Am Soc Nephrol* 2019; 30:493–504
27. Tacke F, Nuraldeen R, Koch A, et al: Iron parameters determine the prognosis of critically ill patients. *Crit Care Med* 2016; 44:1049–1058
28. Lasocki S, Lefebvre T, Mayeur C, et al; FROG-ICU study group: Iron deficiency diagnosed using hepcidin on critical care discharge is an independent risk factor for death and poor quality of life at one year: An observational prospective study on 1161 patients. *Crit Care* 2018; 22:314–321
29. Marik PE, Corwin HL: Efficacy of RBC transfusion in the critically ill: A systematic review of the literature. *Crit Care Med* 2008; 36:2667–2674
30. Napolitano LM: Anemia and red blood cell transfusion: Advances in critical care. *Crit Care Clin* 2017; 33:345–364
31. Carson JL, Stanworth SJ, Guyatt G, et al: Red blood cell transfusion: 2023 AABB international guidelines. *JAMA* 2023; 330:1892–1902
32. Fasano RM, Doctor A, Stowell SR, et al: Optimizing RBC transfusion outcomes in patients with acute illness and in the chronic transfusion setting. *Transfus Med Rev* 2023; 37:150758
33. Vlaar AP, Oczkowski S, deBruin S, et al: Transfusion strategies in non-bleeding critically ill adult: A clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Med* 2020; 46:673–696
34. Cable CA, Razavi SA, Roback JD, et al: RBC transfusion strategies in the ICU: A concise review. *Crit Care Med* 2019; 47:1637–1644
35. Pieracci FM, Henderson P, Rodney JR, et al: Randomized double-blind placebo-controlled trial of the effects of enteral iron supplementation on anemia and risk of infection during surgical critical illness. *Surg Infect* 2009; 10:9–19
36. Pieracci FM, Stovall RT, Jaouen B, et al: A multicenter randomized clinical trial of IV iron supplementation for anemia of traumatic critical illness. *Crit Care Med* 2014; 42:2048–2057
37. Litton E, Baker S, Erber WN, et al; IRONMAN Investigators: Intravenous iron or placebo for anaemia in intensive care: The IRONMAN multicentre randomized blinded trial. *Intensive Care Med* 2016; 42:1715–1722
38. Shah A, Fisher SA, Wong H, et al: Safety and efficacy of iron therapy on reducing red blood cell transfusion requirements and treating anaemia in critically ill adults: A systematic review with meta-analysis and trial sequential analysis. *J Crit Care* 2019; 49:162–171
39. Geneen LJ, Kimber C, Doree C, et al: Efficacy and safety of intravenous iron therapy for treating anaemia in critically ill adults: A rapid systematic review with meta-analysis. *Transfus Med Rev* 2022; 36:97–106
40. Shah A, Chester-Jones M, Dutton SJ, et al; INTACT Investigators: Intravenous iron to treat anaemia following critical care: A multicentre feasibility randomised trial. *Br J Anaesth* 2022; 128:272–282
41. Warner MA, Johnson ML, Hanson AC, et al: Practical anemia bundle and hemoglobin recovery in critical illness: A randomized clinical trial. *JAMA Netw Open* 2025; 8:e252353
42. Walsh TS: Invited commentary: Active prevention and treatment of post-critical illness anemia. Is it time for large effectiveness trials? *JAMA Netw Open* 2025; 8:e252368
43. Shah A, Wray K, James T, et al: Serum hepcidin potentially identifies iron deficiency in survivors of critical illness at the time of hospital discharge. *Br J Haematol* 2019; 184:279–281
44. Lasocki S, Baron G, Driss F, et al: Diagnostic accuracy of serum hepcidin for iron deficiency in critically ill patients with anemia. *Intensive Care Med* 2010; 36:1044–1048
45. Litton E, Lim J: Iron metabolism: An emerging therapeutic target in critical illness. *Crit Care* 2019; 23:81
46. Litton E, Baker S, Erber W, et al; IRONMAN Study investigators: Hepcidin predicts response to IV iron therapy in patients admitted to the intensive care unit: A nested cohort study. *J Intensive Care* 2018; 6:60
47. Lasocki S, Asfar P, Jaber S, et al; Hepcidane study group: Impact of treating iron deficiency, diagnosed according to hepcidin quantification, on outcomes after a prolonged ICU stay compared to standard care: A multicenter, randomized, single-blinded trial. *Crit Care* 2021; 25:62
48. Dave CV, Brittenham GM, Carson JL, et al: Risks of anaphylaxis with iron formulations. *Ann Intern Med* 2022; 175:656–664
49. Arastu AH, Elstott BK, Cohen JL, et al: Analysis of adverse events and intravenous iron formulations in adults with and without prior infusion reactions. *JAMA Network Open* 2022; 5:e224488
50. VanDoren L, Auerbach M: IV iron formulations and use in adults. *Hematology Am Soc Hematol Educ Program* 2023; 2023:622–629
51. Weinberg ED: Nutritional immunity. *JAMA* 1975; 231:39–41
52. Ganz T, Nemeth E: Iron homeostasis in host defense and immunity. *Nat Rev Immunol* 2015; 15:500–510
53. Shah AA, Donavan K, Seely C, et al: Risk of infection with administration of IV iron: A systematic review and meta-analysis. *JAMA Open Network* 2021; 4:e2133935
54. Ganz T: Anemia of inflammation. *N Engl J Med* 2019; 381:1148–1157
55. Corwin HL, Gettinger A, Rodriguez RM, et al: Efficacy of recombinant human erythropoietin in the critically ill patient: A

randomized double-blind placebo-controlled trial. *JAMA* 2002; 288:2827–2835

56. Corwin HL, Gettinger A, Fabian T, et al: Efficacy and safety of epoetin alpha in the critically ill. *N Engl J Med* 2007; 357:965–976
57. Corwin HL, Napolitano LM: Erythropoietin for critically ill trauma patients: Are we missing an opportunity? *J Trauma Acute Care Surg* 2014; 77:774–779
58. Zarychanski R, Turgeon AF, McIntyre L, et al: Erythropoietin receptor agonists in critically patients: A meta-analysis of randomized controlled trials. *CMAJ* 2007; 177:725–734
59. Mesgarpour B, Heidinger BH, Kienbacher C, et al: Safety of off-label erythropoiesis stimulating agents in critically ill patients: A meta-analysis. *Intensive Care Med* 2013; 39:1896–1908
60. Wijnberge M, Rullum SR, de Bruin S, et al: Erythropoiesis-stimulating agents as replacement therapy for blood transfusions in critically ill patients with anemia: A systematic review and meta-analysis. *Transfusion Med* 2020; 30:433–441
61. Litton E, Latham P, Inman J, et al: Safety and efficacy of erythropoiesis-stimulating agents in critically ill patient admitted to the intensive care unit: A systematic review and meta-analysis. *Intensive Care Med* 2019; 45:1190–1199
62. French CJ, Glassford NJ, Gantner D, et al: Erythropoiesis-stimulating agents in critically ill trauma patients: A systematic review and meta-analysis. *Ann Surg* 2017; 265:54–62
63. Yoshihiro S, Hongo T, Yamamoto M, et al: Pharmacotherapy for reducing RBC transfusion for patients in the ICU: A systematic review and network meta-analysis. *Crit Care Med* 2024; 52:618–625
64. Leger M, Auchabie J, Ferrandiere M, et al: Erythropoietin to treat anemia in critical care patients: A multicenter feasibility study. *Anesthesia* 2023; 78:979–987
65. Litton E, French C, Herschtal A, et al: Iron and erythropoietin to heal and recover after intensive care (ITHRIVE): A pilot randomized clinical trial. *Crit Care Resusc* 2023; 25:201–206
66. National Institute for Health and Care Research: INtravenous Iron and eryThropoietin to treat Anaemia following CriTical care-2 (INTACT-2): A Multi-Centre, Randomised, Parallel Group, Double Blind, Placebo Controlled, Clinical Efficacy Trial. 2023. Available at https://fundingawards.nihr.ac.uk/award/NIHR153014. Accessed November 6, 2025
67. French C, Nichol A: EPO-Trauma Trial. Available at: https://www.monash.edu/medicine/sphpm/anzicrc/research/epo-trauma. Accessed November 6, 2025
68. Lasocki S, Pene F, Ait-Oufella H, et al: Management and prevention of anemia (acute bleeding excluded) in adult critical care patients. *Ann Intensive Care* 2020; 10:97
69. Lasocki S, Kimmoun A, Chanques G, et al: Treating critically ill anaemic patients with erythropoietin: Why not? *Intensive Care Med* 2020; 46:1794–1795
70. Oczkowski S, Shah A, Aubron C, et al; ESICM Transfusion Guideline Part 1 Task force: Treating critically ill anemic patients with erythropoietin: Less is more. *Intensive Care Med* 2021; 47:256–257
71. Sager P, Angmo S, Sandhir R, et al: Effect of hepcidin antagonists on anemia during inflammatory disorders. *Pharmacol Ther* 2021; 226:107877
72. Stefanova D, Raychev A, Arezes J, et al: Endogenous hepcidin and its agonist mediate resistance to selected infections by clearing non-transferrin bound iron. *Blood* 2017; 130:245–257
73. Kaplan JM, Sharma N, Dikdan S: Hypoxia-inducible factor and its role in the management of anemia in chronic kidney disease. *Int J Mol Sci* 2018; 19:389
74. Haase V: Regulation of erythropoiesis by hypoxia-inducible factors. *Blood Rev* 2013; 27:41–53
75. Haase VH, Tanaka T, Koury MJ: Hypoxia-inducible factor activators: A novel class of oral drugs for the treatment of anemia of chronic kidney disease. *Hematology Am Soc Hematol Educ Program* 2024; 2024:409–418
76. Siegal DM, Belley-Côté EP, Lee SF, et al: Small-volume blood collection tubes to reduce transfusions in intensive care: The STRATUS randomized clinical trial. *JAMA* 2023; 330:1872–1881
77. Shander A, Javidroozi M, Lobel G: Patient blood management in the intensive care unit. *Transfus Med Rev* 2017; 31:264–271
78. Littlejohn J, Shen L, Srivastava A, et al: Patient blood management for the critically-ill patient. *Curr Anesthesiol Rep* 2024; 14:376–387
79. World Health Organization: Guidance on Implementing Patient Blood Management to Improve Global Blood Health Status. 2024. Available at: https://iris.who.int/bitstream/handle/10665/380784/9789240104662-eng.pdf?sequence=1&isAllowed=y. Accessed November 6, 2025