

REVIEW

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Iron Metabolism: An Emerging Therapeutic Target in Critical Illness



Edward Litton^{1,2*} and Jolene Lim¹

Abstract

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Introduction

Iron is required for erythropoiesis and is also essential for many other life-sustaining functions including deoxyribonucleic acid (DNA) and neurotransmitter synthesis, mitochondrial function and the innate immune response. Despite its importance in maintaining health, iron deficiency is the most common nutritional deficiency worldwide and many of the risk factors for iron deficiency are also risk factors for developing critical illness. The result is that iron deficiency is likely to be over-represented in critically ill patients, with an estimated incidence of up to 40% at the time of intensive care unit (ICU) admission [1].

Critical illness results in profound and characteristic changes to iron metabolism that are highly conserved from an evolutionary perspective. These changes are mediated predominantly by the polypeptide hepcidin, which acts to decrease the absorption and availability of iron, despite acute phase increases in iron-binding proteins, such as ferritin, which may suggest normal or increased iron stores. The result is a state of functional iron deficiency. This may be protective in the short term, providing a form of 'nutritional immunity' against invading microbes by diminishing access to free iron in response to infection. However, by reducing the capacity of the

body to access iron for vital processes, persistent functional iron deficiency can become harmful. For patients with prolonged ICU admission, this may contribute to critical illness-associated cognitive, neuromuscular and cardiopulmonary dysfunction.

Historically, the possibility of iron deficiency was largely unexplored in critically ill patients due to the confounding effects of acute inflammation on commonly available iron measures, the lack of safe and effective treatments and uncertainty as to the clinical significance of deranged iron metabolism. However, assays, including hepcidin, offer the potential to identify iron restriction despite the presence of inflammation and may be coupled with promising therapeutic options to address issues including nosocomial infection and functional recovery for patients admitted to the ICU.

These advances are timely as emerging data suggest that disordered iron metabolism is of substantial prognostic significance in critical illness. High serum transferrin saturation and iron concentration are independent predictors of mortality in patients admitted to the ICU [2]. These data are consistent with findings of increased infection risk and organ failure associated with deranged iron metabolism in studies of patients undergoing hematopoietic stem cell and renal transplantation [3, 4]. Failure to maintain iron homeostasis early after a profound insult may result in an accumulation of highly reactive free iron, or non-transferrin bound iron, inflicting further oxidative stress on vulnerable organs or scavenged by invading microorganisms. The requirement for tight homeostatic control of iron metabolism is further demonstrated by population data from Norway, suggesting an association between severe iron deficiency and risk of bloodstream infection [5].

In summary, the available evidence suggests that both iron deficiency and iron excess may be harmful for critically ill patients and that clinical assessment of iron status in the ICU is important and should include consideration of both possibilities. The risks related to

* Correspondence: ed.litton@health.wa.gov.au

¹Intensive Care Unit, Fiona Stanley Hospital, Perth, Australia

²School of Medicine, University of Western Australia, Perth, Australia



different iron states and associated iron study patterns are provided in Fig. 1.

The advent of safe and effective intravenous iron preparations provides an opportunity to explore the potential benefits of treating patients diagnosed with functional iron deficiency in the ICU, when enteral iron is ineffective due to the actions of hepcidin. Intravenous iron therapies have largely been investigated in the context of erythropoiesis. There are high quality data that intravenous iron, compared to either oral iron or no iron, significantly decreases anemia and red blood cell (RBC) transfusion requirement in hospitalized patients, albeit with a potential increased risk of infection [6]. The evidence for patients admitted to the ICU is less clear. To date few randomized controlled trials (RCTs) have been conducted in critically ill patients, although a recent multicenter study suggested that intravenous iron is biologically active in this population, increasing hemoglobin without any signal of harm [7].

Whilst much of the focus of iron has been as a treatment for anemia, a risk factor for adverse outcomes in patients admitted to the ICU, non-anemic iron deficiency impairs aerobic metabolism and is associated with reduced maximal oxygen consumption (VO_{2max}), muscle endurance and cognitive performance [8–10]. It is plausible that interventions to address disrupted iron metabolism may have much wider benefit for reducing complications and improving functional recovery after critical illness, independent of erythropoiesis.

The similarities are striking between the pathological consequences of the alterations in iron metabolism during critical illness and many common and characteristic complications, particularly those associated with functional impairment, in patients requiring prolonged ICU admission. Exploring the role of iron dysmetabolism in nosocomial infection and cognitive, neuromuscular and

cardiopulmonary dysfunction may uncover novel therapeutic targets to help to address the substantial public health burden of these conditions in survivors of critical illness.

Iron metabolism and critical illness

Critical illness precipitates an inflammatory response that results in early and profound changes in iron metabolism. An acquired form of iron dysmetabolism can be said to occur when these changes are persistent and contribute to impaired end-organ function. Ferritin, a major repository of intracellular iron, and the iron-binding glycoprotein, lactoferrin, are acute phase reactants and are upregulated in proportion to the severity of the inflammatory response [11]. The higher affinity of ferritin and lactoferrin to bind iron relative to transferrin, the circulating iron transporter and a negative acute phase reactant, results in hypoferremia [11]. This pattern of low serum iron, low transferrin and high ferritin occurs in more than 75% of critically ill patients within 3 days of ICU admission [12, 13]. Akin to the partial uncoupling of intravascular volume status from total body water as a common consequence of ICU treatment in critical illness, total body iron stores may become uncoupled from available and circulating iron.

Although the immediate changes in ferritin and transferrin are initiated directly by cytokines, it is the effect of hepcidin, described as the master regulator of iron, that determines the severity and duration of an iron-restricted state. Hepcidin, a 25-amino acid peptide hormone synthesized predominantly by hepatocytes, is secreted in response to a variety of stimuli including inflammatory cytokines and iron excess. Hepcidin acts by binding to and degrading ferroportin, a cellular iron exporter found in duodenal cells, macrophages and hepatocytes. Increasing hepcidin secretion decreases the

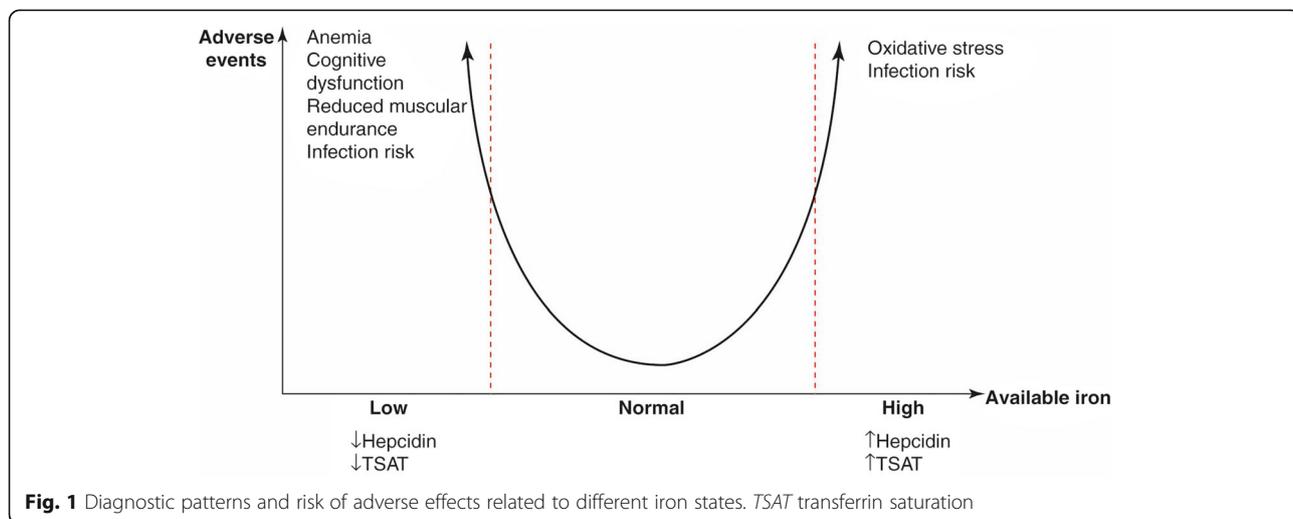


Fig. 1 Diagnostic patterns and risk of adverse effects related to different iron states. *TSAT* transferrin saturation

intestinal absorption of dietary iron, decreases the release of recycled heme iron by macrophages, increases the sequestration of iron stores in hepatocytes and reduces circulating free iron [14].

There are two key clinical consequences of the changes in iron metabolism associated with critical illness. The first is that diagnosis of functional iron deficiency is problematic and cannot be reliably excluded on the basis of standard iron study parameters. The second is that a persistent state of dysmetabolism predisposes a vulnerable population to the consequences of iron-restricted metabolism, a state most commonly considered in the context of erythropoiesis but with important implications for the risk and severity of nosocomial infection and critical illness-associated cognitive, neuromuscular and cardiopulmonary dysfunction.

Diagnosing Iron deficiency

The inflammatory response that occurs in critical illness confounds the interpretation of commonly available assays to diagnose iron deficiency, including ferritin and transferrin. To address this, one approach has been to alter the threshold values of these markers to account for the acute phase response [15]. In patients with anemia requiring long term dialysis, a serum ferritin of < 200 µg/L is highly suggestive of iron deficiency and predicts a good response to intravenous iron, whereas patients with a ferritin of between 500 and 1200 µg/L and a transferrin saturation < 25% may also show an increase in hemoglobin in response to intravenous iron [15]. By applying similar criteria in critical illness, iron-restricted erythropoiesis has been reported to occur in more than a fourth of patients on admission to ICU [16]. However, validation studies against a gold standard of iron deficiency in critically ill patients are lacking and the accuracy of these criteria in predicting response to intravenous iron in this setting remains uncertain. Given the association between high transferrin saturation and adverse outcomes in critically ill patients, it may be that standard measures of iron metabolism are of greater use in identifying patients with potential iron overload, in whom intravenous iron therapy may pose greater risks, than in diagnosing functional iron deficiency per se.

In contrast, serum hepcidin concentration appears to provide a more reliable signal of iron-restricted erythropoiesis, decreasing in concentration with the onset of iron deficiency in patients admitted to the ICU even in the presence of inflammation [17]. In a recent study in critically ill patients with anemia, serum hepcidin concentration, but not ferritin or transferrin saturation, was able to identify patients in whom intravenous iron therapy was effective in reducing RBC transfusion requirement [18]. These findings require validation in further studies but are similar to findings in oncology, where

hepcidin concentration appears to predict response to intravenous iron therapy in patients with chemotherapy-induced anemia [19]. In order for large validation studies to occur, accurate, clinically-available hepcidin assays are required.

A two-stage process may be of value, in which standard iron assays are first used to exclude patients at risk of iron excess and identify clear cases of iron deficiency. For patients not clearly overloaded or deficient, hepcidin concentration is then measured. As the evidence base grows and the role of hepcidin becomes more clearly defined, studies investigating its association with functional outcomes after ICU may also be of substantial interest.

Anemia

Anemia is associated with adverse outcomes and remains the most common indication for RBC transfusion in patients admitted to the ICU, even when adherence to a conservative transfusion threshold is high [20]. Preventing the onset and progression of anemia requires a multifaceted approach adapted to the specific clinical context. Major surgery requiring elective ICU admission represents a large patient cohort where a pre-emptive approach is preferable [21]. Approximately one in three patients scheduled to undergo major surgery is anemic, a potentially modifiable risk for perioperative adverse events, including myocardial infarction, stroke and mortality [22]. A recent international consensus statement recommends routine screening of all patients undergoing surgery with an expected blood loss > 500 mL and consideration of intravenous iron for patients with anemia and evidence of iron deficiency when oral iron is inefficacious, not tolerated or surgery is planned to occur in less than 6 weeks [23]. In contrast, a Cochrane review on the use of preoperative iron therapy to correct anemia identified only three small RCTs and found no significant reduction in allogeneic RBC transfusion requirements [24]. The safety and efficacy of preoperative intravenous iron therapy is now the focus of several ongoing large scale RCTs in cardiac, abdominal and orthopedic surgery. A summary of major completed and ongoing RCTs of preoperative intravenous iron is provided in Table 1.

For patients admitted to the ICU there is some evidence to guide decisions on the use of intravenous iron therapy. A systematic review and meta-analysis on the efficacy of intravenous iron in the treatment of anemia in ICU patients did not demonstrate a significant decrease in anemia or RBC transfusion requirements but only included five relatively small studies [25]. More recently, a multicenter RCT including 140 patients demonstrated that intravenous iron administered within 48 h of ICU admission resulted in a significant increase in hemoglobin concentration at hospital discharge (107 g/L

Table 1 Randomized controlled trials of intravenous (i.v.) iron in major surgery

Study, year [ref], number (n) of patients	Population	Intervention	Outcomes
Kim, 2017 (FAIRY trial) [48] n = 454	Anemia post-radical gastrectomy	500–1000 mg i.v. FCM	Significantly more Hb responders No significant differences in QoL
Johansson, 2015 (PROTECT trial) [49] n = 60	Non-anemic patients undergoing cardiac surgery	100 mg i.v. iron isomaltoside	More non-anemic patients in i.v. iron group Higher Hb 1 month postoperative in i.v. iron group
Bernabeu-Wittel, 2016 [50] n = 306	Hip fracture surgery	1 g i.v. FCM+ 40,000 IU s.c. EPO	Higher Hb at discharge and 60-days post-discharge No significant differences in ABT, mortality, HRQoL, adverse events.
Froessler, 2016 [51] n = 72	Abdominal surgery with IDA	500–1000 mg i.v. FCM	Reduced ABT Improved preoperative Hb Improved postoperative Hb Reduced LOS
Intravenous iron for Treatment of Anemia before Cardiac Surgery (ITACS; ClinicalTrials.gov Identifier: NCT02632760)	Anemic patients before elective cardiac surgery	1 g i.v. FCM (or similar product)	Primary outcome: Number of days alive and out of hospital from surgery to 30 days post-surgery
Preoperative Intravenous Iron to Treat Anemia in Major Surgery (PREVENTT; ClinicalTrials.gov Identifier: NCT01692418)	Anemic patients before major open abdominal surgery	1 g i.v. FCM	Primary outcome: ABT requirement
Intravenous Iron, Functional Recovery and Delirium in Patients with Hip Fracture (FEDEREF; EudraCT: 2014-001923-53)	Hip fracture patients	200 mg iron sucrose on days 1, 3 and 5 from admission	Primary outcome: Functional variables, including ability to perform activities of daily living and walking. Cognitive variables, including cognitive status and incidence of delirium ABT requirement

ABT allogeneic blood transfusion, EPO erythropoietin, FCM ferric carboxymaltose, Hb hemoglobin, HRQoL health-related quality of life, IDA iron-deficiency anemia, LOS length of stay, QoL quality of life, s.c. subcutaneous

vs. 100 g/L, $p = 0.02$) without any infusion-related adverse event, but no difference in RBC transfusion rates, hospital length of stay or mortality [7]. Although these data suggest biological activity, the available evidence is currently insufficient to assess the effect of early intravenous iron administration on patient outcomes, or to exclude increased infection risk.

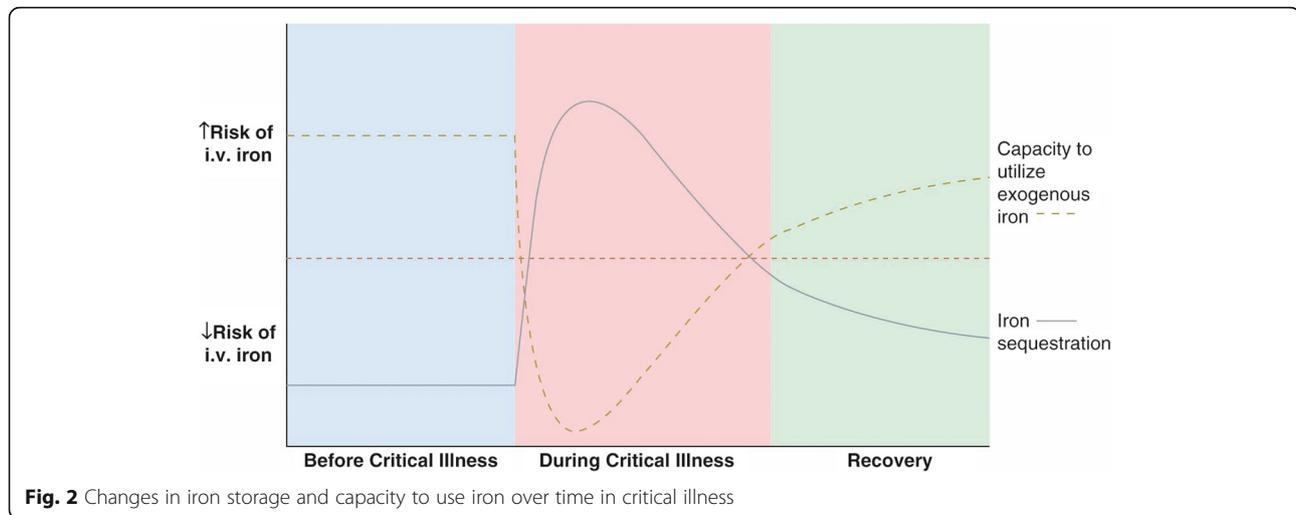
The timing of intravenous iron administration in patients admitted to the ICU may also be a strong determinant of whether the benefits outweigh the risks. The period of greatest physiological stress generally occurs early after ICU admission. The effects of critical illness and related treatments, such as RBC transfusion and catecholamine infusions, increase the risks and also exacerbate the consequences of iron dysmetabolism and excess free iron. A diminished capacity to process exogenous parenteral iron may worsen this situation. In vitro data suggest dose-dependent and formulation-dependent effects of intravenous iron compounds on macrophage handling and the extent of oxidative stress [26]. Early initiation of intravenous iron provides time to develop an erythropoietic response. However, this neglects a wider therapeutic window after the most acute period of critical illness has abated when the risk benefit ratio may be more favorable and addressing the functional outcomes of prolonged ICU admission can be prioritized. The temporal changes in iron metabolism and response

to intravenous iron therapy in critical illness are summarized in Fig. 2.

Cognitive dysfunction

Cognitive dysfunction is common in survivors of critical illness, affecting more than one in four patients and often persisting after physical recovery [27]. The pathophysiology is multifactorial and characterized by new deficits or deterioration of pre-existing mild deficits in global cognition or executive function. However, the underlying causes remain poorly understood and there are no established treatments [27].

Iron is essential for neurotransmitter synthesis, uptake and degradation and is necessary for mitochondrial function in metabolically active brain tissue [28]. Iron deficiency has cerebral and behavioral effects consistent with dopaminergic dysfunction, manifesting as poor inhibitory control and diminished executive and motor function [29]. In both children and pre-menopausal women with non-anemic iron deficiency, iron supplementation is associated with improved mental quality-of-life and cognitive function [9, 30]. Studies on the effects of intravenous iron on cognitive outcomes in patients recovering from critical illness are currently lacking and will need to consider the optimal timing, dose and duration of therapy.



Neuromuscular dysfunction

Critical illness myopathy is a frequent complication of prolonged acute illness, affecting a substantial proportion of patients admitted to ICU. Weakness is often prolonged with many patients experiencing decreased exercise capacity and compromised quality of life years after the acute event [31]. Even in healthy non-anemic subjects, adequate iron status is essential for efficient aerobic capacity [10]. Fatigue is also a significant factor in recovery after critical illness, influencing a patient's ability to engage with rehabilitation. Iron deficiency persisted in more than one in three patients at 6 months after prolonged ICU admission and is associated with increased fatigue independent of anemia [32]. Given the catabolic state conferred by critical illness and role of iron in myoglobin and muscle oxidative metabolism, further evaluation of the relationship between iron deficiency and critical illness myopathy may provide insight into the role of iron supplementation in improving physical recovery after acute severe illness.

Cardiopulmonary dysfunction

Iron is an essential component of structural proteins in cardiomyocytes and an obligate co-factor for hypoxia-inducible factor (HIF), a mediator of the systemic cardiovascular response to hypoxia. As a consequence, iron plays an important role in systolic heart function and hypoxic pulmonary vasoconstriction.

Independent of anemia, iron deficiency is associated with increased risk of death in patients with heart failure [33]. High quality evidence suggests that intravenous iron for patients with systolic heart failure improves exercise capacity, survival and quality of life [34]. Critical illness may impair myocardial iron use through a number of mechanisms including catecholamine-induced downregulation of myocardial transferrin receptor 1

(TfR1) and upregulation of hepcidin [35]. Emerging data also suggest disrupted iron metabolism may be important in various subtypes of pulmonary artery hypertension and that altitude-associated pulmonary artery hypertension is improved by intravenous iron therapy [36]. Pulmonary artery hypertension, and associated right ventricular dysfunction, is common in patients admitted to the ICU with severe acute respiratory distress syndrome (ARDS) and is a poor prognostic indicator [37]. Whether the beneficial effects of intravenous iron for patients with isolated systolic heart failure and pulmonary artery hypertension are translatable to patients being treated in the ICU requires further investigation, but assessment of iron status and potential initiation of iron therapy in patients with severe cardiac failure and markers of iron deficiency should be considered on an individual patient basis.

Infection

The term 'nutritional immunity' describes the changes in iron metabolism of the mammalian host during infection, in which the acute phase response acts to limit the availability of free iron for microbes including invasive fungi and avid iron-binding bacteria [38, 39]. Hereditary iron overload disorders increase the risk and severity of infection with siderophilic bacteria, such as *Vibrio vulnificus* and *Yersinia enterocolitica*, although these bacteria are only moderately pathogenic in other settings [39]. Iron overload not only predisposes to infection from particular organisms, but also then impairs components of the innate immune response including chemotaxis, phagocytosis, lymphocyte and macrophage function [40].

Investigating a potential causal link between iron supplementation and infection risk is complex. The relationship is likely to depend on a large range of factors, including the setting, participant population and

particular iron dosing strategy. For example, oral iron supplementation for children in malaria endemic areas does not appear to increase the risk of malaria overall, but may increase the risk where malaria prevention strategies are unavailable and decrease the risk where they are available [41]. Although an increased risk of infection has been suggested in a systematic review of RCTs investigating hospitalized patients treated with intravenous iron, infection was only reported in a minority of trials and the risk, including in critically ill patients, remains uncertain [6]. A RCT of intravenous iron sucrose compared with oral iron in patients with chronic kidney disease was stopped early due to increased serious adverse events, including infection requiring hospitalization, in the intravenous iron group [42]. On the other hand a RCT of intravenous ferric carboxymaltose for patients with cardiac failure demonstrated improved functional capacity and quality of life with no significant between-group differences in serious adverse events, including infection [43]. These contrasting findings demonstrate the need for context-specific assessment of infection risk and the potential for dose and formulation-dependent differences [26]. For patients admitted to the ICU, it is plausible that the risk of infection related to parenteral supplementation is not uniform, but may vary between patients and within a patient over time (see Fig. 2).

Whilst uncertainty regarding the risk of infection may still limit widespread use of intravenous iron in the acute phase of critical illness, the relationship between changes in iron metabolism and infection also provides therapeutic opportunities. Nosocomial infection remains a major source of morbidity in patients admitted to the ICU. Oral supplementation with the iron-binding glycoprotein, lactoferrin, appears to reduce nosocomial infection in preterm infants, although the results of large studies are awaited; results have not been replicated in the adult ICU setting [44, 45].

Other potential therapeutic targets of iron metabolism exist or are in development that may also be of relevance to reducing nosocomial infection. For example, the nutritional immunity conferred by reducing iron availability during infection is mediated by hepcidin, secreted in response to inflammatory mediators. However, inhibitors of hepcidin secretion, including anemia and hypoxia, may exert a counterbalancing effect in critically ill patients resulting in relative hepcidin deficiency and increased free iron available for invading microbes. For critically ill patients with early sepsis and low hepcidin concentrations, hepcidin agonists currently in development may attenuate the severity of the infective insult [46]. Likewise, iron chelators are known to be synergistic with some antifungal therapies in managing a range of fungal infections and may be beneficial in the prevention and treatment of nosocomial infections [47].

Conclusion

Iron deficiency is common in the general population and likely to be over-represented in patients admitted to the ICU. Critical illness exacerbates this situation by initiating a form of functional iron deficiency in which iron absorption and recycling is diminished and stored iron is less accessible for use. Although there may be beneficial short-term effects from this process by conferring a form of nutritional immunity against invading microbes, there are also risks. Homeostatic control of iron may be lost leading to the risk of iron excess, as suggested by emerging evidence that high transferrin saturation is a poor prognostic marker early after ICU admission. Perhaps most importantly, whether or not critical illness is initiated by an infection, it is often prolonged. Persistent functional iron deficiency may lead to iron dysmetabolism in which reduced iron availability contributes to impaired end-organ function.

The reduced availability of iron in critical illness is often considered in the context of anemia, but the consequences are much broader than this and overlap extensively with many of the issues faced by ICU survivors. Correction of non-anemic iron deficiency improves cognitive and cardiopulmonary dysfunction and aerobic performance and reduces fatigue. Recent data suggest that hepcidin measurement may be useful in targeting intravenous iron therapy at those most likely to benefit. For patients requiring prolonged ICU admission, considering iron dysmetabolism may be of substantial therapeutic benefit in improving functional recovery after critical illness.

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Consent for publication

Not applicable.

Competing interests

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