Commentary

Role of iron in anaemic critically ill patients: it's time to investigate!

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Abstract

Anaemia is a common problem in critically ill patients admitted to intensive care units. Many factors can be involved in its development, including rapid alterations in iron metabolism. Maintenance of iron homeostasis is a prerequisite for many essential biological processes and is a central element for the development of erythroid precursors and mature red blood cells. With the inflammatory process, iron distribution is disturbed, with decreased serum iron levels and increased iron stores. Little information is available on the precise role of alterations in iron metabolism in the development of iron anaemia in critically ill patients.

Keywords anaemia, erythropoietin, iron, red blood cell

Anaemia is a major cause of morbidity and mortality worldwide and is often observed in critically ill patients, not just at admission but particularly during intensive care unit (ICU) stay [1]. The time course of anaemia during an ICU stay depends on the underlying pathologies [1], but at least a third of ICU patients receive a transfusion at some point during their ICU stay [2,3]. The rationale behind blood transfusion is to restore oxygen delivery and provide a reserve should further bleeding occur. Several recent studies have modified transfusion practice, in terms of the level of pretransfusion haemoglobin concentration [3] and in view of the adverse effects of blood transfusion, including haemodynamic and immunomodulatory effects, and transmission of micro-organisms [2,3].

The aetiology of anaemia is often multifactorial, including overt or occult blood loss (e.g. resulting from frequent blood sampling or surgical procedures), haemodilution, reduced red blood cell (RBC) production caused by decreased synthesis of endogenous erythropoietin (EPO), and probably also reduced RBC lifespan due to increased uptake by the reticuloendothelial system [4,5]. Alteration in iron metabolism plays a central role in the development of anaemia [6]. The majority of the body's iron content is incorporated into haemoglobin in developing erythroid precursors and mature RBCs, but this process is rapidly altered with the acute phase reaction. Typically, the inflammatory process is associated with low concentrations of serum iron, high ferritin (the protein responsible for iron storage), and low transferrin (the principal iron transporting glycoprotein) [7]. The underlying mechanisms are very complex and not well understood, although the final teleological aim is primarily to deprive bacteria of nutritionally required iron. In fact, in just a few hours, proinflammatory and anti-inflammatory cytokines cause a decrease in the iron level in blood.

Proinflammatory cytokines such as tumour necrosis factor-α, IL-1β and IL-6 induce the transcription and the translation of ferritin; modulate the binding affinity of cytoplasmic iron regulatory protein (IRP)-1 and IRP-2, which contain iron-responsive elements; and rapidly decrease the mRNA expression of transferrin receptor [8]. Interferon-γ stimulates

EPO = erythropoietin; ICU = intensive care unit; IL = interleukin; IRP = iron regulatory protein; RBC = red blood cell.

iron absorption by enterocytes via the divalent metal transporter-1, but it has an inhibitory effect on ferroprotein – another enterocyte protein that transfers oxidized iron into the circulation. These alterations result in increased iron storage in enterocytes [9]. Anti-inflammatory cytokines such as IL-4, IL-10 and IL-13 induce haem oxygenase-1 expression to promote haem degradation and iron storage in monocytes and thereby contribute to iron storage in the reticulo-endothelial system [10]. Nitric oxide reduces RBC production by stimulating IRP and reducing ferrochelatase activity, which inhibits the final step in heme synthesis [11].

In the present issue of *Critical Care*, Darveau and coworkers [12] review the literature on iron supplementation in anaemic critically ill patients. That article reveals the lack of studies evaluating alterations in iron metabolism in ICU patients. Darveau and coworkers [12] also provide a summary of studies using EPO therapy, the rationale behind this strategy in anaemic ICU patients being that EPO levels are inappropriately low [6] as a result of the effects of proinflammatory cytokines (interferon-γ, tumour necrosis factor-α, IL-1) that inhibit EPO receptors on erythroid progenitor cells. In randomized, double-bind, placebo-controlled studies, Corwin and coworkers [13,14] demonstrated the safety of EPO treatment plus iron administration and the resulting decrease in number of RBC transfusions needed, but regrettably they reported no effects on outcome in terms of ICU infection rates or mortality. Only one study [15] compared the effect of iron administration (20 mg/day intravenously) with that of treatment with EPO (300 mg subcutaneously on days 1, 3, 5, 7 and 9) and iron. Surprisingly, in that study the reticulocyte count increased significantly at day 6 in the EPO-treated group as compared with the iron and control groups, but it rapidly decreased thereafter, with no apparent difference between groups at day 18. Moreover, there were no differences in ICU length of stay or the total number of RBC transfusions after 3 weeks between the iron and EPO groups. Although the number of patients was limited, this is probably the only study comparing iron administration and EPO therapy in the ICU. Importantly, both treatments have possible side effects: for EPO treatment, anti-EPO antibodies with severe aplasia [16], transient alterations in RBC rheology [17] and anaemia secondary to cessation of intensive treatment [18]; and for iron administration, anaphylactoid reactions with increased risk for infection [7].

As highlighted by Darveau and coworkers [12], before supplementing critically ill patients with iron we need additional studies to investigate and better define the role played by iron, including the place of primordial regulators of iron metabolism such as hepcidin and transferrin receptor [19,20], in the development of anaemia in this population.

Competing interests

The authors declare that they have no competing interests.

References

1. Nguyen Ba V, Peres Bota D, Melot C, Vincent JL: **Time course of hemoglobin concentrations in non-bleeding ICU patients.** *Crit Care Med* 2003, **31:**406-410.
2. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D: **Anemia and blood transfusion in critically ill patients.** *JAMA* 2002, **288:**1499-1507.
3. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: **A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care.** *N Engl J Med* 1999, **340:**409-417.
4. Piagnerelli M, Boudjeltia KZ, Vanhaeverbeek M, Vincent JL: **Red blood cell rheology in sepsis.** *Intensive Care Med* 2003, **29:** 1052-1061.
5. Piagnerelli M, Zouaoui Boudjeltia K, Brohee D, Piro P, Carlier E, Vincent JL, Lejeune P: **Alterations of red blood cell shape and sialic acid membrane content in septic patients.** *Crit Care Med* 2003, **31:**1052-1061.
6. Rogiers P, Zhang H, Leeman M, Nagler J, Neels H, Mélot C, Vincent JL: **Erythropoietin response is blunted in critically ill patients.** *Intensive Care Med* 1997, **23:**159-162.
7. Patruta SI, Horl WH: **Iron and infection.** *Kidney Int Suppl* 1999, **69:**S125-S130.
8. Rogers JT: **Ferritin translation by interleukin-1and interleukin-6: the role of sequences upstream of the start codons of the heavy and light subunit genes.** *Blood* 1996, **87:**2525-2537.
9. Ludwiczek S, Aigner E, Theurl I, Weiss G: **Cytokine-mediated regulation of iron transport in human monocytic cells.** *Blood* 2003, **101:**4148-4154.
10. Lee TS, Chau LY: **Heme oxygenase-1 mediates the anti-inflammatory effect of interleukin-10 in mice.** *Nat Med* 2002, **8:** 240-246.
11. Rafferty SP, Domachowske JB, Malech HL: **Inhibition of hemoglobin expression by heterologous production of nitric oxide synthase in the K562 erythroleukemic cell line.** *Blood* 1996, **88:**1070-1078.
12. Darveau M, Denault AY, Blais N, Notebaert E: **Bench-to-bedside review: Iron metabolism in critically ill patients.** *Crit Care* 2004, **8:**356-362.
13. Corwin HL, Gettinger A, Rodriguez RM, Pearl RG, Gubler KD, Enny C, Colton T, Corwin MJ: **Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial.** *Crit Care Med* 1999, **27:** 2346-2350.
14. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ, Corwin MJ, Colton T: **Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial.** *JAMA* 2002, **288:**2827-2835.
15. van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A: **Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients.** *Crit Care Med* 2000, **28:**2773-2778.
16. Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, Michaud P, Papo T, Ugo V, Teyssandier I, Varet B, Mayeux P: **Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin.** *N Engl J Med* 2002, **346:**469-475.
17. Bor-Kucukatay M, Yalcin O, Meiselman HJ, Baskurt OK: **Erythropoietin-induced rheological changes of rat erythrocytes.** *Br J Haematol* 2000, **110:**82-88.
18. Piron M, Loo M, Gothot A, Tassin F, Fillet G, Beguin Y: **Cessation of intensive treatment with recombinant human erythropoietin is followed by secondary anemia.** *Blood* 2001, **97:**442-448.
19. Ganz T: **Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation.** *Blood* 2003, **102:**783-788.
20. Fillet G, Beguin Y: **Monitoring of erythropoiesis by the serum transferrin receptor and erythropoietin.** *Acta Clin Belg* 2001, **56:**146-154.

Review

Bench-to-bedside review: Iron metabolism in critically ill patients

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Abstract

Critically ill patients frequently develop anemia due to several factors. Iron-withholding mechanisms caused by inflammation contribute to this anemia. The iron metabolism imbalances described or reported in all intensive care studies are similar to the values observed in anemia of inflammation. The administration of iron could be useful in the optimization of recombinant human erythropoietin activity, but this could be at the expense of bacterial proliferation. Since there is a lack of evidence to support either oral or intravenous iron administration in intensive care patients, further studies are necessary to determine the efficacy and safety of iron supplementation in conjunction with recombinant human erythropoietin in critically ill patients. We review the mechanisms leading to iron sequestration in the presence of inflammation. The present article also reviews the literature describing the iron status in critically ill patients and explores the role of iron supplementation in this setting.

Keywords critical illness, erythropoiesis, iron metabolism

Introduction

Recent observational studies have shown that most patients in the intensive care unit (ICU) become anemic within a few days [1–3]. In Europe, approximately 37% of patients receive transfusions and just over 70% of those remaining in the ICU for longer than 7 days are transfused [1]. The CRIT Study showed similar results in the United States [2]. A number of factors contribute to this anemia, including the acute inflammatory reaction typical of these patients [3,4]. Anemia of inflammation has been clearly described in patients with cancer, with chronic inflammatory disease and with chronic infection [5–10]. This type of anemia is related to the release of mediators that cause a blunted erythropoietic response and an activation of red blood cell catabolism by macrophages. The inflammatory state also results in decreased mobilization of iron stores from the reticuloendothelial system, leading to the development and persistence of anemia [5–10].

Special attention has been paid in recent years to limiting the number of transfusions received by ICU patients. Limiting blood collection [1] and restrictive transfusion thresholds [11] are among the strategies that have been adopted for blood conservation. Although the optimal dose of recombinant human erythropoietin (rHuEPO) in the intensive care setting has yet to be determined, its use constitutes another blood conservation strategy [12,13]. Erythropoietin's ability to stimulate erythrocyte production is highly dependent on the availability of iron. Understanding iron metabolism in this patient population is important in order to act on the mechanisms of and the causes of anemia in critically ill patients. The decrease in iron availability seen in inflammatory diseases may contribute to inadequate erythropoiesis in ICU patients.

Is the iron metabolism imbalance seen in chronic inflammatory states similar to that found in ICU patients? To

APACHE = Acute Physiology and Chronic Health Evaluation; FID = functional iron deficiency; ICU = intensive care unit; IL = interleukin; IV = intravenous; rHuEPO = recombinant human erythropoietin.

what extent do these disturbances affect erythropoiesis and the patient's response to exogenous erythropoietin? Should iron supplements be administered? The purpose of the present article is to review the impact of inflammation on iron status and to review the studies that describe iron metabolism in ICU patients. We also explore the role of iron supplementation in this setting.

Iron-withholding mechanisms in the presence of inflammation

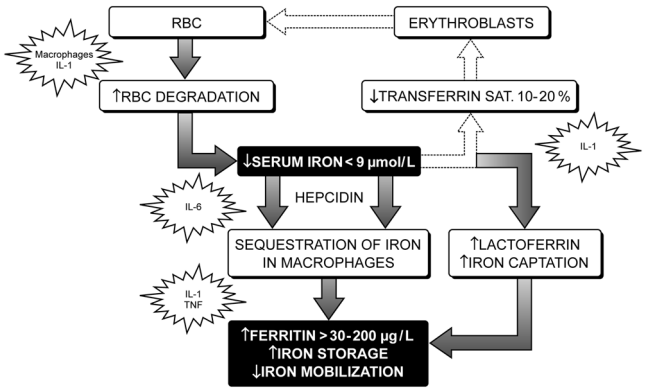
Most of the iron available for erythropoiesis comes from the catabolism of senescent red blood cells by the macrophages in the reticuloendothelial system [6–10]. The iron, transported by transferrin, binds to receptors on the surface of the erythroblasts and is used in hemoglobin synthesis [6–10]. The iron also binds to apoferritin to produce iron stored in the form of ferritin. Under normal conditions, there is a balance between the iron transport paths and the iron stores [6–10].

Ferritin is an inflammatory protein (acute-phase reactant). The synthesis of ferritin is increased by circulating cytokines such as IL-1 and tumor necrosis factor. When these inflammation mediators are present, iron stored in the form of ferritin tends to increase and the mobilization of iron stored from the reticuloendothelial system tends to decrease. The balance between the amount of iron available for erythropoiesis and the stored iron is disturbed (Fig. 1) [6–10]. Hypoferremia rapidly sets in due to an increase in the iron-binding capacity of ferritin, to the detriment of transferrin. The severity of the hypoferremia depends on the severity of the underlying inflammatory disease [6].

IL-1 also stimulates lactoferrin synthesis. Lactoferrin is a circulating protein that binds iron with greater affinity than transferrin [6,7,9]. In the presence of inflammation, iron bound to lactoferrin is captured by the macrophages and is then stored in the form of ferritin, thereby withholding iron from the erythroid precursors (Fig. 1) [6,7,9]. The recent demonstration that a novel protein, hepcidin, is greatly upregulated in response to inflammation via IL-6 is yet another potential mechanism of iron sequestration [14]. Hepcidin could be a central mediator of decreased iron absorption through the gut and of sequestration of iron in macrophages, and its structure has also shown homology to naturally occurring antimicrobial proteins [14]. Changes related to inflammation therefore lead to less iron bound to transferrin and to less iron available for erythropoiesis [6–10]. This process has been hypothesized to have evolved as a 'tug-of-war' phenomenon resulting in an iron-deficient milieu that would lead to compromised microorganism proliferation (Fig. 1) [7,9].

Overall, these mechanisms result in a decrease in serum iron <9 μmol/l, in a decrease in transferrin levels <3 g/l and in a decrease in the transferrin saturation percentage between 10% and 20%, with normal or elevated ferritin levels

Figure 1



Decrease in iron recycling in the presence of inflammation: iron metabolism in critically ill patients. Most of the iron available for erythropoiesis comes from the catabolism of senescent red blood cells (RBC) by the macrophages in the reticuloendothelial system. Under normal conditions, there is a balance between the iron transport paths and the iron stores: serum iron, 9–27 μmol/l; transferrin, 3–6 g/l; transferrin saturation (sat.), 30–50%; ferritin, 50–150 μg/l. In the presence of inflammation, the synthesis of ferritin is increased by IL-1 and by tumor necrosis factor (TNF). Hypoferremia rapidly sets in due to an increase in the iron-binding capacity of ferritin to the detriment of transferrin. IL-l also stimulates lactoferrin synthesis. Iron bound to lactoferrin is captured by the macrophages and is stored in the form of ferritin. Hepcidin could be a central mediator of iron sequestration in macrophages. Grey arrows, pathways increased by inflammation; broken arrows, pathways decreased by inflammation.

>300 μg/l [8,10]. Elevated ferritin levels in inflammatory states make it difficult to evaluate iron stores. However, a patient presenting with a ferritin concentration >200 μg/l probably does not have an iron deficiency, whereas a value <30 μg/l does indicate iron deficiency (ferritin levels between 30 and 200 μg/l in inflammatory conditions) [6,10].

In contrast with these iron-deprivation mechanisms, it seems that iron deficiency could impair immune defense. Little evidence is available on iron and its effects on direct immunity. However, *in vitro* studies have suggested that iron deficiency depresses some aspects of cell-mediated immunity [15]. In a review of the literature, Oppenheimer reported deleterious effects of iron deficiency on lymphocyte, neutrophil and macrophage function [15]. Whether these effects depend on the severity of iron deficiency is not known. Not only iron deficiency but also iron overload seems to impair polymorphonuclear leucocyte function, reducing phagocytic function and bacterial killing [16]. Data regarding iron and its effect on the immune system are conflicting. More studies are needed to clearly elucidate the role of iron on immunity.

Iron metabolism in ICU patients

Inflammation is implicated in many critically ill disorders. Indeed, clinical evidence of systemic inflammation is present

Table 1

Studies describing iron metabolism in intensive care unit (ICU) patients

Study	Time of measurement	Iron (μmol/l)	Ferritin (μg/l)	Transferrin saturation (%)	Transferrin (g/l)
Reference value with inflammation [8,10]		< 9	30–200	10–20	< 3
Surgical ICU patients [18]	Week 1	4.1	652	12.8	1.7
	Week 2	4.1	1234	11.9	1.5
	Week 3	4.6	1536	13.4	1.4
	Week 4	6.9	1367	18.7	1.4
Medical ICU patients ≥ 4 days [3]	Days 1–2	4.8[a]	471[a,b]	16[a]	1.4[a,c]
	Days 6–8	6.0[a]	767[a,b]	15[a]	1.3[a,c]
	Days 13–15	6.5[a]	795[a,b]	22[a]	1.3[a,c]
	Days 20–25	8.1[a]	774[a,b]	24[a]	1.4[a,c]
	Days 31–40	7.8[a]	723[a,b]	20[a]	1.5[a,c]
Medical and surgical ICU patients [19]	Days 2–3	4.9[d]	727[b]	16	Not reported
General ICU patients [21]					
Functional iron deficiency	Day 1	Not reported	342	Not reported	Not reported
No functional iron deficiency	Day 1	Not reported	292	Not reported	Not reported
Multiple mechanical trauma patients [20]	Day 1	9.5	832	Not reported	1.7[c]
	Day 2	3.9	547	Not reported	1.7[c]
	Day 4	3.4	466	Not reported	1.5[c]
	Day 6	4.0	530	Not reported	1.6[c]
	Day 9	5.0	842	Not reported	1.6[c]

Data presented as mean values, except [a] median values. [b] Ferritin (ng/ml or μg/ml). [c] Transferrin (mg/dl) multiplied by 0.01 to convert to transferrin (g/l). [d] Iron (μg/dl) multiplied by 0.1791 to convert to iron (μmol/l).

in almost all patients developing multiple organ dysfunction syndrome, a common complication observed in critically ill patients [17]. The severity of the host inflammatory response is highly related to the development of multiple organ dysfunction syndrome and is frequently seen in patients with sepsis. The anemia of inflammation is a hypoproliferative anemia defined by a low serum or plasma iron concentration in the presence of adequate reticuloendothelial iron stores [5]. It is possible that iron metabolism involved in the anemia of chronic disease is similar to the anemia seen in critically ill patients because of the presence of inflammatory mediators in both conditions.

To describe iron metabolism in critically ill patients, a search was performed on the MEDLINE database from 1966 to December 2004 for articles describing iron metabolism in adult critically ill patients. The term 'critical illness' was combined with the terms 'iron', 'erythropoiesis' and 'anemia'. All English-language articles describing iron metabolism in the ICU setting were retained. The bibliographies of these articles were reviewed for additional references. Five observational studies described iron metabolism in ICU patients [3,18–21], and one study provided indicators of iron status [22]. All studies described iron metabolism in a population of nonbleeding, acutely ill patients. Studies on iron metabolism mediators are summarized in Table 1.

Two studies described iron metabolism throughout the ICU stay [3,18]. The earliest of these described the iron status in critically ill surgical patients. In 1989, in a study involving 51 patients, Bobbio-Pallavicini and colleagues observed a decrease in serum iron and elevated ferritin levels in more than 75% of patients on their third day of hospitalization in the surgical ICU [18]. Table 1 presents the variations in iron metabolism indicators during intensive care for all patients. Ferritin values remained abnormally elevated among all patients during their stay in the ICU. Patients with sepsis leading to multiple organ dysfunction syndrome had the highest ferritin values. Indeed, among patients who developed postoperative sepsis, there was a significant drop in hemoglobin (107.3 g/l versus 125.7 g/l, $P < 0.001$), a significant increase in ferritin levels (1585 μg/l versus 641 μg/l, $P < 0.001$) and a significant decrease in transferrin (1.44 g/l versus 1.95 g/l, $P < 0.001$) compared with their

presepsis state. However, sepsis did not significantly affect serum iron levels. When sepsis resolved, the transferrin and hemoglobin values increased. Ferritin decreased dramatically with sepsis resolution (1585 μg/l versus 472 μg/l, $P < 0.001$).

The incidence, severity, characteristics and causes of anemia in 96 patients who had been in a medical ICU for longer than 3 days were assessed in the second study [3]. Fifteen percent of the patients experienced acute bleeding, and 39% of the patients were transfused during their stay in the ICU. While they were in the ICU, 71 patients (74%) developed anemia (hemoglobin < 110 g/l) that could not be explained by blood loss alone. Elevated ferritin values and decreased transferrin saturation values were observed in these patients (Table 1). During the first 2 weeks of the ICU stay, more than 50% of patients had abnormal serum iron concentrations. These values continued to be observed for longer than 4 weeks, as reported in the study performed by Bobbio-Pallavicini and colleagues [18]. Increased iron sequestration secondary to inflammation could explain the increased ferritin levels and the reduced serum iron concentration and transferrin saturation observed in these studies.

Two other studies in critically ill patients reported their observations on iron metabolism on the first few days of admission [19,22]. Rodriguez and colleagues present iron metabolism values for patients with hematocrit < 38% on the second or third day in the ICU [19]. These values come from screening data for a study comparing rHuEPO administration with placebo in surgical and medical ICU patients [23]. Of the 184 patients screened for this study, 16 had transferrin saturation < 15% or ferritin < 50 μg/l and were not included. Eight patients had a vitamin B_{12} deficit or a folate deficit and were also excluded. The remaining 160 patients were included. The admitting diagnoses were pneumonia (24%), respiratory diseases (21%) and trauma (15%). The values for serum iron, ferritin and transferrin saturation for the 160 patients are comparable with values seen in anemia of inflammation, and are presented in Table 1. The mean hemoglobin at the beginning of the study was 103 ± 12 g/l. Although these values were measured at baseline, prior to the administration of the first dose of study medication, this study was not designed to study iron metabolism in consecutive patients.

The second study, conducted by Elliot and colleagues, reported iron metabolism abnormalities in 25 ICU patients with acute failure of at least one organ [22]. Patients with chronic renal failure, coagulopathy or active bleeding were excluded. In the majority of patients in the ICU for longer than 12 hours, they found decreased mean serum iron levels (1.0–12.6 μmol/l), increased mean ferritin levels (37–2376 μg/l) and decreased mean transferrin levels (0.57–2.46 g/l). Ferritin values were abnormally elevated (> 300 μg/l) in 16 patients and were greater than 1000 μg/l in three patients. Iron metabolism imbalances set in fairly quickly after ICU admission, along with the inflammatory process reflected by the increased concentrations of IL-6 and C-reactive protein. The mean hemoglobin at admission was between 80 and 110 g/l.

The anemia observed in the studies of Rodriguez and colleagues and of Elliot and colleagues was not secondary to active bleeding or coagulopathy because these etiologies were exclusion criteria [19,22]. However, an abnormal iron metabolism could have contributed to this disorder. Mean values are not reported in the study of Elliot *et al.* and therefore are not presented in Table 1. It should be noted that the patients in this observational study received a daily 200 mg supplement of oral ferrous sulfate (or equivalent) that may have affected the results.

Finally, patients admitted to the ICU for multiple trauma also seem to quickly develop hypoferremia secondary to inflammation. Iron metabolism in 23 severely traumatized patients was evaluated by Hobisch-Hagen and colleagues [20]. On admission to the ICU, they presented with an average hemoglobin level of 100 g/l (68–129 g/l). Twelve hours after admission to the ICU, ferritin levels were markedly elevated (> 300 μg/l). The elevated levels persisted beyond 1 week. Reduced serum iron concentrations on the second day of hospitalization were statistically significant, compared with admission, and remained lower for longer than 1 week. Serum transferrin was low and did not change during the ICU stay. Indicators of iron status for this study are presented in Table 1 and are compatible with iron parameters usually seen in the presence of inflammation.

In summary, these observational studies all demonstrate that critically ill patients present a decrease in the availability of iron along with an elevation of ferritin levels. In light of the data presented, iron metabolism in ICU patients seems to behave in the same way as it does in chronic inflammatory disease. The iron metabolism imbalances described or reported in all of the studies are similar to the values observed in anemia of inflammation. Indeed, elevated ferritin > 300 μg/l, serum iron < 9 μmol/l, transferrin saturation between 10% and 20%, and transferrin levels < 3 g/l are generally observed in critically ill patients (Table 1). Iron metabolism disorders set in within the first few days. Ferritin remained at particularly elevated levels throughout the ICU stay, reflecting the inflammatory condition of these patients. Iron metabolism disorders therefore probably contribute to the anemia observed in ICU patients.

Functional iron deficiency

Patients with anemia of inflammation, unlike iron deficiency anemia, may have normal iron stores but might present a functional iron deficiency (FID). FID refers to the inability to use iron efficiently for erythropoiesis, in spite of adequate iron stores. FID may develop with rHuEPO therapy and might be a cause of poor response. FID is observed in chronic dialysis patients receiving rHuEPO. The increased erythropoiesis

activity induced by rHuEPO exceeds the amount of functional iron available. FID may also occur in inflammatory conditions when the iron is locked away and stored by the reticuloendothelial system, preventing the release of the iron required for erythropoiesis. A decrease in transferrin saturation will occur in spite of normal or elevated ferritin.

FID has been defined by the presence of more than 10% hypochromic red blood cells. An observational study on the prevalence of FID on admission to the ICU for 51 patients was conducted by Patteril and colleagues [21]. A patient in that study was considered to have a FID if more than 10% of the red blood cells were hypochromic. Upon admission to the ICU, 35% of patients (95% confidence interval, 22–48%) presented FID. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II scores of patients with and without FID were comparable. Anemia was no more severe among patients with FID than in those without FID (average hemoglobin concentration, 107 g/l versus 108 g/l, respectively). The mean length of stay in the ICU was statistically increased among patients with FID (7.6 days versus 3.3 days, $P < 0.0007$). The severity of FID also correlated with the duration of the ICU stay.

FID could thus reflect the severity of the critical illness. However, FID was not associated with APACHE II scores and no difference in the mortality was observed between the two groups. This could of course be due to a lack of power, and further studies are needed to determine whether FID in critically ill patients is simply a marker of nutritional status or is a predictor for outcome. Iron stores are difficult to evaluate in the presence of inflammation because ferritin is frequently increased. The ferritin values of both groups of patients are presented in Table 1.

Should we supplement critically ill anemic patients with iron?

Considering the physiopathology of the anemia of inflammation, it is unlikely that iron supplementation would further stimulate erythropoiesis unless iron deficiency is masked by elevated ferritin levels [6,7]. Only one randomized open-label prospective study evaluated erythropoietic response to the administration of iron supplementation in anemic critically ill patients [24]. In this study, all patients (36 patients) received 1 mg folic acid daily. One-third of the patients received no additional therapy. The iron group (12 patients) received 20 mg intravenous (IV) iron supplementation daily for 14 days. The rHuEPO group (12 patients) received IV iron with 300 U/kg rHuEPO every 2 days for 14 days. Compared with the levels in the other two groups, the elevation in reticulocyte counts was statistically significant only in the rHuEPO group. Reticulocyte counts increased in the rHuEPO group from $56 \pm 33 \times 10^9$/l to a maximum of $189 \pm 97 \times 10^9$/l on day 13. No such increase was seen in the iron group. No significant difference was observed between the three groups in terms of hemoglobin concentration.

Iron supplementation with rHuEPO

Administration of rHuEPO generally makes it possible to alleviate anemia secondary to chronic inflammatory disease. A few studies have shown that rHuEPO administration also stimulates erythropoiesis in ICU patients with acute inflammatory states [12,13]. A large-scale study recently demonstrated that rHuEPO together with oral iron supplementation reduced the need for blood transfusions in ICU patients [13]. The amplification of erythropoiesis that results from the administration of rHuEPO increases the need for iron. Consequently, rHuEPO must be used in conjunction with an iron supplement to optimize the eryhropoietic response and to prevent FID. Given the high prevalence of FID in ICU patients [21], it would appear essential to provide iron supplementation for critically ill patients receiving rHuEPO.

Oral supplementation such as that used recently by Corwin and colleagues [13] may not be optimal for all ICU patients because the gastrointestinal tract is not always functional and iron absorption is poor and erratic. Moreover, decreased iron gut absorption by increased hepcidin production and other mechanisms (particularly related to the underlying condition of the patient) may predispose to inadequacy of oral iron therapy. Nevertheless, a significant reduction in transfusion needs was shown in their study [13].

Whether iron supplementation is necessary in these patients or whether the response might have been improved with IV iron remain to be determined. Iron supplementation clearly improves the response to rHuEPO. It has been shown that IV iron administration with rHuEPO is beneficial for many dialysis patients and has become standard therapy for several patients [25]. Furthermore, administering an IV iron supplement with rHuEPO could make it possible to optimize the erythropoietic response in inflammatory states, as demonstrated in patients with rheumatoid arthritis [26] and in patients with Crohn disease [27]. IV iron supplementation in the ICU setting may prove hazardous, however, given the hemodynamic adverse effects that are possible with certain formulations of parenteral iron and the risk to promote the growth of bacteria.

Iron supplementation and risk of infection

Iron is an essential component of bacterial growth [9,28]. Iron sequestration during inflammation could represent a defense mechanism [9,28]. However, iron chelation with siderophores allows bacterial proliferation in a reduced-iron environment [9,28]. Iron administration could therefore, in theory, increase the host susceptibility for bacterial infections.

No data on critically ill patients are available to support such a hypothesis. The EPIBACDIAL study, performed in 988 patients with chronic renal failure requiring hemodialysis, did not observe a relationship between iron administration and bacteremia (54.0% in those supplemented with iron versus 52.9% in those without, $P = 0.88$) [29]. The data from the

EPIBACDIAL trial were revised by Hoen and colleagues to evaluate the potential role of IV iron administration on the risk of bacteremia [30]. High-frequency iron administration and high-dose IV iron administration could be associated with an increased incidence of bacteremia. The incidence also increased if the patients were given rHuEPO (relative risk, 5.5; 95% confidence interval, 1.29–23.5). These data from chronic renal failure patients could suggest a link between IV iron administration and infection. IV iron administration to ICU patients who are already infected could therefore be risky.

In the Corwin and colleagues' study, oral iron supplementation was given with rHuEPO to all patients [13]. If oral iron was not tolerated, patients received IV iron supplementation. Despite the fact that oral iron administration did not appear to produce deleterious effects in the Corwin and colleagues' study, the safety of iron administration should be further investigated before a widespread utilization of iron replacement occurs in the ICU.

Conclusion

Six studies have so far described iron metabolism in critically ill patients. A decrease in the availability of iron is generally observed, along with elevated ferritin levels. In these patients, iron metabolism is similar to that found in inflammatory diseases and may contribute to the anemia observed in ICU patients. Iron deficiency is difficult to evaluate in the presence of inflammation. Future studies using a novel approach based on hematologic indices would be useful [31]. Additional studies are necessary to determine the utility of iron supplementation alone in critically ill patients.

At the present time, there is a lack of evidence to support either oral or IV iron administration in critically ill patients. Further studies are needed to determine the safety of iron supplementation in ICU patients, especially the link between iron and clinical infectious risk. A large randomized study comparing IV iron supplementation, oral iron supplementation and no iron supplementation in rHuEPO-treated critically ill patients would be of interest.

Competing interests

MD, AYD and EN received financial support for research from Ortho-Biotech. NB has none to declare.

References

1. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D: **Anemia and blood transfusion in critically ill patients.** *JAMA* 2002, **288:**1499-1507.
2. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot M, Duh MS, Shapiro MJ: **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.
3. von Ahsen N, Müller C, Serke S, Frei U, Eckardt KU: **Important role of nondiagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients.** *Crit Care Med* 1999, **27:**2630-2639.
4. Ba VN, Bota DP, Mélot C, Vincent J: **Time course of hemoglobin concentrations in non bleeding intensive care unit patients.** *Crit Care Med* 2003, **31:**406-410.
5. Means RT: **Recent developments in the anemia of chronic disease.** *Curr Hematol Rep* 2003, **2:**116-121.
6. Means RT: **The anemia of chronic disorders.** In *Wintrobe's Clinical Hematology*. Edited by Lee GR, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM. Baltimore, Maryland: Williams & Wilkins; 1999:1011-1021.
7. Sears DA: **Anemia of chronic disease.** *Med Clin North Am* 1992, **76:**567-579.
8. Adamson JW: **Iron deficiency and other hypoproliferative anemias.** In *Harrison's Principles of Internal Medicine*. Edited by Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. New York: McGraw-Hill; 2001:660-666.
9. Jurado RL: **Iron, infections, and anemia of inflammation.** *Clin Infect Dis* 1997, **25:**888-895.
10. Hillman RS: **Iron deficiency and other hypoproliferative anemias.** In *Harrison's Principles of Internal Medicine*. Edited by Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL, Longo DL. New York: McGraw-Hill; 1998:638-645.
11. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Scheitzer I, Yetisir E: **A multicenter, randomized, controlled clinical trial of transfusion requirement in critical care.** *N Engl J Med* 1999, **340:**409-417.
12. Darveau M, Notebaert E, Denault AY, Bélisle S: **Recombinant human erythropoietin use in intensive care.** *Ann Pharmacother* 2002, **36:**1068-1074.
13. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ, Corwin MJ, Colton T: **Efficacy of recombinant human erythropoietin in critically ill patients.** *JAMA* 2002, **288:**2827-2835.
14. Ganz T: **Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation.** *Blood* 2003, **102:**783-788.
15. Oppenheimer SJ: **Iron and its relation to immunity and infectious disease.** *J Nutr* 2001, **131:**S616-S635.
16. Patruta SI, Edlinger R, Sunder-Plassman G, Hörl WH: **Neutrophil impairment associated with iron therapy in hemodialysis patients with functional iron deficiency.** *J Am Soc Nephrol* 1998, **9:**655-663.
17. Marshall JC: **Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome.** *Crit Care Med* 2001, **29:**S99-S106.
18. Bobbio-Pallavicini F, Verde G, Spriano P, Losi R, Bosatra MG, Iotti G, Chiranda M, Villa S: **Body iron status in critically ill patients: significance of serum ferritin.** *Int Care Med* 1989, **15:**171-178.
19. Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG: **Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness.** *J Crit Care* 2001, **16:**36-41.
20. Hobisch-Hagen P, Wiedermann F, Mayr A, Fries D, Jelkmann W, Fuchs D, Hasibeder W, Mutz N, Klinger A, Schobersberger W: **Blunted erythropoietic response to anemia in multiply traumatized patients.** *Crit Care Med* 2001, **29:**743-747.
21. Patteril MV, Davey-Quinn AP, Gedney JA, Murdoch SD, Bellamy MC: **Functional iron deficiency, infection and systemic inflammatory response syndrome in critical illness.** *Anaesth Intensive Care* 2001, **29:**473-478.
22. Elliot JM, Virankabutra T, Jones S, Tanudsintum S, Lipkin G, Todd S, Bion J: **Erythropoietin mimics the acute phase response in critical illness.** *Crit Care* 2003, **7:**R35-R40.
23. Corwin HL, Gettinger A, Rodriguez RM, Pearl RG, Gubler KD, Enny C, Colton T, Corwin MJ: **Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, doubled-blind, placebo-controlled trial.** *Crit Care Med* 1999, **27:**2346-2350.
24. van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A: **Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients.** *Crit Care Med* 2000, **28:**2773-2778.
25. Goodnough LT, Skikne B, Brugnara C: **Erythropoietin, iron, and erythropoiesis.** *Blood* 2000, **96:**823-833.
26. Kaltwasser JP, Kessler U, Gottschalk R, Stucki G, Möller B: **Effect of recombinant human erythropoietin and intravenous iron on anemia and disease activity in rheumatoid arthritis.** *J Rheumatol* 2001, **28:**2430-2436.
27. Gasché C, Dejaco C, Waldhoer T, Tillinger W, Reinisch W, Fueger GF, Gangl A, Lochs H: **Intravenous iron and erythro-**

poietin for anemia associated with Crohn disease. *Ann Intern Med* 1997, **126:**782-787.
28. Fishbane S: **Review of issues relating to iron and infection.** *Am J Kidney Dis* 1999, **34:**S47-S52.
29. Hoen B, Paul-Dauphin A, Hestin D, Kessler M: **EPIBACDIAL: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients.** *J Am Soc Nephrol* 1998, **9:**869-876.
30. Hoen B, Paul-Dauphin A, Kessler M: **Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients.** *Clin Nephrol* 2002, **57:**457-461.
31. Brugnara C: **Iron deficiency and erythropoiesis: new diagnosis approaches.** *Clin Chem* 2003, **49:**1573-1578.