Review
Bench-to-bedside review: Iron metabolism in critically ill patients
Martin Darveau[1,2], André Y Denault[3], Normand Blais[4] and Éric Notebaert[5]

[1]Research student, Faculty of Pharmacy, University of Montreal, Quebec, Canada
[2]Cité de la Santé de Laval, Québec, Canada
[3]Clinical Assistant Professor of Anesthesia, University of Montreal, Montreal Heart Institute and Centre Hospitalier de l'Université de Montréal, Québec, Canada
[4]Hematologist, Hematology Department, Cité de la Santé de Laval, Québec, Canada
[5]Clinical Assistant Professor of Medicine, Critical Care Department, Cité de la Santé de Laval, Québec, Canada

Corresponding author: Martin Darveau, martin_darveau@ssss.gouv.qc.ca

See *Commentary*, page 306

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
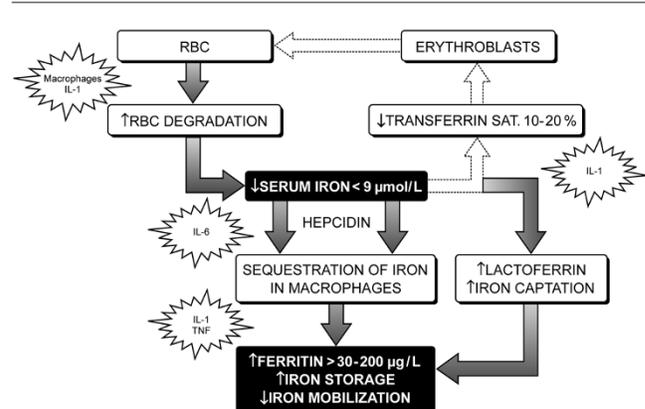
Decrease in iron recycling in the presence of inflammation: iron metabolism in critically ill patients. Most of the iron available for erythropoiesis comes from the catabolism of senescent red blood cells (RBC) by the macrophages in the reticuloendothelial system. Under normal conditions, there is a 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

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.