



Iron Administration in the Critically Ill

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Anemia is a common pathology in intensive care unit (ICU) patients. The pathophysiology of anemia includes altered iron metabolism with decreased erythropoiesis. Under normal conditions, there is a balance between iron transport by transferrin, making iron available for incorporation in hemoglobin, and iron storage as ferritin. In inflammatory processes, this balance is disturbed and plays a central role in the development of anemia. Typically, the inflammatory process is associated with a low concentration of serum iron, high ferritin and low transferrin. Effective erythropoiesis requires both erythropoietin (EPO) and iron. Critically ill patients have inappropriately low EPO levels, and several studies have been conducted to assess the potential benefits of exogenous EPO supplementation. EPO treatment plus iron administration reduced the number of red blood cell (RBC) transfusions needed but had no effects on outcome in terms of ICU infection rates or mortality. Iron can have adverse effects, including inhibition of phagocytosis, inhibition of intracellular killing of bacteria, and altered polymorphonuclear cell function. Iron overload has also been shown to cause increased apoptosis in patients with hemochromatosis. Further study is needed to accurately define the precise role of iron in the development of anemia in critically ill patients, and to determine the potential benefits and risks of iron supplementation.

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Iron is essential for oxygen transport by hemoglobin and myoglobin; hemoglobin contains 80% of the total body iron stores.¹ Under physiologic conditions, there is a balance between iron transport and iron storage. Iron transport is provided by transferrin, which makes iron available for incorporation into hemoglobin. Iron storage is in the form of ferritin.¹ This transport/storage balance is disturbed in inflammatory processes, both acute—as often seen in acutely ill patients in the intensive care unit (ICU)—and chronic. These disturbances play a central role in the development of anemia in these patients.²

Typically, the inflammatory process is associated with decreased concentrations of serum iron, increased ferritin, and decreased transferrin concentrations.³ The underlying mechanisms are very complex and not entirely understood, although the final teleologic aim is primarily to deprive bacteria of their nutritionally required iron.⁴ In fact, already within a few hours following exposure to an inflammatory stimulus, pro- and anti-inflammatory cytokines can decrease blood

iron levels. Pro-inflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6 induce the transcription and the translation of ferritin, modulate the binding affinity of cytoplasmic iron regulatory proteins (IRP)-1 and -2 with iron-responsive elements, and rapidly decrease the mRNA expression of transferrin receptors.⁵ Interferon (INF)- γ stimulates iron absorption by enterocytes via the divalent metal transporter-1 (DMT-1) but has an inhibitory effect on ferroportin internalization into these cells. These alterations result in iron storage in enterocytes.⁶ Anti-inflammatory cytokines like IL-4, IL-10, and IL-13 induce the expression of heme-oxygenase-1 to favor heme degradation and iron storage in monocytes and in the reticuloendothelial system.^{7,8}

Nitric oxide (NO) reduces red blood cell (RBC) production by stimulating IRP and by reducing ferrochelatase activity, which inhibits the final step of heme synthesis.⁹ Recent studies have highlighted the fundamental role of hepcidin, a 25-amino acid protein that is produced by the liver in response to inflammation. This production occurs very rapidly, even before acute-phase reactants like C-reactive protein (CRP).¹⁰⁻¹² Hepcidin decreases iron absorption in the gut and downregulates the iron exporter ferroportin at the plasma membrane of macrophages and enterocytes.¹¹

This review will focus on some of the key studies on iron metabolism in the critically ill patient and the effects of iron administration in animals and critically ill patients, especially in septic conditions.

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Alterations of Iron Metabolism in Critically Ill Patients

A number of studies have reported alterations of iron metabolism in nonbleeding ICU patients (postsurgery, trauma or medical, septic or nonseptic patients). These studies were recently reviewed by Darveau et al¹³ and are summarized in Table 1. Four studies evaluated the prognostic value of ferritin concentration on the risk of development of acute respiratory distress syndrome (ARDS) in ICU patients.¹⁴⁻¹⁷ In these studies, ferritin concentration was significantly increased at the time of ICU admission in patients who devel-

oped ARDS. There are two possible explanations for this finding. One is that pro-inflammatory cytokines, which are implicated in the development of ARDS, do increase ferritin synthesis. A second is that the oxidative stress present in patients at risk of developing ARDS might liberate iron from ferritin, accelerating the formation of toxic hydroxyl radicals.¹⁶

The time course of these measurements is of great importance. This was recently demonstrated by Kemna et al,¹² who observed a significant decrease in blood iron concentrations as early as 22 hours after administration of a small dose of endotoxin in human healthy volunteers. Only a few of the studies listed in Table 1 included blood iron measurements

Table 1 Studies Describing Iron Metabolism in ICU Patients

Study	Type of Patients (no.)	Time of Measurement	Iron ($\mu\text{mol/L}$)	Ferritin ($\mu\text{g/L}$)	Transferrin (g/L)	Transferrin Saturation (%)
Risk of ARDS						
Gutteridge ¹⁴	ARDS (10)	ND	2.7	ND	3.06 \pm 0.41	26 \pm 9
	ARDS retrospective (5)	ND	3.3	ND	0.82 \pm 0.13	71 \pm 7
Gutteridge ¹⁵	ARDS proven (10)	When ARDS developed	2.7 \pm 0.4	ND	1.76 \pm 0.13	34 \pm 4
Connelly ¹⁶	At risk of ARDS (10)	Before surgery	3.7 \pm 0.4	ND	1.98 \pm 0.14	41 \pm 5
	Medicosurgical (83)					
	At risk of ARDS (75)	ND	ND	280 [230–500] females 480 [270–738] males	ND ND	ND ND
Sharkey ¹⁷	With ARDS (8)	ND	ND	293 [180–758] females 1,450 [928–3,750] males	ND ND	ND ND
	Trauma plus ARDS (42)	At admission	ND	240 [12–4,500]	ND	ND
Medical and/or surgical						
Bobbio-Pallavicini ³⁰	Surgical (51)	Week 1	4.1	652	1.7	12.8
von Ahsen ³¹	Medical (71)	Day 1–2	4.8	471	1.4	16
Rodriguez ³²	Medicosurgical (160)	Day 2 to 3	4.9	727	ND	16
Patteril ³³	Medicosurgical (51)					
	Functional iron deficiency	Day 1	ND	342	ND	ND
	No functional iron deficiency	Day 1	ND	292	ND	ND
Piagnerelli ¹⁹	Medicosurgical (29)	Day 1				
	Septic		ND	ND	1.2 [1.1–1.7]	ND
	Nonseptic		ND	ND	2.2 [2.0–2.6]	ND
Muñoz ²²	Medicosurgical (131)	Day 0 to 6	7.5 \pm 6.8	387 \pm 462	1.9 \pm 0.7	28 \pm 25
Piagnerelli ²⁰	Medicosurgical (51)	Day 1				
	Nonseptic		7.2 [5.0–14.0]	461 [215–973]	2.2 \pm 0.6	14 [9–39]
	Septic		3.6 [2.9–5.7]	204 [69–404]	1.7 \pm 0.5	11 [7–13]
Septic shock						
Mumby ³⁴	Septic shock (15)	At diagnosis of infection	7.8 \pm 1.8	ND	0.87 \pm 0.01	35 \pm 7
Trauma						
Hobish-Hagen ¹⁸	Trauma (23)	At admission	9.5	832	1.7	ND
Erythropoietin studies						
van Iperen ²¹	Medicosurgical (36)	At admission				
	Control group		2.05 \pm 0.8	891 \pm 469	1.4 \pm 0.4	12 \pm 6
	Iron group		2.7 \pm 1.3	900 \pm 909	1.5 \pm 0.4	15 \pm 12
	EPO group		3.4 \pm 1.9	1042 \pm 487	1.5 \pm 0.3	16 \pm 9
Corwin ²⁵	Medicosurgical					
	Placebo group (652)	Day 1 to 3	5.03 \pm 6.1	562 \pm 1,169	ND	17 \pm 19
	EPO group (650)	Day 1 to 3	6.5 \pm 8.8	684 \pm 1,385	ND	20 \pm 21
Vincent ²⁶	Medicosurgical (73)					
	Placebo group (25)	Day 1 to 3	6.9 \pm 7.6	642 \pm 781	ND	26 \pm 26
	EPO group (48)	Day 1 to 3	4.4 \pm 3.7	435 \pm 299	ND	15 \pm 14

on ICU admission,^{14,15,17-21} and, unfortunately, the time delay between hospital and ICU admission was usually not defined. Yet, this information is important in order to exclude patients with alterations in iron metabolism due to an inflammatory syndrome that was present prior to ICU admission.

We recently studied iron metabolism in patients admitted to the ICU with a previous hospital length of stay of 2 days or less.²⁰ Despite identical hemograms at ICU admission, septic patients had more severe alterations in iron metabolism, characterized by decreased iron and transferrin concentrations and increased ferritin concentration. No difference was observed for the transferrin saturation and the concentration of soluble transferrin receptor. Interestingly, for all patients at admission, CRP concentration was directly correlated with ferritin and inversely correlated with transferrin concentration.²⁰ Muñoz et al²² also observed a correlation between CRP, iron and transferrin concentration but blood sampling was performed just 1 day per week, and in addition some patients had abnormal RBC mean corpuscular volume (range, 78.4 to 109.7 fL), suggesting prior hematologic disease.

All studies except two^{19,20} excluded patients who had received a RBC transfusion prior to ICU admission or during the ICU stay. Indeed, these patients should be excluded from studies on iron metabolism due to the large quantity of iron provided with RBC transfusions.

In summary, alterations in iron metabolism are frequent in ICU patients, but studies evaluating this phenomenon are limited. To understand the primordial role of iron in the development of anemia, we need more studies exploring the time course of events and, particularly, the role of other major regulators of iron metabolism, such as hepcidin or soluble transferrin receptor.²³

Iron Administration in the Critically Ill

The effects of iron administration in ICU patients have not been well studied. The only available data concern subgroups of patients in studies comparing the effects of iron alone or with erythropoietin (EPO) administration in ICU patients.^{21,24-26} In vitro studies have shown that iron can have adverse effects on polymorphonuclear cell functions, including inhibition of phagocytosis and intracellular killing of bacteria.²⁷ Mice without the *hfe* gene (*hfe*^{-/-}) represent a clinically relevant model of hemochromatosis. When these mice were submitted to cecal ligation and puncture (CLP), Wizek et al²⁸ observed a higher mortality rate after a high than after a low iron diet (75% v 45% at day 7; $P < .001$). Also after CLP, Javadi et al²⁹ observed a higher mortality rate in mice who received high-dose exogenous iron (daily subcutaneous injection of 5 mg of iron dextran). Interestingly, these authors observed increased apoptosis in the intestinal epithelium and in the spleen in the 24 hours following the onset of infection but no difference in bacteremia, suggesting that causes other than bacterial overgrowth may explain these higher mortality rates.

Four studies in adult ICU patients compared the effects of iron administration alone or with EPO.^{21,24-26} These studies actually focused on the potential benefit of EPO rather than the effect of iron administration. Van Iperen et al²¹ studied the effects of intravenous administration of 20 mg of iron sucrose daily for 14 days in 12 ICU patients. These authors observed an insignificant increase in reticulocyte count compared to 12 patients treated with 1 mg of folic acid. Iron administration had no effect on EPO or ferritin concentrations, or on transferrin saturation (remaining below 20%). Serum transferrin and iron concentrations increased significantly only after 10 and 21 days, respectively. These modifications could be due to a significant decrease in the inflammatory syndrome (CRP concentrations decreased from 150 ± 71 to 48 ± 53 mg/L; $P < .05$ at day 10) rather than to an effect of the iron administration. This suggestion was confirmed by the absence of change in serum transferrin receptor concentration during iron therapy, indicating the lack of resumption of erythropoiesis. The limit of this study was the small number of patients studied in each group, the very low dose of iron administered, and the non-exclusion of patients who had received a blood transfusion during the study period. This latter factor could modify iron metabolism quite substantially, as this group received a total of 63 units of RBCs (5 ± 7 U per patient).²¹

In 1999, Corwin et al²⁴ studied the efficacy of 300 U/kg of EPO started 3 days after ICU admission and continued daily for a total of 5 days, versus placebo in a series of 160 ICU patients. Both groups received oral iron (liquid preparation), at a dose of at least 150 mg of elemental iron, either orally or via a nasogastric tube, starting on ICU day 3 or whenever bowel sounds were present. Parenteral iron was given to patients who were either unable to take oral iron or who demonstrated an inadequate response to oral iron, as reflected by a transferrin saturation below 20% and a decrease in serum ferritin to less than 100 μ g/L. For the same hematocrit value (around 30%) in both groups before treatment, the increase in reticulocyte count was more pronounced in the EPO group than in the iron group (2.5% v 0.8%). There were fewer RBC transfusions in the EPO than in the iron groups (166 v 305). No differences were observed in adverse events, including mortality, but the incidence of new infections was not specified. A limitation of this study is the lack of information about the iron metabolism parameters at baseline and during treatment.

In a larger prospective, randomized, double-blind, placebo-controlled, multicenter trial, Corwin et al²⁵ compared the effect of EPO to a placebo in patients who received the same dosage of iron as in the first study. They also observed fewer RBC transfusions in patients who received 40,000 units of EPO weekly (50.5% v 60.4%; $P < .001$) but no difference in mortality (14% in the EPO and 15% in the placebo group). No data were provided about the time course of iron metabolism during treatment but the alterations in iron metabolism were more marked at baseline in the placebo than in the EPO group. Indeed, iron concentration and transferrin saturation were significantly lower (28.1 ± 34.3 v 36.2 ± 48.9 μ g/dL, $P < .001$, and 17.2 ± 18.5 v $20.3 \pm 21.2\%$, $P = .006$,

respectively). Moreover, ferritin concentration was also somewhat lower in the placebo than in the EPO group ($562 \pm 1,169$ v $684 \pm 1,385$ $\mu\text{g/L}$, $P = .09$). More pronounced alterations in iron metabolism in the placebo group at baseline may perhaps explain the limited erythropoiesis in this group. In this study, there were no differences in serious adverse events, including sepsis.²⁵

In a recent multicenter trial, we observed,²⁶ until day 29, a more elevated reticulocyte count in 73 medicosurgical ICU patients receiving 40,000 units of EPO weekly plus 150 mg/d of iron compared to those receiving iron only. After day 29, the mean change in reticulocyte count remained identical, but the area under the curve for reticulocyte count in the initial and the last samples was greater in the EPO group, indicating an augmented erythropoietic response. In contrast to the study by Corwin et al,²⁵ iron metabolism was more altered at baseline in the EPO group than in the placebo group (serum iron concentration 24.4 ± 20.7 v 38.7 ± 42.5 $\mu\text{g/dL}$; ferritin 435 ± 299 v 642 ± 781 $\mu\text{g/L}$; transferrin saturation $16.5\% \pm 13.5\%$ v $26.0\% \pm 26.2\%$).²⁶ Sepsis was the most frequently reported serious complication in both groups (12% in the placebo group and 6% in the EPO group).

Conclusion

In summary, iron metabolism is rapidly altered in ICU patients. Nevertheless, we need additional studies on selected patient populations (without RBC transfusions, without a long hospital stay before ICU admission, without hematologic disease) to better define the role of iron in the development of anemia in critically ill patients. Only then will we be able to study the effects of iron supplementation on anemia in non-infected critically ill patients.

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