Anesthesiology 2010; 112:1211–5

Low Reticulocyte Hemoglobin Content Is Associated with a Higher Blood Transfusion Rate in Critically Ill Patients

A Cohort Study

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ABSTRACT

Background: Intensive care unit (ICU) patients often need blood transfusion, but no reliable predictors of transfusion requirements are available at ICU admission. The authors hypothesized that ICU patients with functional iron deficiency may be at higher risk for developing anemia, requiring blood transfusion. Their objective was to determine whether low reticulocyte hemoglobin content (CHr) was associated with transfusion requirements in ICU patients.

Methods: This is a prospective cohort study in a general ICU. The authors studied 62 patients, after excluding those transfused on or before ICU admission. The authors recorded age, diagnosis, severity score, presence of sepsis, ICU complications, ICU treatments, and transfusion-free interval. Threshold for low CHr was 29 pg. The authors also recorded ICU and hospital outcome. The statistical analysis included Cox proportional hazard function for transfusion.

Results: Twenty-three patients (37%) presented with low CHr on ICU admission and tended to be sicker and more likely to have sepsis than those with normal CHr. They were also more prone to complications, particularly acute renal failure (39 *vs.* 13% $P = 0.02$) and ICU-acquired infection (30 *vs.* 10% $P = 0.04$). The overall transfusion rate was 22.6%, being higher in low-CHr patients than in normal-CHr patients (39.1 *vs.* 12.8%, $P = 0.02$). After adjusting for severity of illness, age, trauma, and hemoglobin level, low CHr remained significantly associated with transfusion, with a hazard ratio of 3.6 (95% CI, 1.2–10.7; $P = 0.02$). Median ICU stay was also longer in patients with low CHr (8 *vs.* 5 days, $P = 0.01$). Differences in mortality did not reach statistical significance.

Conclusion: Low CHr is common at ICU admission and is associated with higher transfusion requirements.

What We Already Know about This Topic

- Anemia occurs commonly in patients in the intensive care unit (ICU), yet simple tests to determine risk for anemia and transfusion are not available
- Reticulocyte hemoglobin content (CHr) has been suggested as a measure of functional iron deficiency and might serve as such a test

What This Article Tells Us That Is New

- In 62 ICU patients, low CHr was common and was associated with higher transfusion requirements

INTENSIVE care unit (ICU) patients often receive blood transfusions. A descriptive analysis of adult ICUs in the United States found that approximately 3,500 transfusions are given to ICU patients daily.[1,2] A large epidemiologic study in European ICUs validated the common occurrence of anemia in critically ill patients and reported that lower hemoglobin levels were associated with longer ICU stay and greater in-hospital mortality.[3] Furthermore, this study reported that 73% of patients with ICU stay more than 7 days received a blood transfusion, even though transfusion was indicated only in patients with hemoglobin less than 8.4 g/dl. Two different approaches to avoid the risks of secondary anemia and the potentially deleterious effects of transfusions have been studied: preemptive treatments (mostly iron, folates, and erythropoietin) and prediction of ICU patients with higher likelihood of developing secondary anemia. The preventive treatment of wide ICU populations proved effective in replenishing body stores or accelerating erythropoiesis, but it failed to improve relevant clinical outcomes.[4,5] Aiming to tailor treatments more closely to patients' needs,

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

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Received from the Intensive Care Unit, Hospital Sant Joan de Deu—Fundació Althaia, CIBER Enfermedades Respiratorias, Manresa, Spain. Submitted for publication September 21, 2009. Accepted for publication January 27, 2010. Support was provided solely from institutional and/or departmental sources. Presented, in part, at the 22nd Annual Congress of European Society of Intensive Care Medicine, Vienna, Austria, October 11–14, 2009. The authors state that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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Milbrandt *et al.*[6] tried to determine the predictors of late anemia. They developed a model with five variables on admission (abnormal lactate, surgical patient, nonemergent surgery, inotropic support, and hemoglobin deficit) that succeeded in discriminating patients who would develop late anemia but failed to predict the need for transfusion. Furthermore, these clinical scores were unable to demonstrate the pathophysiology of the anemia and, thus, precluded the choice of a suitable preemptive treatment.

Iron deficiency is a common cause of anemia in outpatients and inpatients, but in ICU patients, the classic diagnosis of iron deficiency is blunted by the inflammatory status induced by most critical illnesses. Moreover, ICU patients commonly exhibit "metabolic iron deficiency," which refers to a decrease in the amount of iron available for metabolic processes. This is a problem of supply and demand, rather than of total body iron deficiency.[7] A common cause of metabolic iron deficiency is known as reticuloendothelial blockade, which usually occurs in the setting of acute or chronic inflammation, when stored iron is not released for transferring. The administration of erythropoietin may even exacerbate metabolic iron deficiency because of the lack of iron available for erythrocyte production. At present, no single test is invariably accurate when compared with the gold standard of stained bone marrow smears. Erythrocyte zinc protoporphyrin and serum transferrin assays are often not routinely available or, alternatively, may require secondary laboratory analysis.[7]

Reticulocyte hemoglobin content (CHr) was recently reported to be a fast method for diagnosing "functional" iron deficiency because of either lack of iron or lack of available iron for metabolic activity. Its diagnostic accuracy was slightly better than those of ferritin, transferrin saturation, or mean cellular volume.[8] Moreover, CHr proved a good predictor of the response to intravenous iron in chronic hemodialysis patients who were receiving erythrocyte-stimulating agents.[9] Currently, the prevalence of this so-called functional iron deficiency in critically ill patients is unknown.

Our hypothesis was that ICU patients with functional iron deficiency may be at a higher risk for developing anemia requiring blood transfusion. Our objective was to determine the prevalence of low CHr in ICU patients on admission and to determine whether it is associated with ICU transfusion requirements.

Materials and Methods

We screened all patients on admission to our 16-bed general ICU in a 2-month period (April to May 2007). Exclusion criterion were as follows: need for transfusion on or before ICU admission, previous treatment with intravenous iron, thalassemia, macrocytic anemia, transfer to another hospital, moribund state, orders to withhold transfusion, and anticipated ICU stay less than 48 h. Informed consent was waived by the Institutional Research Committee (Sabadell, Barcelona, Spain) because of the noninterventional design of the study. In our institution, intravenous iron is used only to treat symptomatic iron deficient anemia in the ward. Intravenous iron administration is extremely uncommon in the ICU because packed erythrocytes, always leukodepleted in our country, are routinely indicated for anemia in critically ill patients. The protocol for transfusion in our ICU uses restrictive criteria: stable patients are transfused only when hemoglobin reaches 7 g/dl, whereas patients in septic shock or with acute cardiac conditions are transfused when hemoglobin reaches 9 g/dl.[10]

At ICU admission, we recorded age, diagnosis, severity score (Simplified Acute Physiologic Score 3), and its associated risk of mortality, diagnosis of sepsis (Surviving Sepsis Campaign criteria[11]), reticulocyte count, and CHr. During the ICU stay, we recorded specific ICU treatments (tracheal intubation, mechanical ventilation, tracheotomy, dialysis, vasoactive drugs, thermodilution catheter, parenteral nutrition, pacemaker placement, and interventional radiology procedures) and transfusion-free interval. We also recorded ICU complications (acquired infections, barotrauma, reintubation, and acute renal failure) and the length of ICU stay, and ICU and hospital outcome.

CHr was measured using the reticulocyte channel of the Sysmex XE-2100 Automated Hematology Analyzer (TOA Medical Electronics, Kobe, Japan). We measured CHr in the first blood sampled on arrival at the ICU, and CHr less than 29 pg was considered functional iron deficiency.[8] Moreover, to avoid interferences with standard clinical treatment, these data were not available to attending physicians.

Statistics

Sample size calculation: no specific sample size was necessary for the descriptive analysis of the prevalence of functional iron deficiency. To determine the association between low CHr and transfusion requirements, we estimated that 30–40% of patients would need transfusion and that 20–40% would have low CHr at ICU admission. Thus, for a power of 80%, a 0.05 α-error, and a two-tailed hypothesis of a difference greater than 20% in transfusion rate, the required sample size ranged from 30 to 54 patients. We decided to study 62 patients to allow for a 10% loss during the study.

Because of the small sample, we used nonparametric tests to describe (median, 25 and 75 percentiles) and compare (Fisher exact test and Kruskal-Wallis test) variables, with significance set at 0.05. Analysis was performed using EpiInfo 3.5 software (Centre for Disease Control, Atlanta, GA).

Variables associated with transfusion in the univariate analysis at $P \leq 0.1$ were included in a Cox proportional hazard function for transfusion. Proportional hazards models are a subclass of survival models in statistics, in which the effect of a treatment under study has a multiplicative effect on the subject's hazard rate.

Results

In the study period, 75 patients were admitted; 13 were excluded because of less than 48-h ICU stay, and 62 were

Table 1. Descriptive [Mean ± SD, or Median (95% CI)] Patients' Characteristics at ICU Admission

	Low CHr (n = 23)	Normal CHr (n = 39)	*P* Value
Age, yr	66.1 ± 17.4	61.1 ± 17.1	0.2
Female	6 (26.1%)	14 (35.9%)	0.3
Trauma	1 (4.5%)	6 (15.8%)	0.08
Acute coronary syndrome	4 (17%)	8 (20%)	0.5
Clinical bleeding	3 (13%)	4 (10%)	0.5
Surgery before ICU admission	4 (17%)	4 (10%)	0.3
Surgery during ICU stay	1 (4%)	4 (10%)	0.3
Cancer	2 (9.1%)	4 (11.1%)	0.6
Sepsis	12 (52.2%)	13 (33.3%)	0.1
Hemoglobin on admission, g/dl	12.2 (10.3–13.5)	13.0 (11.2–14.9)	0.1
Reticulocytes, $\times 10^{-9}$/l	47 (38–69)	68 (42–90)	0.07
SAPS3 risk of death, %	40 (11–61)	29 (7–45)	0.1

CHr = reticulocyte hemoglobin content; CI = confidence interval; ICU = intensive care unit; SAPS3 = Simplified Acute Physiologic Score 3.

included in the study. At ICU admission, 23 (37%) had low CHr; we observed a trend toward a greater likelihood of having sepsis and toward a higher risk of mortality based on Simplified Acute Physiologic Score 3 in patients with low CHr. Conversely, trauma patients were less likely to have low CHr. Because of the exclusion criteria, no patients were overtly anemic on inclusion in the study (table 1). During the study period, no patients received intravenous iron or erythropoietin.

Table 2 depicts the intensity of ICU treatment needed by patients according to their iron status at ICU admission and, thus, describes the case mix of the cohort. More patients with low CHr received vasoactive drugs (69.6 *vs.* 33.3%), central venous catheter (91.3 *vs.* 56.4%), and arterial catheter (70.6 *vs.* 38.5%) in comparison with those with normal CHr.

Table 3 shows the outcome of patients according to their iron status at ICU admission. Patients with low CHr were more prone to major ICU complications such as acute renal failure (39 *vs.* 13%, $P = 0.02$) and ICU-acquired infection (30 *vs.* 10%, $P = 0.04$), and they stayed in the ICU longer (8 *vs.* 5 days, $P = 0.01$). Differences in hospital mortality (30 *vs.* 23%) did not reach statistical significance and closely followed the predicted Simplified Acute Physiologic Score 3 mortality risk at ICU admission.

The overall rate of erythrocyte transfusion during the ICU stay was 22.6%, but this rate was much higher in patients with low CHr than in those with normal CHr (39.1 *vs.* 12.8%, $P = 0.02$). After adjusting for clinically significant variables on ICU admission (severity of illness, age, trauma, and hemoglobin level), low CHr remained significantly associated with transfusion, with a hazard ratio of 3.6 (95% CI, 1.2–10.7, $P = 0.02$), as shown in figure 1. The accuracy of low CHr for predicting the need for transfusion showed a positive predictive value of 40% (20–60%), a negative predictive value of 87% (77–98%), a positive likelihood ratio of 2.2, and a negative likelihood ratio of 0.5. A separate analysis after excluding septic patients did not substantially modify these values.

The median time to transfusion tended to be slightly shorter in patients with low CHr (9 *vs.* 12 days, $P = 0.8$). There were no differences in the number of packed erythrocyte units administered during the first transfusion in the two groups (1.9 units in low CHr patients *vs.* 2.2 units in normal CHr patients, $P = 0.9$) or in the hemoglobin level before transfusion (6.7 [6.3–7.1] g/dl in low CHr patients *vs.* 7.05

Table 2. Descriptive [Median (95% CI)] Process-of-Care Variables during Intensive Care Unit Stay

	Low CHr (n = 23)	Normal CHr (n = 39)	*P* Value
Central venous catheter	21 (91%)	22 (56%)	0.003
Vasoactive drugs	16 (70%)	13 (33%)	0.006
Erythrocytes transfusion	9 (39%)	5 (13%)	0.02
Platelets transfusion	1 (4%)	1 (3%)	0.6
Fresh frozen plasma transfusion	2 (9%)	4 (10%)	0.6
Pretransfusion hemoglobin, g/dl	6.7 (6.3–7.1)	7.05 (6.8–7.2)	0.9
Interventional radiology	5 (22%)	1 (3%)	0.02
Arterial catheter	12 (71%)	10 (38%)	0.04
Mechanical ventilation > 96 h	10 (43%)	8 (21%)	0.06
Thermodilution catheter	5 (22%)	3 (8%)	0.1
Tracheal intubation	14 (61%)	18 (46%)	0.1
Dialysis	4 (17%)	3 (8%)	0.2
Tracheostomy	2 (9%)	1 (3%)	0.3
Parenteral nutrition	2 (9%)	4 (10%)	0.6

CHr = reticulocyte hemoglobin content; CI = confidence interval.

Table 3. Descriptive [Median (95% CI)] Outcome Variables

	Low CHr (n = 23)	Normal CHr (n = 39)	*P Value*
Reintubation	4 (17.4%)	1 (2.6%)	0.06
Acute renal failure	9 (39.1%)	5 (12.8%)	0.02
ICU-acquired infection	7 (30.4%)	4 (10.3%)	0.04
Length of ICU stay, d	8 (4–20)	5 (3–7)	0.01
ICU mortality	5 (21.7%)	7 (17.9%)	0.5
Hospital mortality	7 (30.4%)	9 (23.1%)	0.4

CHr = reticulocyte hemoglobin content; CI = confidence interval; ICU = intensive care unit.

[6.8–7.2] g/dl in normal CHr patients, $P = 0.9$). Mortality was significantly higher in transfused patients than in nontransfused patients, both during the ICU stay (50 *vs.* 10.4%, $P = 0.003$) and during the entire hospital stay (57.1 *vs.* 16.5%, $P = 0.005$).

Discussion

Our study adds to the evidence that functional iron deficiency is very common in patients admitted to the ICU. Moreover, we found that low CHr is strongly associated with higher transfusion requirements. Therefore, critically ill patients with low CHr seem to be suitable subjects for future studies to determine whether early treatment with intravenous iron after ICU admission can reduce transfusion requirements.

Efforts to improve the outcome of critically ill patients by reducing the need for transfusion have focused on different aspects of critical care. First, the amount of blood extracted for laboratory analysis has been minimized through the widespread use of (1) noninvasive monitoring tools, such as pulse oximeters, capnographs, and continuous venous saturation catheters, which reduce the number of blood samples acquired daily, (2) new analyzers that provide reliable results with smaller amounts of blood, and (3) blood-sparing devices that reinfuse part of the blood withdrawn from indwelling catheters. A second approach consists of lowering the threshold for transfusion; this method gained extraordinary acceptance after Hébert *et al.*[12] showed that most ICU patients with hemoglobin levels as low as 7 g/dl can forgo transfusion without detectable side effects.

A third approach to reducing the need for transfusion is the preemptive treatment of critically ill patients with bone marrow–stimulating agents. The most commonly studied line is the erythropoietin-stimulating proteins. Preliminary trials were promising, but a recent meta-analysis concluded that the real efficiency of erythropoietin was lower than was previously thought.[13] Although, compared with a placebo, erythropoietin significantly reduced the odds of a patient receiving at least 1 transfusion (odds ratio 0.73), most of the studies included were performed before the widespread adoption of the restrictive transfusion strategy. Finally, the most recent study published found that the use of epoetin alpha not only failed to reduce the rate of erythrocyte transfusion among critically ill patients but

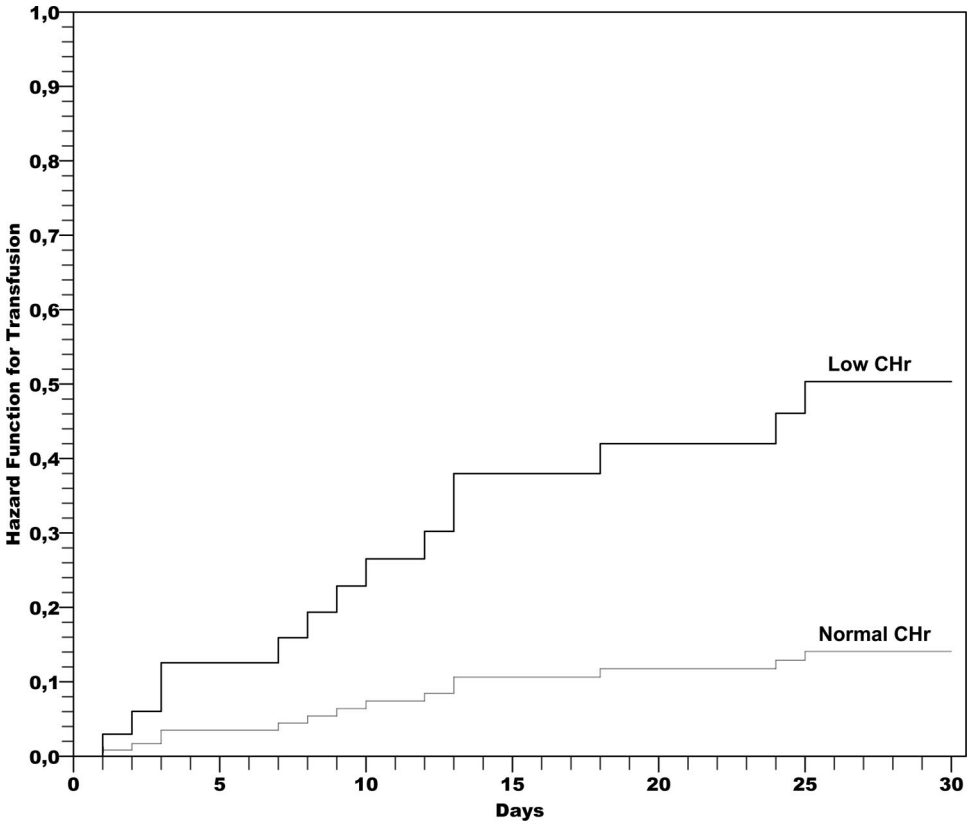

Fig. 1. Time to transfusion in the groups of patients with low and normal reticulocyte hemoglobin content (CHr).

was also associated with an increase in the incidence of thrombotic events.[5] Therefore, this option remains restricted to research scenarios.[14]

Although iron replacement is invaluable in the outpatient treatment of iron deficiency anemia, the effect of iron supplementation on morbidity and mortality in critically ill patients with functional iron deficiency has not been studied thoroughly. Again, the inflammatory response associated with critical illness may limit the amount of supplemental iron ultimately available for erythropoiesis. The use of iron replacement therapy in critical illness has also been questioned because of the possible link between iron and infection, but recent retrospective studies observed no relationship between the parenteral iron replacement therapy and the likelihood of infection.[15] Our separate analysis of patients without sepsis on admission yielded comparable results in terms of the ability of CHr to detect patients with a higher likelihood of needing a transfusion; thus, a conservative approach to avoid the harmful effects of iron in infected patients might be a starting point for future studies of preemptive treatment with intravenous iron.

Patient selection can improve the signal-to-noise ratio in preemptive treatments. By using this approach, Milbrandt *et al.*[6] designed a model with high positive predictive power for the development of anemia, although it is less accurate for predicting the need for transfusion. Our data suggest that a single parameter obtained at ICU admission, CHr, can clearly separate patients with a higher likelihood of needing a transfusion from those with a lower likelihood. In addition, these "functionally" iron deficient patients might conceivably be a suitable target for preemptive treatment options such as intravenous iron therapy. In this line, Kim *et al.*[9] described low CHr as a good predictor of the response to intravenous iron in chronic hemodialysis patients.

Limitations of the Study

Although the sample was large enough to demonstrate differences in the prevalence of transfusion, our study is underpowered to reach conclusions about clinically important outcomes, such as ICU length of stay, morbidity, or mortality. Sample size also precluded the possibility of studying whether the need for transfusion correlated with low bone marrow capacity or intercurrent events during the ICU stay. Moreover, our small sample made it impossible for us to clarify whether low CHr was the cause of transfusion requirements or a marker of severity associated with longer ICU stay. Adherence to transfusion guidelines was good in terms of hemoglobin trigger for transfusion, but somewhat lower for the amount of transfused units. Case mix is always an issue in single-center studies, but our levels of severity, length of stay, and mortality suggest a case mix that is easily applicable to most ICUs.

We conclude that low CHr is common at ICU admission, and it is associated with higher transfusion requirements. Whether low CHr is a marker of severity or a modifiable factor remains to be elucidated.

The authors thank Albert Altes, M.D. (Hematology Department, Fundacio Althaia, Manresa, Spain), for his critical insights on the article.

References

1. Groeger JS, Guntupalli KK, Strosberg M, Halpern N, Raphaely RC, Cerra F, Kaye W: Descriptive analysis of critical care units in the United States: Patient characteristics and intensive care unit utilization. Crit Care Med 1993; 21:279–91
2. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, 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. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D; ABC (Anemia and Blood Transfusion in Critical Care) Investigators: Anemia and blood transfusion in critically ill patients. JAMA 2002; 288:1499–507
4. 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; 27:2346–50
5. Corwin HL, Gettinger A, Fabian TC, May A, Pearl RG, Heard S, An R, Bowers PJ, Burton P, Klausner MA, Corwin MJ; EPO Critical Care Trials Group: Efficacy and safety of epoetin alfa in critically ill patients. N Engl J Med 2007; 357:965–76
6. Milbrandt EB, Clermont G, Martinez J, Kersten A, Rahim MT, Angus DC: Predicting late anemia in critical illness. Crit Care 2006; 10:R39
7. Pieracci FM, Barie PS: Diagnosis and management of iron-related anemias in critical illness. Crit Care Med 2006; 34:1898–905
8. Mast AE, Blinder MA, Lu Q, Flax S, Dietzen DJ: Clinical utility of the reticulocyte hemoglobin content in the diagnosis of iron deficiency. Blood 2002; 99:1489–91
9. Kim JM, Ihm CH, Kim HJ: Evaluation of reticulocyte haemoglobin content as marker of iron deficiency and predictor of response to intravenous iron in haemodialysis patients. Int J Lab Hematol 2008; 30:46–52
10. Hébert PC, Tinmouth A, Corwin HL: Controversies in RBC transfusion in the critically iIl. Chest 2007; 131:1583–90
11. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36:296–327
12. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: Transfusion requirements in critical care: A multicenter randomized controlled clinical trial. N Engl J Med 1999; 340:409–17
13. Zarychanski R, Turgeon A, Fergusson D: Erythropoietin receptor agonists in critically ill patients: A meta-analysis of randomized control trials. Can Med Assoc J 2007; 177:725–34
14. Cook D, Crowther M: Targeting anemia with erythropoietin during critical illness. N Engl J Med 2007; 357:1037–9
15. Torres S, Kuo YH, Morris K, Neibart R, Holtz JB, Davis JM: Intravenous iron following cardiac surgery does not increase the infection rate. Surg Infect (Larchmt) 2006; 4:361–6