

Anemia, Erythropoietin, and the Trauma Patient

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Learning Objectives: 1) To review the etiology of anemia of critical illness. 2) To review the current risks and complications associated with allogeneic blood transfusions. 3) To review the use of human recombinant erythropoietin.

Abstract

Anemia develops in many intensive care unit (ICU) patients during their ICU course. As a result, as many as 50% of ICU patients will receive a transfusion of packed red blood cells (RBCs). The etiology of anemia is attributable to a combination of blood loss and impaired RBC production. These include acute and occult blood losses as well as repeated phlebotomy. Decreased RBC production is due to the combined effects of an inappropriately low erythropoietin response and abnormal iron metabolism as a direct suppression by inflammatory mediators. RBC transfusions are commonly used to correct anemia, but evidence is emerging that transfusions may confer an additional risk rather than provide a benefit. Erythropoietic-stimulating agents along with iron supplementation are used to overcome the blunted endogenous erythropoietin response and iron-restricted erythropoiesis seen in anemia of critical illness.

Anemia is common in critically ill patients. Multiple studies have shown that approximately 95% of patients in intensive care units (ICUs) admitted for more than 3 days develop anemia.^{1,2} In fact, a study conducted in 1995 demonstrated that 50% of all ICU patients were transfused with at least one red blood cell (RBC) unit,

with an average number transfused of five to six units during their ICU stay.^{3,4} In a post hoc analysis of critically injured trauma patients evaluated in the CRIT study, the trauma subset were more likely to be transfused one additional unit of blood when compared with the full study population.

Transfusion practices have not changed significantly during the past decade. The CRIT study had an overall transfusion rate of 44%³ and a recent study conducted in Western Europe had a transfusion rate of 37% in the ICU with an overall rate of 42% in the 28 days of the study.⁵

The etiology of ICU-associated anemia is multifactorial (Table 1). Blood loss can occur from obvious bleeding due to trauma, surgery, and/or invasive procedures as well as from phlebotomy and occult losses (i.e., gastric stress ulcers, renal replacement therapy).⁶⁻⁸ Decreased RBC production is due to the combined effects of an inappropriately low erythropoietin response, abnormal iron metabolism, and direct suppression by inflammatory mediators.^{7,10}

Blood Loss

Multiple studies support the idea that phlebotomy in the ICU contributes to a patient's anemia. Approximately 17% of all blood loss in the ICU is due to diagnostic tests.⁶ A study conducted 2 decades ago compared the phlebotomy records of 50 ICU patients with 50 general medical-surgical ward patients.¹¹ The ICU patients had a threefold increase in blood draws than the ward patients (3.4 times vs. 1.1 times; $P < .001$). This corresponded to an increase in blood volume drawn (41.5 mL vs. 12.4 mL; $P < .001$). The ward patients were phlebotomized a mean of 175 mL for the entire hospitalization compared with 762.2 mL in patients admitted to the ICU. Of the ICU patients, those with arterial lines had more blood drawn (944 mL) and more often (4 times) than those who did not have arterial lines (300.9 mL and 1.9 times). The investigators concluded that the large blood losses contributed to transfusion requirements. In a retrospective chart review of all patients admitted to a multidisciplinary ICU, 85% of all patients who had a length of stay >1 week were transfused.⁷ Of those patients who were transfused, the mean blood volume phlebotomized was 60 to 70 mL/day compared with 40 mL/day in the patients who did not receive transfusions ($P < .05$). The authors concluded that phlebotomy accounted for 49% of the variation in RBCs transfused.

Table 1. Etiology of Anemia in Critically Ill Trauma Patients

- Acute hemorrhage
 - Trauma-related bleeding
 - Acute gastrointestinal bleeding
- Surgical blood losses
- Occult gastrointestinal bleeding
- Dialysis-dependent renal failure/renal replacement therapy
- Phlebotomy
- Restrictive erythropoiesis
 - Abnormal iron utilization
 - Inappropriate low production of erythropoietin (blunted EPO response)
 - Direct suppression of bone marrow RBC production
- Nutritional deficiencies
 - Iron
 - Folate
 - Vitamin B₁₂

A study conducted in 1993 reported similar results. Patients in the ICU had a mean weekly blood draw of 550 mL compared with 208 mL in ward patients.¹²

When blood is taken from indwelling catheters such as arterial lines, an initial amount of blood is discarded based on local nursing practices. A discard volume of twice the dead space provides accurate results for arterial blood gas measurements.¹³ The use of closed-system sampling devices (i.e., venous arterial blood management and protection system, or VAMP) with the return of sterile blood has been used to avoid this “wasting” of discarded blood.¹⁴

Decreased Red Blood Cell Production

Besides phlebotomy, obvious and occult blood losses, critically ill patients with anemia are found to have a blunted erythropoietin response and abnormal iron utilization. Normally, erythropoietin levels increase >100-fold in response to acute anemia (normal range, 10–30 IU/mL; Fig. 1). Multiple studies have shown that anemic critically ill patients have inappropriately low levels of erythropoietin. Rogiers et al¹⁵ compared serum erythropoietin concentrations of critically ill patients with those of ambulatory patients with iron deficiency anemia. Although erythropoietin levels were elevated compared with healthy, nonanemic controls, they were significantly decreased compared with erythropoietin concentrations of iron-deficient anemic controls with comparable hemoglobin levels.

Various authors have implicated that inflammatory mediators have a role in the blunted erythropoiesis seen in the critically ill.^{6,16} In a prospective observational study of 23 multiple trauma patients, blood samples were collected from day 1 to day 9 measuring serum erythropoietin, tumor necrosis factor- α (TNF- α), interleukin-1 receptor antagonist (IL-1ra), interleukin-6 (IL-6), ferritin, hemoglobin, and iron levels.¹⁶ Fifteen of the 23 patients were transfused RBC units. Measured inflammatory mediators, TNF- α , IL-1ra, and IL-6 levels were elevated on day 1 and remained elevated on day 9. The investigators found that there was an

inappropriately low endogenous erythropoietin response (mean value, <50 U/L) to the degree of anemia and that iron levels fell on day 2 and remained low. They concluded that anemia in this patient population is a result of bleeding, a blunted erythropoietin response, and iron-restricted erythropoiesis. This blunted erythropoietin response has been shown in critically ill patients with multiple organ dysfunction syndrome.¹⁷ In this prospective, randomized, placebo-controlled study of 19 surgical/trauma patients with multiorgan failure and baseline anemia, the levels of TNF- α , IL-2, and IL-6 were 2 to 12 times higher than normal. Both groups had slightly elevated erythropoietin levels at baseline (39.8 IU/mL in the recombinant human erythropoietin [rHuEPO] group and 29.6 IU/mL in the control group). The control group had a slight decrease in erythropoietin levels that returned to baseline by week 3 and a reticulocyte count of 1.9%; however, the rHuEPO group showed an increase in erythropoietin levels to 149 IU/mL by week 2 with a reticulocyte count of 4%.

These studies support the role of inflammatory mediators in a blunted erythropoietin response. Furthermore, the presence of inflammatory markers in critically ill may cause a functional iron deficiency. In a randomized open trial conducted in a multidisciplinary ICU, markers of iron metabolism were evaluated in 36 critically ill patients.¹⁸ All patients were found to have low levels of serum iron and transferrin, low transferrin saturation, and low-to-normal serum transferrin receptor levels with elevated levels of ferritin on admission to the ICU, thus supporting the hypoferric state in the presence of adequate iron stores seen in anemic critically ill patients.

Hepcidin, a 25 amino acid peptide, is the principal iron regulatory hormone that regulates the intestinal absorption of iron and its mobilization from fixed macrophage stores.^{8,20} Hepcidin expression increases in patients with an inflammatory stimulus.²¹ Anemia, tissue hypoxia, erythropoietin, erythropoiesis, and iron utilization all regulate the expression of hepcidin mRNA.¹⁹ Hepcidin is a negative regulator of intestinal iron absorption and macrophage iron release.²² Thus, in anemia of inflammation, iron retention by reticuloendothelial macrophages and duodenal enterocytes causes low transferrin saturation and iron-restricted erythropoiesis.²⁰

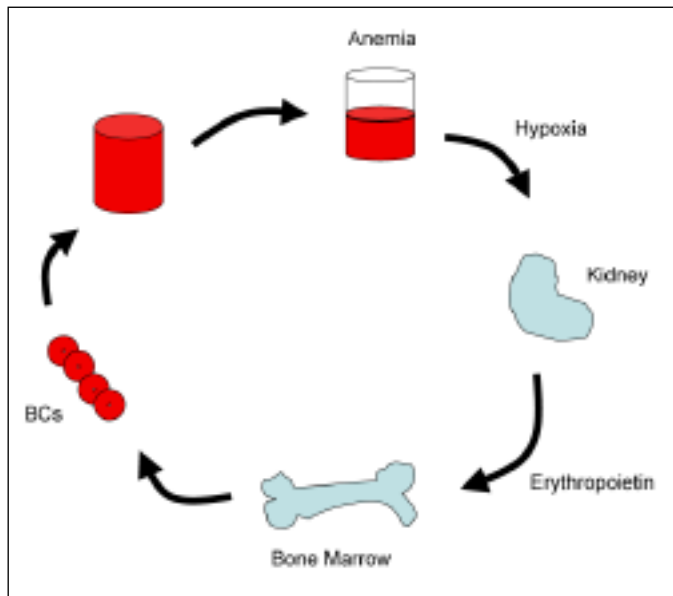


Figure 1. During anemia, the kidneys respond to relative hypoxia by releasing erythropoietin. The erythropoietin stimulates erythropoiesis in the bone marrow and an increase in red blood cell production and release into circulation.

Red Blood Cell Transfusion in the Intensive Care Unit

Transfusion practice in the United States has not changed during the last few decades. Anywhere from 37% to 44% of patients admitted to ICUs were transfused RBCs in two large studies conducted in the United States and in Western Europe recently.^{2,5} Of those patients who have an ICU length of stay >1 week, the transfusion rate increases to 85%.² The “transfusion trigger” in both of these studies was similar: a mean pretransfusion hemoglobin of 8.6 g/dL and 8.4 g/dL, respectively. In the TRICC trial,²³ the investigators enrolled 838 euvolemic critically ill patients with hemoglobin concentrations <9 g/dL within 72 hours of ICU admission. Patients were randomly assigned to either a restrictive transfusion group, in which the patients received RBC units if the hemoglobin levels fell below 7 g/dL and maintained at hemoglobin concentrations of 7 to 9 g/dL, or a liberal transfusion group, in which the patients received RBC units to maintain hemoglobin concentration >10 g/dL. Overall, the mortality rates at 30 days, 60 days, and length of stay in the ICU were statistically similar. However, the in-hospital mortality rates were lower in the restrictive strategy group compared with the liberal group (22.2% vs. 28.1%, respectively; *P* = .05). Also, the mortality rates in the restrictive group were lower in the less critically ill and younger patients (age <55 years).

Risks associated with RBC transfusions include transmission of infectious diseases and transfusion-related reactions. With better screening parameters of donors and improved viral screening tests, the incidence of transmission has decreased substantially. The reported estimated risks for transmission of human immunodeficiency virus is down to 1 in 2 million blood transfusions in the United States, while the incidence of hepatitis B is 1 in 250,000.²⁴

However, RBC transfusions are associated with longer hospital stays and an increase in mortality. In the Western European study, those who received a transfusion were older (mean, 63.6 vs. 59.2 years, respectively; $P < .001$), had higher acute physiology and chronic health evaluation (APACHE) II scores (mean, 16.5 vs. 13.5, respectively; $P < .001$), a lower admission baseline hemoglobin (mean, 10.1 vs. 12.2 g/dL, respectively; $P < .001$), and longer hospital stays (mean, 15.8 vs. 10.9 days, respectively; $P < .001$). In addition, the ICU mortality rates were significantly higher in those patients who received transfusion (18.5% vs. 10.1%, respectively; $P < .001$), as well as 28-day overall mortality (29% vs. 14.9%, respectively; $P < .001$).⁴ These findings were independent of severity of illness or hemoglobin level. A recent U.S. study had similar findings.² The investigators found increased sequential organ failure assessment (SOFA) scores, increased hospital and ICU length of stays, and longer duration of mechanical ventilation in those patients who received blood transfusion ($P < .007$).

Some investigators have discussed the possible role of immunomodulatory effects of RBC transfusions and their potential to increase the risk of nosocomial infection.²⁵ In a retrospective analysis of 1,717 patients admitted to a medical-surgical trauma ICU, the rate of nosocomial infections was significantly higher in those patients who received transfusion compared with those who did not (15.4% vs. 2.9%, respectively; $P < .005$). The authors also found a dose-dependent increase in risk for infection: 1.5-fold increase for each unit transfused. Mortality, ICU, and hospital length of stay were all significantly increased in the transfused group ($P < .001$). A follow-up prospective, observational analysis by the same investigators in 2006 showed that the same pattern still exists, although the rate of nosocomial infection has decreased secondary to improved infection-control interventions. The use of leukoreduced RBC units did not significantly reduce the rate of nosocomial infection. Multiple studies demonstrated that the incidence of nosocomial infections correlate with RBC transfusions in trauma patients.⁹⁻²⁸

Is older blood associated with increased complications? The concentration of 2,3-diphosphoglycerate in the stored blood decreases over time, thus interfering with the ability of RBCs to unload oxygen. In addition, the RBCs become less deformable, which may impede their ability to access capillary beds.^{29,30} Investigators measured gastric pH at baseline and <6 hours after transfusion in 23 critically ill, ventilated patients with a diagnosis of sepsis and with a hemoglobin level <10 g/dL.³¹ Patients who had received blood stored >15 days had a decrease in mucosal pH, which represents gastric ischemia.

Erythropoietic Agents

In order to avoid potential complications of RBC transfusions, other methods to reduce the amount of RBCs transfused are being sought. Recombinant human erythropoietin (epoetin alfa) is approved to treat anemia in patients with chronic renal failure, cancer, and human immunodeficiency virus, and in patients undergoing elective major nonvascular, noncardiac surgery. Use of erythropoietic agents in these populations has been associated with successful reduction of allogeneic blood transfusions. Several studies

have been conducted to evaluate the use of rHuEPO in critically ill patients (Table 2).

To overcome the blunted erythropoietin response in critically ill patients, Gabriel et al¹⁷ conducted a randomized, prospective, controlled trial in 19 patients with multiple organ dysfunction syndrome. The patients were randomized to receive rHuEPO 600 IU/kg intravenously 3 times a week or saline; both groups were given iron, folic acid, and vitamin B₁₂. Reticulocyte counts were similar at baseline in both groups; however, in the rHuEPO-treated group there was a significant increase in reticulocyte levels by the 3rd week (rHuEPO group 4% vs. 1.9% placebo group; $P < .05$). The investigators found that there was an inverse correlation between IL-6 and serum erythropoietin levels. They concluded that despite the immunosuppressive effects of circulating cytokines on erythropoiesis in patients with multiple organ dysfunction syndrome, exogenous erythropoietin can stimulate the erythropoietic system with high-dose rHuEPO.

Another study was conducted in the late 1990s to determine whether the use of rHuEPO reduced the number of RBC transfusions.¹⁶ In a prospective, randomized, double-blind, multicenter trial, 160 patients were randomized to receive either rHuEPO or placebo. The study drug (rHuEPO 300 U/kg or placebo) was administered daily starting on day 3 to day 7, then every other day to a target hematocrit of 38% or until discharge from the ICU or to a maximum of 6 weeks. All patients were given supplemental iron therapy; RBC transfusions were given based on the patient's attending physician. The number of transfusions was significantly less in the rHuEPO group (166 units vs. 305 units, respectively; $P < .002$). Between days 8 and 42, 55% of the patients in the placebo group either received transfusions or died, compared with 45% in the rHuEPO group. Overall, there was an increase in reticulocytosis and final hematocrit in the rHuEPO group compared with the placebo group, despite the fewer transfusions. The two groups had similar mortality and adverse outcomes. The investigators concluded that the use of rHuEPO increased hematocrit and reduced RBC transfusions by 45%.

van Iperen and colleagues¹⁸ investigated the response of erythropoiesis to iron and rHuEPO therapy in a small, prospective, randomized trial. Thirty-six critically ill patients were randomized into either control, iron, or rHuEPO groups. All patients were given supplemental folic acid therapy; additionally, the subjects in the iron group received 200 mg of intravenous (IV) iron saccharate, and the rHuEPO group received 200 mg of IV iron saccharate and rHuEPO 300 U/kg for every other day for five doses. Transfusions were given based on a transfusion algorithm. There was an inverse correlation between erythropoietin levels relative to the degree of anemia in all study patients. The serum transferrin receptor, which quantitatively estimates erythropoiesis, increased only in the rHuEPO group, but after day 6. The reticulocyte counts were significantly higher in the rHuEPO group than either the control or iron groups from day 8 to day 15, but were similar by day 21. Hemoglobin concentrations were similar in all the groups throughout the study period. The control group was transfused a total of 140 units compared with 63 units in the iron group and 82 units in the rHuEPO group. Thus, this study reaffirmed the concept of a blunted erythropoiesis in critically ill patients that responds to exogenous erythropoietin.

The response to exogenous erythropoietin may be decreased because of iron-restricted erythropoiesis. Relative iron deficiency occurs because of increased erythron iron requirements that exceed available iron stores.^{32,33} Adding IV iron may overcome this relative iron deficiency.

Corwin and colleagues⁴ followed up their initial small study with a larger randomized controlled trial of 1,302 critically ill

Table 2. Studies Evaluating the Use of Recombinant Human Erythropoietin (rHuEPO) in Critically Ill Patients

Study	Design	Population	Transfusion	Epo Regimen	Findings	Conclusion
Gabriel et al, ¹⁷ 1998	Single center prospective, randomized, placebo-controlled	19 adults with multiple organ dysfunction syndrome	To keep HCT >30%	Randomized to receive rHuEPO 600 IU/kg IV TIW or placebo for 3 weeks	1. rHuEPO group had increase in reticulocyte count 4% vs. 1.9% ($P < .05\%$) 2. Inverse correlation between IL-6 and serum EPO levels	Exogenous EPO can stimulate the erythropoietic system with high-dose rHuEPO
Corwin et al, ¹⁶ 1999	Multicenter prospective, randomized, placebo-controlled, double-blind	160 adults in 2 mixed medical/surgical ICUs and 1 surgical ICU	As ordered by attending physician	Randomized to receive rHuEPO 300 IU/kg IV or placebo daily for 4 days then every other day for target HCT >38%, discharge or 6 weeks	1. Number of patients receiving transfusions less in rHuEPO group ($P < .05\%$) 2. Decreased number of units transfused in rHuEPO group ($P < .05\%$)	The use of rHuEPO increased HCT and reduced RBC transfusions by 45%
van Iperen et al, ¹⁸ 2000	Single center prospective, randomized, placebo-controlled, open-label	36 adults admitted to a mixed medical, surgical, trauma, and neurologic ICU	All patients for Hb <8.9 g/dL. Patients with cardiac history transfused at Hb <9.7 g/dL or when clinically needed	Randomized to receive either rHuEPO 300 IU/kg SC every other day for 5 doses, IV iron and folate for 14 days (rHuEPO group), or IV iron and folate for 14 days (iron group) or folate for 14 days (control group)	1. Reticulocyte count increased in the rHuEPO group significantly compared with the iron and control groups from day 8 to day 15 but similar by day 21 2. rHuEPO group had a increase in transferrin receptor from day 6 3. Hb counts were similar in all groups 4. ICU LOS was shorter in rHuEPO and iron groups 5. Serum EPO levels were higher in the rHuEPO group compared with the iron and control groups from day 2 to day 6	Blunted erythropoiesis in critically ill patients who respond to exogenous erythropoietin
Corwin et al, ⁴ 2002	Multicenter prospective, randomized, placebo-controlled, double-blind	1,302 adults admitted to medical, surgical, and mixed medical/surgical ICUs at 65 medical centers	No preset transfusion trigger	Randomized to receive either rHuEPO 40,000 units weekly or placebo for a total of 3 doses and those who stayed in the ICU on day 21 received a fourth dose	1. Percentage of patients treated with placebo was transfused significantly more than those treated with rHuEPO (60.4% vs. 50.5%, respectively; $P < .001$) 2. Significant reduction in the cumulative number of units transfused, 1,590 units (rHuEPO group) and 1,963 units (placebo group); $P = .001$ 3. The mean pretransfusion hemoglobin was similar in both groups (8.5 g/dL)	The use of rHuEPO in critically ill patients reduces the number of units transfused. The findings support the hypothesis that anemia of critical illness is one of relative erythropoietin deficiency
Georgopoulos et al, ³⁴ 2005	Multicenter prospective, randomized	148 adults admitted to ICUs	Transfusion trigger of 7 g/dL in all patients except in patients with active cardiac ischemia or neurologic impairment or active bleeding	Randomized to receive either IV iron (control group), IV iron and rHuEPO 40,000 units weekly (group A), or IV iron and rHuEPO 40,000 units 3 times per week (group B) for a maximum of 3 weeks	1. Number of RBC units transfused was higher in the control group compared with groups A and B (138 units, 33 units, and 23 units, respectively; $P < .05$) 2. Percentage of patients transfused was higher in the control group compared with groups A and B (58.3%, 37.3%, and 26.5%; $P < .05$) 3. There was a dose response of Hb to rHuEPO	The total reduction in the number of RBC units transfused did not differ between the two dosing regimens; the use of rHuEPO 40,000 units weekly is sufficient to reduce the need for RBC transfusion in critically ill patients

HCT, hematocrit; IV, intravenously; IL-6, interleukin-6; EPO, erythropoietin; ICU, intensive care unit; RBC, red blood cell; SC, subcutaneously; LOS, length of stay.

patients to assess the efficacy of weekly rHuEPO in reducing RBC transfusion. The patients were randomized to receive either rHuEPO 40,000 units weekly or placebo for a total of three doses, and those who stayed in the ICU on day 21 received a fourth dose. The percentage of patients who were treated with placebo was transfused significantly more than those treated with rHuEPO (60.4% vs. 50.5%, respectively; $P < .001$). There was also a significant reduction in the cumulative number of units transfused: 1,590 units in the rHuEPO group and 1,963 units in the placebo group. This demonstrates a 19% reduction in RBC units transfused per day alive ($P = .04$). The mean pretransfusion hemoglobin was similar in both groups (8.5 g/dL). The results of this larger trial confirmed the findings in the earlier trial. The use of rHuEPO in critically ill patients leads to an overall reduction in the total number of RBC units transfused. The results support the evidence that anemia of critical illness is one of relative erythropoietin deficiency.

Although the above-mentioned studies all support the use of rHuEPO in critically ill patients to overcome the blunted endogenous erythropoietin response to anemia, the doses of rHuEPO were all different. In a recent prospective, randomized, multicenter study, Georgopoulos et al³⁴ evaluated the efficacy of two dosing regimens. One hundred forty-eight patients were enrolled and randomized to receive either IV iron saccharate (control), IV iron saccharate and rHuEPO 40,000 units once weekly (group A), or IV iron saccharate and rHuEPO 40,000 units 3 times per week (group B) for a maximum of 3 weeks of therapy. All groups were given 100 mg of IV iron saccharate 3 times a week. There was a standardized transfusion protocol. The pretransfusion hemoglobin was not significantly different in the three groups (7.9, 7.6, and 7.7 g/dL, respectively, in the control group, group A, and group B). The total number of RBC units transfused was significantly higher in the control group compared with groups A and B (138 units, 33 units, and 23 units, respectively; $P < .05$); the difference between groups A and B were not significantly different. There was also a dose response of hemoglobin to rHuEPO. Thus, the authors concluded that because the total reduction in the number of RBC units transfused did not differ between the two dosing regimens, the use of rHuEPO 40,000 units weekly is sufficient to reduce the need for RBC transfusion in critically ill patients, when restrictive doses of IV iron are administered concomitantly.

Livingston et al³⁵ published a study to assess the bone marrow response in critically ill trauma patients. They obtained bone marrow aspirates and peripheral blood smears from days 1 to 9 in 45 trauma patients admitted to a surgical ICU and from gender- and age-matched healthy volunteers (who served as controls). The mean hemoglobin level was 8.3 g/dL, with a significantly elevated erythropoietin levels and a slight reticulocytosis of 2.6% in the trauma patients. Thus, the authors concluded that there was an impairment in the production of RBCs in the bone marrow. They further investigated whether the effect of exogenous erythropoietin would stimulate the bone marrow. Increasing amounts of exogenous erythropoietin increased bone marrow progenitor growth in the control group; however, there was a decline of 38% in the trauma group bone marrow. The investigators caution the use of exogenous erythropoietin to improve erythropoiesis in the critically ill trauma population.

In a recent prospective, randomized placebo controlled trial, 1,460 critically ill medical, surgical, and trauma patients were randomized to receive placebo or 40,000 units of epoetin alfa weekly for three doses.³⁶ There was no difference in transfusion practices (pretransfusion Hb 8.0 ± 1 g/dL in the placebo group and 8.2 ± 0.9 g/dL in the study group) and percentages of patients transfused (48.3% in the placebo group and 46% in the study group). However, at day 29 there was a significant reduction in mortality in trauma

patients in the epoetin alfa group versus placebo group (3.5% vs. 6.6%, respectively; $P = 0.04$).

Conclusion

Anemia is common in the critically ill trauma patient. By day 3 of ICU stay, 95% of critically ill patients are anemic and approximately 50% will receive large numbers of allogeneic transfusions. Most trauma patients develop anemia because of ongoing blood losses, occult losses, and/or decreased RBC production in the ICU. Phlebotomy is one of the major contributors to these ongoing blood losses. The amount of blood drawn in this population directly relates to transfusion needs. In an effort to reduce this population's exposure to allogeneic transfusions, ICUs should develop strategies to decrease daily blood volume drawn, minimize the number of blood draws, and eliminate wasting of discarded blood by returning sterile blood and/or using closed-system sampling devices. The critically ill trauma patients have been found to have decreased RBC production from a combined effect of blunted erythropoietin response, abnormal iron utilization, and iron-restricted erythropoiesis. Inflammatory mediators, TNF- α , IL-1ra, IL-2, and IL-6, have been implicated in the blunted erythropoietic response in the trauma ICU patients.

Because RBC transfusions remain an integral part of anemia management and are associated with increased morbidity and mortality, reduction or elimination of transfusion is a necessity. Transfusion practice in the United States and Western Europe has not changed over the past decade. The hemoglobin "trigger" for transfusion appears to be around 8.5 g/dL, despite the results of the TRICC trial that showed that maintaining hemoglobin concentrations of 7 to 9 g/dL in certain ICU populations lowers mortality rates. In addition, lowering and/or eliminating a transfusion trigger in most ICU patients will minimize or eliminate the exposure to RBC transfusions. Allogeneic RBC transfusions are associated with complications in the critically ill trauma patient, including higher mortality rates, longer hospital and ICU length of stays, higher incidence of nosocomial infections, and longer duration of mechanical ventilation.

Erythropoietic-stimulating agents along with iron supplementation are used to overcome the blunted endogenous erythropoietin response and iron-restricted erythropoiesis seen in anemia of critical illness. Because of scarce evidence, no strict criteria can be recommended on the use of exogenous erythropoietin in critically ill trauma patients. Consensus guidelines for the management of anemia in critical care patients that address the role(s) of blood transfusion, iron supplementation, and/or erythropoietic agents are needed.

References

1. Rodriguez RM, Corwin HL, Gettinger A, et al. Nutritional deficiencies and blunted erythropoietin response as causes of anemia of critical illness. *J Crit Care* 2001;16:36-41.
2. Corwin HL, Gettinger A, Pearl RG, et al. 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. Littenberg B, Corwin HL, Gettinger A, et al. A practice guideline and decision aide for blood transfusion. *Immunohematology* 1995;11:88-92.
4. Corwin HL, Gettinger A, Pearl RG, et al. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. *JAMA* 2002;288:2884-6.
5. Vincent JL, Baron J-F, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA* 2002;288:1499-507.

6. von Ahsen N, Muller C, Serke S, et al. Important role of nondiagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients. *Crit Care Med* 1999;27:2630-9.
7. Corwin HL, Parsonnet KC, Gettinger A. RBC transfusion in the ICU. Is there a reason? *Chest* 1995;108:767-71.
8. Napolitano LM. Current status of blood component therapy in surgical critical care. *Curr Opin Crit Care* 2004;10:311-7.
9. Stubbs JR. Alternatives to blood product transfusion in the critically ill: Erythropoietin. *Crit Care Med* 2006;34(Suppl):S160-9.
10. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;352(10):1011-23.
11. Smoller BR, Kruskall MS. Phlebotomy for diagnostic laboratory tests in adults: Pattern of use and effect on transfusion requirements. *N Engl J Med* 1986;314:1233-5.
12. Dale JC, Pruett SK. Phlebotomy—a minimalist approach. *Mayo Clin Proc* 1993;68:249-55.
13. Rickard CM, Couchmann BA, Schmidt SJ, Dank A, Purdie DM. A discard volume of twice the vascular line deadspace ensures clinically accurate arterial blood gases and electrolytes and prevents unnecessary blood loss. *Crit Care Med* 2003;31:1654-8.
14. Fowler RA, Berenson M. Blood conservation in the intensive care unit. *Crit Care Med* 2003;31:S715-20.
15. Rogiers P, Zhang H, Leeman M, et al. Erythropoietin response is blunted in critically ill patients. *Intensive Care Med* 1997;23:159-62.
16. Corwin HL, Gettinger A, Rodriguez RM, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1999;27:2346-50.
17. Gabriel A, Kozek S, Chiari A, et al. High-dose recombinant human erythropoietin stimulates reticulocyte production in patients with multiple organ dysfunction syndrome. *J Trauma* 1998;44:361-7.
18. van Iperen CE, Gaillard CA, Kraaijenhagen RJ, et al. Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. *Crit Care Med* 2000;28:2773-8.
19. Pak M, Lopez MA, Gabayan V, Ganz T, Rivera S. Suppression of hepcidin during anemia requires erythropoietic activity. *Blood* 2006;108:3730-5.
20. Fleming RE, Bacon BR. Orchestration of iron homeostasis. *N Engl J Med* 2005;352:1741-4.
21. Weinstein DA, Roy CN, Fleming MD, et al. Inappropriate expression of hepcidin is associated with iron refractory anemia. *Blood* 2002;100:3776-81.
22. Fleming RE, Sly WS. Hepcidin: a putative iron-regulatory hormone relevant to hereditary hemochromatosis and the anemia of chronic disease. *Proc Natl Acad Sci U S A* 2001;98:8160-2.
23. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340:409-17.
24. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. First of two parts: blood transfusion. *N Engl J Med* 1999;340:438-47.
25. Taylor RW, Manganaro L, O'Brien J, et al. Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. *Crit Care Med* 2002;30:2249-54.
26. Claridge JA, Sawyer RG, Schulman AM. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. *Am Surg* 2002;68:566-72.
27. Nichols RL, Smith JW, Klein DB, et al. Risk of infection after penetrating abdominal trauma. *N Engl J Med* 1984;311:1065-70.
28. Edna TH, Bjerkeset T. Association between blood transfusion and infection in injured patients. *J Trauma* 1992;33:659-61.
29. Corwin HL. Blood transfusion in the critically ill patient. *Dis Mon* 1999;45:409-26.
30. Surgenor SD, Hampers MJ, Corwin HL. Is blood transfusion good for the heart? *Crit Care Med* 2001;29:S189-91.
31. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993;269:3024-9.
32. Finch CA. Erythropoiesis, erythropoietin, and iron. *Blood* 1982;60:1241-6.
33. Goodnough LT, Skikne B, Brugnara C. Erythropoietin, iron, and erythropoiesis. *Blood* 2000;96:823-33.
34. Georgopoulos D, Matamis D, Routsis C, et al. Recombinant human erythropoietin therapy in critically ill patients: a dose-response study. *Crit Care* 2005;9:R508-15.
35. Livingston DH, Anjaria D, Wu J, et al. Bone marrow failure following severe injury in humans. *Ann Surg* 2003;238:748-53.
36. Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med*. 2007;357(10):965-76.