Critical Care Medicine
Volume 27 • Number 11 • November 1999

2346

FEATURE ARTICLES

Efficacy of recombinant human erythropoietin in the critically ill patient: A randomized, double-blind, placebo-controlled trial

Howard L. Corwin MD, FCCM; [1]
Andrew Gettinger MD, FCCM; [1]
Robert M. Rodriguez MD; [2]
Ronald G. Pearl MD, PhD, FCCM; [2]
K. Dean Gubler DO, MPH; [3]
Christopher Enny BS; [4]
Theodore Colton ScD; [5]
Michael J. Corwin MD [5]

[1] From the Departments of Critical Care Medicine and Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, NH (HLC, AG);
[2] the Department of Anesthesiology, Stanford University, Stanford, CA (RMR, RGP);
[3] the Naval Medical Center, San Diego, CA (KDG);
[4] Ortho Biotech, Raritan, NJ (CE);
[5] and the School of Public Health, Boston University, Boston, MA (TC, MJC).

Supported, in part, by Ortho Biotech, Raritan, NJ.

Objective: **To determine whether the administration of recombinant human erythropoietin (rHuEPO) to critically ill patients in the intensive care unit (ICU) would reduce the number of red blood cell (RBC) transfusions required.**

Design: **A prospective, randomized, double-blind, placebo-controlled, multicenter trial.**

Setting: **ICUs at three academic tertiary care medical centers.**

Patients: **A total of 160 patients who were admitted to the ICU and met the eligibility criteria were enrolled in the study (80 into the rHuEPO group; 80 into the placebo group).**

Interventions: **Patients were randomized to receive either rHuEPO or placebo. The study drug (300 units/kg of rHuEPO or placebo) was administered by subcutaneous injection beginning ICU day 3 and continuing daily for a total of 5 days (until ICU day 7). The subsequent dosing schedule was every other day to achieve a hematocrit (Hct) concentration of >38%. The study drug was given for a minimum of 2 wks or until ICU discharge (for subjects with ICU lengths of stay >2 wks) up to a total of 6 wks (42 days) postrandomization.**

Measurements and Main Results: **The cumulative number of units of RBCs transfused was significantly less in the rHuEPO group than in the placebo group (*p* <.002, Kolmogorov-Smirnov test). The rHuEPO group was transfused with a**

total of 166 units of RBCs vs. 305 units of RBCs transfused in the placebo group. The final Hct concentration of the rHuEPO patients was significantly greater than the final Hct concentration of placebo patients (35.1 ± 5.6 vs. 31.6 ± 4.1; *p* <.01, respectively). A total of 45% of patients in the rHuEPO group received a blood transfusion between days 8 and 42 or died before study day 42 compared with 55% of patients in the placebo group (relative risk, 0.8; 95% confidence interval, 0.6, 1.1). There were no significant differences between the two groups either in mortality or in the frequency of adverse events.

Conclusions: **The administration of rHuEPO to critically ill patients is effective in raising their Hct concentrations and in reducing the total number of units of RBCs they require. (Crit Care Med 1999; 27:2346-2350)**

K EY W ORDS: erythropoietin; anemia; blood transfusion; transfusion medicine; blood substitutes; critical care; intensive care unit

Anemia is a problem that commonly complicates the course of critically ill patients admitted to the intensive care unit (ICU). We have found that 85% of patients admitted to the ICU with a length of stay >1 wk are transfused with ≥1 unit of red blood cells (RBCs) (mean, 9.5 ± 0.8 units) while in the ICU [1] . Similarly, Groeger et al. [2] reported that on any given day, as many as 14% of patients in ICU receive a blood transfusion. Most of the transfusions in the ICU are not associated with acute blood loss, but rather ICU patients appear to have a constant transfusion requirement of 2-4 units/wk [1] .

Why critically ill patients are unable to mount an erythropoietic response sufficient to compensate for the anemia that they develop while in the ICU is not completely clear. A blunted erythropoietic response to physiologic stimuli has been noted in both critically ill adults and children [3] [4] . This is particularly evident in patients with sepsis and may reflect the action of inflammatory mediators. Recently, the administration of pharmacologic doses of recombinant human erythropoietin (rHuEPO) to patients with multiple organ dysfunction was reported to result in an erythropoietic response, despite the presence of elevated cytokine concentrations [5] . Similarly, although the iron status of patients in the ICU has not been well studied, critically ill patients with multiple organ dysfunction have iron studies consistent with the anemia seen in patients with chronic inflammatory states (anemia of chronic disease) [5] . Taken together, these findings suggest that patients in the ICU may have inadequately elevated erythropoietin concentrations and/or are unable to respond appropriately to endogenous erythropoietin. We conducted a randomized, double-blind, placebo, controlled trial to determine whether the administration of rHuEPO to critically ill patients in the ICU is effective in reducing the number of units of RBCs these patients require.

MATERIALS AND METHODS

General Description.

The study was a prospective, randomized, double-blind, placebo, controlled, multicenter trial conducted at three academic medical centers between November 1993 and July 1997. Approval of the study was obtained from the Institutional Review Committee at each participating institution,

and informed consent was obtained from each patient (or their surrogate). The Food and Drug Administration via an investigator-sponsored investigational new drug application also approved the study. The objective of the study was to determine whether the administration of rHuEPO to critically ill ICU patients would reduce the number of units of RBCs these patients required.

Patients.

All patients admitted to the multidisciplinary ICU at Dartmouth-Hitchcock Medical Center (November 1993-July 1997), the multidisciplinary ICU at Stanford University Medical Center (May 1995-July 1997), and the surgical ICU at the Naval Medical Center San Diego (November 1995-July 1997) were evaluated for study eligibility before ICU day 3 (study day 1). Inclusion/exclusion criteria are displayed in Table 1 . Patients who qualified for the study and who gave informed consent were randomized and entered into the study on ICU day 3 (study day 1). Patients were randomized using computer-generated random numbers. Randomization was stratified by site.

Study Design.

Patients were randomized and entered into the study on ICU day 3 (study day 1). The study drug (300 units/kg rHuEPO [Procrit, Ortho Biotech, Raritan, NJ] or placebo) was administered by subcutaneous injection beginning on ICU day 3 and continuing

TABLE 1 -- Inclusion/exclusion criteria

Inclusion criteria
Age, 18 yrs or older
Gender, male or female; female subjects must be postmenopausal for at least 1 yr or surgically sterile (hysterectomy or tubal ligation); female subjects of childbearing potential must have a negative pregnancy test (serum human chorionic gonadotropin radioimmunoassay) immediately before study entry
No deficiency of B_{12} (<200 pg/mL) or folate (<2.5 ng/mL)
No iron deficiency (transferrin saturation, <15%, and ferritin, <50 ng/mL)
Hematocrit, <38%
Subject (or next of kin) must read and sign the informed consent form
Exclusion criteria
Presence of any primary hematologic disease or B_{12} (<200 pg/mL), folate (<2.5 ng/mL), or iron deficiency (transferrin saturation, <15%, and ferritin, <50 ng/mL)
Risk of hospital death (Acute Physiology and Chronic Health Evaluation), >80%
Neutropenia (<500 neutrophils) or thrombocytopenia (<20,000 platelets)
Vasopressor requirement for blood pressure support (other than low-dose dopamine <5 μg/kg/min) and severe respiratory compromise (Fio_2 > 60% and/or positive end-expiratory pressure > 10)
Chronic renal failure on maintenance dialysis
Liver failure, cirrhosis, varices, hepatic encephalopathy
Seizures within prior 6 months
Hypertension not controlled on medication (systolic, >200; diastolic, >110)
Severe head injury
Recent neurosurgical procedure or cerebrovascular accident (within 1 month)
Recent androgen therapy (within 1 month)
Recent cytotoxic or immunosuppressive therapy (within 1 month)
Autoimmune hemolysis (Coombs' test, positive)
Subjects who have received an experimental drug within 30 days before this study
Previous or involvement in prior recombinant human erythropoietin clinical study
Subjects prohibited from receiving blood transfusions
Pregnancy or lactation
Human immunodeficiency virus positive
Active collagen-vascular disease
Recent thromboembolic disease (within 6 months)
Active bleeding

daily for a total of 5 days (until ICU day 7, study day 5). The subsequent dosing schedule was every other day. The study drug was given for a minimum of 2 wks or until ICU discharge (for subjects with ICU lengths of stay of >2 wks) up to a total of 6 wks (42 days) postrandomization. The study drug was temporarily withheld when the hematocrit (Hct) concentration reached >38% and resumed if the Hct again fell to <38%. The study drug was given intravenously if the platelet count was <20,000. All subjects were followed for a total of 42 days after randomization (study day 42).

All patients began receiving oral iron (liquid preparation), $\geq$150 mg of elemental iron, either orally or via a nasogastric tube starting on study day 1 (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 (a transferrin saturation of <20% and a decrease of serum ferritin to <100 ng/mL).

The need for a blood transfusion was determined by the subject's attending physician. There was no specific transfusion protocol used in this study. The frequency and severity of either adverse or unusual events associated with drug administration were monitored.

Study Outcomes.

There were two primary end points prospectively identified: a) the cumulative blood transfusion requirement from study day 1; and b) transfusion independence between study day 8 and study day 42.

Statistical Analysis.

The sample size for the study was calculated based on study outcome 2. A sample size of 206 (103 per group) was planned to achieve a power of 80% to detect a reduction with rHuEPO from 50% to 30% in the percent of subjects either receiving a transfusion between study days 8 and 42 or dying before study day 42. However, study enrollment was stopped early (at 160 subjects) because a slowing of the pace of enrollment made it impractical to continue further enrollment of subjects.

All patients were followed up for a total of 42 days (6 wks) from the date of randomization, unless death occurred earlier. Final laboratory studies were obtained on day 42 or at hospital discharge for those patients discharged before day 42. An analysis of outcomes was on an intention-to-treat basis.

To assess changes in laboratory values from baseline value, we used analysis of covariance with baseline value and number of days between baseline and final value as covariates. For study outcome 1, namely, the comparison of cumulative blood transfusion requirements in the two study groups, we used the Kolmogorov-Smirnov test [6] . For study outcome 2, namely, being transfusion independent during the period of 8-42 days postrandomization, we used the chi^2 test. We dichotomized this outcome as the patient being alive on day 42 and not having received a blood transfusion between days 8 and 42 (success) vs. death before day 42 or having received a blood transfusion at any time between days 8 and 42 (failure). We also conducted a survival analysis of study outcome 2 using the combined outcome of death and/or transfusion as the end point; we compared the survival curves for the two groups by means of the log rank test. For all statistical tests, a two-tailed $p \leq .05$ was considered significant.

RESULTS

Patients.

There were 1,778 patients in the ICU on day 3; all were screened for enrollment. Of these, 329 were found to be eligible for the study and 160 were subsequently enrolled and randomized (Dartmouth, 47; Stanford, 89; and the Naval Hospital, 24). There were 80 subjects enrolled in each group. The most common reasons for exclusion were hematologic disease, recent thromboembolic event, seizures or severe head injury, renal failure, and active bleeding (Table 1). Similarly, the most common reason for nonenrollment of eligible patients was the refusal to consent. There were no significant differences between groups at enrollment in either patient characteristics or ICU admitting diagnosis

---

(Tables 2 and 3). Patients eligible for the study but not enrolled were similar to the enrolled patients. The study outcomes are summarized in Table 4 .

Blood Transfusions.

The cumulative number of RBC units transfused was significantly less in the rHuEPO group than in the placebo group (Fig. 1 ; $p < .002$, Kolmogorov-Smirnov test). The rHuEPO group received a total of 166 units of RBCs vs. 305 units of RBCs received by the placebo group. The pretransfusion Hct in the rHuEPO and placebo groups was not significantly different (27.5 ± 3.8 vs. 27.0 ± 4.0, respectively).

Patients in the rHuEPO group received a mean of 8.3 ± 4.5 doses of rHuEPO (23,000 ± 7,000 units/dose). A total of 20 patients (16 rHuEPO, 4 placebo) reached a Hct concentration of 38% and had further study drug withheld.

Transfusion Independence.

A total of 45% of patients in the rHuEPO group either received a blood transfusion between study days 8 and 42 or died before study day 42 compared with 55% of patients in the placebo group (relative risk, 0.8; 95% confidence interval [CI], 0.6, 1.1).

Laboratory Studies.

Despite the reduced number of total units of RBCs transfused, the change in Hct from baseline to final measurement was

significantly greater in the rHuEPO patients (4.8; 95% CI, 3.8, 5.9) than in the placebo patients (1.4; 95% CI, 0.3, 1.4; p <.001, analysis of covariance). Likewise, the change in percentage of reticulocytes from baseline to final measurement was significantly greater in the rHuEPO patients (2.5; 95% CI, 1.9, 3.0) than in the placebo patients (0.8; 95% CI, 0.3, 1.3; p <.001, analysis of covariance). The final Hct of the rHuEPO patients was significantly greater than the final Hct of the placebo patients (35.1 ± 5.6 vs. 31.6 ± 4.1, respectively; p <.01). Final values were obtained day 21.5 ± 13.8 in the rHuEPO group and day 22.8 ± 15.2 in the placebo group.

Adverse Events.

There were no significant differences observed between the two groups either in mortality (Fig. 2) or in the frequency of adverse events (Table 5).

DISCUSSION

The volume of blood transfused in the ICU is staggering. In the current study, 55% of patients in the placebo group received

TABLE 2 -- Characteristics of subjects at enrollment [a]

	Group	
	Recombinant Human Erythropoietin (n = 80)	**Placebo (n = 80)**
% Male	55	53
Age (yrs)	59.1 ± 20.5	60.4 ± 18.8
Acute Physiology and Chronic Health Evaluation II	18.2 ± 5.3	18.4 ± 5.4
Hematocrit	30.2 ± 4.2	30.4 ± 3.7
Reticulocyte (%)	1.7 ± 1.1	1.7 ± 1.1
Erythropoietin (nL 25 mU/mL)	39 ± 40	30 ± 29

[a] No significant differences observed.

TABLE 3 -- Primary intensive care unit (ICU) diagnosis at enrollment [a]

	Group	
Primary ICU Diagnosis	**Recombinant Human Erythropoietin (n = 80)**	**Placebo (n = 80)**
Respiratory infection	18	20
Postoperative respiratory insufficiency	10	8
Other respiratory	18	16
Trauma	12	12
Gastrointestinal surgery	5	5
Sepsis	3	3
Other	14	16

[a] No significant differences observed.

TABLE 4 -- Study outcomes

	Group	
	Recombinant Human Erythropoietin	**Placebo**
Total units transfused [a]	166	305

%Transfused or died days 8-42	45	55
Hct change (baseline to final) [b]	4.8 (95% CI, 3.8, 5.9)	1.4 (95% CI, 0.3, 2.8)
Final Hct [c]	35.1 ± 5.6	31.6 ± 4.1
Reticulocyte %Change (baseline to final) [b]	2.5 (95% CI, 1.9, 3.0)	0.8 (95% CI, 0.3, 1.3)

Hct, hematocrit; CI, confidence interval.

[a] p <.002 (Kolmogorov-Smirnov test);
[b] p <.001 (analysis of covariance), baseline vs. final, recombinant human erythropoietin vs. placebo;
[c] p <.01.

transfusion and, on average, received almost four units of RBCs. This is similar to other reports of ICU patients [7] . We demonstrated, however, that the administration of rHuEPO to ICU patients resulted in a 45% reduction in the number of units of RBCs transfused (305 units for the placebo group vs. 166 units for the rHuEPO group). This was highly significant and was accomplished without any significant adverse events attributable to the rHuEPO therapy.

Our finding of a marked response to pharmacologic doses of erythropoietin supports the concept that critically ill patients have a blunted erythropoietic response to physiologic stimuli as well as an impaired ability to respond to endogenous erythropoietin. Although rHuEPO has been widely used and is highly effective in a variety of clinical settings, little data exist regarding its use in the critically ill [8] . Gabriel et al. [5] , in a small trial of patients with multiple organ dysfunction and elevated cytokine concentrations, also noted evidence of an erythropoietic response to pharmacologic doses of erythropoietin. Their study was of shorter duration (3 wks) than was our study and only examined a small number

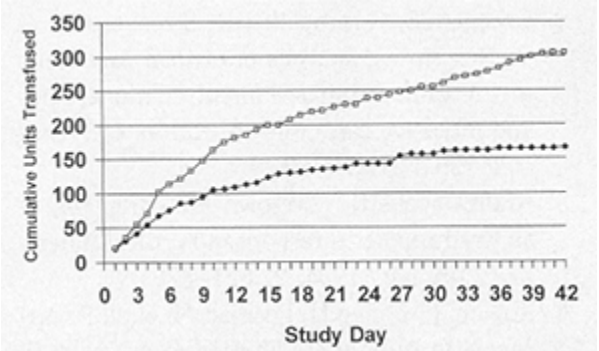

Figure 1. Cumulative units of red blood cells transfused by study day. *Diamonds*, the recombinant human erythropoietin group; *squares*, the placebo group. p =.002 by the Kolmogorov-Smirnov test.

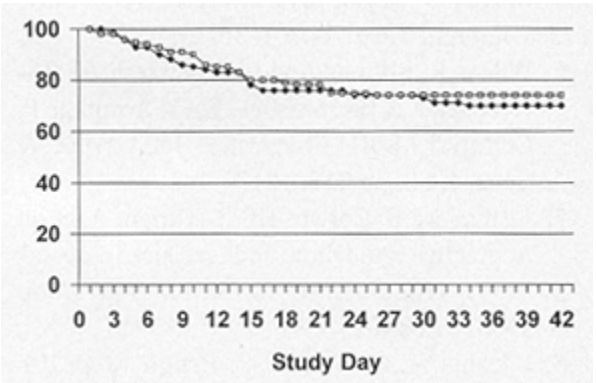

Figure 2. Mortality by study day. *Diamonds*, the recombinant human erythropoietin group; *squares*, the placebo group.

TABLE 5 -- Adverse events [a]

Adverse Event	Recombinant Human Erythropoietin	Placebo
Death	24	21

Deep vein thrombosis	4	4
Thrombocytopenia	9	3
Thrombocytosis	6	2

No other category of adverse event was observed in more than four individuals.

[a] No significant differences were observed.

of patients. They were, therefore, not able to demonstrate any effect on the amount of blood transfused, despite the evidence of a marrow response to rHuEPO. In a study of patients with acute burns, rHuEPO therapy did not prevent anemia or result in a decrease in RBC transfusion requirement [9] . This also was a small trial, using a lower rHuEPO dose; however, increased erythropoiesis was noted in the subgroup of patients having smaller burns. This is of interest because these latter patients would be the subgroup of burn patients who would be predicted to have less bone marrow suppression and, therefore, more likely to respond to a lower rHuEPO dose.

The second outcome that we examined was the ability to make patients "transfusion independent" with rHuEPO therapy. We chose to examine the days 8-42 time period to account for the expected lag time from initiation of rHuEPO therapy to the onset of marrow response. Although patients in the rHuEPO group were less likely to die or receive a blood transfusion between study days 8 and 42 (45% vs. 55%), this difference was not statistically significant. The relative risk for either death before day 42 or transfusion between days 8 and 42 with rHuEPO was 0.8 (95% CI, 0.6, 1.1). This, in part, may reflect the fact that even day 8 is on the early side for an expected erythropoietic response. In addition, the study was underpowered to detect the difference in the transfusion rate observed. The sample size in this study would have allowed the detection of a relative risk in the range of 0.6; however, a sample size of ~300 subjects per group would have been required for a power of 80% to detect the 0.8 relative risk observed.

It is clear that significant variability exists in the transfusion practice of physicians. This is driven more by the physician's "transfusion trigger" than by the patient's physiologic need for blood [1] [7] . We did not use a transfusion protocol in our study; however, given the nature of the study, it is unlikely that variability in physician transfusion practice significantly influenced the reduction in cumulative blood transfusions that we observed. The fact that the pretransfusion Hct was comparable in the two groups suggests that physician transfusion practice was, in fact, similar in both groups. One could speculate, however, that if the "transfusion trigger" in general was lowered by virtue of this study, if anything, it might have made the demonstration of "transfusion independence" more difficult because of a disproportionate reduction in RBC transfusions in the placebo group. Given the similar pattern of mortality in the two groups (Fig. 2), it is also unlikely that mortality had an important effect on study outcomes.

Transfused RBCs, especially during the acute time period after transfusion, are not "normal." Storage of RBCs temporarily decreases 2,3-diphosphoglycerate concentrations, interfering with the ability of RBCs to unload oxygen, and temporarily impairs RBC deformability. In particular, "older" RBCs are a greater problem. Marik and Sibbald [10] , in a study of septic patients undergoing mechanical ventilation, not only failed to demonstrate acute improvement in oxygen uptake after the transfusion of 3 units of RBCs (hemoglobin, 9.0-11.9 g/dL), but also found that patients receiving "old" transfused blood (>15 days) developed evidence of splanchnic ischemia. A subsequent study using a rat sepsis model found that whereas transfusion of "fresh" RBCs acutely increased systemic oxygen uptake, this effect was impaired with transfusion of RBCs stored for 28 days [11] . On the other hand, rHuEPO therapy, in contrast to blood transfusion, has been shown to improve extractable oxygen in patients undergoing open-heart surgery [12] . In these patients, treatment with rHuEPO resulted in a right shift in the oxygen dissociation curve (vs. left shift with transfusion). In patients in the rHuEPO group, both P50 and 2,3-diphosphoglycerate concentrations were increased in contrast to a decrease in these variables in patients in the placebo group. Finally, there was a lower occurrence rate and severity of postoperative lactic acidosis in the group of patients receiving rHuEPO. We did not measure oxygen status in our patients; however, the changes demonstrated in the open-heart surgery patients would clearly be beneficial to the critically ill ICU patient. The transfusion of RBCs may not only "not help" but, in some circumstances, may also harm the critically ill patient.

The use of rHuEPO provides a unique opportunity to achieve higher hemoglobin concentrations in the critically ill patient, without exposing them to the risk of RBC transfusion. In our study, the final Hct in the patients receiving rHuEPO was significantly higher than in the placebo patients (35 vs. 31, respectively), despite receiving 45% fewer units of RBCs. We did not find an increase in either mortality or other adverse events with rHuEPO therapy. This is consistent with the literature, which has repeatedly demonstrated that rHuEPO therapy is very well tolerated [8] . The adverse reactions that have occurred with rHuEPO therapy appear to be mostly limited to the chronic renal failure population.

The optimal dose of rHuEPO and the timing of rHuEPO administration remain to be determined. These factors clearly have cost

as well as efficacy implications. We used a relatively high dose of rHuEPO (300 units/kg), initially administered daily, followed by an every other day dosing schedule. However, recent data suggest that a weekly rHuEPO dose of 600 units/kg weekly should yield comparable results [13] . Because of the lag time for marrow response to rHuEPO, early initiation of rHuEPO would be expected to improve efficacy. The importance of early initiation of rHuEPO therapy has been well demonstrated in other clinical settings [8] . We initiated rHuEPO on ICU day 3 to allow for screening and to exclude the short-term ICU patient. Ideally, it would be preferable to initiate rHuEPO at ICU admission (or before), in particular, for the "long-term" ICU patient who stands to gain the most benefit from rHuEPO therapy. However, identification of these patients prospectively can be difficult. Administration of rHuEPO to those patients who leave the ICU within 1 or 2 days would clearly be less cost-effective than restricting therapy to the more long-term ICU patients. Key in developing guidelines for rHuEPO use in the ICU will be balancing the early initiation of therapy vs. selection of those patients most likely to benefit.

The cost of rHuEPO as used in our study was on average $1,890 per patient. If we had used the weekly dosing protocol (600 units/kg) in the present study, it would have resulted in a cost of $840 to $1,260 per patient rather than the $1,890 we observed. If the cost of a unit of transfused RBCs is assumed to be ~$200 [14] , the additional cost per unit of RBC saved with rHuEPO in this study was $900/unit saved (not transfused). On the other hand, if a weekly dosing protocol had been used, assuming equal efficacy, the cost would have been $300-$500/unit saved.

The cost of a blood transfusion will clearly vary between centers. In addition, the $200 estimate may underestimate the actual cost of a transfusion. In cancer patients, for example, the mean cost of blood transfusions per year has been reported to be $1,668, or ~$400-$450 per unit transfused [15] . Similarly, Cantor et al. [16] has placed the cost of transfusing a unit of blood at $270. Our analysis also does not take into account the potential savings resulting from the avoidance of the deleterious effects of RBC transfusion, i.e., infection, or benefits derived from the higher Hct concentrations achieved in patients receiving rHuEPO. Our study was focused on the efficacy of rHuEPO therapy. Finally, the benefit of conservation of an increasingly scarce resource, i.e., blood, also needs to be considered. This latter issue will become increasingly important in the future, with projections of a 4 million-unit annual shortfall in RBCs in the United States by the year 2030 [14] . It is very likely rHuEPO therapy, particularly using a weekly dosing schedule of 600 units/kg, will be demonstrated to be a cost-effective therapy in the future.

In conclusion, the use of rHuEPO is effective in reducing the number of units of RBCs that critically ill ICU patients receive. Despite this reduction in the units of RBCs transfused, Hct concentrations are significantly increased in patients receiving rHuEPO. No adverse effects associated with rHuEPO therapy were noted. The potential benefits to the critically ill patient resulting from the avoidance of RBC transfusion still remains to be more fully examined.

REFERENCES

1. Corwin HC, Parsonnet KC, Gettinger A: RBC transfusion in the ICU: Is there a reason? *Chest* 1995; 108:767-771 Abstract

2. Groeger JS, Guntupalli KK, Strosberg M, et al: Descriptive analysis of critical care units in the United States: Patient characteristics and intensive care unit utilization. *Crit Care Med* 1993; 21:279-291 Abstract

3. Krafte-Jacobs B, Levetown ML, Bray GL, et al: Erythropoietin response to critical illness. *Crit Care Med* 1994; 22:821-826 Abstract

4. Rogiers P, Zhang H, Leeman M, et al: Erythropoietin response is blunted in critically ill patients. *Intensive Care Med* 1997; 23: 159-162 Abstract

5. 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; 44:361-367 Abstract

6. Wilcox R: Kolmogorov-Smirnov test. *In:* Enclycopedia of Biostatistics. Vol 3. Armitage P, Colton T (Eds). Chichester, John Wiley & Sons, 1998, pp 2174-2176

7. Littenberg B, Corwin HC, Gettinger A, et al: A practice guideline and decision aide for blood transfusion. *Immunohematology* 1995; 11:88-94

8. Cazzola M, Mercuriali F, Brugnara C: Use of recombinant erythropoeitin outside the setting of uremia. *Blood* 1997; 89: 4248-4267 Citation

9. Still JM, Belcher K, Law EJ, et al: A double-blinded prospective evaluation of recombinant human erythropoietin in acutely burned patients. *J Trauma* 1995; 38: 233-236 Abstract

10. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; 269:3024-3029 Abstract

11. Fitzgerald RD, Martin CM, Dietz GE, et al: Transfusing red blood cells stored in citrate phosphate dextrose adenine-1 for 28 days fails to improve tissue oxygenation in rats. *Crit Care Med* 1997; 25:726-732 Full Text

12. Sowade O, Gross J, Sowade B, et al: Evaluation of oxygen availability with oxygen status algorithm in patients undergoing open heart surgery treated with epoetin beta. *J Lab Clin Med* 1997; 129:97-105 Abstract

13. Goldberg MA, McCutchen JW, Jove M, et al: A safety and efficacy comparison study of two dosing regimens of epoetin alfa in patients undergoing major orthopedic surgery. *Am J Orthop* 1996; 25:544-552 Abstract

14. Nucci ML, Abuchowski A: The search for blood substitutes. *Sci Am* 1998; 278:72-79 Citation

15. Mohandas K, Aledort L: Transfusion requirements, risks, and costs for patients with malignancy. *Transfusion* 1995; 35:427-430 Abstract

16. Cantor SB, Hudson DV, Lichtiger B, et al: Costs of blood transfusion: A process flow analysis. *J Clin Oncol* 1998; 16:2364-2370 Abstract

