

Efficacy of Recombinant Human Erythropoietin in Critically Ill Patients

A Randomized Controlled Trial

Howard L. Corwin, MD

Andrew Gettinger, MD

Ronald G. Pearl, MD, PhD

Mitchell P. Fink, MD

Mitchell M. Levy, MD

Marc J. Shapiro, MD

Michael J. Corwin, MD

Theodore Colton, ScD

for the EPO Critical Care Trials Group

BLOOD TRANSFUSION, AN INTEGRAL part of clinical practice for most of the last century, has been looked upon as relatively “risk free” and with obvious clinical benefit.¹ A dramatic change in thinking occurred in the early 1980s, when concerns about transfusion-related infections, particularly those caused by hepatitis C and the human immunodeficiency virus (HIV), prompted a re-evaluation of the risks of allogeneic transfusion. Although advances in transfusion medicine have greatly decreased the risk of viral transmission during blood transfusion, other concerns now drive the debate over transfusion practice and have led to a re-examination of the approach to red blood cell (RBC) transfusion.

Critically ill patients typically receive multiple RBC transfusions.²⁻⁴ Recent data from both the United States and Western Europe demonstrate that between 35% and 50% of all patients admitted to ICUs today receive on average almost 5 RBC units during their

For editorial comment see p 2884.

Context Anemia is common in critically ill patients and results in a large number of red blood cell (RBC) transfusions. Recent data have raised the concern that RBC transfusions may be associated with worse clinical outcomes in some patients.

Objective To assess the efficacy in critically ill patients of a weekly dosing schedule of recombinant human erythropoietin (rHuEPO) to decrease the occurrence of RBC transfusion.

Design A prospective, randomized, double-blind, placebo-controlled, multicenter trial conducted between December 1998 and June 2001.

Setting A medical, surgical, or a medical/surgical intensive care unit (ICU) in each of 65 participating institutions in the United States.

Patients A total of 1302 patients who had been in the ICU for 2 days and were expected to be in the ICU at least 2 more days and who met eligibility criteria were enrolled in the study; 650 patients were randomized to rHuEPO and 652 to placebo.

Intervention Study drug (40000 units of rHuEPO) or placebo was administered by subcutaneous injection on ICU day 3 and continued weekly for patients who remained in the hospital, for a total of 3 doses. Patients in the ICU on study day 21 received a fourth dose.

Main Outcome Measures The primary efficacy end point was transfusion independence, assessed by comparing the percentage of patients in each treatment group who received any RBC transfusion between study days 1 and 28. Secondary efficacy end points identified prospectively included cumulative RBC units transfused per patient through study day 28; cumulative mortality through study day 28; change in hemoglobin from baseline; and time to first transfusion or death.

Results Patients receiving rHuEPO were less likely to undergo transfusion (60.4% placebo vs 50.5% rHuEPO; $P < .001$; odds ratio, 0.67; 95% confidence interval [CI], 0.54-0.83). There was a 19% reduction in the total units of RBCs transfused in the rHuEPO group (1963 units for placebo vs 1590 units for rHuEPO) and reduction in RBC units transfused per day alive (ratio of transfusion rates, 0.81; 95% CI, 0.79-0.83; $P = .04$). Increase in hemoglobin from baseline to study end was greater in the rHuEPO group (mean [SD], 1.32 [2] g/dL vs 0.94 [1.9] g/dL; $P < .001$). Mortality (14% for rHuEPO and 15% for placebo) and adverse clinical events were not significantly different.

Conclusions In critically ill patients, weekly administration of 40000 units of rHuEPO reduces allogeneic RBC transfusion and increases hemoglobin. Further study is needed to determine whether this reduction in RBC transfusion results in improved clinical outcomes.

JAMA. 2002;288:2827-2835

www.jama.com

ICU stay.^{5,6} However, the view of RBC transfusion as risk free is no longer tenable. In addition to well-described transfusion complications, recent studies have raised the issue of immunosup-

Author Affiliations, Financial Disclosures, and Members of the EPO Critical Care Trials Group are listed at the end of this article.

Corresponding Author and Reprints: Howard L. Corwin, MD, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756 (e-mail: howard.l.corwin@hitchcock.org).

pression related to allogeneic blood transfusion,^{1,7-10} as well as concerns regarding the age of RBCs transfused.^{11,12} Adding to the controversy about risk-benefit ratio for RBC transfusion are recent data showing that an aggressive RBC transfusion strategy may decrease the likelihood of survival in selected subgroups of critically ill adults.¹³ Accordingly, limiting exposure to allogeneic RBC transfusions would be advantageous in critically ill patients.

Production of RBCs by the bone marrow is impaired in critically ill patients, and this phenomenon contributes to both the development and the persistence of anemia. Critically ill patients tend to be anemic early in their ICU course and hemoglobin levels fall during the ICU stay.^{3,6} The anemia associated with critical illness is probably fundamentally similar to the anemia of chronic inflammatory disease.¹⁴ A major feature of the anemia of critical illness is a failure of circulating erythropoietin concentrations to increase appropriately in response to physiologic stimuli.¹⁵⁻¹⁹ Thus, we hypothesized that treatment with pharmacologic doses of recombinant human erythropoietin (rHuEPO) might decrease exposure to allogeneic blood and raise the hemoglobin level in critically ill patients.

Recently, a small, randomized, placebo-controlled trial of critically ill patients who received a combination of daily administration of rHuEPO for 5 days followed by every-other-day administration reported an almost 50% reduction in the number of RBC transfusions.²⁰ Despite receiving fewer RBC transfusions, patients receiving rHuEPO had a significantly greater increase in hematocrit. The efficacy of rHuEPO in this trial has raised the question whether rHuEPO would also be effective at reducing transfusions in a larger, more diverse critically ill population. Furthermore, in other clinical settings a weekly rHuEPO dose of 40 000 units has been shown to be as effective as more frequent dosing regimens.²¹⁻²⁴ Our study was designed to assess the efficacy of a weekly dosing schedule of rHuEPO in

reducing the exposure to allogeneic RBCs in a large, diverse group of critically ill patients.

METHODS

This study was a prospective, randomized, double-blind, placebo-controlled, multicenter trial conducted at 65 US medical centers between December 1998 and June 2001 (study group members are listed at the end of this article). Approval of the study was obtained from the institutional review committee at each participating institution and written informed consent was obtained from each patient (or surrogate). Each institutional review committee determined who could qualify as a patient surrogate for the purpose of giving consent at their institution. The study was monitored for safety by an independent data and safety monitoring board, which met 11 times during the course of the study; the stopping rule was a mortality difference of $P < .001$ (DSMB listed at the end of this article). The study objective was to determine if administration of rHuEPO to critically ill patients admitted to the ICU would reduce the occurrence of any RBC transfusion as well as reduce the cumulative number of RBC units transfused.

The study was designed by the principal investigators with input from the data coordinating center and was reviewed by the study sponsor. Patient enrollment was done at each site and supervised by the data coordinating center. Randomization and data analysis were done by the data coordinating center. The principal investigators and manuscript committee, with assistance from the data coordinating center, interpreted the data and were responsible for the manuscript. The final manuscript was reviewed by the study sponsor. The manuscript committee determined the final manuscript content and had full access to all data.

Study Population

All patients admitted to either a medical, surgical, or a medical/surgical ICU in each of the 65 participating institutions, who remained in the ICU for at

least 2 days, were evaluated for study eligibility prior to ICU day 3 (study day 1). Inclusion criteria included stay in the ICU for 3 days; age at least 18 years; hematocrit less than 38%; and provision of signed informed consent. Exclusion criteria included renal failure with dialysis; uncontrolled hypertension; new onset or uncontrolled seizures; acute burns; pregnancy or lactation; acute ischemic heart disease; acute gastrointestinal bleeding; prior treatment with rHuEPO; participation in another research protocol; and expected ICU discharge within 48 hours of ICU day 2. Patients who met entry criteria and who gave informed consent were randomized and entered into the study on ICU day 3 (study day 1). Randomization was stratified by site and entailed use of computer-generated random numbers (FIGURE 1).

Study Design

Study drug (40 000 units of rHuEPO [Procrit; Ortho Biotech Products, LP, Bridgewater, NJ]) or a placebo identical in appearance was administered by subcutaneous injection on ICU day 3 and continued once weekly for patients who remained in the hospital, for a total of 3 doses (study days 1, 7, and 14). Patients who remained in the ICU on study day 21 received a fourth dose. Syringes were prepared either in the hospital's pharmacy or in the patient care area. Study drug was withheld if the hematocrit was 38% prior to the scheduled administration. All patients were to be followed up for 28 days following randomization (study day 28).

Patients received oral iron (liquid preparation), at least 150 mg/d of elemental iron, either orally or via nasogastric tube beginning on study day 1 (ICU day 3), unless they could not tolerate oral feeding. Parenteral iron was to be given to patients demonstrating an inadequate response to oral iron (transferrin saturation $< 20\%$ and a decrease of serum ferritin to < 100 ng/mL [< 225 pmol/L]).

The need for RBC transfusion was determined by each patient's physician. The following transfusion guideline was

established for the study: no RBC transfusion if the hemoglobin level was at least 9 g/dL or the hematocrit concentration was at least 27%, unless there was a specific clinical indication (active bleeding, ischemia, or other); RBC transfusion for a hemoglobin level less than 9 g/dL or a hematocrit concentration less than 27% was at a physician's discretion. There was no hemoglobin level or hematocrit concentration that mandated an RBC transfusion. Transfusion indication, pretransfusion hemoglobin level, and pretransfusion hematocrit concentration were recorded for each RBC transfusion. In addition, patients were monitored for all adverse events associated with either drug administration or RBC transfusion.

Study Outcomes

The primary efficacy end point was transfusion independence, assessed by comparing the percentage of patients in each treatment group who received any RBC transfusion between study days 1 and 28.

Secondary efficacy end points identified prospectively were cumulative RBC units transfused per patient through study day 28; cumulative mortality through study day 28; change in hemoglobin from baseline; and time to first transfusion or death. Additional data recorded included ICU length of stay, hospital length of stay, and days receiving mechanical ventilation.

Baseline Assessment

Baseline demographic, diagnostic, and laboratory data were obtained at randomization. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were based on data obtained within the first 24 hours after ICU admission. Admitting diagnosis was selected from a list of diagnostic categories; all that applied were noted. Comorbidities identified from the medical history included cardiac disease, chronic pulmonary disease, diabetes mellitus, hypertension, malignancy, peripheral vascular disease, primary hematologic disease, and thromboembolic disease.

Study Regimen and Follow-up

Adverse events were assessed daily. Laboratory data were obtained weekly, within 24 hours prior to the weekly administration of study drug, and at study completion. Patients discharged from the hospital prior to study day 28 had final laboratory data obtained within 7 days of study day 28. Mechanical ventilation was recorded on a daily basis, as was a patient's presence in the ICU.

Statistical Analysis

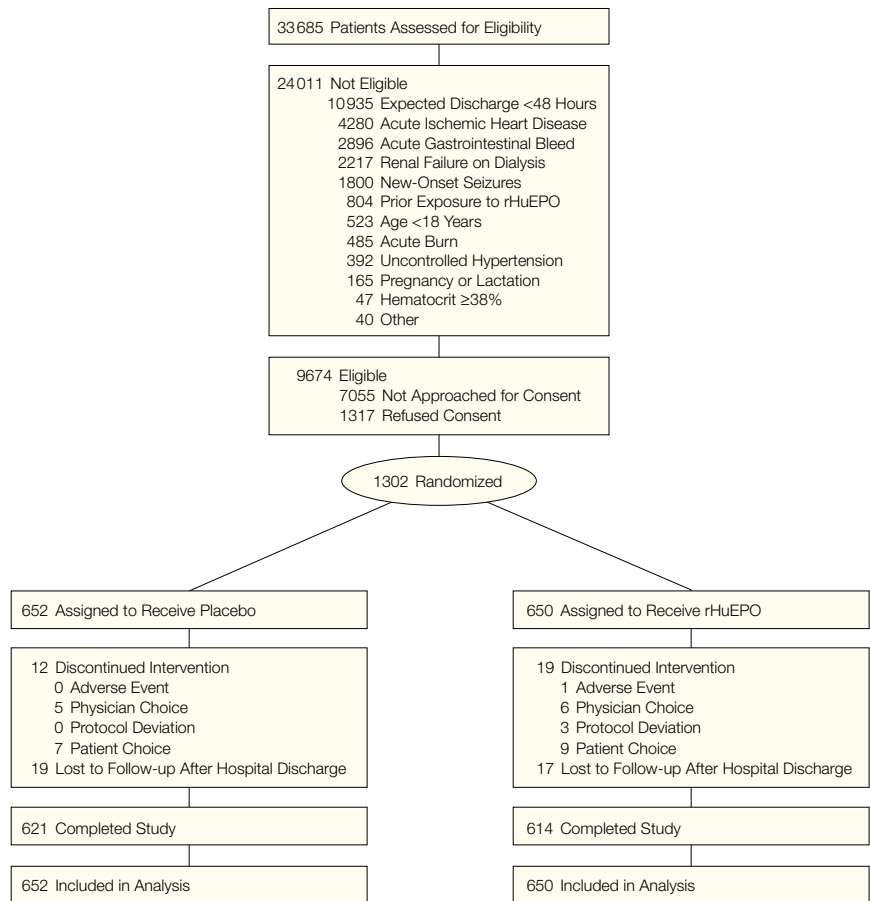
A sample size of 1300 was calculated to provide at least 90% power to detect an absolute treatment difference of 10% with respect to the primary efficacy end point, percentage of patients receiving any RBC transfusion. All patients were followed up for 28 days, unless death oc-

curred earlier. Analysis of outcomes was on an intent-to-treat basis.

The primary efficacy end point was evaluated using a 2-sided Fisher exact test. Patients not receiving transfusion at the time of study withdrawal or lost to follow-up were considered not transfused for this analysis. In addition, a second analysis was done in which all patients withdrawn or lost to follow-up were considered transfused.

Secondary analyses were specified in the original study protocol. To compare the number of RBC units transfused per patient in the 2 study groups, we used the Mann-Whitney test. Transfusion rate, expressed as RBC units transfused per day alive while in the study, was determined by dividing the total number of RBC units transfused for each group by

Figure 1. Screening and Enrollment of Study Patients



rHuEPO indicates recombinant human erythropoietin. Individuals could have more than 1 reason for exclusion.

the total number of days alive for the patients in that group (sum of the number of days alive for each individual patient in the group, maximum of 28 for a patient surviving to study day 28).

Mechanical ventilation was analyzed as ventilator-free days, defined as the number of days a patient was alive and did not receive mechanical ventilation through study day 28. Patients were included whether mechanical ventilation was initiated on or after study day 1. Patients who were reventilated were also included. Patients were excluded only if they withdrew from the study, were lost to follow-up, or had a

missing ventilator stop date with a hospital discharge date prior to study day 28. Reventilation was analyzed only for those patients who were candidates for reventilation, ie, discontinued initial mechanical ventilation prior to study day 28 and who did not die on the day of or the day after discontinuation of mechanical ventilation. Ventilator-free days were compared using the Mann-Whitney test. Similarly, ICU length of stay was analyzed as ICU-free days, defined as the number of days a patient was alive and not in the ICU through study day 28. Patients were excluded only if they withdrew from the

study or were lost to follow-up. Readmission to the ICU was analyzed only for those patients who were candidates for readmission, ie, discharged from their initial ICU stay prior to study day 28 and did not die on their last day in the ICU. Number of ICU-free days was compared using the Mann-Whitney test.

Several survival analyses of time to event (death, first transfusion, first transfusion or death, ICU readmission, ventilation, reventilation) were performed. Kaplan-Meier survival curves for the 2 groups were compared using the log-rank test.

Logistic regression was performed to adjust the odds ratio (OR) for RBC transfusion. Covariates entered included age, sex, diagnostic categories, comorbidities, APACHE II score, baseline hemoglobin, baseline iron, baseline erythropoietin level, and baseline serum creatinine. Two statistical approaches, Cox semiparametric modeling assuming proportional hazards and recursive partitioning, were used to explore the association of mortality with treatment and other variables.

To assess changes in laboratory values from baseline to final value, analysis of covariance was used with baseline value and number of days between baseline and final value as covariates.

Results are presented as mean (SD) unless otherwise indicated. All statistical tests were 2-tailed at the .05 significance level, except for the tests of treatment-by-covariate interactions, which were at the .10 significance level. Analyses were conducted with SAS OnlineDoc version 8 (SAS Institute Inc, Cary, NC).

Subgroup Analysis

In addition to the main analysis of all patients, several subgroups of patients were analyzed separately for both percentage of patients undergoing transfusion and mortality. Although these subgroups were not prospectively identified, they were identified prior to knowledge of treatment assignment and prior to the locking of the database and the conduct of the final data analysis.

Table 1. Demographics and Baseline Characteristics*

	Placebo (n = 652)	rHuEPO (n = 650)	P Value
Age, mean (SD), y	51 (19.40)	51 (19.97)	.98
Sex, No. (%)			
Men	415 (63.7)	391 (60.2)	.21
Women	237 (36.3)	259 (39.8)	
APACHE II score, mean (SD)	19.6 (7.99)	19.7 (7.60)	.79
Admitting diagnosis, No. (%)†			
Postoperative	277 (42.5)	312 (48.0)	.05
Trauma	316 (48.5)	314 (48.3)	.96
Neurologic	118 (18.1)	109 (16.8)	.56
Cardiovascular	35 (5.4)	36 (5.5)	.90
Other respiratory	88 (13.5)	81 (12.5)	.62
Pneumonia	57 (8.7)	61 (9.4)	.70
ARDS	18 (2.8)	18 (2.8)	>.99
SIRS	4 (0.6)	4 (0.6)	>.99
Sepsis	46 (7.1)	59 (9.1)	.18
Primary hematologic disease	4 (0.6)	13 (2.0)	.03
Other nonsurgical	47 (7.2)	37 (5.7)	.31
Medical history, No. (%)†			
Cardiac disease	143 (21.9)	125 (19.2)	.24
Chronic pulmonary disease	97 (14.9)	100 (15.4)	.82
Diabetes mellitus	83 (12.7)	81 (12.5)	.93
Hypertension	177 (27.1)	170 (26.2)	.71
Malignancy	100 (15.3)	88 (13.5)	.39
Peripheral vascular disease	33 (5.1)	27 (4.2)	.51
Primary hematologic disease	16 (2.5)	18 (2.8)	.73
Thromboembolic disease	56 (8.6)	59 (9.1)	.77
Baseline laboratory values, mean (SD)			
Hemoglobin, g/dL	9.97 (1.19)	9.97 (1.17)	.95
Reticulocytes, %	1.82 (0.93)	1.85 (1.05)	.56
Erythropoietin, mU/mL	57.25 (69.37)	55.40 (62.52)	.62
Iron, µg/dL‡	28.1 (34.26)	36.2 (48.90)	<.001
Ferritin, ng/dL‡	561.7 (1169)	683.8 (1385)	.09
Transferrin saturation, %	17.2 (18.46)	20.3 (21.23)	.006

*rHuEPO indicates recombinant human erythropoietin; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; and SIRS, systemic inflammatory response syndrome. There was a small number of missing values for some variables.

†Admitting diagnosis and medical history categories are not mutually exclusive.

‡To convert iron to µmol/L, multiply values by 0.179; to convert ferritin to pmol/L, multiply values by 2.247.

The DSMB identified 3 mutually exclusive admitting diagnostic categories for safety monitoring during the study: trauma; surgical, nontrauma; and medical, nonsurgical, nontrauma. These 3 admitting diagnostic categories were determined independently of the baseline admitting diagnoses. Four other subgroups identified were identical to the subgroups studied by Hebert et al¹³ to allow for comparison of our findings with theirs: age younger than 55 years; age 55 years or older; APACHE II score 20 or lower; and APACHE II score higher than 20.

RESULTS

Among the 33 685 patients screened on ICU day 2 (Figure 1), more than 70% were ineligible for the study, primarily because of expected ICU discharge within 24 to 48 hours. Of those eligible, approximately two thirds were not approached for consent to participate, in most instances because of inability to identify and contact the appropriate patient surrogate(s) during the window of time for study enrollment. Of those patients (or surrogates) asked to consent, 50% agreed.

A total of 1302 patients were enrolled in the study, with 650 randomized to receive rHuEPO and 652 to receive placebo. The 2 groups were generally comparable at enrollment with respect to baseline demographic characteristics and laboratory values as well as admitting diagnosis and comorbidities (TABLE 1). There were some statistically significant differences; however, the magnitudes were not clinically meaningful and multivariate analysis took these variables into account. The study drug exposure was as follows: 15% received 1 dose; 31% received 2 doses; 37% received 3 doses; and 17% received 4 doses.

Blood Transfusions

The percentage of patients who received any RBC transfusion during the 28-day follow-up was significantly lower in the rHuEPO group than in the placebo group ($n=328$ [50.5%] vs $n=394$ [60.4%]; $P<.001$; OR, 0.67; 95% con-

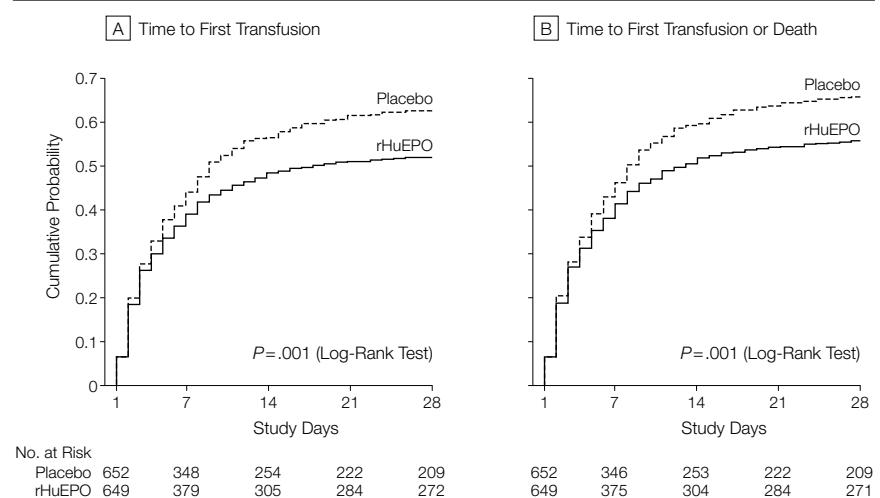
fidence interval [CI], 0.54-0.83). After adjustment for baseline characteristics, the effect of rHuEPO was essentially unchanged (adjusted OR, 0.65; 95% CI, 0.51-0.83). The results of an additional analysis in which all patients withdrawn or lost to follow-up were considered to have had transfusion were similar to those described above (63.3% placebo vs 53.4% rHuEPO; OR, 0.66; 95% CI, 0.53-0.83).

A Kaplan-Meier plot of the time to first transfusion indicates that a difference between the 2 treatment groups commenced near the end of the first week following randomization and increased progressively over the course of the 28-day follow-up (FIGURE 2A). A similar pattern occurred for the com-

posite end point of time to first transfusion or death (Figure 2B).

The cumulative number of RBC transfusions for each treatment group over the 28-day follow-up appears in TABLE 2. The total number of RBC units transfused was 1590 units for rHuEPO therapy compared with 1963 units for placebo therapy. The cumulative RBC transfusions were significantly lower in patients receiving rHuEPO compared with placebo patients. This was initially assessed based on the cumulative RBC units per subject (median units per subject, 1 vs 2; $P<.001$). A second analysis that accounted for time at risk for transfusion demonstrated a 19% reduction in RBC units transfused per day alive (ratio of transfusion rates, 0.81; 95% CI,

Figure 2. Kaplan-Meier Plots of Time to First Transfusion and First Transfusion or Death



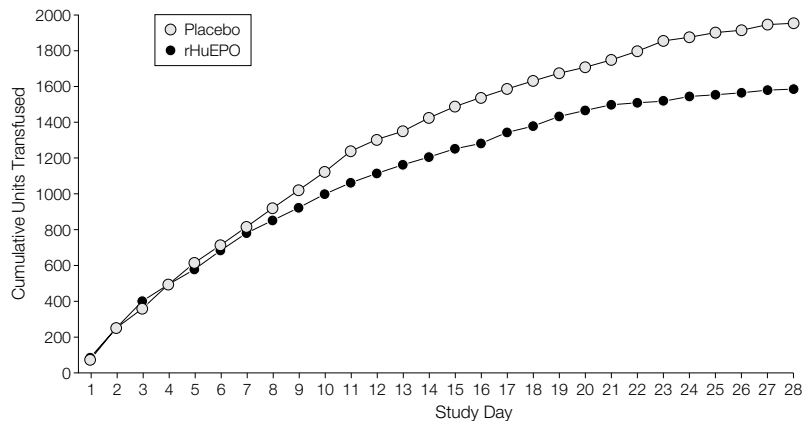
The date of transfusion was not known for 1 patient and is thus excluded from the analysis. A, Median time to event was 18 days for the rHuEPO (recombinant human erythropoietin) group and 9 for the placebo group. B, Median time to event was 13 days for the rHuEPO group and 8 days for the placebo group.

Table 2. Cumulative Units of Red Blood Cells Transfused per Patient and per Day Alive*

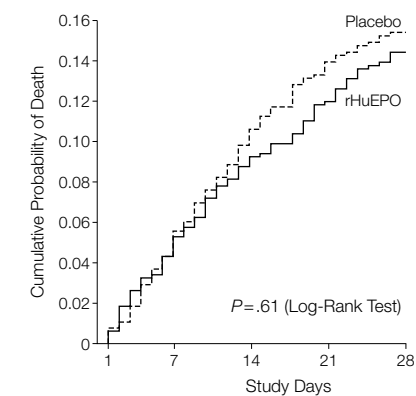
	Placebo (n = 652)	rHuEPO (n = 650)	P Value†
Units transfused per patient, No.			
Mean (SD)	3.0 (5.42)	2.4 (4.79)	
Median (IQR)	2 (0-4)	1 (0-3)	<.001
Total No. of days alive	16 235	16 247	
Total No. of units transfused	1963	1590	
Transfusion rate/days alive (SE)	0.121 (0.0085)	0.098 (0.0074)	.04

*rHuEPO indicates recombinant human erythropoietin; IQR, interquartile range; and CI, confidence interval. The effect estimate for the difference in transfusion rates (rHuEPO–placebo) was -0.02 (95% CI, -0.04 to -0.001). The effect estimate for the ratio of transfusion rates (rHuEPO–placebo) was 0.81 (95% CI, 0.79 to 0.83).

†Units transfused comparison was calculated with the Mann-Whitney test and transfusion comparison rate was based on normal distribution.

Figure 3. Cumulative Units of Red Blood Cells Transfused

rHuEPO indicates recombinant human erythropoietin.

Figure 4. Kaplan-Meier Plot of Time to Death

No. at Risk	1	7	14	21	28
Placebo	652	618	568	544	523
rHuEPO	650	612	574	544	523

rHuEPO indicates recombinant human erythropoietin.

0.79-0.83; $P = .04$). FIGURE 3 displays the cumulative units transfused by study day. This plot suggests that the treatment groups do not begin to differ with regard to RBC units transfused until approximately 1 week following treatment.

Hemoglobin Levels

The mean (SD) increase in hemoglobin from baseline to final determination was significantly greater for patients who received rHuEPO (1.32 [2] g/dL vs 0.94 [1.9] g/dL for placebo; $P < .001$). The mean day the final hemoglobin measurement was obtained was identical for both groups at study day 23.

Transfusion practices were similar in the 2 treatment groups. The mean pretransfusion hemoglobin was 8.57 (0.96) g/dL for the placebo group and 8.53 (1.08) g/dL for the rHuEPO group. Among those patients undergoing transfusion, pretransfusion hemoglobin was similar in the 2 treatment groups for the first RBC transfusion as well as for all subsequent RBC transfusions. Similarly, 21% of patients in each group underwent transfusion at a hemoglobin level greater than 9 g/dL or hematocrit greater than 27%.

Mortality and Adverse Events

There was no significant difference in 28-day mortality between the 2 groups (14% in rHuEPO vs 15% in placebo; $P = .61$, FIGURE 4). The incidence of severe adverse events reported was comparable between the 2 treatment groups (TABLE 3).

Length of Stay and Mechanical Ventilation

Median hospital length of stay (19 days for rHuEPO vs 21 days for placebo; $P = .82$) and median ICU-free days (18 days for rHuEPO vs 17 days for placebo; $P = .25$) did not differ between groups. However, there was a higher, but not statistically significant, ICU readmission rate in the placebo group compared with the rHuEPO group (13.3% vs 9.8%, respectively; $P = .07$).

Median ventilator-free days did not differ between the 2 groups (22 days for rHuEPO vs 20 days for placebo; $P = .27$). There were also no statistically significant differences between the 2 treatment groups in either reventilation rate (16.6% for rHuEPO vs 20.5% for placebo; $P = .17$) or new-onset ventilation (20.8% for rHuEPO vs 24.4% for placebo; $P = .38$).

Subgroup Analyses

The subgroups analyzed were admitting diagnosis (trauma; surgical, nontrauma; and medical, nonsurgical, nontrauma); age younger than 55 years; age 55 years or older; APACHE II score 20 or lower; and APACHE II score higher than 20.

The percentage of patients undergoing transfusion and the OR for RBC transfusion for the entire group and for each subgroup are shown in TABLE 4. The reduction in the percentage of rHuEPO patients undergoing transfusion was consistent across all the subgroups analyzed, as well as for the range of baseline hemoglobin levels (Table 4).

Mortality in each subgroup for patients receiving rHuEPO and patients receiving placebo is shown in TABLE 5. Overall mortality varied widely by subgroup, with the expected increase in mortality with older age and higher APACHE II scores. There was also considerable variation in mortality across the subgroups by treatment group. However, multivariate analysis using Cox semiparametric and recursive partitioning approaches demonstrated no treatment or treatment-by-baseline variable interaction with mortality.

COMMENT

In a previous randomized, placebo-controlled trial conducted in 160 patients, a combination of daily administration of rHuEPO (300 U/kg) followed by administration every other day resulted in an almost 50% reduction in total RBC transfusions.²⁰ There was also a trend toward an increase in the percentage of patients receiving no RBC transfusions (transfusion independence) with rHuEPO therapy. Our study, in a much

larger and more diverse group of critically ill patients, expands the findings of the prior trial. A weekly dosing schedule of 40 000 units of rHuEPO significantly increased the percentage of patients achieving transfusion independence as well as reduced the cumulative number of RBCs transfused compared with placebo patients. The RBC transfusion reduction was consistent across all of the subgroups examined, although not all comparisons were statistically significant. In both studies, despite the reduction in the number of RBC transfusions, the increase in hemoglobin level was significantly greater with rHuEPO therapy.

The reduction in total RBC units transfused and the increase in hemoglobin level were more modest in this study. This smaller transfusion effect is in part a consequence of the 2-week shorter follow-up period. If the total RBC units transfused in the 2 studies are compared at 28 days following randomization, the reduction in RBC transfusion in the earlier trial²⁰ is approximately 30%, closer to the 19% reduction seen in this trial. Therefore, it is possible that a longer follow-up period would have demonstrated a greater reduction in RBC transfusion than the 19% reduction observed. An additional contributing factor to the difference in effect size may be the decrease in total rHuEPO dose received by patients in our trial. In the current study patients received, on average, half the amount of rHuEPO that was given in the earlier trial (80 000 units vs 160 000 units).

Transfusion practice varies greatly among physicians and institutions.²⁵ Recently, a transfusion strategy in critically ill patients to maintain a hemoglobin level between 7 and 9 g/dL has been shown to be as effective as, and in some subgroups superior to, a transfusion strategy to maintain a hemoglobin level between 10 and 12 g/dL.^{13,26} However, recent reports suggest that the "transfusion trigger" in most ICUs remains higher than the more conservative transfusion strategy.^{5,6} Clearly, transfusion practice could affect our results and the magnitude of any potential benefit re-

sulting from rHuEPO therapy. In the current study, 60% of the patients in the placebo group underwent transfusion. This rate of transfusion, as well as the number of units transfused per patient, was comparable to the transfusion practice pattern observed in the prior trial as well as the restrictive group in the TRICC trial.^{13,20} Similarly, the pretransfusion hemoglobin level (8.5 g/dL) was identical in both the placebo and the rHuEPO groups, and importantly, transfusion practice in the current trial is con-

sistent with recent reports of transfusion practices in ICUs across the United States⁶ and Western Europe.⁵ Therefore, the results of this study reflect the efficacy of rHuEPO in a setting representative of the predominant transfusion practice in ICUs today.

In view of questions that have been raised regarding the safety and efficacy of RBC transfusions,¹³ does a reduction in RBC transfusions with rHuEPO therapy lead to better clinical outcomes? In the present study there were

Table 3. Serious Adverse Events*

	Placebo (n = 652)	rHuEPO (n = 650)	P Value
Any serious adverse event	249 (38)	235 (36)	.45
Respiratory system disorders	91 (14)	95 (15)	.75
Respiratory insufficiency	39 (6)	28 (4)	.21
Dyspnea	22 (3)	25 (4)	.66
Pneumonia	16 (2)	19 (3)	.61
Resistance mechanism disorders	43 (7)	45 (7)	.83
Sepsis	30 (5)	31 (5)	.90
Abscess	8 (1)	12 (2)	.38
Heart rate and rhythm disorders	41 (6)	36 (6)	.64
Cardiac arrest	31 (5)	27 (4)	.69
Vascular (extracardiac) disorders	30 (5)	21 (3)	.25
Thrombophlebitis (deep)	15 (2)	14 (2)	>.99
Urinary system disorders	21 (3)	25 (4)	.55
Renal failure (acute)	19 (3)	20 (3)	.87
General disorders	26 (4)	19 (3)	.36
Multiple organ failure	18 (3)	11 (2)	.26
Gastrointestinal system disorders	23 (4)	15 (2)	.25
Platelet, bleeding, and clotting disorders	13 (2)	14 (2)	.85
Central and peripheral nervous system disorders	15 (2)	6 (1)	.08
Cardiovascular disorders, general	5 (1)	10 (2)	.21

*All adverse events are presented as No. (%). rHuEPO indicates recombinant human erythropoietin.

Table 4. Transfusions by Subgroup and by Baseline Hemoglobin Level*

Subgroup	Placebo Transfused		rHuEPO Transfused		Odds Ratio (95% CI)
	Total No.	No. (%)	Total No.	No. (%)	
All patients	652	394 (60.4)	650	328 (50.5)	0.67 (0.54-0.83)
APACHE II score					
≤20	377	206 (54.6)	370	175 (47.3)	0.74 (0.56-0.99)
>20	272	185 (68.0)	278	153 (55.0)	0.58 (0.41-0.81)
Admitting diagnosis					
Trauma	316	195 (61.7)	314	168 (53.5)	0.71 (0.52-0.98)
Surgical nontrauma	163	102 (62.6)	169	83 (49.1)	0.58 (0.37-0.89)
Medical nontrauma	173	97 (56.1)	167	77 (46.1)	0.67 (0.44-1.03)
Age, y					
<55	361	209 (57.9)	367	187 (51.0)	0.76 (0.56-1.01)
≥55	291	185 (63.6)	283	141 (49.8)	0.57 (0.41-0.79)
Baseline hemoglobin, g/dL					
<9	121	81 (66.9)	119	69 (58.0)	0.68 (0.40-1.15)
≥9	531	313 (58.9)	529	258 (48.8)	0.66 (0.52-0.85)

*rHuEPO indicates recombinant human erythropoietin; CI, confidence interval; and APACHE, Acute Physiology and Chronic Health Evaluation. In some categories, some patients had missing values.

Table 5. Mortality by Subgroup*

Subgroup	Placebo Transfused		rHuEPO Transfused		Odds Ratio (95% CI)
	Total No.	No. (%)	Total No.	No. (%)	
All patients	652	120 (18.4)	650	111 (17.1)	0.91 (0.69-1.21)
APACHE II score					
≤20	377	57 (15.1)	370	34 (9.2)	0.57 (0.36-0.89)
>20	272	63 (23.2)	278	77 (27.7)	1.27 (0.86-1.87)
Admitting diagnosis					
Trauma	316	33 (10.4)	314	15 (4.8)	0.43 (0.23-0.81)
Surgical nontrauma	163	29 (17.8)	169	28 (16.6)	0.92 (0.52-1.62)
Medical nontrauma	173	58 (33.5)	167	68 (40.7)	1.36 (0.88-2.12)
Age, y					
<55	361	42 (11.6)	367	35 (9.5)	0.80 (0.50-1.29)
≥55	291	78 (26.8)	283	76 (26.9)	1.00 (0.69-1.45)

*rHuEPO indicates recombinant human erythropoietin; CI, confidence interval; and APACHE, Acute Physiology and Chronic Health Evaluation. Some patients were missing values for APACHE score.

no significant differences in morbidity or mortality observed between the 2 groups. Clearly, the current study does not have the power to identify small differences in clinical outcomes among subgroups.

As in the prior study,²⁰ rHuEPO therapy did not increase serious clinical events. As with clinical outcomes, even a study as large as the current one does not have the power to identify less common adverse events. Recently, the occurrence of pure red-cell aplasia associated with the presence of antierythropoietin antibodies was reported in a small number of patients with chronic renal failure treated with rHuEPO administered subcutaneously.^{27,28} This phenomenon was not observed in our trial, although our follow-up time was short.

The individuals studied represent a diverse group of critically ill patients from multiple ICUs across the United States. The major reason for ineligibility for the study was early discharge from the ICU. The intent of the study was to focus on “long-term” ICU patients, those with the highest transfusion burden.³ The 30% of patients found eligible for the study is consistent with other reports regarding the number of patients remaining in the ICU for longer than 1 week.^{2,5,6} Only one third of eligible patients were approached for consent, reflecting the difficulty of performing research in a critically ill patient population.^{29,30} Regulations governing who can serve as a surrogate to provide consent for participation in a research study when patients are unable to consent for themselves are becoming stricter.

This is a particularly important issue for research in the ICU, where patients often are not able to provide consent for themselves. The difficulty in identifying and contacting the appropriate surrogate in the relatively short time frame prior to randomization was responsible for the majority of the instances in which consent was not requested. There did not appear to be any systematic exclusion of patients other than for the reasons delineated in the protocol, but no information about excluded patients was collected to assess whether the group studied was representative.

The cost of rHuEPO is approximately \$400 for each 40000-unit dose while the cost of a unit of RBCs is generally in the \$300 to \$400 range. The average patient received 2 or 3 doses of rHuEPO (\$800-\$1200) and avoided approximately 1 unit of RBCs (\$300-\$400). However, the reduction in the number of RBC units transfused (19%) may itself be beneficial, independent of any additional clinical outcome effects. For example, not transfusing “unnecessary” units of RBCs avoids the morbidity and mortality directly associated with each RBC unit transfused (ie, transfusion reactions, transfusion-related infection) as well as the potential for medical errors associated with the transfusion process itself.^{31,32} The avoidance of unnecessary RBC transfusions would also save a resource that is becoming increasingly scarce. Establishing whether rHuEPO therapy is cost-effective will involve the consideration of all these fac-

tors as well as any additional benefit in clinical outcome achieved.

Could similar benefit be achieved by changing transfusion practice? Clearly, as demonstrated by Hebert et al,¹³ changing transfusion practice will substantially impact the number of RBC units transfused. However, even in the restrictive group of the study by Hebert et al, two thirds of the patients received at least 1 RBC transfusion, a rate of transfusion similar to that observed in the placebo group in the current study. Therefore, the potential to reduce transfusion with the use of rHuEPO remains at even more restrictive transfusion thresholds. Key in identifying critically ill patients who will be most likely to benefit from rHuEPO is selecting the more “long-term” critically ill patient (ie, longer than 1 week length of stay), who represent 25% to 30% of critically ill patients.^{3,5,6}

In conclusion, weekly therapy with 40000 units of rHuEPO in critically ill patients results in a significant reduction in their exposure to allogeneic RBC transfusion. Despite receiving fewer RBC transfusions, patients treated with rHuEPO achieve a higher hemoglobin level, consistent with the hypothesis that the anemia of critical illness is an underproduction anemia characterized in part by a relative erythropoietin deficiency.^{14,15} No differences in clinical outcomes were demonstrated between the rHuEPO and placebo groups. Therefore, while it is clear that rHuEPO treatment reduces RBC transfusions in critically ill patients, further study is necessary to establish whether this reduction in RBC transfusions will also result in improved clinical outcomes for some critically ill patients.

Author Affiliations: Critical Care Medicine (Dr H. Corwin) and Department of Anesthesiology (Dr Gettinger), Dartmouth-Hitchcock Medical Center, Lebanon, NH; Department of Anesthesia, Stanford University Medical Center, Stanford, Calif (Dr Pearl); Department of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pa (Dr Fink); Rhode Island Hospital, Providence (Dr Levy); St Louis University Health Science Center, St Louis, Mo (Dr Shapiro); and Department of Pediatrics, Boston University School of Medicine (Dr M. Corwin), Department of Epidemiology, Boston University School of Public Health (Dr Colton), and CareStat Inc (Drs M. Corwin and Colton), Boston, Mass. **Financial Disclosures:** Drs H. Corwin, Gettinger, and Pearl have received honoraria from Ortho Biotech; Drs H. Corwin and Gettinger have received research fund-

ing from Ortho Biotech; Drs H. Corwin, Gettinger, Fink, Levy, Shapiro, and Pearl have been paid consultants to Ortho Biotech; and Drs Colton and M. Corwin are partners in CareStat Inc, the study contract research organization.

Author Contributions: As principal investigators of this study, Drs Howard Corwin and Gettinger had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the analysis. *Study concept and design:* H. Corwin, Gettinger, M. Corwin, Colton.

Acquisition of data: H. Corwin, Gettinger.

Analysis and interpretation of data: H. Corwin, Gettinger, Pearl, Fink, Levy, Shapiro, M. Corwin, Colton.

Drafting of the manuscript: H. Corwin, Fink, M. Corwin, Colton.

Critical revision of the manuscript for important intellectual content: H. Corwin, Gettinger, Pearl, Fink, Levy, Shapiro, M. Corwin, Colton.

Statistical expertise: M. Corwin, Colton.

Obtained funding: H. Corwin, Gettinger.

Administrative, technical, or material support: H. Corwin, Gettinger.

Study supervision: H. Corwin, Gettinger, M. Corwin.

EPO Critical Care Trials Group: *Principal Investigators:* Howard L. Corwin, MD, Dartmouth-Hitchcock Medical Center; Andrew Gettinger, MD, Dartmouth-Hitchcock Medical Center. *Steering Committee:* Howard L. Corwin, MD; Andrew Gettinger, MD; Ronald G. Pearl, MD, PhD, Stanford University Medical Center. *Data and Safety Monitoring Board:* Janet Wittes, PhD, Chair, Statistics Collaborative, Inc; Gordon Bernard, MD, Vanderbilt University School of Medicine; David Henry, MD, Pennsylvania Oncology/Hematology Associates; Margaret Parker, MD, SUNY, Stonybrook. *Data Coordinating Center:* CareStat Inc in collaboration with the Boston University School of Public Health. *Study Sponsor:* Ortho Biotech Products, LP; Christopher Enny, Brenda Sarokhan.

Members of the EPO Critical Care Trials Group: Edward Abraham, University of Colorado Health Sciences Center, Denver; Timothy Albertson, UC-Davis Medical Center, Sacramento, Calif; Dennis Amundson, Naval Medical Center, San Diego, Calif; Paula Anderson, University of Arkansas for Medical Sciences, Little Rock; David Antonenko, Altru Health System, Grand Forks, ND; Robert Balk, Rush Medical College, Chicago, Ill; Robert Bartlett, University of Michigan Medical Center, Ann Arbor; Gregory Beilman, Fairview University Medical Center, Minneapolis, Minn; Bruce Bonnell, Spectrum Health, Grand Rapids, Mich; Roy Brower, Johns Hopkins Hospital, Baltimore, Md; Susan Brundage, Baylor College of Medicine, Houston, Tex; Timothy Buchman, Washington University Medical Center, St Louis, Mo; Marianne Cinat, University of California at Irvine, Orange; Stephen Cohn, University of Miami, Miami, Fla; Robert Cooney, The Milton S. Hershey Medical Center, Hershey, Pa; Douglas Coursin, University of Wisconsin, Madison; Timothy Fabian, University of Tennessee Health Science Center, Memphis; Mitchell Fink, University of Pittsburgh Medical Center, Pittsburgh, Pa; Lewis Flint and Mark Rumbak, Tampa General Hospital, Tampa, Fla; John Fortune, University Medical Center, Tucson, Ariz; T. James Gallagher, Shands Hospital, Gainesville, Fla; Andrew Gettinger and Howard Corwin, Dartmouth-Hitchcock Medical Center, Lebanon, NH; Joseph Govert, Duke University Medical Center, Durham, NC; Michael Gropper, UCSF Medical Center, San Francisco, Calif; Jesse Hall, University of Chicago, Chicago, Ill; C. William Hanson, Hospital of the University of Pennsylvania, Philadelphia; Stephen Heard, University of Massachusetts Medical Center, Worcester; John Heffner, Medical University of South Carolina, Charleston; Mathilda Horst, Henry Ford Hospital, Detroit, Mich; David Hoyt, UCSD Medical Center, San Diego, Calif; Gary Iwamoto and Howard Levy, University of New Mexico, Albuquerque; Carl Kaplan, University of Missouri at Columbia; Gary Kinasewitz, University of Oklahoma Health Science Center, Oklahoma

City; Mitchell Levy, Rhode Island Hospital, Providence; Alan Lisbon, Beth Israel Deaconess Medical Center, Boston, Mass; Steven Lisco, Brigham and Women's Hospital, Boston, Mass; Robert Lodato, Memorial Hermann Hospital, Houston, Tex; Stephen Lowry and Harold Paz, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ; Dana Lustbader, North Shore University Hospital, Manhasset, NY; Drew MacGregor, Wake Forest University Baptist Medical Center, Winston-Salem, NC; Mali Mathru, University of Texas Medical Branch at Galveston; John Mayberry and Betsy Ellen Soifer, Oregon Health Sciences University Hospitals and Clinics, Portland; Norman McSwain, Charity Hospital/Tulane University Hospital, New Orleans, La; Sherry Melton and Addison May, University of Alabama at Birmingham; Michael Murray and Martin De Ruyter, Mayo Clinic, Rochester, Minn; Stanley Nasraway, New England Medical Center, Boston, Mass; Patrick Offner, Denver Health Medical Center, Denver, Colo; R. Pearl, Stanford University Medical Center, Stanford, Calif; Susan Pingleton, University of Kansas Medical Center, Kansas City; Hiram Polk, University of Louisville Hospital, Louisville, Ky; James Ramsay, Emory University Hospital, Atlanta, Ga; George Rodman, Methodist Hospital of Indianapolis, Indianapolis, Ind; Robert Rodriguez, Highland Hospital, Oakland, Calif; Jeffrey Salomone, Grady Memorial Hospital, Atlanta, Ga; Miren Schinco-Schaffer and Gianna Scannell, University Medical Center, Jacksonville, Fla; M. Michael Shabot, Cedars-Sinai Medical Center, Los Angeles, Calif; Marc Shapiro, St Louis University, St Louis, Mo; Robert Sladen, Columbia Presbyterian Medical Center, New York, NY; Kenneth Steinberg, Harborview Medical Center, Seattle, Wash; Ronald Stewart, University of Texas Health Science Center, San Antonio; Jonathon Truitt, University of Virginia Health System, Charlottesville; Jeffrey Vender, Evanston Hospital, Evanston, Ill; Kenneth Waxman, Santa Barbara Cottage Hospital, Santa Barbara, Calif; Lucy Wibbenmeyer, University of Iowa Medical Center, Iowa City; and Mihae Yu, University of Hawaii-The Queen's Medical Center, Honolulu.

Funding/Support: This study was supported by Ortho Biotech Products LP, manufacturer of rHuEPO.

REFERENCES

- Spence RK, Cernaianu AC, Carson J, DelRossi AJ. Transfusion and surgery. *Curr Probl Surg.* 1993;30:1101-1180.
- Littenberg B, Corwin H, Gettinger A, Leichter J, AuBuchon J. A practice guideline and decision aid for blood transfusion. *Immunohematology.* 1995;11:88-92.
- Corwin HC, Parsonnet KC, Gettinger A. RBC transfusion in the ICU: is there a reason? *Chest.* 1995;108:767-771.
- 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.
- Vincent JL, Baron JF, Gattinoni L, et al. Anemia and blood transfusion in critically ill patients. *JAMA.* 2002;288:1499-1507.
- Corwin HL, Abraham E, Fink MP, et al. Anemia and blood transfusion in the critically ill: current clinical practice in the US—The CRIT Study [abstract]. *Crit Care Med.* 2001;29(suppl):A2.
- Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine: first of two parts—blood transfusion. *N Engl J Med.* 1999;340:438-447.
- Blumberg N, Heal JM. Effects of transfusion on immune function: cancer recurrence and infection. *Arch Pathol Lab Med.* 1994;118:371-379.
- Landers DF, Hill GE, Wong KC, Fox JJ. Blood transfusion-induced immunomodulation. *Anesth Analg.* 1996;82:187-204.
- Mickler TA, Longnecker DE. The immunosuppressive aspects of blood transfusion. *J Intensive Care Med.* 1992;7:176-188.
- Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA.* 1993;269:3024-3029.

12. Fitzgerald RD, Martin CM, Dietz GE, Doig GS, Potter RF, Sibbald WJ. 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.

13. Hebert PC, Wells G, Blajchman MA, et al, for the Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med.* 1999;340:409-417.

14. Corwin HL, Krantz S. Anemia in the critically ill: "acute" anemia of chronic disease. *Crit Care Med.* 2000;28:3098-3099.

15. Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG. Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. *J Crit Care.* 2001;16:36-41.

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

17. Krafte-Jacobs B, Levettown ML, Bray GL, Ruttimann UE, Pollack MM. Erythropoietin response to critical illness. *Crit Care Med.* 1994;22:821-826.

18. Frede S, Fandrey J, Pagel H, Hellwig T, Jelkmann W. Erythropoietin gene expression is suppressed after lipopolysaccharide or interleukin-1 beta injections in rats. *Am J Physiol.* 1997;273:R1067-R1071.

19. Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. *J Interferon Cytokine Res.* 1998;18:555-559.

20. 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;27:2346-2350.

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

22. Monk TG, Goodnough LT, Brecher ME, Colberg JW, Andriole GL, Catalona WJ. A prospective randomized comparison of three blood conservation strategies for radical prostatectomy. *Anesthesiology.* 1999;91:24-33.

23. Qvist N, Boesby S, Wolff B, Hansen CP. Recombinant human erythropoietin and hemoglobin concentration at operation and during the postoperative period: reduced need for blood transfusions in patients undergoing colorectal surgery—prospective double-blind placebo-controlled study. *World J Surg.* 1999;23:30-35.

24. Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E, Einhorn LH. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times weekly dosing. *J Clin Oncol.* 2001;19:2875-2882.

25. Goodnough LT, Johnston MF, Toy PT, for the Transfusion Medicine Academic Award Group. The variability of transfusion practice in coronary artery bypass surgery. *JAMA.* 1991;265:86-90.

26. Hebert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med.* 2001;29:227-234.

27. Casadevall N, Nataf J, Viron B, et al. Pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med.* 2002;346:469-475.

28. Casadevall. Antibodies against rHuEPO: native and recombinant. *Nephrol Dial Transplant.* 2002;17(suppl 5):42-47.

29. McRae AD, Weijer C. Lessons from everyday lives: a moral justification for acute care research. *Crit Care Med.* 2002;30:1146-1151.

30. Burck R. Minimal risk: the debate goes on. *Crit Care Med.* 2002;30:1180-1181.

31. Myhre BA, McRuer D. Human error: a significant cause of transfusion mortality. *Transfusion.* 2000;40:879-885.

32. Spahn DR, Casutt M. Eliminating blood transfusions: new aspects and perspectives. *Anesthesiology.* 2000;93:242-255.