

The CRIT Study: Anemia and blood transfusion in the critically ill—Current clinical practice in the United States*

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Objective: To quantify the incidence of anemia and red blood cell (RBC) transfusion practice in critically ill patients and to examine the relationship of anemia and RBC transfusion to clinical outcomes.

Design: Prospective, multiple center, observational cohort study of intensive care unit (ICU) patients in the United States. Enrollment period was from August 2000 to April 2001. Patients were enrolled within 48 hrs of ICU admission. Patient follow-up was for 30 days, hospital discharge, or death, whichever occurred first.

Setting: A total of 284 ICUs (medical, surgical, or medical-surgical) in 213 hospitals participated in the study.

Patients: A total of 4,892 patients were enrolled in the study.

Measurements and Main Results: The mean hemoglobin level at baseline was 11.0 ± 2.4 g/dL. Hemoglobin level decreased throughout the duration of the study. Overall, 44% of patients received one or more RBC units while in the ICU (mean, 4.6 ± 4.9 units). The mean pretransfusion hemoglobin was 8.6 ± 1.7 g/dL. The mean time to first ICU transfusion was 2.3 ± 3.7 days. More

RBC transfusions were given in study week 1; however, in subsequent weeks, subjects received one to two RBC units per week while in the ICU. The number of RBC transfusions a patient received during the study was independently associated with longer ICU and hospital lengths of stay and an increase in mortality. Patients who received transfusions also had more total complications and were more likely to experience a complication. Baseline hemoglobin was related to the number of RBC transfusions, but it was not an independent predictor of length of stay or mortality. However, a nadir hemoglobin level of <9 g/dL was a predictor of increased mortality and length of stay.

Conclusions: Anemia is common in the critically ill and results in a large number of RBC transfusions. Transfusion practice has changed little during the past decade. The number of RBC units transfused is an independent predictor of worse clinical outcome. (Crit Care Med 2004; 32:39–52)

KEY WORDS: anemia; blood transfusion; transfusion practice; transfusion risks

The value of red blood cell (RBC) transfusion in clinical practice was unchallenged through most of this century (1). However, in the early 1980s, transfusion practice began to come under systematic scrutiny (2–4). Initially, the primary concerns related to the risks of transfusion-related

infections, particularly human immunodeficiency virus and hepatitis. However, the issues are now much more complex. The examination and debate over RBC transfusion risks during the last two decades has led to a more critical examination of transfusion benefits. Further complicating these issues has been the growing shortage of RBCs available for transfusion.

The issues surrounding RBC transfusion are particularly important in the critically ill. Anemia is very common in the critically ill; almost 95% of patients admitted to the intensive care unit (ICU) have a hemoglobin level below normal by ICU day 3 (5). As a consequence of this anemia, critically ill patients receive a large number of RBC transfusions. More than 50% of patients admitted to the ICU receive RBC transfusions during their ICU stay (6, 7). In those patients with an ICU length of stay (LOS) of >1 wk, the proportion of patients transfused increases to 85% (6). In a survey of ICUs across the United States conducted

a decade ago, 14% of ICU patients on the day of the survey received at least one unit of transfused RBCs (8).

Recent data suggest that many critically ill patients can tolerate hemoglobin levels as low as 7 g/dL and that a “liberal” RBC transfusion strategy may in fact lead to worse clinical outcomes (9). However, a hemoglobin level of 7 g/dL represents a threshold or “trigger” for transfusion that is much lower than the level generally regarded as standard practice (6, 7). The impact of the scrutiny of transfusion practice during the last decade on current clinical practice is not known. The present study was undertaken to determine current transfusion practice in ICUs in the United States and to examine the impact of anemia and RBC transfusion on the clinical outcomes of critically ill patients.

METHODS

Design. The study was a prospective, multiple center, observational study of ICU pa-

*See also p. 290.

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tients in the United States. The enrollment period was August 2000 through April 2001. Patients were enrolled within 48 hrs of ICU admission. Inclusion criteria included: age of ≥ 18 yrs; admission to a medical, surgical, or combined medical-surgical ICU; anticipated ICU stay of >48 hrs; and informed consent. Exclusion criteria included: admission to a pediatric, cardiothoracic, cardiac, neurologic, or burn ICU; renal failure on dialysis; patients prohibited from receiving RBC transfusions; and patients involved in other transfusion research protocols. Patients were followed for either 30 days or until hospital discharge or death if these occurred before day 30. The study protocol was approved by the institutional review board of each participating institution.

Data Collection. Data collected included: hospital and ICU characteristics; patient demographics; admitting diagnostic categories; co-morbidities; ICU admission Acute Physiology and Chronic Health Evaluation (APACHE) II score; ICU admission and weekly Sequential Organ Failure Assessment (SOFA) scores; RBC transfusions; age of each RBC unit transfused; baseline (value closest to enrollment), weekly, and pretransfusion hemoglobin levels; mortality; ventilator days; ICU and hospital LOS; and clinical complications (see "APPENDIX 1" for definitions).

Statistical Analysis. The primary end point of the study was to quantify the RBC transfusion practice in critically ill patients. The secondary end point was to describe the clinical outcomes and complications associated with anemia and RBC transfusions in these patients. SAS PROC MEANS procedure (SAS Institute, Cary, NC) was used to analyze the mean, standard deviation, and median of continuous variables, such as age and hemoglobin level. The significance of differences between two continuous measurements was determined by Student's *t*-test. Analysis of variance (ANOVA) was used when more than two measurements were compared. Results are presented as mean \pm SD. SAS PROC FREQ procedure (SAS Institute) was used to tabulate the frequencies of categorical variables, such as number of transfusions and number of complications. Chi-square tests were used to test statistical significance. Pearson's correlation coefficients were used to assess the degree of linear correlation between two continuous variables. A two-sided alpha error of $<.05$ was considered to indicate statistical significance. Bonferroni adjustment was used when multiple comparisons were made.

Accelerated failure time models were used (PROC LIFEREG procedure, SAS Institute) to assess the factors associated with ICU LOS or hospital LOS. Adjustment was made for potential confounding factors, including patient demographic characteristics, RBC transfusion, nadir hemoglobin level or baseline hemoglobin level, the difference between the maximum and minimum hemoglobin values, mean age of blood transfused, mechanical ventila-

tion status, baseline APACHE II and SOFA scores, origin of admission (e.g., emergency room, operating room), admitting diagnoses, and medical history. The median ICU and hospital LOS by transfusion status were generated conditional on the average values of other covariates in the model.

Mortality was analyzed and presented using two different models. First, logistic regression (PROC LOGISTIC procedure, SAS Institute) was used to examine transfusion and covariate effects after controlling for the duration on study. In a further confirmatory analysis of transfused patients, a Kaplan-Meier survival analysis and log-rank test (PROC LIFETEST procedure, SAS Institute) was performed, after 1:1 matching of transfused patients with nontransfused patients using propensity scores technique. Because the assignment of transfusion vs. no transfusion could not be randomized, potential selection bias was addressed by developing a propensity score for transfusion. Baseline attributes, including patient demographics, baseline APACHE II and SOFA scores, origin of admission, admitting diagnoses, medical history, and hospital LOS, that are potentially associated with receiving a transfusion were gathered into a single composite-predicted probability in logistic regression that summarized the likelihood for a patient with a given set of characteristics to receive a transfusion. A transfused patient was then matched to a non-

transfused patient who had similar propensity (i.e., conditional probability) to receive a blood transfusion, using a greedy matching method. In this study, a subcohort of 44.8% of transfused patients had a match from the nontransfused patients. The remaining transfused patients with whom none of the nontransfused patients had a similar propensity to match were excluded from the propensity score analysis because their great baseline differences from the nontransfused patients hampered the ability to investigate the independent effect of transfusion on mortality.

RESULTS

Institution/ICU Characteristics. A total of 284 ICUs in 213 hospitals participated in the study. Hospital and ICU size are displayed in Table 1. Of the 213 hospitals, 70% were characterized as urban, 26% suburban, and 4% rural. Of the ICUs, 31% were medical, 29% were surgical, and 40% were medical-surgical. Seventy-one percent of the ICUs were managed as "open" units. There was a full-time ICU director in 84% of the ICUs. Residents and fellows were present in 76% and 39% of ICUs, respectively. Only 19% of hospitals had an institutional transfusion protocol in place at the time of the study.

Table 1. Hospital and Intensive Care Unit (ICU) Size

	<200	200-300	300-400	400-500	>500
Hospitals ^a	12	31	48	36	83
			ICU beds		
ICUs	<10	11-20	21-30	31-40	>40
	36	163	50	23	12

^aNumber of beds was missing for three hospitals.

Table 2. Patients' Characteristics

Total no. of patients	4892	
No. of enrolling hospitals	213	
No. of enrolling ICUs	284	
	Mean \pm SD	LQ/Median/UQ
Age, yrs	60.0 \pm 18.3	46.6/62.5/74.5
Sex, %		
Male	55	
Female	45	
Baseline APACHE II score	19.7 \pm 8.2	14.0/19.0/25.0
Baseline SOFA score	6.2 \pm 3.7	3.0/6.0/9.0
Baseline hemoglobin level, g/dL	11.0 \pm 2.4	9.4/10.8/12.6
ICU length of stay, days	7.4 \pm 7.3	3.0/4.0/9.0
Hospital length of stay, days	13.2 \pm 8.9	6.0/10.0/19.0
Mechanical ventilation, %	61	
Ventilator duration, days	7.1 \pm 7.4	2.0/4.0/10.0
ICU mortality, %	13	
Hospital mortality, %	18	

ICU, intensive care unit; LQ, lower quartile; UQ, upper quartile; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

Table 3. Admitting Diagnostic Categories

Admitting Diagnostic Category	% of Patients
Respiratory failure	32
Postoperative	20
Pneumonia	15
Cardiovascular	12
Trauma	12
Sepsis/SIRS	11
Hemodynamic instability	10
Neurologic	8
Gastrointestinal bleed	8
ARDS	3
Primary hematologic disease	1
Other	23

SIRS, systemic inflammatory response syndrome; ARDS, acute respiratory distress syndrome.

Forty percent of patients had more than one admitting diagnosis.

Table 4. Co-morbid Conditions

Co-Morbid Condition	% of Patients
Hypertension	45
Cardiac disease	39
Pulmonary disease	33
Gastrointestinal disease	27
Diabetes	24
Cancer	18
Musculoskeletal disease	15
Central nervous system disease	13
Anemia	13
Renal disease	12
Peripheral vascular disease	10
Thromboembolic disease	5
Immunologic disease	4
Primary hematologic disease	3

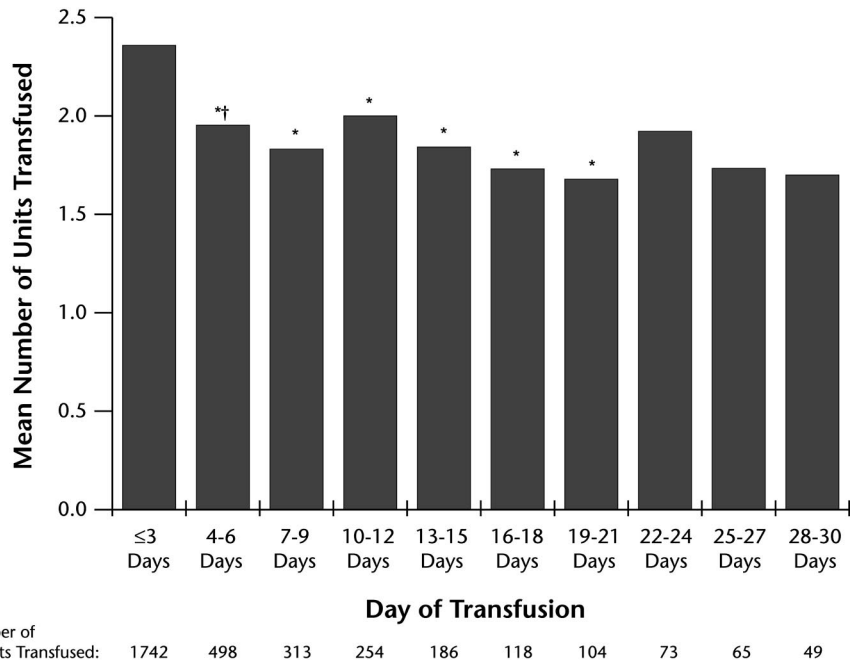
Patient Characteristics. During the 9-month study period, a total of 4,892 patients were enrolled in the study. Patient characteristics are summarized in Table 2. The mean age of the patients was 60 ± 18 yrs; 35% were >70 yrs old, and 30% were <50 yrs of age. The mean ICU LOS was 7.4 ± 7.3 days; 39% of patients remained in the ICU for ≤ 3 days, 36% stayed in the ICU for >1 wk, and 15% stayed for >2 wks. Admitting diagnostic categories and co-morbidities are shown in Tables 3 and 4, respectively. Sixty-one percent of patients required mechanical ventilatory support during their ICU stay, and 46% were mechanically ventilated at the time of ICU admission. The mean duration of mechanical ventilation was 7.1 ± 7.4 days for ventilated patients. ICU and hospital mortality rates for patients were 13% and 18%, respectively.

RBC Transfusion. RBC transfusions performed in the ICU, after ICU discharge, and during the combined ICU and post-ICU periods are summarized in Table 5. In total, 11,391 RBC units were

Table 5. Transfusion Results

	Mean \pm SD	LQ/Median/UQ
ICU		
Total no. of RBC units transfused	9990	
Percentage of patients with transfusions	44.1	
No. of units transfused (for patients with transfusions)	4.6 ± 4.9	2.0/3.0/6.0
Pretransfusion hemoglobin, g/dL	8.6 ± 1.7	7.7/8.5/9.4
Days to first transfusion	2.3 ± 3.7	0.0/1.0/3.0
Age of blood, days	21.3 ± 11.4	12.0/19.0/30.0
Post-ICU		
Total no. of RBC units transfused	1401	
Percentage of patients with transfusions	13.4	
No. of units transfused (for patients with transfusions)	2.7 ± 2.8	2.0/2.0/3.0
Pretransfusion hemoglobin, g/dL	8.5 ± 1.5	7.7/8.3/9.0
Age of blood, days	21.0 ± 11.4	12.0/19.0/31.0
ICU and Post-ICU		
Total no. of RBC units transfused	11391	
Percentage of patients with transfusions	48.2	
No. of units transfused (for patients with transfusions)	4.8 ± 5.1	2.0/3.0/6.0
Pretransfusion hemoglobin, g/dL	8.6 ± 1.7	7.7/8.5/9.3
Days to first transfusion	2.8 ± 4.3	0.0/1.0/3.0
Age of blood, days	21.2 ± 11.4	12.0/19.0/30.0

LQ, lower quartile; UQ, upper quartile; ICU, intensive care unit; RBC, red blood cell.

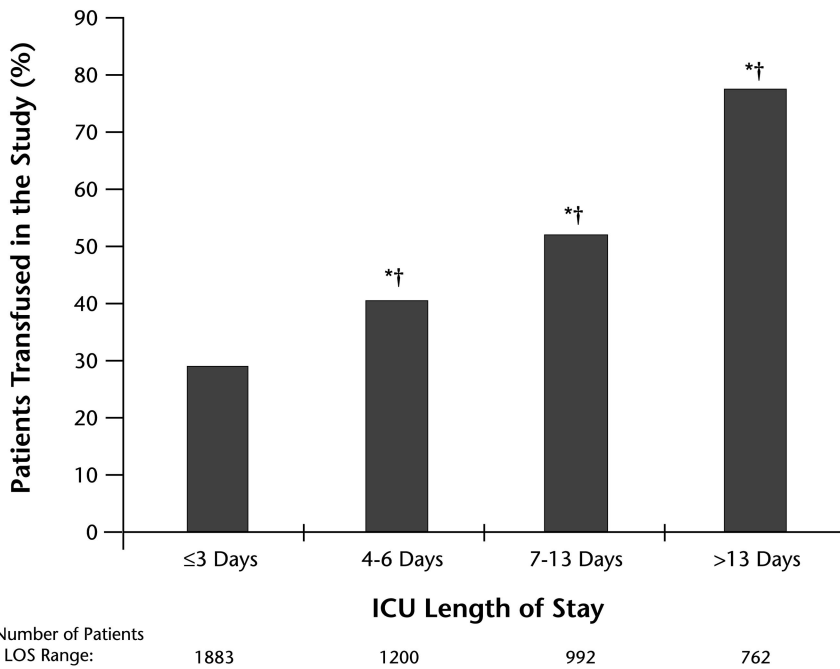


*The difference is significant at $p < .003$ (using ANOVA and Bonferonni adjustment) compared with ≤ 3 days.
 †The difference is significant at $p < .003$ (using ANOVA and Bonferonni adjustment) compared with previous period.

Figure 1. Number of red blood cell (RBC) units transfused between day 1 and day 30. ANOVA, analysis of variance.

transfused during the study period, including 9,990 RBC units in the ICU and 1,401 RBC units after ICU discharge. Overall, 44% of patients admitted to the ICU received one or more RBC units while in the ICU. The mean time to first transfusion was 2.3 ± 3.7 days (median, 1.0; lower quartile, 0.0; upper quartile, 3.0). More RBC transfusions were given in week 1; however, in subsequent weeks,

patients received one to two RBC units per week (Fig. 1). Longer ICU stays were associated with both a higher percentage of patients transfused and more RBC units transfused per patient (Figs. 2 and 3, respectively). Thirteen percent of patients received one or more RBC units after ICU discharge. Among these patients, 60% also received an RBC transfusion while in the ICU. Transfusion in-

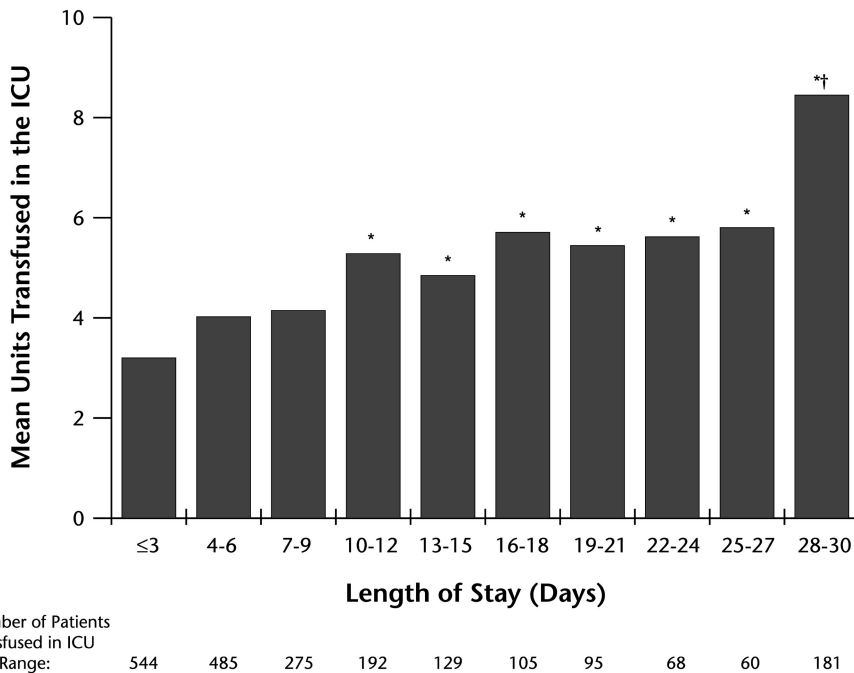


ICU, intensive care unit.

*The difference is significant at $p < .01$ (Bonferroni adjustment) compared with the first ICU stay group.

†The difference is significant at $p < .01$ (Bonferroni adjustment) compared with the previous ICU stay group.

Figure 2. Percentage of patients receiving transfusions by intensive care unit (ICU) length of stay (LOS).



*The difference is significant at $p < .003$ (Bonferroni adjustment) compared with the first ICU stay group.

†The difference is significant at $p < .003$ (Bonferroni adjustment) compared with previous ICU stay group.

23 transfused patients do not have an Intensive Care Unit length of stay.

Figure 3. Mean number of red blood cell (RBC) units transfused by length of stay (LOS). ICU, intensive care unit.

dications are shown in Table 6. The most common indication (90%) reported was for low hemoglobin level.

Patients who were transfused had more total complications and were more likely to experience a complication (Table

Table 6. Reason for Red Blood Cell Transfusion^a

Reason for Transfusion	% of Transfusions
Low hemoglobin	90
Active bleeding	24
Ischemia	3
Increased cardiac output	2
Surgical procedure	19
Hemodynamic instability/hypotension	21
Clinical condition	26

^aThere could be more than one reason for a transfusion.

7). Approximately 4% of RBC transfusions were associated with a transfusion-related complication. The most common transfusion-related complications reported were fever (1.9%), fluid overload (1.7%), and hypotension (1%). The number of RBC units transfused was directly related to mortality. Mortality was 10% for patients who received no transfusions and 25% among patients who received six or more RBC units.

The pretransfusion hemoglobin levels are shown in Figure 4. The mean pretransfusion hemoglobin was 8.6 ± 1.7 g/dL. The same value pertained, irrespective of whether transfusions were given during the ICU stay or after discharge from the ICU (Table 5). The pretransfusion hemoglobin was remarkably consistent across the range of ICU characteristics (Table 8). The pretransfusion hemoglobin was also comparable for all transfusions (e.g., first, second, third) and ICU LOS. There were no clinically meaningful differences associated with age, sex, diagnostic category, APACHE II, or baseline SOFA score.

Baseline Hemoglobin Levels. The mean hemoglobin level at baseline was 11.0 ± 2.4 g/dL, and almost two thirds of patients had a baseline hemoglobin level of <12 g/dL. Hemoglobin level decreased throughout the duration of the study (Fig. 5). Individuals with a lower baseline hemoglobin level were more likely to receive an RBC transfusion. Almost 90% of patients with a baseline hemoglobin of ≤ 8 g/dL received an RBC transfusion. In contrast, only 20% of patients with a baseline hemoglobin of >12 g/dL received an RBC transfusion. Both time to first ICU transfusion (1.8 ± 1.7 days for baseline hemoglobin of ≤ 8 g/dL vs. 6.3 ± 6.2 days for baseline hemoglobin of >12 g/dL, $p < .05$) and total RBC units transfused (6.3 ± 7.1 units for baseline hemo-

Table 7. Complications in the Intensive Care Unit

	n	% ^a	Patients Who Received Transfusions, n	% ^b
One or more complications	1552	31.7	1049	67.6
ARDS	227	5.7	217	78.3
Pulmonary edema	234	4.8	158	67.5
Sepsis	452	9.2	329	72.8
Septic shock	355	7.3	273	76.9
Infection	461	9.4	324	70.3
Pneumonia	638	13.0	421	66.0
Deep venous thrombosis	69	1.4	53	76.8
Pulmonary embolus	29	0.6	22	75.9
Significant bleeding	277	5.7	269	97.1
Transfusion reactions	—	—	86	4.0

ARDS, acute respiratory distress syndrome.

^aDenominator is the total number of patients (4,892); ^bdenominator is the total number of patients with the corresponding condition.

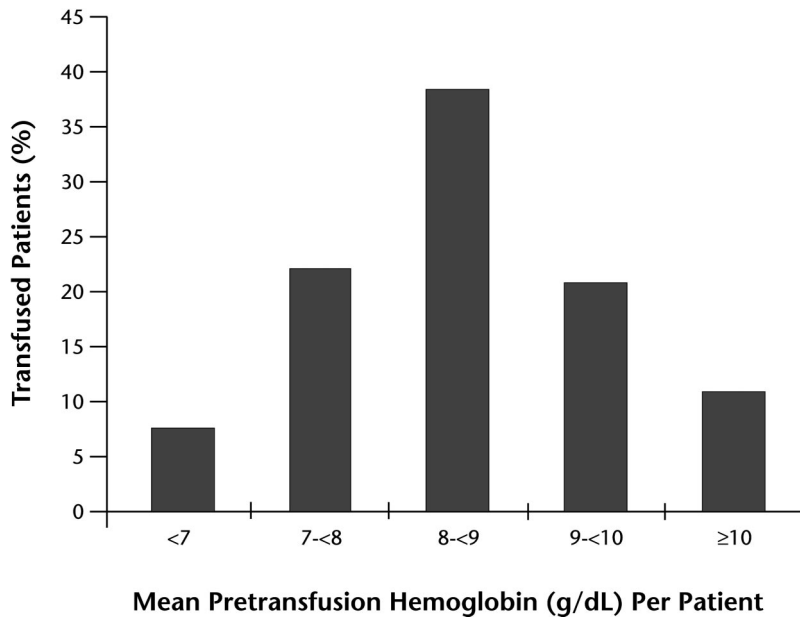


Figure 4. Pretransfusion hemoglobin.

globin of ≤ 8 g/dL vs. 4.6 ± 4.4 units for baseline hemoglobin of >12 g/dL, $p < .05$) were significantly different between the low and high baseline hemoglobin groups.

Patients with a low baseline hemoglobin level (≤ 8 g/dL) presented with more hemodynamic instability, sepsis, and gastrointestinal bleeding, whereas patients with a higher baseline level (>12 g/dL) presented with more respiratory and cardiovascular problems (Table 9). Similarly, a lower baseline hemoglobin level was associated with preexisting anemia or conditions often associated with anemia (e.g., cancer, renal disease), whereas a higher baseline hemoglobin level was associated with more pulmonary disease (Table 10). Baseline hemoglobin levels of ≤ 10 g/dL were associated with higher

APACHE II and SOFA scores and higher mortality and complication rates.

Age, Co-morbidity, and Admitting Diagnosis. There was little association between age and either RBC transfusion rate (42% for patients of ≤ 50 yrs vs. 47% for patients of ≥ 70 yrs) or pretransfusion hemoglobin concentration (8.5 g/dL for patients of ≤ 50 yrs vs. 8.7 g/dL for patients of ≥ 70 yrs). In general, the incidence of RBC transfusion was relatively consistent across the co-morbidities; however, patients with preexisting anemia and hematologic disease tended to receive transfusions more frequently (58.3% and 58.7%, respectively), whereas patients with preexisting pulmonary disease tended to receive transfusions less frequently (37.5%). This pulmonary group tended to have a relatively higher

proportion of patients with a baseline hemoglobin level of >12 g/dL and a lower proportion of patients with a baseline hemoglobin level of ≤ 8 g/dL (Table 10). On the other hand, transfusions were much more frequent in patients with an admitting diagnosis of gastrointestinal hemorrhage (80%) and less frequent in patients admitted with a pulmonary (35%) or neurologic diagnosis (30%).

APACHE II and SOFA. The mean baseline APACHE II and SOFA scores were 19.7 ± 8.2 and 6.2 ± 3.7 , respectively. Both baseline APACHE II and SOFA score were significantly higher for patients with a baseline hemoglobin level of ≤ 10 g/dL. Low baseline APACHE II (≤ 15) and low baseline SOFA (≤ 6) scores were associated with a significantly decreased likelihood of RBC transfusion and fewer total RBC units transfused. There was a significant association between mean SOFA score during the course of the ICU stay and the number of RBC units transfused (no transfusions, SOFA scores 4–5; one to six RBC units, SOFA scores 6–7; more than six RBC units, SOFA scores 8–9).

Age of RBC Units Transfused. The distribution of the age of RBC units transfused is shown in Figure 6. The mean age of all RBC units transfused was 21.2 ± 11.4 days. There was no difference in the age of RBC units whether transfused within or outside of the ICU, nor was there any difference in the age of RBC units transfused among different types of institutions or ICUs. There was no difference between the median age of the RBC units a patient received and any clinical outcome.

Multivariate Analyses. The number of RBC units transfused was significantly associated with increased ICU and hospital LOS compared with patients who did not receive transfusions (Table 11). Patients with a transfusion amount of 1–2, 3–4, and >4 units had a corresponding increase in median ICU LOS of 2.1, 3.8, and 10.1 days, respectively; and an increase in median hospital LOS of 3.5, 6.7, and 16.6 days, respectively, as compared with the median ICU LOS of 4.6 days and hospital LOS of 11.0 days observed in the patients who did not receive transfusions. Baseline hemoglobin level was not statistically significantly associated with ICU or hospital LOS; however, a separate analysis shows that lower nadir hemoglobin levels were correlated with longer LOS.

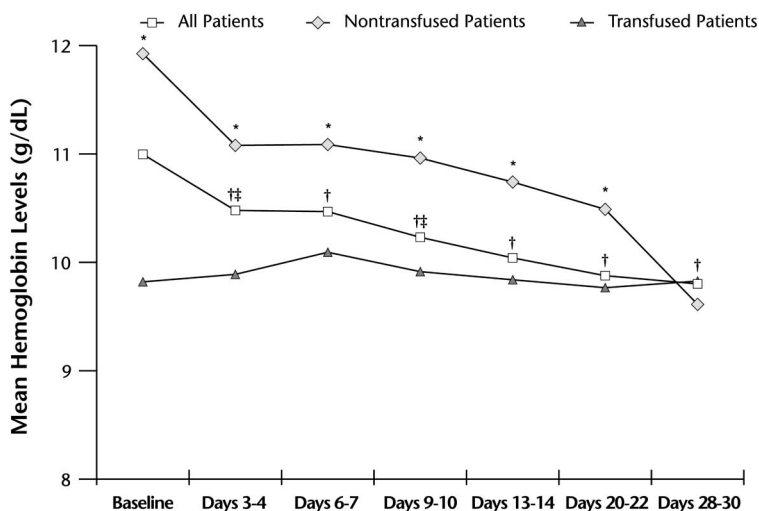
RBC transfusion was also independently associated with higher mortality

Table 8. Pretransfusion Hemoglobin Level and Patients Who Received Transfusions

Factors	Patients Who Received Transfusions n (%)	Pretransfusion Hemoglobin, g/dL		p Value
		Mean ± SD	LQ/Median/UQ	
ICU type				
Medical, n = 1742	711 (40.8)	8.2 ± 1.6	7.4/8.2/9.0	<.001
Surgical, n = 1057	587 (55.5)	8.8 ± 1.8	7.9/8.7/9.6	
Combined, n = 2093	859 (41.0)	8.7 ± 1.7	7.8/8.6/9.4	
ICU characteristics				
Opened, n = 3406	1491 (43.8)	8.6 ± 1.7	7.8/8.6/9.4	<.001
Closed, n = 1486	666 (44.8)	8.4 ± 1.7	7.5/8.3/9.2	
Small, n = 672 ^a	282 (42.0)	8.1 ± 1.8	7.4/8.2/9.0	
Medium, n = 2650 ^b	1228 (46.3)	8.6 ± 1.7	7.7/8.6/9.4	<.001
Large, n = 1570 ^c	647 (41.2)	8.7 ± 1.6	7.8/8.6/9.4	
Public, n = 1504	679 (45.2)	8.6 ± 1.7	7.8/8.7/9.4	
Private, n = 1476	596 (40.4)	8.7 ± 1.8	7.7/8.6/9.5	.34
Academic, n = 1841	844 (45.8)	8.5 ± 1.7	7.6/8.4/9.3	.14
Community, n = 911	408 (44.8)	8.6 ± 1.6	7.7/8.4/9.3	
Transfusion protocol				
Yes, n = 1078	521 (48.3)	8.6 ± 1.8	7.7/8.6/9.5	.009
No, n = 3643	1565 (43.0)	8.5 ± 1.7	7.7/8.5/9.3	

LQ, lower quartile; UQ, upper quartile; ICU, intensive care unit.

^aSmall ICU, ≤11 beds; ^bmedium ICU, 11–20 beds; ^clarge ICU, >20 beds.



N (Hb)= 4892 3778 2042 1306 822 431 207

N (Hb)=

Trans/No Trans: 2157/2735 1903/1875 1272/770 911/395 638/184 365/66 182/25

*The difference across groups (transfused vs. nontransfused) is significant at $p < 0.007$ (using Bonferroni adjustment).

†The difference is significant at $p < .0045$ (using ANOVA and Bonferroni adjustment) compared with baseline (all patients sample).

‡The difference is significant at $p < .0045$ (using ANOVA and Bonferroni adjustment) compared with previous period (all patients sample).

Figure 5. Hemoglobin (Hb) levels day 1 through day 30. Trans/No Trans, ratio of patients who received transfusions to those who did not; ANOVA, analysis of variance.

rates (Table 12). Neither a baseline hemoglobin level of <10 g/dL nor a mean age of RBC units transfused of >2 wks was independently associated with an increase in mortality. However, in a separate model, nadir hemoglobin of <9.0 g/dL was associated with an increase in mortality. For the analysis using matching by propensity score to study mortality rate, 1,059 transfused patients (44.8%) were matched to 1,059 patients (41.8%) who did not receive transfusions. After

adjusting for the propensity for receiving a blood transfusion, RBC transfusion remained statistically significantly associated with an increased risk for death (adjusted mortality ratio, 1.65; 95% confidence interval, 1.35–2.03; log-rank, $p < .001$) (Fig. 7).

DISCUSSION

Anemia is common in critically ill patients and is seen early in their ICU

course. By 48 hrs after ICU admission, almost 70% of patients admitted to the ICU had a baseline hemoglobin level of <12 g/dL, and half of these had a level of <10 g/dL. The anemia in these critically ill patients persisted throughout the duration of their ICU and hospital stay, with or without RBC transfusion. The extent of anemia observed is consistent with previous studies (6).

Transfusion practice in response to this anemia has changed little over the last decade. Based on our survey, almost 50% of patients admitted to ICUs across the United States today receive transfusions. Although the initial RBC transfusion tended to occur early in the ICU stay (<3 days), there were ongoing RBC transfusions in these patients throughout their ICU stay. These observations are virtually identical to those made in earlier studies (6–8). Similarly, the mean pretransfusion hemoglobin observed (i.e., the transfusion trigger) was 8.6 ± 1.7 g/dL in the present study, a value that is comparable with that described in earlier reports (6, 7). RBC transfusions were not restricted to the ICU. Thirteen percent of patients discharged from the ICU received an average of 2.7 ± 2.8 units after ICU discharge. Post-ICU RBC transfusions increased the total number of RBC units transfused by almost 15% and therefore had a significant impact on the total number of RBC units consumed by critically ill patients.

The ICUs and institutions that participated in the study are a representative cross-section of ICUs in the United States, including large and small hospitals and teaching and nonteaching hospitals. Therefore, the results of the study likely reflect general transfusion practice patterns in ICUs in the United States today. A minority of ICUs (<20%) participating in the current study had an institutional or ICU transfusion protocol in place at the time of the study; however, the existence of such a protocol did not seem to affect transfusion-related practices. Although transfusion practice was reasonably consistent across institutions and ICUs, surgical patients tended to receive transfusions more frequently. This observation is consistent with the study by Groeger et al. (8), which reported that as many as 25% of patients in surgical ICUs receive transfusions on any given day, as compared with 14% in the overall population.

Recently, a similar observational study of transfusion practice in ICUs across

Table 9. Admitting Diagnostic Categories (Baseline Hemoglobin [Hb] of ≤ 8 and Baseline Hb of >12)

	Baseline Hb $\leq 8^a$		Baseline Hb $> 12^b$	
	n	%	n	%
Respiratory failure	97	23	533	35 ^c
Postoperative	55	13	220	14
Pneumonia	46	11	226	15
Cardiovascular	34	8	217	14 ^c
Trauma	48	12	182	12
Sepsis/SIRS	59	14	113	7 ^c
Hemodynamic instability	60	14	122	8 ^c
Neurologic	16	4	194	13 ^c
Gastrointestinal bleed	121	29	38	3 ^c
ARDS	10	2	37	2
Primary hematologic disease	14	3	0	0 ^c
Other	101	24	395	26

SIRS, systemic inflammatory response syndrome; ARDS, acute respiratory distress syndrome.

^aA total of 174 patients had at least two diagnoses (including other), 133 patients had at least two diagnoses (excluding other), 30 patients only had other as a diagnosis, and two patients had no diagnosis; ^b573 patients had at least two diagnoses (including other), 419 patients had at least two diagnoses (excluding other), 176 patients only had other as a diagnosis, and four patients had no diagnosis; ^cthe baseline Hb > 12 group is statistically different from baseline Hb ≤ 8 group ($p < .05$).

Table 10. Co-morbidities (Baseline Hemoglobin (Hb) of ≤ 8 and Baseline Hb of >12)

Preexisting Conditions	Percentage of Patients	
	Baseline Hb ≤ 8	Baseline Hb > 12
Hypertension	38	43
Cardiac disease	39	37
Pulmonary disease	21	38 ^a
Gastrointestinal disease	34	20 ^a
Diabetes	23	21
Cancer	18	14 ^a
Musculoskeletal disease	13	13
Central nervous system disease	12	12
Anemia	29	3 ^a
Renal disease	16	6 ^a
Peripheral vascular disease	12	8 ^a
Thromboembolic disease	5	3
Immunologic disease	6	2 ^a
Primary hematologic disease	6	1 ^a

^aThe baseline Hb > 12 group was statistically different from baseline Hb ≤ 8 group ($p < .05$).

Western Europe was performed (9). Data were collected on 3,534 patients admitted to ICUs during a 2-wk period in late 1999. The similarity of the results of this study with our study is striking and suggests a remarkable consistency in current transfusion practice within the critical care community. A total of 37% of patients received transfusions of a mean of 4.8 RBC units while in the ICU, and 12.7% of patients received transfusions in the post-ICU period. In total, 42% of patients received transfusions during the 28-day study period. The mean pretransfusion hemoglobin level was 8.4 g/dL.

The magnitude of RBC transfusion in the critically ill today is surprising, given the scrutiny to which transfusion practice has been subjected during the last

decade. In a prospective randomized study of critically ill patients, Hebert et al. (10) demonstrated that maintaining hemoglobin levels in the 7–9 g/dL range is at least equivalent, and in some patients (APACHE II of ≤ 20 or age of < 55 yrs) superior, to maintaining hemoglobin levels of > 10 g/dL with RBC transfusion. This finding also seemed to apply to patients with underlying cardiac disease, although other data suggest that patients with active ischemic cardiac disease may require a higher hemoglobin level (11). The studies by Hebert et al. (10, 11) and Dietrich et al. (12) have raised questions regarding the validity of the historic assumption that RBC transfusion is beneficial for all critically ill patients with anemia. Recent recommendations have

advocated that empirical automatic transfusion thresholds be abandoned in favor of a practice of RBC transfusion only for defined physiologic need (2, 3). However, the suggestion for a more conservative approach to RBC transfusion does not as yet seem to have resulted in any major alteration in practice patterns.

Decisions about transfusing RBCs are often made without a complete understanding of the risks and benefits of transfusion (13). Although a much clearer understanding of the risks of RBC transfusion has developed since the 1980s, the risks of anemia and the benefit of RBC transfusion are much less well characterized. For more than five decades, a hemoglobin level of 10 g/dL and a hematocrit of 30% were generally accepted minimum levels, particularly in the surgical setting. First proposed in 1942 (14), the “10/30” rule has become more a matter of faith than data. Although it is clear that transfusions at hemoglobin levels in the 10 g/dL range are much less common today, we observed that only about 25% of RBC transfusions occur in a range consistent with the findings reported by Hebert et al (10).

This transfusion behavior is consistent with previous studies, which noted that transfusion decisions tend to be driven by individual transfusion triggers rather than specific physiologic indications (6). In these studies, pretransfusion hematocrit was the same, regardless of transfusion indication. In the present study, there was little evidence that either age or co-morbidities significantly influenced transfusion practice. On the other hand, a low baseline hemoglobin level was associated with more RBC transfusions. The time to first transfusion was significantly longer in those patients who presented with a high baseline hemoglobin level (1.8 ± 1.7 days with baseline hemoglobin of ≤ 8 g/dL vs. 6.3 ± 6.2 days with baseline hemoglobin of > 12 g/dL, $p < .05$). These results support the hypothesis that RBC transfusion in many critically ill patients is driven by arbitrary transfusion triggers rather than physiologic findings (6). The fact that a low hemoglobin level was noted as one of the transfusion indications in 90% of transfusions is consistent with this hypothesis. The similarity between the apparent transfusion thresholds in the ICU and after ICU discharge also supports the view that hemoglobin level rather than clinical or physiologic factors drives transfusion decisions.

In general, more severely ill patients, as measured by either APACHE II or

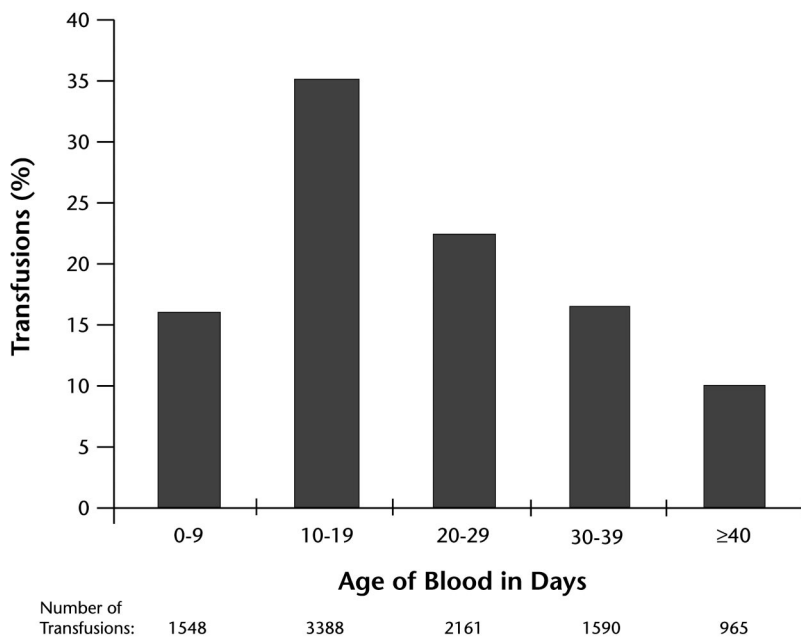


Figure 6. Age of red blood cell units transfused.

Table 11. Accelerated Failure Time Model on Intensive Care Unit (ICU) and Hospital Length of Stay (LOS)

	LOS Ratio			p Value
	Point Estimate	95% Confidence Limits		
ICU LOS				
RBC transfusion status in ICU				
Units transfused: 1–2	1.47	1.35	1.59	<.0001
Units transfused: 3–4	1.84	1.66	2.03	<.0001
Units transfused: >4	3.20	2.88	3.55	<.0001
No transfusion	Reference	—	—	—
Baseline hemoglobin level, g/dL				
<8	0.94	0.85	1.05	0.278
8 to <9	0.96	0.88	1.04	0.338
9 to <10	0.97	0.90	1.03	0.324
≥10	Reference	—	—	—
Nadir hemoglobin level, g/dL ^a				
<8	1.41	1.29	1.53	<.0001
8 to <9	1.57	1.47	1.69	<.0001
9 to <10	1.30	1.23	1.39	<.0001
≥10	Reference	—	—	—
Hospital LOS				
RBC transfusion status in hospital				
Units transfused: 1–2	1.32	1.22	1.42	<.0001
Units transfused: 3–4	1.61	1.47	1.75	<.0001
Units transfused: >4	2.51	2.28	2.76	<.0001
No transfusion	Reference	—	—	—
Baseline hemoglobin level, g/dL				
<8	1.01	0.91	1.11	0.918
8 to <9	0.96	0.89	1.03	0.244
9 to <10	0.96	0.91	1.02	0.240
≥10	Reference	—	—	—
Nadir hemoglobin level, g/dL ^a				
<8	1.17	1.08	1.27	<.0001
8 to <9	1.23	1.16	1.31	<.0001
9 to <10	1.14	1.08	1.21	<.0001
≥10	Reference	—	—	—

RBC, red blood cell.

^aEstimates from a separate model in which nadir hemoglobin replaces baseline hemoglobin level.

SOFA score, had a low baseline hemoglobin level and received more RBC transfusions. However, after correcting for baseline hemoglobin level and severity of illness, more RBC transfusions were independently associated with worse clinical outcomes. This is similar to the finding by Vincent et al (9). On the other hand, although both studies found that baseline hemoglobin level was not associated with mortality, we did find that a nadir hemoglobin level of <9 g/dL was associated with a higher mortality. Given the observational design of these studies, these findings should be interpreted with caution. However, the transfusion results are consistent with recent data suggesting that a liberal RBC transfusion policy may be deleterious for some critically ill patients (10, 15).

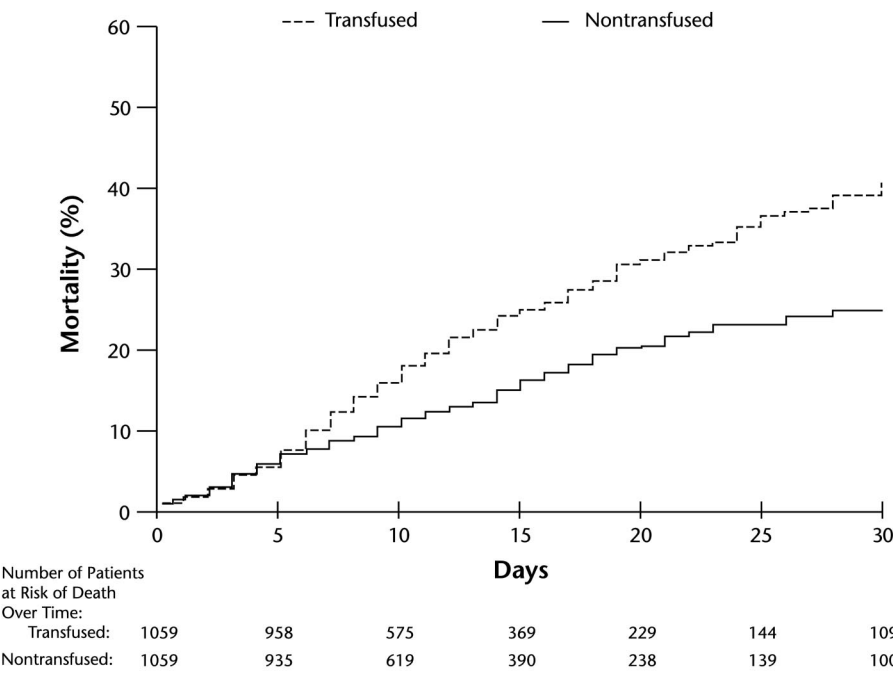
Why RBC transfusions are associated with worse clinical outcomes is unclear. A substantial amount of literature has developed since the early 1980s suggesting that exposure to allogeneic leukocytes in transfusions may trigger an immune system response in the recipient leading to increased risk of infection, earlier recurrence of malignancy, and increased likelihood of mortality (16). A significant association between the number of RBC transfusions and risk of subsequent infection has been reported in patients after trauma, burns, and a variety of surgical procedures, both elective and emergency (17–19). In the critically ill, Taylor et al. (20) demonstrated an association between RBC transfusion and nosocomial infection and mortality in the critically ill. These data have in turn led to the hypothesis that giving patients transfusions with leuko-reduced blood should result in reduced morbidity and mortality compared with patients receiving transfusions with non-leuko-reduced blood. However, most of the studies bearing on these questions have been flawed by retrospective design and inadequate consideration of the effects of co-morbidities, whereas the few prospective studies in specific patient populations have reached contradictory conclusions. Meta-analyses of this substantial literature have failed to identify a statistically significant effect of leuko-reduction (16, 21, 22). A recent study evaluating clinical outcomes after the institution of a universal leuko-reduction program in Canada noted a reduction in hospital mortality after introduction of this program (23). On the other hand, a randomized prospective study comparing outcomes in patients receiving either leuko-reduced

Table 12. Logistic regression for 30-day mortality

Factors	Odds Ratio			p Value
	Point Estimate	95% Confidence Limits		
RBC transfusion status in hospital				
Units transfused: 1–2	1.48	1.07	2.05	.018
Units transfused: 3–4	2.62	1.80	3.81	<.0001
Units transfused: >4	4.01	2.74	5.87	<.0001
No transfusion	Reference	—	—	—
Baseline hemoglobin level, g/dL				
<8	1.05	0.71	1.56	.799
8 to <9	0.85	0.61	1.17	.314
9 to <10	0.90	0.70	1.16	.424
≥10	Reference	—	—	—
Nadir hemoglobin level, g/dL ^a				
<8	1.54	1.12	2.12	<.009
8 to <9	1.49	1.13	1.95	<.004
9 to <10	1.17	0.91	1.49	.227
≥10	Reference	—	—	—
Mean age of blood transfused in hospital				
>2 wks	1.00	0.75	1.32	.975
≤2 wks or no transfusion	Reference	—	—	—

RBC, red blood cell.

^aEstimates from a separate model in which nadir hemoglobin replaces baseline hemoglobin level.



Log-Rank=24.02; p<.0001.

Figure 7. Mortality by transfusion status for propensity-matched patients.

or non-leuko-reduced RBCs failed to demonstrate any beneficial effect of leuko-reduction on clinical outcome (24). The question therefore still remains as to whether there are in fact clinical benefits associated with leuko-reduction of transfused RBCs (25). We do not have data from the current study that would allow us to answer this question.

Recent data have also raised the issue that transfusion of “old” blood may be

associated with worse outcomes (26, 27). The current study provides robust data regarding the age of RBCs critically ill patients receive. The mean age of RBCs transfused was 3 wks, and >25% of transfused RBCs were >1 month old. This is somewhat older than the mean 16 ± 6.7 days for RBCs transfused in Western Europe (9). There were no differences in the age of RBCs transfused across institutions or ICUs. Although there was a trend

A *nemia is common in the critically ill and results in a large number of red blood cell transfusions.*

toward worse clinical outcome among patients receiving transfusions with relatively old blood, this relationship was weak and did not achieve statistical significance. The clinical significance of the age of blood remains controversial and will require further study.

Why critically ill patients are anemic is multifactorial. Phlebotomy and blood loss undoubtedly play a role (6, 9). Nevertheless, a number of studies suggest that an underproduction of erythrocytes similar to that observed in chronic inflammatory diseases significantly contributes to the anemia in critical illness (28). More than 90% of ICU patients have low serum iron, total iron binding capacity, and iron–total iron binding capacity ratio (5, 29). In addition, these patients typically have an elevated serum ferritin level (5, 19). At a time when the iron studies are abnormal, serum erythropoietin levels are only mildly elevated, with little evidence of a reticulocyte response to endogenous erythropoietin (5). Therefore, the anemia of critical illness is a distinct clinical entity characterized by a blunted erythropoietin production and abnormalities in iron metabolism. This is reflected in the fall in hemoglobin level observed during the course of a patient’s critical illness.

The data from this study should be interpreted recognizing that this is an observational study. Although the analysis attempted to control for confounding factors, it was limited to only the factors recorded. Given the complexity of critical illness, all of the factors influencing outcome may not have been included. For example, although there are considerable baseline clinical data available, fewer data are available regarding a patient’s clinical status at the time of a RBC transfusion. The inferences drawn between variables can only indicate association not causation.

In conclusion, anemia is common in the critically ill patient, and persists throughout the ICU and hospital stay. Despite the scrutiny of transfusion practice during recent years, practice in the

United States in 2000–2001 is little changed as compared with the preceding decade (6–8). Transfusion practice in the United States is also very similar to transfusion practice as recently reported in Western Europe (9). Current data regarding RBC transfusion thresholds and risks of RBC transfusion have not as yet significantly altered practice patterns (10). RBC transfusions seem to be associated with worse clinical outcomes. Clearly, approaches to reduce RBC transfusion would be desirable (10, 30). However, further study is required to more fully explore the risk of anemia, optimal hemoglobin level, and the risk and efficacy of RBC transfusion in the critically ill.

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APPENDIX 1

Definitions of Terms

Acute Respiratory Distress Syndrome. Acute respiratory distress syndrome manifested by acute onset, PaO_2/FiO_2 of ≤ 200 torr, bilateral infiltrates on frontal chest radiograph, pulmonary artery occlusion pressure of ≤ 18 mm Hg when measured, or no clinical evidence of left atrial hypertension.

Deep Vein Thrombosis. Clinical suspicion of deep vein thrombosis confirmed by either duplex ultrasonography or venography.

Pulmonary Embolism. Clinical suspicion of pulmonary embolism confirmed by either ventilation/perfusion scan or pulmonary angiogram, particularly in the presence of deep vein thrombosis.

Organ Failure/Dysfunction. Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention; Sequential Organ Failure Assessment scoring was used in this study to track organ failure/dysfunction.

Infection. Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

- Bacteremia: positive blood cultures for bacteria.
- Wound infection: presence of signs and symptoms consistent with a wound infection (erythema, edema, tenderness, and pus) along with positive wound cultures.
- Catheter infection: confirmed using semiquantitative cultures of the catheter portion residing in the intracutaneous area with ≥ 15 colony-forming units present.
- Pneumonia: presence of fever, leukocytosis, purulent secretions, new or progressive chest radiograph infiltrates, or pathologic bacteria in tracheobronchial secretions.
- Urinary tract infection: presence of signs/symptoms consistent with a urinary tract infection (e.g., pyuria, dysuria, frequency, urgency, flank pain)

along with positive urine cultures (from a good-quality specimen) containing >100,000 colony-forming units, >5 white blood cells per high-power field.

- Fungal infection: presence of fungi as determined by culture from any sterile site (e.g., blood, cerebrospinal fluid, urine, sputum).

Reintubation. Intubation occurring after extubation by a healthcare professional.

Failed Weaning Attempt. Failed definitive attempt to remove patient from ventilatory support.

Respiratory Failure. Presence of one or more of the following: 1) respiratory rate of ≤ 5 breaths/min or ≥ 49 breaths/min, 2) P_{aCO_2} of ≥ 50 torr (≥ 6.7 kPa), 3) alveolar-arterial oxygen tension difference ($P[A-a]O_2$) of ≥ 350 torr ($P[A-a]O_2 = 713 F_{IO_2} - P_{aCO_2} - P_{aO_2}$), or 4) dependent on ventilator on day 4 of organ system failure (e.g., not necessarily applicable for the initial 72 hrs of organ system failure).

Acute Lung Injury. Acute onset, P_{aO_2}/F_{IO_2} of ≤ 300 torr, bilateral infiltrates on frontal chest radiograph, pulmonary artery occlusion pressure of ≤ 18 mm Hg, or no clinical evidence of left atrial hypertension (not as serious as acute respiratory distress syndrome).

Pulmonary edema. Edema in the lung tissues, best evidenced by chest radiograph.

Sepsis. Known or suspected infection. The systemic response to infection, manifested by two or more of the following conditions as a result of infection: 1) temperature of $>38^\circ C$ ($100.4^\circ F$) or $<36^\circ C$ ($96.8^\circ F$); 2) heart rate of >90 beats/min; 3) respiratory rate of >20 breaths/min or P_{aCO_2} of <32 torr; and 4) white blood cell count of $>12,000/mm^3$, $<4,000/mm^3$, or $>10\%$ immature (band) forms.

Septic Shock. Sepsis-induced hypotension or the requirement for vasopressors/inotropes to maintain blood pressure despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or acute alteration in mental status.

Systemic Inflammatory Response Syndrome. The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: 1) temperature of $>38^\circ C$ ($100.4^\circ F$) or $<36^\circ C$ ($96.8^\circ F$); 2) heart rate of >90

beats/min; 3) respiratory rate of >20 breaths/min or P_{aCO_2} of <32 torr (<4.3 kPa); or 4) white blood cell count of $>12,000$ cells/ mm^3 , <4000 cells/ mm^3 , or $>10\%$ immature (bands) cells.

Cardiac Arrest. Arrest of cardiac function, even if patient is successfully resuscitated.

Myocardial Infarction. Electrocardiographic and laboratory (creatinine kinase, isoenzyme of creatine kinase with muscle and brain subunits, troponin) abnormalities suggestive of myocardial infarction.

Cerebrovascular Accident. Diagnosis confirmed by computed tomographic scan.

Disseminated Intravascular Coagulopathy. Clinical suspicion of disseminated intravascular coagulopathy confirmed with the following laboratory tests: prolonged prothrombin time, activated partial thromboplastin time, and thrombin time; decreased fibrinogen and platelets; positive fibrin degradation products, D-dimer; and decreased factors V, VIII, and II (late).

Major Bleed on Study. Significant bleeding (>1 unit of blood) from a single source, typically resulting in a decrease in hemoglobin/hematocrit and the need for transfusion.

APPENDIX 2

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