Anemia and Blood Transfusion in Critically Ill Patients

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A NEMIA IS A COMMON PROBLEM in critically ill patients admitted to intensive care units (ICUs).[1] Deleterious effects of anemia include increased risk of cardiac-related morbidity[2] and mortality,[2,3] as well as a generalized decrease in oxygen-carrying capacity. Consequences of anemia may be compounded in this population since critical illness often increases metabolic demands.

Among the many causes of anemia in the critically ill, some of the most important are sepsis,[4] overt or occult blood loss (including frequent blood sampling[5]), decreased production of endogenous erythropoietin, and immune-associated functional iron deficiency.[6] However, the specific impact of anemia on ICU patient morbidity and mortality is poorly defined, as is the optimal hemoglobin level for this population.

Anemia is typically treated with blood transfusions to help maintain adequate oxygen delivery. Groeger et al[7] found that 16% of patients in medical ICUs and 27% of those in surgical ICUs

Context Anemia is a common problem in critically ill patients admitted to intensive care units (ICUs), but the consequences of anemia on morbidity and mortality in the critically ill is poorly defined.

Objectives To prospectively define the incidence of anemia and use of red blood cell (RBC) transfusions in critically ill patients and to explore the potential benefits and risks associated with transfusion in the ICU.

Design Prospective observational study conducted November 1999, with 2 components: a blood sampling study and an anemia and blood transfusion study.

Setting and Patients The blood sampling study included 1136 patients from 145 western European ICUs, and the anemia and blood transfusion study included 3534 patients from 146 western European ICUs. Patients were followed up for 28 days or until hospital discharge, interinstitutional transfer, or death.

Main Outcome Measures Frequency of blood drawing and associated volume of blood drawn, collected over a 24-hour period; hemoglobin levels, transfusion rate, organ dysfunction (assessed using the Sequential Organ Failure Assessment score), and mortality, collected throughout a 2-week period.

Results The mean (SD) volume per blood draw was 10.3 (6.6) mL, with an average total volume of 41.1 (39.7) mL during the 24-hour period. There was a positive correlation between organ dysfunction and the number of blood draws ($r=0.34$; $P<.001$) and total volume drawn ($r=0.28$; $P<.001$). The mean hemoglobin concentration at ICU admission was 11.3 (2.3) g/dL, with 29% (963/3295) having a concentration of less than 10 g/dL. The transfusion rate during the ICU period was 37.0% (1307/3534). Older patients and those with a longer ICU length of stay were more commonly transfused. Both ICU and overall mortality rates were significantly higher in patients who had vs had not received a transfusion (ICU rates: 18.5% vs 10.1%, respectively; $\chi^2=50.1$; $P<.001$; overall rates: 29.0% vs 14.9%, respectively; $\chi^2=88.1$; $P<.001$). For similar degrees of organ dysfunction, patients who had a transfusion had a higher mortality rate. For matched patients in the propensity analysis, the 28-day mortality was 22.7% among patients with transfusions and 17.1% among those without ($P=.02$); the Kaplan-Meier log-rank test confirmed this difference.

Conclusions This multicenter observational study reveals the common occurrence of anemia and the large use of blood transfusion in critically ill patients. Additionally, this epidemiologic study provides evidence of an association between transfusions and diminished organ function as well as between transfusions and mortality.

JAMA. 2002;288:1499-1507   www.jama.com

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Caring for the Critically Ill Patient Section Editor: Deborah J. Cook, MD, Consulting Editor, *JAMA*.
Advisory Board: David Bihari, MD; Christian Brun-Buisson, MD; Timothy Evans, MD; John Heffner, MD; Norman Paradis, MD; Adrienne Randolph, MD.

are transfused on any given day. In a retrospective chart review in the United States, 85% of patients with an ICU length of stay greater than 1 week received at least 1 blood transfusion, and the mean number of units of blood transfused per patient was 9.5.[8] More than two thirds of ICU transfusions were not associated with acute blood losses.[8]

While blood transfusions are prevalent among ICU patients, the criteria for optimal anemia management are not clearly defined.[9] A randomized controlled trial by the Canadian Critical Care Trials Group[10] comparing restrictive (ie, target hemoglobin level, 7-9 g/dL) and liberal (target level, 10-12 g/dL) transfusion strategies in ICU patients indicated that the liberal use of transfusions may have resulted in higher hospital mortality rates.

The use of blood includes health risk and has significant administrative, logistic, and economic implications. Allogeneic blood transfusion is associated with risk of allergic reaction,[11] infection transmission,[12] and immunosuppression.[11,13,14] Additionally, blood transfusion in the critically ill, particularly with "old" stored cells, does not consistently improve tissue oxygenation.[15]

The use of blood transfusions for the treatment of anemia in critically ill patients warrants further evaluation. This prospective observational study was designed to determine the frequency of blood drawing and the volume of blood lost from blood drawing, and to estimate the incidence of anemia and the use of red blood cell (RBC) transfusions in critically ill patients throughout western Europe. Such data could provide an objective basis for the future study of anemia management strategies.

METHODS
Study Design

This prospective, observational study had 2 components: a blood sampling study, and an anemia and blood transfusion study. Institutional recruitment for participation was by open invitation from the study steering com-

mittee to academic and nonacademic ICUs. Institutional participation was limited to general medical and/or surgical ICUs in western Europe. Additionally, participation required a minimum of at least 6 beds to limit any variability in staffing, technology, or practice associated with smaller ICUs. Since this epidemiologic observational study did not require any deviation from routine medical practice, institutional review board approval was either waived or expedited in participating institutions and informed consent was not required.

Blood Sampling Study

The purpose of the blood sampling study was to determine the frequency of blood drawing and the associated volume of blood lost. The number of blood draws and volume per draw was recorded for all patients in each ICU for a 24-hour period 1 week prior to the anemia and blood transfusion study. Data were also collected for the Sequential Organ Failure Assessment (SOFA) score.[16]

Anemia and Blood Transfusion Study

For all patients admitted to participating ICUs during a 2-week period (November 15, 1999, through November 29, 1999), data were collected daily for a maximum of 28 days or until hospital discharge, interinstitutional transfer, or death. Data collected at ICU admission included demographics, type of admission, type of surgery (if applicable), primary diagnostic category, comorbidities, history of anemia and recent acute blood loss, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, SOFA score, and history of recombinant human erythropoietin therapy. Data collected daily included morning hemoglobin, hematocrit, RBC count, SOFA score, indication for transfusion, pretransfusion hemoglobin (if different from the patient's morning value), and number of units transfused. The primary indication for transfusion (assessed by the attending physician) and pretransfusion hemo-

globin levels were collected for the first transfusion of the day only.

Data Management and Statistical Evaluation

Data collected using preprinted case report forms (CRFs) were verified using a series of domain and consistency edits as defined by the study steering committee. Intensive care units were queried when data values were either questionable or were missing for required fields. The CRFs were then scanned electronically using TELEform scanning software (Cardiff Software Inc, Vista, Calif) and a database was created using SPSS v9.01 (SPSS Inc, Chicago, Ill). Unanswered queries concerning required fields were treated as missing and resulted in an overall loss of 0.06% of data.

Descriptive statistics were computed for all study variables. Bivariate and multivariate distributions were evaluated for normality using standard statistical methods and by examining stratified distribution plots. Nonparametric measures of comparison were used for variables evaluated as not normally distributed. Difference testing between groups was performed using the 2-tailed t test, analysis of variance (with Bonferroni post-hoc analyses), or χ^2 test. Significance for main effects was tested at the $\alpha = .05$ level. Logistic regression was conducted to assess determinants of mortality. Kaplan-Meier survival analyses were conducted on the entire sample as well as on a sample of matched pairs of patients (transfused and nontransfused) who were matched on their propensity to receive a transfusion. Propensity scores were obtained through logistic regression of patient characteristics on transfusion status (ie, actual receipt of a transfusion). A greedy matching technique[17] was used to match unique transfused patients with unique nontransfused patients based on propensity scores. The best-match propensity score was identical to 6 digits. Once a match was made, the control patient was removed from the pool. This process was then repeated using 5-digit

matching, then 4-digit matching, etc. If a transfused patient matched with more than 1 control, a match was randomly selected. The process proceeded sequentially to a single-digit match on propensity score. If a match was not obtained at this point, the transfused patient was excluded.

Cohorts reflecting patient groups of specific clinical interest were created post hoc. In particular, cohort was defined of those patients with acute bleeding as an indicator for transfusion at any time or having hemorrhagic shock on admission.

RESULTS

TABLE 1 describes the country participation and the characteristics of the participating ICUs.

Blood Sampling Study

Twenty-four–hour blood sampling data were collected on 1136 patients from 145 participating western European ICUs (see list at end of article). The number and volume of blood samples drawn in the 24-hour period varied widely across patients. A total of 45.9% of patients had 5 or more blood samples drawn. The mean (SD) number of draws per patient was 4.6 (3.2), the mean volume per draw was 10.3 (6.6) mL, and the average total volume was 41.1 (39.7) mL for the 24-hour period. There was a significant positive correlation between organ dysfunction (as measured by the SOFA score) and number of blood draws ($r=0.34$; $P<.001$) and total volume drawn ($r=0.28$; $P<.001$).

Anemia and Blood Transfusion Study

Demographics. Anemia and blood transfusion study data were collected on 3534 patients from 146 ICUs. Mean (SD) patient age was 61 (17) years, with 33.4% older than 70 years. The majority of patients (62%) were men. **TABLE 2** presents the primary clinical data on admission to the ICU. The mean admitting APACHE II score was 14.8 (7.9) and the mean admitting SOFA score was 5.2 (3.8). Overall mean ICU length

of stay was 4.5 (6.7) days (≤1 day, 46.6% of patients; 2-3 days, 21.4%; 4-7 days, 14.2%; and >7 days, 17.8%).

Course of Anemia. The mean (SD) admitting hemoglobin level was 11.3 (2.3) g/dL, with 63% (2078/3295) of patients having an admitting hemoglobin level less than 12 g/dL and 29% (963/3295) less than 10 g/dL. Admitting hemoglobin was correlated with age ($r=-0.11$; $P<.001$). The mean admitting hemoglobin level was 11.7 g/dL for patients younger than 50 years (n=726), but 11.0 g/dL in patients aged 80 through 90 years (n=298), and 9.9 g/dL in patients older than 90 years (n=23) ($F=6.6$; $P<.001$).

On admission, approximately 13% of patients had a recent history of anemia; of those patients, 36.6% had an ad-

mitting hemoglobin less than 10 g/dL. Of all patients with an admitting hemoglobin level less than 10 g/dL, 48.9% had neither a history of anemia nor of acute bleeding.

Hemoglobin patterns over the 28-day period, stratified by the day 1 hemoglobin level, are illustrated in **FIGURE 1**, revealing a convergence of hemoglobin levels over time, irrespective of the admitting hemoglobin level. Hemoglobin evolution was similar both for the cohort of patients without acute bleeding (75% of patients, n=2655) and the cohort with acute bleeding (data not shown). There were weak negative correlations between admitting hemoglobin level and admitting SOFA score ($r=-0.21$, $P<.001$) and ICU length of stay ($r=-0.25$, $P<.001$).

Table 1. Summary of Participating Institutions*

	No. (%)	Hospital Beds, No.	Mean ICU Beds, No.
Hospital Characteristics			
Hospital type			
Academic medical center	71 (49.0)	1052	13.9
City or regional medical center	50 (34.5)	700	11.4
Community hospital	24 (16.5)	554	11.3
ICU type			
General	103 (71.0)	. . .	12.2
Surgical	37 (25.5)	. . .	13.5
Medical	5 (3.4)	. . .	13.6

Country Characteristics			
	Hospitals, No.	Patients in Blood Sampling Study, No.	Patients in Anemia and Blood Transfusion Study, No.
Country			
Austria	15	112	308
Belgium	14	145	558
Denmark	2	10	36
Finland	9	45	307
France	24	227	504
Germany	14	125	461
Greece	4	47	60
Italy	14	84	209
The Netherlands	14	116	397
Norway	3	14	30
Portugal	5	31	53
Spain	6	58	147
Sweden	3	8	76
Switzerland	4	17	115
United Kingdom†	15	97	273
Total	**146**	**1136**	**3534**

*ICU indicates intensive care unit; ellipses, not applicable.
†Only 14 hospitals from the United Kingdom submitted data for the Blood Sampling Survey.

Table 2. Admitting Clinical Data*

	No. (%)	Mean Admitting APACHE II Score†	Mean Admitting SOFA Score†	Mean Admitting Hb Level, g/dL	Prior Transfusion, %‡
Admission type					
Elective surgery	1464 (41.4)	11.6	4.2	11.0	26.1
Medical	1151 (32.6)	17.9	5.9	11.9	6.6
Emergency surgery	586 (16.6)	16.3	6.1	10.8	34.2
Trauma	269 (7.6)	15.1	5.6	11.5	19.6
Other	58 (1.6)	14.5	4.0	12.0	17.2
Shock at ICU admission‡§	705 (20.2)	21.8	8.8	10.5	28.0
Sepsis/septic	271 (38.4)	22.1	9.0	10.4	6.6
Cardiogenic	205 (29.1)	23.4	9.4	11.1	12.1
Hemorrhagic	180 (25.5)	21.0	8.4	9.2	68.4
Other	94 (13.3)	21.8	8.3	11.8	12.9
Primary admission diagnosis					
Coronary ischemic heart disease	637 (18.2)	13.6	5.6	11.2	20.8
Circulatory	579 (16.5)	15.6	5.8	11.0	29.9
Respiratory	549 (15.6)	16.2	5.3	11.5	12.8
Neurologic	397 (11.3)	15.3	5.1	12.3	6.3
Gastrointestinal	353 (10.1)	14.0	4.6	10.8	30.5
Trauma	237 (6.8)	14.9	5.4	11.5	24.6
Kidney/urinary tract	126 (3.6)	14.4	4.9	10.6	27.2
Infectious	115 (3.3)	18.2	6.6	10.7	10.4
Hepatobiliary/pancreatic	94 (2.7)	15.0	5.6	10.8	34.4
Poisoning	88 (2.5)	11.6	3.8	13.3	0
Endocrine/metabolic	52 (1.5)	15.1	3.1	12.7	5.8
Orthopedic	51 (1.5)	10.5	2.5	10.7	35.3
Obstetric/gynecologic	46 (1.3)	9.2	2.6	10.4	26.1
Hematologic/immunologic	18 (0.5)	23.4	8.5	9.0	52.9
Other	166 (4.7)	11.6	3.2	11.3	16.4

*Numbers do not total 3534 because of missing data (some forms incomplete). APACHE II indicates Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; Hb, hemoglobin; and ICU, intensive care unit.
†Range of scores for Apache II, 0-71; for SOFA, 0-24.
‡Within 24 hours prior to ICU admission.
§Types were not mutually exclusive; total percentage exceeds 100%.

Figure 1. Course of Hemoglobin (Hb) Patterns by Admitting Hb Level Category
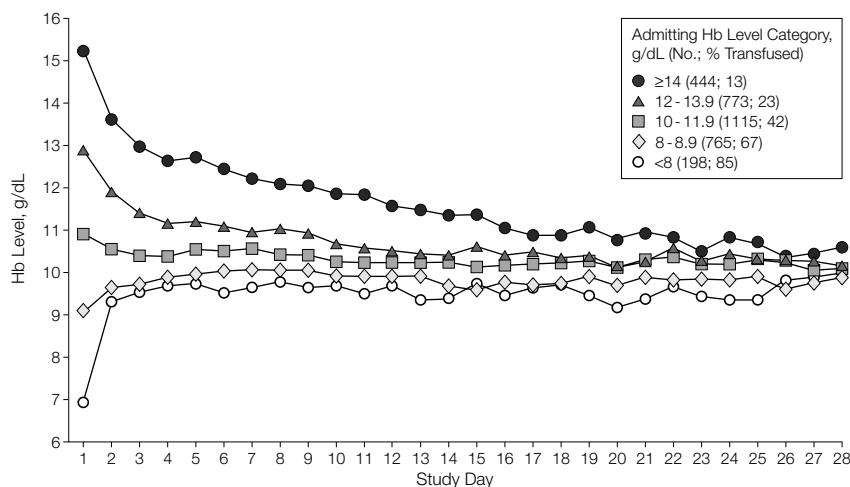
Numbers do not total 3534 because of missing data (some forms incomplete).

Transfusions. The transfusion rate (proportion of 3534 patients transfused) during the ICU period was 37.0%, and the post-ICU transfusion rate was 12.7% (proportion of all patients initially admitted to the ICU). The overall transfusion rate (including both ICU and post-ICU timeframes) was 41.6% over the 28-day period. The mean (SD) age of blood transfused in the ICUs was 16.2 (6.7) days. Leukocyte-depleted blood was used most of the time by 46% of the ICUs surveyed, some of the time in 35%, and never in 19%. Transfusion rates differed significantly by hospital type, with community hospitals transfusing at a rate of 36.4%, regional hospitals at a rate of 39.8%, and academic hospitals at the highest rate of 44.2% ($\chi^2 = 12.1; P < .002$), which reflected the differences in sever-

ity of the patient populations as measured by mean admitting SOFA score across the hospital types (4.5 for patients in community hospitals, 5.1 for patients in regional hospitals, and 5.4 for patients in academic hospitals; $F=9.2$; $P<.001$).

Two thirds of patients transfused within 24 hours prior to ICU admission had subsequent transfusions during the survey. Patients admitted for emergency surgery were transfused more frequently (57.5%), followed by those admitted for trauma (48.0%), elective surgery (42.1%), and medical reasons (32.0%). These differences were statistically significant ($\chi^2=115.0$; $P<.001$).

Transfusion rates increased consistently by age group, from 29.9% (18-30 years) to 54.2% (>80 years) ($\chi^2=63.2$; $P<.001$). However, differences in the mean number of units transfused by age, during both the ICU stay and throughout the 28-day survey, were not statistically significant.

Transfused patients were older, had higher admitting SOFA and APACHE II scores, lower admitting hemoglobin levels, and longer hospital lengths of stay (**TABLE 3**).

The overall mean pretransfusion hemoglobin levels were 8.4 (1.3) g/dL for the entire population and 8.5 (1.1) g/dL for those without acute bleeding. **TABLE 4** shows the distribution of indications for transfusion as well as the pretransfusion hemoglobin levels for both the ICU and the post-ICU periods. There were no significant differences in the mean pretransfusion hemoglobin levels by age, primary admitting diagnosis, or indication for transfusion (data not shown). Pretransfusion hemoglobin concentrations exceeded 9 g/dl in less than 30% of cases.

Higher transfusion rates were associated with increased ICU length of stay (**TABLE 5**). Mean ICU length of stay for transfused patients was 7.2 (median=3) days compared with 2.6 (median=1) days for nontransfused patients. Nearly 70% of all transfused patients received their first transfusion within the first 2 days in the ICU. Patients whose ICU length of stay was

longer than 7 days had an overall transfusion rate of 73.3%, with a transfusion rate of 52.6% during the first 2 days in the ICU.

The association between transfusion rates and degree of organ failure, as assessed by the SOFA score, was statistically significant ($\chi^2=358.5$; $P<.001$). When transfused and nontransfused patients were paired within strata of their admitting SOFA scores, transfused patients had lower mean admitting hemoglobin levels than nontransfused patients at every admitting SOFA category (t tests significant at $P<.05$ within each SOFA category). Within each admitting SOFA category, the nontransfused groups consistently showed greater improvement in organ function over time than the transfused groups (data not shown). Mean daily SOFA scores were significantly higher in transfused patients than in nontransfused patients across the entire 28-day survey ($P<.01$ on all 28 days). Transfused patients both with and without bleeding had similar SOFA evolution (data not shown). The last recorded SOFA score, irrespective of length of stay, was significantly lower in the nontransfused group than in the transfused group (2.8 vs 4.8; $t=-12.8$; $P<.001$).

Mortality. ICU mortality was 13.5% and 28-day overall mortality was 20.2%. Both ICU and overall mortality rates were significantly higher for trans-

Table 3. Patient Characteristics by Transfusion Status*

Variable	Transfused	Not Transfused	P Value†
Age, mean (SD), y	63.6 (15.8)	59.2 (17.0)	<.001
Men, No. (%)	920 (63.3)	1231 (60.6)	.11
Admission characteristics			
Admitting Hb level, mean (SD), g/dL	10.1 (2.1)	12.2 (2.1)	<.001
Admitting SOFA score, mean (SD)	6.6 (3.7)	4.2 (3.5)	<.001
Admitting APACHE II score, mean (SD)	16.5 (7.9)	13.5 (7.7)	<.001
Recent history of anemia, No. (%)	254 (17.5)	188 (9.2)	<.001
Recent history of blood loss, No. (%)	594 (4.1)	353 (17.4)	<.001
In shock at admission, No. (%)	445 (30.7)	268 (12.7)	<.001
Admission type, No. (%)			
Elective surgery	617 (41.9)	847 (41.1)	.61
Emergency surgery	338 (23.3)	248 (12.0)	<.001
Medical	368 (25.0)	781 (37.9)	<.001
Trauma	129 (8.8)	140 (6.8)	.03
Other	16 (1.1)	42 (2.0)	.03
Hospital length of stay, mean (SD), d	15.8 (9.0)	10.9 (7.9)	<.001

*Hb indicates hemoglobin; SOFA, Sequential Organ Failure Assessment; and APACHE II, Acute Physiology and Chronic Health Evaluation II.
†Due to missing data, the group sizes vary for each comparison.

Table 4. Summary of Indications for Transfusion*

Indication for Transfusion†	ICU Transfusion (n = 1307)		Post-ICU Transfusion (n = 326)	
	Transfusions, No. (%)	Pretransfusion Hb, Mean (SD), g/dL	Transfusions, No. (%)	Pretransfusion Hb, Mean (SD), g/dL
Acute bleeding	702 (55.5)	8.4 (1.4)	80 (27.4)	8.4 (1.0)
Inadequate Hb with: Diminished physiological reserves	355 (28.0)	8.4 (1.0)	35 (44.2)	8.3 (1.1)
Altered tissue perfusion	213 (16.8)	8.4 (1.2)	26 (12.0)	8.4 (0.8)
Coronary artery disease	104 (8.2)	8.7 (0.9)	129 (8.9)	8.7 (0.8)
Other indications	142 (11.2)	8.4 (1.2)	47 (16.1)	8.3 (1.0)

*ICU indicates intensive care unit; Hb, hemoglobin.
†Since many patients were transfused on multiple days, indications for transfusions are not mutually exclusive.

Table 5. Intensive Care Unit (ICU) Transfusion Rate and Mean Number of Units Transfused by ICU Length of Stay (LOS)

ICU LOS, d	All Patients (n = 3534)			Acute Bleeding (n = 794 [22.5%])*			No Acute Bleeding (n = 2655 [75.1%])*		
	No.	Transfused, %	Units Transfused, Mean No. (SD)	No.	Transfused, %†	Units Transfused, Mean No. (SD)‡	No.	Transfused, %†	Units Transfused, Mean No. (SD)‡
All patients	3534	37.0	4.8 (5.2)	794	92.8	5.5 (6.1)	2655	20.0	3.5 (3.3)
≤2	2136	24.5	2.9 (2.6)	380	90.0	3.1 (3.0)	1700	9.5	2.1 (1.1)
>2	1398	56.1	6.0 (6.1)	192	95.4	7.7 (7.3)	955	38.6	4.1 (3.7)
>7	629	73.3	7.2 (7.0)	222	98.7	9.7 (8.5)	397	58.9	4.9 (4.3)

*Total does not add to 100% since 2.4% of patients had missing data related to bleeding status.
†Differences in transfusion rates between patients with and without acute bleeding were statistically significant at every LOS category (P<.01).
‡Difference between patients with and without acute bleeding in mean number of units transfused was statistically significant at every LOS category (P<.01).

Table 6. Difference in Mortality by Number of Units Transfused

Units Transfused	No.	Mortality, %		P Value*
		Survived (n = 2422)	Died (n = 614)	
0	1896	85.1	14.9	
1	157	84.1	15.9	
2	377	79.6	20.4	<.01
3	157	70.7	29.3	
4	130	69.2	30.8	
>4	319	55.2	44.8	

*Numbers do not total 3534 because of missing data (some forms incomplete). χ^2 = 171.46.

Table 7. Summary of Logistic Regression on Mortality*

Variable	β	SE	Wald χ^2	P Value	OR (95% CI)
Constant	−6.71	0.52	168.57	<.001	NA
Transfusion	0.31	0.15	4.28	.04	1.37 (1.02-1.84)
Admitting SOFA score	0.26	0.02	119.43	<.001	1.30 (1.24-1.36)
Admitting APACHE II score	0.11	0.01	106.02	<.001	1.11 (1.09-1.14)
Age	0.01	0	4.38	.04	1.01 (1.00-1.02)
Admitting Hb	0.04	0.03	1.35	.24	1.04 (0.98-1.10)

*Nagelkerke R^2 = 0.440; χ^2_5 = 815.87; P<.01; 89.43% correctly classified. OR indicates odds ratio; CI, confidence interval; NA, not applicable; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Assessment II; and Hb, hemoglobin.

fused vs nontransfused patients (ICU: 18.5% vs 10.1%, respectively; χ^2=50.1; P<.001; overall: 29.0% vs 14.9%, respectively; χ^2=88.1; P<.001). Higher 28-day mortality rates in transfused patients than in nontransfused patients persisted across all SOFA categories in all but the sickest patients (data not shown).

The 28-day survival curves differed significantly by admitting hemoglobin category in transfused patients (Kaplan-Meier log-rank=30.3; P<.001) but not in nontransfused patients. Mortality rates were higher in transfused patients than in nontransfused patients at every hemoglobin category. There was a dose-response relationship between the number of RBC units transfused and mortality, with patients receiving the most units having the highest mortality rates (**TABLE 6**).

Hierarchical logistic regression was conducted to determine the associations between various patient characteristics and death in the ICU. In the first step, patients' admission characteristics (age, admitting hemoglobin level, APACHE II score, and SOFA score) were entered into the model; in the second step, transfusion status (yes/no) was entered. In this model (**TABLE 7**), the associations of transfusion, APACHE II, SOFA, and age with mortality were statistically significant but admitting hemoglobin level was not.

Receipt of a transfusion in the ICU increased a patient's odds of dying by a factor of 1.37 (95% confidence interval, 1.02-1.84).

To examine the specific association between transfusion and mortality, propensity scores[18] were used to adjust for differences in all observed background characteristics in the estimation of the effects of transfusion.[19] A logistic regression model was used to generate a propensity score that reflected the probability of being transfused for each patient. Variables chosen were age, sex, admission type, diagnosis on admission, admitting SOFA score, admitting APACHE II score, day 1 hemoglobin concentration, recent history of anemia, recent acute blood loss, whether the patient was in shock on admission, and hospital length of stay. The logistic regression model was able to correctly classify 76% of patients and produced a Nagelkerke R^2 of 0.415. The probability of being transfused ranged from 0.01 to 0.97.

The matching process yielded 516 unique transfused and 516 unique nontransfused patients who were matched by their propensity scores. Postmatched comparisons of patient characteristics (from Table 3) are presented in **TABLE 8** and illustrate that the differences between transfused and nontransfused patients along these parameters were no longer evident.

Among the matched patients, 205 died during the 28-day follow-up period. Mortality of the transfused patients was 22.7% vs 17.1% for nontransfused patients (χ^2_1=5.1; P=.02). In other words, of those who died, 57.1% were transfused, and 42.9% were not.

FIGURE 2 illustrates the different survival curves for the matched transfused and nontransfused patients. The Kaplan-Meier log-rank statistic testing the equality of the survival distributions for the matched groups was 3.99 ($df=1$; $P=.05$), indicating significantly different survival patterns.

COMMENT

Course of Anemia

This large, epidemiologic study in European ICUs validates the common occurrence of anemia in critically ill patients and also reports that lower mean hemoglobin levels were associated with higher SOFA scores, longer lengths of stay, and higher mortality rates.

Our findings also underline that blood loss through blood sampling is considerable, averaging 41 mL per day. Sicker patients had more blood draws per 24 hours resulting in a higher total loss of blood than patients of lower acuity. Mechanisms to reduce blood sampling losses can include use of point-of-care testing[20] and microchemistry techniques, use of tubing that eliminates the need for discard,[21] a thorough knowledge and communication of the minimum volume needed for each laboratory test, and storage of blood specimens for potential subsequent use.[22] Education and guideline development on such sparing mechanisms may lead to greater implementation.

Transfusion

The overall transfusion rate during the 28-day study period was 42%, with an ICU transfusion rate of 37%. While most transfusions were given within the first week of ICU admission, many transfusions continued to be given throughout the 28-day follow-up period. In patients with ICU length of stay longer than 1 week, 73% received a blood transfusion. This is slightly lower than the rate found in a 1995 study by Corwin et al,[8] in which 85% of US patients with length of stay longer than 1 week received a blood transfusion.

The overall mean pretransfusion hemoglobin level was 8.4 g/dL, a value

Table 8. Patient Characteristics by Transfusion Status for Propensity-Matched Patients*

Variable	Transfused	Not Transfused	P Value†
Age, mean (SD), y	64.0 (15.5)	64.1 (15.0)	.10
Men, No. (%)	193 (37.4)	203 (39.3)	.52
Admission characteristics			
Admitting Hb level, mean (SD), g/dL	10.8 (2.0)	10.9 (1.8)	.92
Admitting SOFA score, mean (SD)	5.5 (3.3)	5.5 (4.0)	.92
Admitting APACHE II score, mean (SD)	14.6 (7.0)	12.0 (7.5)	.54
Recent history of anemia, No. (%)	80 (15.5)	66 (12.8)	.21
Recent history of red blood loss, No. (%)	162 (31.4)	170 (32.9)	.59
In shock at admission, No. (%)	117 (22.7)	106 (20.5)	.41
Admission type, No. (%)			
Elective surgery	271 (52.5)	261 (50.6)	.53
Emergency surgery	83 (16.1)	89 (17.2)	.62
Medical	128 (24.8)	130 (25.2)	.89
Trauma	29 (5.6)	31 (6.0)	.79
Other	5 (1.0)	5 (1.0)	>.99
Hospital length of stay, mean (SD), d	11.4 (6.8)	12.0 (7.5)	.21

*Hb indicates hemoglobin; SOFA, Sequential Organ Failure Assessment; and APACHE II, Acute Physiology and Chronic Health Evaluation II.
†For every comparison, n = 516 in each group.

Figure 2. Survival Analysis by Transfusion Status Among Propensity-Matched Patients
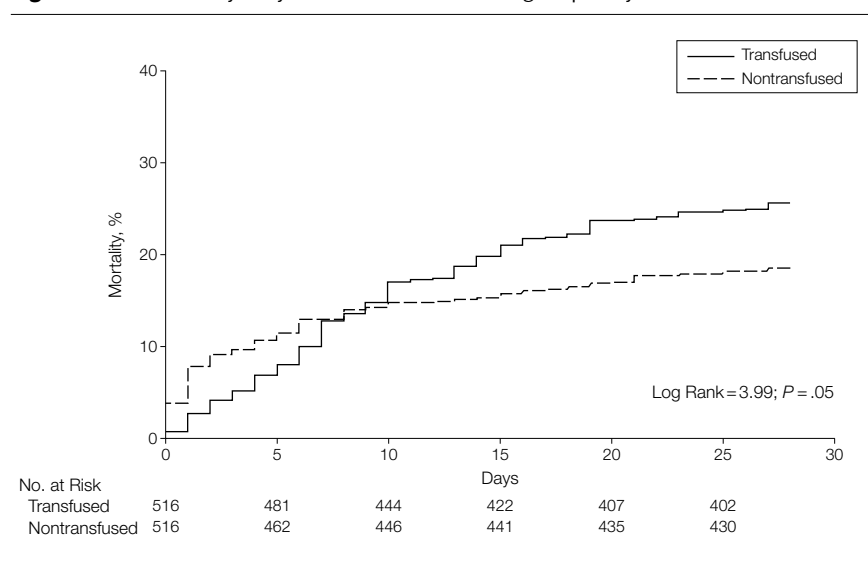
perhaps lower than expected. Actually, the distribution of pretransfusion hemoglobin levels indicated that transfusions were given at a hemoglobin level greater than 9 g/dL in less than 30% of cases. The important results of the Canadian Critical Care Trials Group[10] have probably influenced practice. Surprisingly, there was no significant difference in the mean pretransfusion hemoglobin by age, primary admitting diagnosis, or indication for transfusion. Even patients whose transfusion

indication was acute bleeding had pretransfusion hemoglobin levels similar to those of patients who had other indications for transfusion. Hence, it seems that the hemoglobin value is still the major determinant of the decision to transfuse.

While elderly patients had pretransfusion hemoglobin levels similar to those of younger patients, they had lower daily mean hemoglobin levels than younger patients (ie, had a higher incidence of reaching the transfusion

trigger) and higher transfusion rates than younger patients. In addition to acute blood loss, common causes of anemia in elderly patients can include iron deficiency, chronic disorders, cancer, and nutritional or metabolic disorders.[23] Aging itself may influence erythropoiesis, with possible contributors being a reduction in pluripotent hematopoetic stem cell reserve, reduced production of growth factors, reduced sensitivity of stem cells and progenitors to growth factors, and microenvironmental abnormalities.[24]

Transfused patients had longer ICU length of stay, more severe organ failure, and higher mortality rates than nontransfused patients, but these associations may be explained by different underlying clinical conditions. An altered or blunted erythropoietic response characteristic of anemia of chronic disease may also contribute to anemia in these sickest patients.[1,4]

We found that mortality rates differed significantly by organ failure and transfusion status. As expected, mortality increased in all patients as organ failure increased, but mortality was higher for transfused patients at all levels of organ dysfunction with the exception of those with the most severe organ failure.

Transfused patients had higher mortality rates at every admitting hemoglobin level when compared with nontransfused patients. Mortality rates also differed significantly by admitting hemoglobin group for transfused, but not for nontransfused, patients. There was a dose-response relationship with increasing mortality rates as the number of RBC units transfused increased. Receipt of a blood transfusion increased the risk of dying by a factor of 1.4 (all other variables being equal). Matching patients by their propensity scores for receipt of a transfusion (and hence controlling for age, admission type, diagnosis, admitting SOFA score, admitting APACHE II score, and length of stay) likewise revealed higher mortality rates in transfused patients.

Of the deleterious effects of RBC transfusion, the likely contributing fac-

tor to mortality in the critically ill population is related to immunosuppression as opposed to allergic reaction or infectious transmission. Red blood cell transfusion has been associated with a higher incidence of postoperative infection in various populations.[25-27] The use of leukodepleted blood may result in shorter lengths of stay and fewer complications.[28,29] At the time of this study, the use of deleukocyted blood in participating institutions was variable. Variability in storage techniques may also contribute to RBC deformability that may influence cell oxygen availability.

Due to the risks associated with blood transfusions, alternative treatments of anemia in the critically ill are being explored. The administration of exogenous human recombinant erythropoietin (epoetin alfa) has been shown to raise reticulocyte counts[26,27] and hematocrit levels, and to reduce the total number of units of transfused blood required in critically ill patients.[28]

Interpretation of findings from this observational study should be limited to identification and description of associations between variables of interest. No intervention was implemented, no attempt to control or influence provision of care was made, and the physicians were not blinded to the study purpose. Additionally, the illnesses and treatments of the critically ill are complex and confounded by a multitude of factors. Moreover, data collection in studies of this design is necessarily limited, and not all factors that may have influenced physicians' transfusing practice may not have been collected. Therefore, no causal inferences for associations can be drawn.

The findings from this study reveal that anemia in critically ill patients is common. Transfusions are also common, especially in elderly patients and those with longer ICU lengths of stay. Even though transfusions currently seem to be given primarily in response to decreased hemoglobin levels, the trigger for blood transfusions averaged only 8.4 g/dL. This study provides evidence of the associations be-

tween transfusion and diminished organ function as well as between low hemoglobin level, transfusion, and mortality. Clearly, further study is needed to clarify the place of transfusion in critically ill patients and to evaluate other treatments for anemia that reduce the need for blood transfusions, such as the use of recombinant human erythropoietin (epoetin alfa).

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