Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature*

Paul E. Marik, MD, FACP, FCCM, FCCP; Howard L. Corwin, MD, FACP, FCCM, FCCP

Background: **Red blood cell (RBC) transfusions are common in intensive care unit, trauma, and surgical patients. However, the hematocrit that should be maintained in any particular patient because the risks of further transfusion of RBC outweigh the benefits remains unclear.**

Objective: **A systematic review of the literature to determine the association between red blood cell transfusion, and morbidity and mortality in high-risk hospitalized patients.**

Data Sources: **MEDLINE, Embase, Cochrane Register of Controlled Trials, and citation review of relevant primary and review articles.**

Study Selection: **Cohort studies that assessed the independent effect of RBC transfusion on patient outcomes. From 571 articles screened, 45 met inclusion criteria and were included for data extraction.**

Data Extraction: **Forty-five studies including 272,596 were identified (the outcomes from one study were reported in four separate publications). The outcome measures were mortality, infections, multiorgan dysfunction syndrome, and acute respiratory distress syndrome. The overall risks vs. benefits of RBC transfusion on patient outcome in each study was classified as (i) risks outweigh benefits, (ii) neutral risk, and (iii) benefits outweigh risks. The odds ratio and 95% confidence interval for each outcome measure was recorded if available. The pooled odds ratios were determined using meta-analytic techniques.**

Data Synthesis: **Forty-five observational studies with a median of 687 patients/study (range, 63–78,974) were analyzed. In 42 of the 45 studies the risks of RBC transfusion outweighed the benefits; the risk was neutral in two studies with the benefits outweighing the risks in a subgroup of a single study (elderly patients with an acute myocardial infarction and a hematocrit <30%). Seventeen of 18 studies, demonstrated that RBC transfusions were an independent predictor of death; the pooled odds ratio (12 studies) was 1.7 (95% confidence interval, 1.4−1.9). Twenty-two studies examined the association between RBC transfusion and nosocomial infection; in all these studies blood transfusion was an independent risk factor for infection. The pooled odds ratio (nine studies) for developing an infectious complication was 1.8 (95% confidence interval, 1.5–2.2). RBC transfusions similarly increased the risk of developing multiorgan dysfunction syndrome (three studies) and acute respiratory distress syndrome (six studies). The pooled odds ratio for developing acute respiratory distress syndrome was 2.5 (95% confidence interval, 1.6–3.3).**

Conclusions: **Despite the inherent limitations in the analysis of cohort studies, our analysis suggests that in adult, intensive care unit, trauma, and surgical patients, RBC transfusions are associated with increased morbidity and mortality and therefore, current transfusion practices may require reevaluation. The risks and benefits of RBC transfusion should be assessed in every patient before transfusion. (Crit Care Med 2008; 36:2667–2674)**

KEY WORDS: blood; blood transfusion; anemia; infections; immunomodulation; transfusion-related acute lung injury; acute respiratory distress syndrome; mortality; systematic analysis; meta-analysis

In recent years red blood cell (RBC) transfusion requirements in western nations has been increasing because of the increasing burden of chronic disease in an aging population, improvement in life-support technology, and blood-intensive surgical procedures (1, 2). In the United States alone, nearly 15 million units of blood are donated and 13 million units are transfused annually (2). For much of the last century, RBC transfusion has been viewed as having obvious clinical benefit. However, over the last 20 yrs RBC transfusion practice has come under increased scrutiny. Initially, this was driven by concerns over transfusion-related infections, human immunodeficiency virus in particular. Although the risk of transfusion-transmitted infections has received considerable attention, the risks of this complication, with modern blood banking techniques is now exceedingly remote (3). On the other hand, it is now becoming clear that there are other important, less recognized risks of RBC transfusion related to RBC storage effects and to immunomodulating effects of RBC transfusions, which occur in almost all recipients (4). These immunomodulating effects may increase the risk of the recipients developing nosocomial infections, acute lung injury, and the possible development of autoimmune diseases later in life (4, 5). In recent years, the recognition of these risks has led to a more critical examination of the benefits associated with RBC transfusion. This is particularly important in critically ill, injured, and postoperative patients, with data in both adults and children suggesting equivalence, and in some groups superior clin-

*See also p. 2707.

From the Division of Pulmonary and Critical Care Medicine (PEM), Thomas Jefferson University, Philadelphia, PA; Section of Critical Care Medicine, Department of Anesthesiology (HLC), Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Dr. Corwin is a consultant, has received research support, and is a speaker for Ortho Biotech and Johnson and Johnson PRD. Ortho Biotech and Johnson and Johnson manufacture and distribute Procrit®. Dr. Marik has not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: paul.marik@jefferson.edu

DOI: 10.1097/CCM.0b013e3181844677

ical outcomes with a lower as opposed to "standard" transfusion thresholds (6, 7).

Despite the increased scrutiny of transfusion practices, RBC transfusions remain common with up to 45% of patients being transfused in the intensive care unit (ICU) (8, 9). The goal of this systematic review was (1) to evaluate the association between RBC transfusions and clinical outcome among hospitalized patients, and (2) to determine which patients (if any) may benefit from a RBC transfusion. We restricted this analysis to adult patients. The primary outcome was mortality, however, secondary outcomes included acquired infections, acute respiratory distress syndrome (ARDS), and multiorgan dysfunction syndrome. As the Canadian Critical Care Trials Group study (Transfusion Requirements in Critical Care [TRICC]) (6) is the only prospective, adequately powered, randomized study which has investigated the impact of blood transfusion on patient outcome, our analysis was limited to observational studies. Although meta-analysis of randomized control studies are preferable to meta-analysis of observational studies, a systematic review of observational studies provide a tool for synthesizing clinical data in the absence of randomized controlled studies. Our meta-analysis was conducted in accord with the consensus recommendations by the Meta-analysis of Observational Studies in Epidemiology Group (10).

METHODS

Identification of Trials. The analysis was restricted to those observational studies that performed multivariate analysis with mortality and/or the risk of infections, multiorgan dysfunction syndrome, or ARDS as the endpoints. The aim was to identify all relevant observational trials that reported the impact of RBC transfusion on these clinical outcomes. A multimethod approach was used to identify relevant studies. The National Library of Medicine's MEDLINE database was searched for relevant studies in any language published between 1966 and June 2007 using the following medical subject headings and keywords: blood transfusion (explode), erythrocyte, AND mortality, ARDS, infection, multiple organ failure, critical care, intensive care, "wound or injury," surgery, and "all adult." In addition, Embase and the Cochrane Database of Systematic Reviews were searched. Bibliographies of all selected articles and review articles that included information on RBC transfusion were reviewed for other relevant articles. This search strategy was done iteratively, until no new potential citations were found on review of the reference lists of retrieved articles.

Data Extraction and Analysis. Both authors independently abstracted data from all studies using a standardized form. Data were abstracted on study design, study size, population, and the effect of blood transfusion on the end points of interest. In addition to the major outcome variables, the myocardial infarction rate and neurologic outcome scores were recorded in the neurosurgical and cardiac studies, respectively. ARDS were defined according to the American-European Consensus Committee Report (11), and infection and sepsis were defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (12). The hospital mortality was recorded. The overall risks vs. benefits of RBC transfusion on patient outcome in each study was classified as (1) risks outweigh benefits, (2) neutral risk, and (3) benefits outweigh risks. This assessment was based on the study end points, such that if the risk of complications or death was statistically higher with blood transfusion, the risks were considered to outweigh the benefits. Likewise, if any outcome variable statistically favored blood transfusion (in the absence of any harmful effect) the benefits of RBC transfusion were considered to outweigh the risks. A study was considered neutral risk if blood transfusion had neither beneficial nor harmful effects. The reinfarction rate and neurologic outcome scores were additionally used in the assessment of the cardiac and neurosurgical studies, respectively. Disagreements regarding values or analysis were resolved by discussion between the reviewers.

To quantitate the effect of blood transfusions on the end points of interest, the odds ratio (OR) and 95% confidence interval (95% CI) for the observed effect was recorded if reported. Comprehensive Meta-analysis 2.0 (Biostat, Englewood, NJ) was used for all analyses; a p value of 0.05 (two-sided) was considered significant. We calculated the Cochran Q statistic to test for statistical heterogeneity. Values of Q significantly >0 ($p < 0.1$) were considered evidence of heterogeneity. Because of anticipated heterogeneity between studies, the random-effects model was used to determine the pooled OR, using the adjusted OR and 95% CI, of each study. Sensitivity analysis was done by grouping patients according to major diagnostic groups as follows: trauma, general surgery, cardiac surgery, neurosurgery, orthopedic surgery, acute coronary syndrome, and general ICU patients.

RESULTS

The search strategy generated 571 citations. Of those, 523 did not report the end points of interest or were not relevant and were excluded. A total of 48 articles from 45 studies, which specifically reported the association between RBC transfusion and one or more relevant end points were identified and included in the analysis (8, 9, 13–60). The results from one study (8) had three separate subgroup analyses reported (56, 57, 60). The number of trials evaluated at each stage of the evaluation is illustrated in Figure 1. A summary of the studies is listed in Table 1. In total 272,596 patients were included in the 45 studies; with a median of 687 patients/study (range, 63 to 78,974). The studies included trauma, general surgery, cardiac surgery, and neurosurgery, orthopedic, cardiac, and general ICU patients. No study reported the use of leukodepleted blood. There were no disagreements between the two reviewers as to study inclusion or data end point analysis.

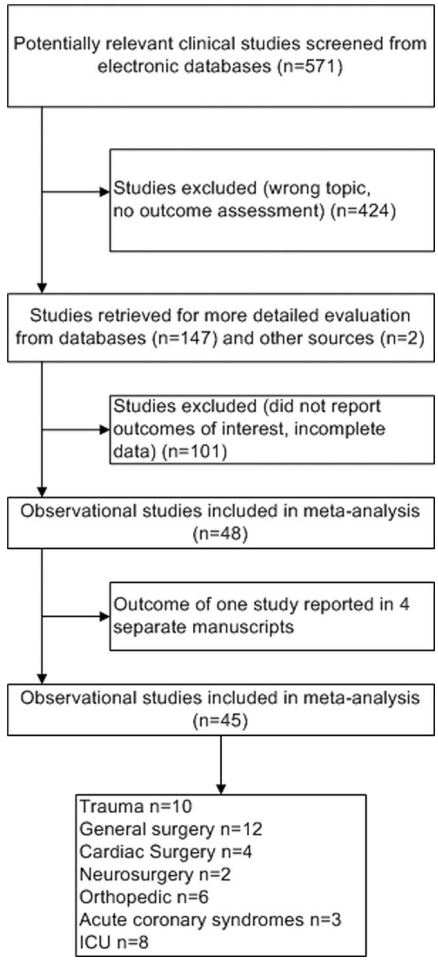

Figure 1. The number of studies evaluated at each stage of the evaluation process. *ICU*, intensive care unit.

In 42 of the 45 studies the risks of RBC transfusion outweighed the benefits, the risk was neutral in two studies, with the benefits outweighing the risks in a subgroup of a single study (elderly patients

Table 1. Studies that have reported the outcomes after blood transfusion

Population, Author, Reference	Design	Number	Outcomes	Risk/Benefit	OR Reported
Trauma (n = 10)					
Edna and Bjerkeset (13)	Retrospective cohort	484	Increased infections	Risks outweigh benefits	No
Moore et al. (14)	Prospective cohort	513	Increased MODS	Risks outweigh benefits	No
Agarwal et al. (15)	Retrospective cohort	5366	Increased infection	Risks outweigh benefits	No
Offner et al. (16, 17)	Prospective cohort	63	Increased MODS, infection	Risks outweigh benefits	No
Claridge et al. (18)	Prospective cohort	1593	Increased infection	Risks outweigh benefits	No
Malone et al. (19)	Prospective cohort	15,534	Increased mortality	Risks outweigh benefits	Yes
Dunn et al. (20)	Prospective cohort	9539	Increased SIRS, ICU admission, mortality	Risks outweigh benefits	Yes
Silverboard et al. (21)	Prospective cohort	102	Increased risk of ARDS, mortality	Risks outweigh benefits	Yes
Croce et al. (22)	Prospective cohort	9,126	Increased infection, ARDS, mortality	Risks outweigh benefits	Yes
Ciesla et al. (23)	Prospective cohort	1344	Increased MODS	Risks outweigh benefits	No
General surgery (n = 12)					
Dawes et al. (24)	Retrospective cohort	117	Increased risk of infection	Risks outweigh benefits	No
Tartter (25)	Retrospective cohort	343	Increased infection	Risks outweigh benefits	No
van Pabst et al. (26)	Retrospective cohort	164	Increased mortality	Risks outweigh benefits	No
Wobbes et al. (27)	Retrospective cohort	548	<4 units blood, no increased infections	Neutral risk	No
			4 units blood, increased infections	Risks outweigh benefits	No
von Doersten et al. (28)	Prospective cohort	104	No increased tumor recurrence or infection	Neutral risk	No
Jahnson and Andersson (29)	Retrospective cohort	217	Increased mortality (less with AB)	Risks outweigh benefits	Yes
Vignali et al. (30)	Prospective cohort	161	Increased infection	Risks outweigh benefits	No
Ford et al. (31)	Retrospective cohort	1032	Increased infection	Risks outweigh benefits	No
Mynster and Nielsen (32)	Prospective cohort	303	Increased infections (with ST >21 days)	Risks outweigh benefits	No
Mynster et al. (33)	Prospective cohort	740	Increased tumor recurrence, mortality	Risks outweigh benefits	No
Chang et al. (34)	Retrospective cohort	1349	Increased infection, mortality	Risks outweigh benefits	No
Lebron-Gallardo et al. (35)	Retrospective cohort	214	Increased post-operative renal failure	Risks outweigh benefits	No
Cardiac surgery (n = 4)					
Vamvakas and Carven (36, 37)	Retrospective cohort	416	Increased MV, pneumonia	Risks outweigh benefits	No
Leal-Noval et al. (38)	Prospective cohort	738	Increased LOS, MV, pneumonia, mortality	Risks outweigh benefits	Yes
Chelemer et al. (39)	Prospective cohort	533	Increased bacterial infections	Risks outweigh benefits	Yes
Koch et al. (40)	Prospective cohort	11,963	Increases complications, mortality	Risks outweigh benefits	Yes
Neuro-surgery (n = 2)					
Smith et al. (41)	Prospective cohort	441	Vasospasm, worse neurological outcome	Risks outweigh benefits	No
Carlson et al. (42)	Retrospective cohort	169	Worse neurological outcome	Risks outweigh benefits	No
Orthopedic (n = 6)					
Murphy et al. (43)	Retrospective cohort	84	Increased infection (less with AB)	Risks outweigh benefits	No
Fernandez et al. (44)	Retrospective cohort	376	Increased infections (less with AB)	Risks outweigh benefits	No
Triulzi et al. (45)	Prospective cohort	102	Increased infections	Risks outweigh benefits	No
Carson et al. (46)	Retrospective cohort	8787	No change in mortality or morbidity	Neutral risk	Yes
Koval et al. (47)	Prospective cohort	687	Increased infection (urinary tract)	Risks outweigh benefits	No
Carson et al. (48)	Retrospective cohort	9598	Increased infections and pneumonia	Risks outweigh benefits	No
Acute coronary syndromes (n = 3)					
Wu et al. (49)	Retrospective cohort	78,974	Decreased mortality with Hct <33	Benefits outweigh risks	Yes
			Increased mortality with Hct >36	Risks outweigh benefits	Yes
Rao et al. (50)	Prospective cohort	24,112	Increased myocardial infarction, mortality	Risks outweigh benefits	Yes
Yang et al. (51)	Prospective cohort	74,271	Increased reinfarction, mortality	Risks outweigh benefits	Yes

Table 1.—*Continued*

Population, Author, Reference	Design	Number	Outcomes	Risk/Benefit	OR Reported
ICU (n = 8)					
Martin et al. (52)	Retrospective cohort	698	Increased mortality	Risks outweigh benefits	No
Vincent et al. (9)	Prospective cohort	1136	Increased MODS, mortality	Risks outweigh benefits	Yes
Taylor et al. (53)	Retrospective cohort	1717	Increased LOS, infections, mortality	Risks outweigh benefits	No
Corwin et al. (8)[a]	Prospective cohort	4892	Increased LOS, mortality	Risks outweigh benefits	Yes
Taylor et al. (54)	Prospective cohort	2085	Increased LOS, infections, mortality	Risks outweigh benefits	No
Gajic et al. (55)	Retrospective cohort	332	Increased ARDS	Risks outweigh benefits	Yes
Shorr et al. (56, 57)[a]	Prospective cohort	—	Increased bacteremia, VAP	Risks outweigh benefits	No
Gong et al. (58)	Prospective cohort	688	Increased risk of ARDS	Risks outweigh benefits	Yes
Kahn et al. (59)	Retrospective cohort	841	Increased risk of ARDS	Risks outweigh benefits	Yes
Zilberberg et al. (60)[a]	Prospective cohort	—	Increased risk of ARDS	Risks outweigh benefits	Yes

[a]Outcomes of CRIT study reported in 4 separate manuscripts.

AB, autologous blood; ARDS, acute respiratory distress syndrome; LOS, length of hospital stay; MODS, multiorgan dysfunction syndrome; Hct, hematocrit; ST, storage time; MV, length of mechanical ventilation; SIRS, systematic inflammatory response syndrome; VAP, ventilator associated pneumonia; ICU, intensive care unit; OR, odds ratio.

with an acute myocardial infarction and a hematocrit <30%) (49). In general, multivariate analysis was performed correcting for age and illness severity (Acute Physiology and Chronic Health Evaluation Score, Injury Severity Score, Sequential Organ Failure Assessment score, etc.). Eighteen studies reported the association between RBC transfusion and mortality. In 17 studies, RBC transfusion was an independent predictor of death; pooled OR (12 studies) was 1.7 (95% CI, 1.4−1.9). The study by Wu et al. (49), which demonstrated a reduction in mortality with blood transfusion in patients with an acute myocardial infarction and HCT <33, and an increased mortality in patients with a HCT >36 was excluded from the calculation of the pooled OR (because of diverging results). The Q statistic revealed moderate heterogeneity between studies. Twenty-two studies examined the association between RBC transfusion and nosocomial infection; in all these studies, blood transfusion was an independent risk factor for infection. The pooled OR (nine studies) for developing an infectious complication was 1.8 (95% CI, 1.5–2.2). Moderate heterogeneity between studies was present. RBC transfusions also increased the risk of developing multiorgan dysfunction syndrome (three studies) and ARDS (six studies). The pooled OR (six studies) for developing ARDS was 2.5 (95% CI, 1.6–3.3). The Q statistic was <1, indicating the absence of heterogeneity between studies. Data were not available for calculating a pooled OR for multiorgan dysfunction syndrome. Forest plots with OR (and 95% CI) for mortality, infectious

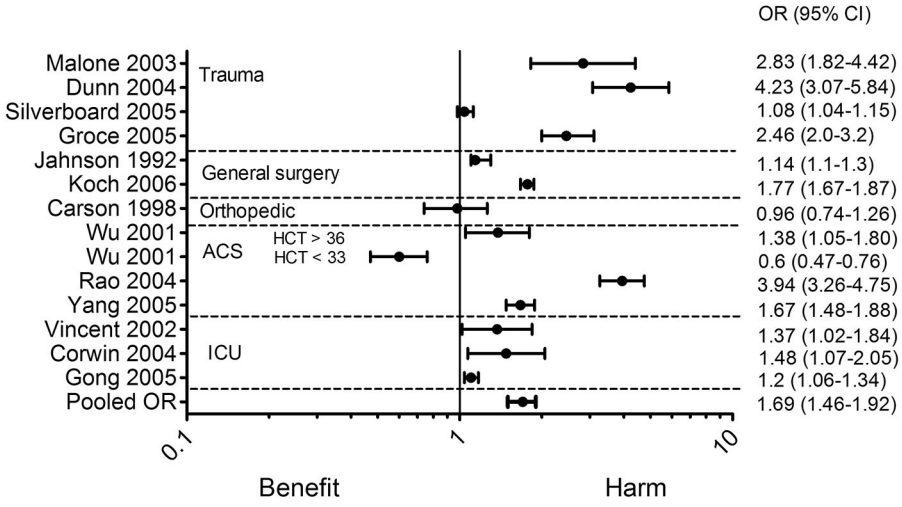

Figure 2. Association between blood transfusion and the risk of death (odds ratio [*OR*] and 95% confidence interval [*CI*]). *ACS*, abdominal compartment syndrome; *ICU*, intensive care unit.

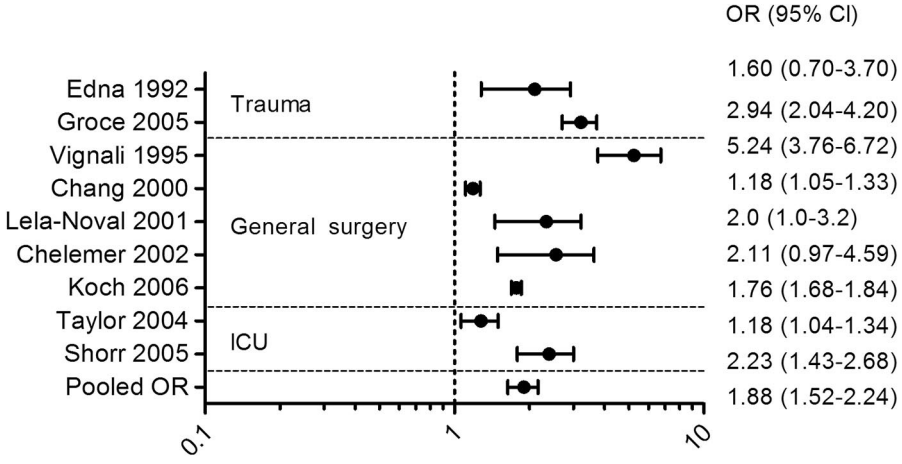

Figure 3. Association between blood transfusion and the risk of infectious complications (odds ratio [*OR*] and 95% confidence interval [*CI*]). *ICU*, intensive care unit.

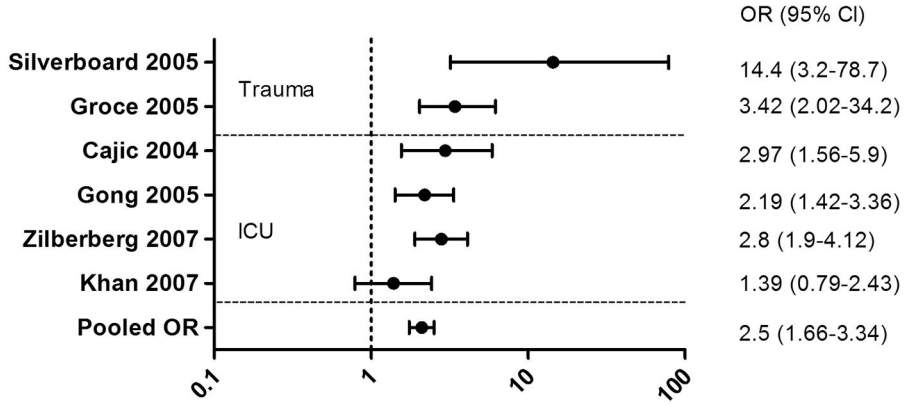

Figure 4. Association between blood transfusion and the risk of developing adult respiratory distress syndrome (odds ratio [*OR*] and 95% confidence interval [*CI*]). *ICU,* intensive care unit.

complications, and ARDS are presented in Figures 2–4.

DISCUSSION

Our study suggests that across a broad spectrum of high risk hospitalized patients, RBC transfusions seem to be associated with increased morbidity and mortality. This was true even in trauma patients, those most likely to benefit from RBC transfusion. The reasons for the apparent lack of benefit of RBC transfusions in the patients included in this meta-analysis cannot be answered from this review. However, recent interest has focused on immunomodulating effects of transfused RBCs and RBC storage lesions (age of transfused RBCs) as possible mechanisms. It has been suggested that leukodepleted blood may have less immunomodulating properties and hence, reduce the complications associated with the transfusion of nonleukodepleted blood (4, 61, 62). However, there is still some debate as to the benefit of leukoreduction (63). Removal of leukocytes from red cell transfusions may have a small but potentially important effect on clinical outcomes, however, cost-effectiveness of universal leukoreduction has yet to be proven, especially in lower risk populations. It should be recognized that the studies included in our review were performed with nonleukodepleted blood. Similarly, age of transfused RBCs has also been suggested as possible explanation for some of the adverse effects associated with RBC transfusion. Numerous abnormalities have been associated with storage of RBCs, and some studies have suggested that transfusion of "older" RBCs may be associated with adverse effects (64–67). If age of transfused RBCs is, in fact, important it would have major ramifications on the already limited blood supply. At this point only limited clinical evidence is available and thus, a definitive clinical trial is necessary to answer this question.

The results of our study need to be interpreted with caution due to the nature of the studies included in our meta-analysis. Observational studies lack the experimental element of random allocation to an intervention and therefore, rely on the association between differences in one characteristic (RBC transfusion) and differences in outcome. Although multivariate analysis may attempt to correct for imbalances, between those exposed and not exposed to the characteristic of interest (RBC transfusion) inherent bias, may be difficult to eliminate. It could therefore be argued that blood transfusion itself is a marker for severity of illness, which cannot be adjusted by multivariate analysis. In addition, observational studies vary considerably in design and analysis. In analyzing a systematic review of observational studies, qualitative clinical end-points (infections, ARDS, risk/benefit ratio) may therefore be as important as quantitative end-points (68–70). It is important to recognize that we were able to identify only a single study in which a subgroup of patients seemed to benefit from RBC transfusion. In the vast majority of studies, the risks associated with blood transfusion outweighed the benefits. This is remarkable, considering the number of patients who receive a RBC transfusion worldwide on a daily basis. Although the pooled OR for mortality and infectious complications should be interpreted with some caution because of heterogeneity between studies, the studies are notable for the consistent direction (harm) of the treatment effect. This suggests that the findings are likely to be true (68–70). As is evident from Figures 2 and 3, the differences in the patient populations largely accounts for the variation in the magnitude of the treatment effect (harm) and the heterogeneity between studies.

TRICC (6) is the only prospective, adequately powered, randomized study, which has investigated the impact of blood transfusion on outcome in adult patients (6). The TRICC study compared a "liberal (10 g/dL)" vs. "restricted (7g/dL)" transfusion trigger threshold in 838 ICU patients. In this study, the restrictive transfusion threshold was at least equivalent, and in some patients (adults <55 yrs of age or Acute Physiology and Chronic Health Evaluation score <20) safer than the more liberal transfusion threshold. A more recent study in pediatric patients reported similar results (7). Our analysis, in combination with these trials, raises questions regarding the validity of the historic assumption that RBC transfusion is beneficial for critically ill, injured, and postoperative patients with anemia. Because of the observational nature of the studies included in our analysis, additional prospective studies are required to test the hypothesis that limiting blood transfusions reduces infections complications, ARDS, organ failure, and overall mortality in high-risk hospitalized patients. It should also be recognized that the TRICC study had no control group receiving routine care and studied two arbitrary fixed treatments for a usually titrated therapy (71). The American Association of Blood Banking has recommended titrating transfusion requirements to parameters of severity of illness rather than arbitrarily defined hemoglobin levels (72). This recommendation is in agreement with the more recent recommendations of the American Society of Anesthesiologists Task Force, (73) and the Canadian Guidelines which suggest "There is no single value of hemoglobin concentration that justifies or requires transfusion; an evaluation of the patient's clinical situation should also be a factor in the decision" (74).

In the absence of acute bleeding, are there any patients who benefit from RBC transfusion or "When do the risks of anemia outweigh the hazards of transfusion?" In health, the amount of oxygen delivered to the whole body exceeds resting oxygen requirements almost four-

fold. An isolated decrease in hemoglobin concentration to 10 g/dL, with all other parameters remaining constant, will result in an oxygen delivery that remains approximately twice that of the resting oxygen consumption. Furthermore, humans have a remarkable ability to adapt to anemia by increasing cardiac output (in the absence of volume depletion), increasing microcirculatory density, and by increasing red cell synthesis of 2,3-diphosphoglycerate with a resultant shift of the oxyhemoglobin dissociation curve (aids oxygen unloading) and by increasing oxygen extraction. Laboratory studies have demonstrated that extreme hemodilution is well tolerated in healthy animals. Animals subjected to acute hemodilution tolerate decreasing hemoglobin concentrations to 30–50 g/dL, with ischemic changes on electrocardiography and depressed ventricular function below these levels (75, 76). Because of the high extraction ratio of oxygen in the coronary circulation, coronary blood flow seems to be the major factor, which limits the tolerance of low hemoglobin concentrations. In experimental animal models of coronary stenosis, depressed cardiac function occurs at hemoglobin concentrations between 70 and 100 g/L (76, 77).

Extensive experience in patients who decline blood for religious reason and in patients with chronic renal disease, myelodysplastic syndromes, and severe autoimmune hemolytic anemias have confirmed that humans tolerate extreme anemia quite well (78–80). The best data come from the Jehovah Witness literature (78). Carson and colleagues (81, 82) performed a retrospective cohort study in 1958 patients who underwent surgery and declined blood transfusions for religious reasons. In those patients without cardiovascular disease and with a blood loss of less than 2.0 g/dL, there was no significant increase in perioperative mortality (for baseline hemoglobin of 6–6.9 g/dL and a decline in hemoglobin of <2 g/dL the OR for death was 1.4; 95% CI, 0.5–4.2). However, in patients with cardiovascular disease, preoperative anemia was associated with a significant increase in perioperative mortality. These data confirm that humans can adapt to very low hemoglobin levels with cardiovascular disease being the major limiting factor.

In our extensive review of the literature, only a single subgroup from a single study reported a beneficial effect associated with RBC transfusion; elderly patients who suffer a myocardial infarction with a baseline HCT below 33% and who did not undergo revascularization (49). Importantly, patients transfused with a HCT >36 had a higher mortality. This study has been well criticized for methodologic problems (62). On the other hand, the study by Rao et al. (50), in patients with acute coronary syndromes found worse outcomes in patients transfused with HCT values greater than 25%. Both the Wu et al. and Rao et al. studies consistently demonstrate that patients who receive RBCs at some higher HCT seem to be harmed by the transfusions. Additional evidence, ideally from a randomized control trial, is still necessary to determine optimal transfusion strategies in this patient population.

Our results suggest that in hemodynamically stable patients without evidence of acute bleeding, limiting blood transfusions may reduce morbidity and mortality. In the absence of acute bleeding, hemoglobin levels consistent with the TRICC trial (7.0–9.0 g/dL) are well tolerated (6). Furthermore, current guidelines suggest titrating transfusion requirements to parameters of illness severity while taking into account the individual patients' clinical situation (73, 74). There remains controversy as to the appropriate transfusion thresholds for patients with ischemic cardiac disease and in the early resuscitation of patients with septic shock (71, 83, 84).

CONCLUSION

Current data suggest that RBC transfusions are associated with increased morbidity and mortality across heterogenous patient groups. There is sparse evidence that routine RBC transfusion in the nonbleeding patient with a hemoglobin concentration greater than 7.0 g/dL leads to improved outcome. In general, we hold that RBC transfusions are only indicated in hemodynamically stable ICU, trauma, and surgical patients with a hemoglobin concentration below 7 g/dL. However, the need for a RBC transfusion should be individualized based on a patient's clinical circumstances rather than an arbitrary hemoglobin concentration. Additional prospective randomized studies are required to determine the risks and benefits of RBC transfusion, in various disease states, their optimal transfusion triggers, the effects of blood storage time, and leukodepletion, on clinical outcomes.

REFERENCES

1. Wells AW, Mounter PJ, Chapman CE, et al: Where does blood go? Prospective observational study of red cell transfusion in north England. *Br Med J* 2002; 325:803–806
2. National Blood Data Resource Center: Comprehensive report on blood collection and transfusion in the United States, 2005. Available at: http://www.aabb.org/Content/Programs_and_Services/Data_Center/NBCUS/. Accessed May 15, 2007
3. Busch MP, Kleinman SH, Nemo GJ: Current and emerging infectious risks of blood transfusions. *JAMA* 2003; 289:959–962
4. Raghavan M, Marik PE: Anemia, allogenic blood transfusion, and immunomodulation in the critically ill. *Chest* 2005; 127:295–307
5. Toy P, Popovsky MA, Abraham E, et al: Transfusion-related acute lung injury: Definition and review. *Crit Care Med* 2005; 33:721–726
6. Hebert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340:409–417
7. Lacroix J, Hebert PC, Hutchinson JS, et al: Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med* 2007; 356:1609–1619
8. Corwin HL, Gettinger A, Pearl RG, et al: The CRIT Study: Anemia and blood transfusion in the critically ill—Current clinical practice in the United States. *Crit Care Med* 2004; 32: 39–52
9. Vincent JL, Baron JF, Reinhart K, et al: Anemia and blood transfusion in critically ill patients. *JAMA* 2002; 288:1499–1507
10. Stroup DF, Berlin JA, Morton SC, et al: Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283:2008–2012
11. Bernard GR, Artigas A, Brigham KL: The American-European Consensus conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818–824
12. Society of Critical Care Medicine Consensus Conference Committee: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20:864–874
13. Edna TH, Bjerkeset T: Association between blood transfusion and infection in injured patients. *J Trauma* 1992; 33:659–661
14. Moore FA, Moore EE, Sauaia A: Blood transfusion: An independent risk factor for postinjury multiple organ failure. *Arch Surg* 1997; 132:620–624
15. Agarwal N, Murphy JG, Cayten CG, et al: Blood transfusion increases the risk of infec-

tion after trauma. *Arch Surg* 1993; 128: 171–176
16. Offner PJ, Moore EE, Biffl WL, et al: Increased rate of infection associated with transfusion of old blood after severe injury. *Arch Surg* 2002; 137:711–716
17. Zallen G, Offner PJ, Moore EE, et al: Age of transfused blood is an independent risk factor for postinjury multiple organ failure. *Am J Surg* 1999; 178:570–572
18. Claridge JA, Sawyer RG, Schulman AM, et al: Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. *Am Surg* 2002; 68:566–572
19. Malone DL, Dunne J, Tracy JK, et al: Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma* 2003; 54:898–905
20. Dunne JR, Malone DL, Tracy JK, et al: Allogenic blood transfusion in the first 24 hours after trauma is associated with increased systemic inflammatory response syndrome (SIRS) and death. *Surg Infect* 2004; 5:395–404
21. Silverboard H, Aisiku I, Martin GS, et al: The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. *J Trauma* 2005; 59:717–723
22. Croce MA, Tolley EA, Claridge JA, et al: Transfusions result in pulmonary morbidity and death after a moderate degree of injury. *J Trauma* 2005; 59:19–23
23. Ciesla DJ, Moore EE, Johnson JL, et al: A 12-year prospective study of postinjury multiple organ failure: Has anything changed? *Arch Surg* 2005; 140:432–438
24. Dawes LG, Aprahamian C, Condon RE, et al: The risk of infection after colon injury. *Surgery* 1986; 100:796–803
25. Tartter PI: Blood transfusion and infectious complications following colorectal cancer surgery. *Br J Surg* 1988; 75:789–792
26. van Lawick van Pabst WP, Langenhorst BL, Mulder PG, et al: Effect of perioperative blood loss and perioperative blood transfusions on colorectal cancer survival. *Eur J Cancer Clin Oncol* 1988; 24:741–747
27. Wobbes T, Bemelmans BL, Kuypers JH, et al: Risk of postoperative septic complications after abdominal surgical treatment in relation to perioperative blood transfusion. *Surg Gynecol Obstet* 1990; 171:59–62
28. von Doersten P, Cruz RM, Selby JV, et al: Transfusion, recurrence, and infection in head and neck cancer surgery. *Otolaryngol Head Neck Surg* 1992; 106:60–67
29. Jahnson S, Andersson M: Adverse effects of perioperative blood transfusion in patients with colorectal cancer. *Eur J Surg* 1992; 158: 419–425
30. Vignali A, Braga M, Dionigi P, et al: Impact of a program of autologous blood donation on the incidence of infection in patients with colorectal cancer. *Eur J Surg* 1995; 161: 487–492
31. Ford CD, VanMoorleghem G, Menlove RL: Blood transfusions and postoperative wound infection. *Surgery* 1993; 113:603–607
32. Mynster T, Nielsen HJ: The impact of storage time of transfused blood on postoperative infectious complications in rectal cancer surgery. *Scan J Gastroenterol* 2000; 35:212–217
33. Mynster T, Christensen IJ, Moesgaard F, et al: Effects of the combination of blood transfusion and postoperative infectious complications on prognosis after surgery for colorectal cancer. *Br J Surg* 2000; 87:1553–1562
34. Chang H, Hall GA, Geerts WH, et al: Allogeneic red blood cell transfusion is an independent risk factor for the development of postoperative bacterial infection. *Vox Sang* 2000; 78:13–18
35. Lebron-Gallardo M, Herrera Gutierrez ME, Seller PG, et al: Risk factors for renal dysfunction in the postoperative course of liver transplant. *Liver Transpl* 2004; 10: 1379–1385
36. Vamvakas EC, Carven JH: Transfusion and postoperative pneumonia in coronary artery bypass graft surgery: Effect of the length of storage of transfused red cells. *Transfusion* 1999; 39:701–710
37. Vamvakas EC, Carven JH: Allogeneic blood transfusion and postoperative duration of mechanical ventilation: Effects of red cell supernatant, platelet supernatant, plasma components and total transfused fluid. *Vox Sang* 2002; 82:141–149
38. Leal-Noval SR, Rincon-Ferrari MD, Garcia-Curiel A, et al: Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. *Chest* 2001; 119:1461–1468
39. Chelemer SB, Prato BS, Cox PM Jr, et al: Association of bacterial infection and red blood cell transfusion after coronary artery bypass surgery. *Ann Thorac Surg* 2002; 73: 138–142
40. Koch CG, Li L, Duncan AI, et al: Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med* 2006; 34:1608–1616
41. Smith MJ, Le Roux PD, Elliott JP, et al: Blood transfusion and increased risk for vasospasm and poor outcome after subarachnoid hemorrhage. *J Neurosurg* 2004; 101:1–7
42. Carlson AP, Schermer CR, Lu SW: Retrospective evaluation of anemia and transfusion in traumatic brain injury. *J Trauma* 2006; 61:567–571
43. Murphy P, Heal JM, Blumberg N: Infection or suspected infection after hip replacement surgery with autologous or homologous blood transfusions. *Transfusion* 1991; 31: 212–217
44. Fernandez MC, Gottlieb M, Menitove JE: Blood transfusion and postoperative infection in orthopedic patients. *Transfusion* 1992; 32:318–322
45. Triulzi DJ, Vanek K, Ryan DH, et al: A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. *Transfusion* 1992; 32:517–524
46. Carson JL, Duff A, Berlin JA, et al: Perioperative blood transfusion and postoperative mortality. *JAMA* 1998; 279:199–205
47. Koval KJ, Rosenberg AD, Zuckerman JD, et al: Does blood transfusion increase the risk of infection after hip fracture? *J Ortho Trauma* 1997; 11:260–265
48. Carson JL, Altman DG, Duff A, et al: Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. *Transfusion* 1999; 39:694–700
49. Wu WC, Rathore SS, Wang Y, et al: Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001; 345:1230–1236
50. Rao SV, Jollis JG, Harrington RA, et al: Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004; 292:1555–1562
51. Yang X, Alexander KP, Chen AY, et al: The implications of blood transfusions for patients with non-ST-segment elevation acute coronary syndromes: Results from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol* 2005; 46:1490–1495
52. Martin CM, Sibbald WJ, Lu X: Age of transfused red blood cells is associated with ICU length of stay. *Clin Invest Med* 1994; 17:124
53. Taylor RW, Manganaro L, O'Brien J, et al: Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. *Crit Care Med* 2002; 30:2249–2254
54. Taylor RW, O'Brien J, Trottier SJ, et al: Red blood cell transfusions and nosocomial infections in critically ill patients. *Crit Care Med* 2006; 34:2302–2308
55. Gajic O, Dara SI, Mendez JL, et al: Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; 32: 1817–1824
56. Shorr AF, Duh MS, Kelly KM, et al: Red blood cell transfusion and ventilator-associated pneumonia: A potential link? *Crit Care Med* 2004; 32:666–674
57. Shorr AF, Jackson WL, Kelly KM, et al: Transfusion practice and blood stream infections in critically ill patients. *Chest* 2005; 127:1722–1728
58. Gong MN, Thompson BT, Williams P, et al: Clinical predictors of and mortality in acute respiratory distress syndrome: Potential role of red cell transfusion. *Crit Care Med* 2005; 33:1191–1198
59. Khan H, Belsher J, Yilmaz M, et al: Fresh frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest* 2007; 131:1308–1314
60. Zilberberg MD, Carter C, Lefebvre P, et al: Red blood cell transfusions and the risk of ARDS amongst critically ill: A cohort study. *Crit Care* 2007; 11:R63
61. Fergusson D, Khanna MP, Tinmouth A, et al: Transfusion of leukoreduced red blood cells may decrease postoperative infections: Two

meta-analyses of randomized controlled trials. *Can J Anaesth* 2004; 51:417–424
62. Hebert PC, Tinmouth A, Corwin HL: Controversies in RBC transfusion in the critically ill. *Chest* 2007; 131:1583–1590
63. Corwin HL, AuBuchon JP. Is leukoreduction of blood components for everyone? *JAMA* 2003; 289:1993–1995
64. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; 269:3024–3029
65. Fitzgerald RD, Martin CM, Dietz GE, et al: Transfusing red blood cells stored in citrate phosphate dextrose adenine-1 for 28 days fails to improve tissue oxygenation in rats. *Crit Care Med* 1997; 25:726–732
66. Tinmouth A, Chin-Yee I: The clinical consequences of the red cell storage lesion. *Transfus Med Rev* 2001; 15:91–107
67. Ho J, Sibbald WJ, Chin-Yee IH: Effects of storage on efficacy of red cell transfusion: When is it not safe? *Crit Care Med* 2003; 31:S687–S697
68. Bigby M, Williams H: Appraising systematic reviews and meta-analyses. *Arch Dermatol* 2003; 139:795–798
69. Ng TT, McGory ML, Ko CY, et al: Meta-analysis in surgery: Methods and limitations. *Arch Surg* 2006; 141:1125–1130
70. Moher D, Cook DJ, Eastwood S, et al: Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. QUOROM Group. *Br J Surg* 2000; 87:1448–1454
71. Klein HG: Blood avoidance for the critically ill: Another blow to liberalism? *Crit Care Med* 2006; 34:2013–2014
72. Consensus conference: Perioperative red blood cell transfusion. *JAMA* 1988; 260: 2700–2703
73. Practice guidelines for perioperative blood transfusion and adjuvant therapies. An Updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2008; 105:198–208
74. Guidelines for red blood cell and plasma transfusion for adults and children. Expert Working Group. *Can Med Assoc J* 2008; 156 (11 suppl):S1–S24
75. Wilkerson DK, Rosen AL, Sehgal LR, et al: Limits of cardiac compensation in anemic baboons. *Surgery* 1988; 103:665–670
76. Levy PS, Kim SJ, Eckel PK, et al: Limit to cardiac compensation during acute isovolemic hemodilution: Influence of coronary stenosis. *Am J Physiol* 1993; 265:H340–H349
77. Leung JM, Weiskopf RB, Feiner J, et al: Electrocardiographic ST-segment changes during acute, severe isovolemic hemodilution in humans. *Anesthesiology* 2000; 93:1004–1010
78. Ott DA, Cooley DA: Cardiovascular surgery in Jehovah's Witnesses. Report of 542 operations without blood transfusion. *JAMA* 1977; 238:1256–1258
79. Slawson KB: Anesthesia for the patient in renal failure. *Br J Anaesthia* 1972; 44: 277–282
80. Campbell R, Marik PE: Severe autoimmune hemolytic anemia treated by paralysis, induced hypothermia, and splenic embolization. *Chest* 2005; 127:678–681
81. Carson JL, Duff A, Poses RM, et al: Effect of anemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; 348:1055–1060
82. Spence RK, Carson JA, Poses R, et al: Elective surgery without transfusion: Influence of preoperative hemoglobin level and blood loss on mortality. *Am J Surg* 1990; 159:320–324
83. 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
84. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377