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CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Controversies in RBC Transfusion in the Critically Ill*

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Transfusion practice has been under great scrutiny over the last 2 decades. The examination of transfusion risks and benefits have been particularly important in the critically ill patient population. This review will examine some of the important controversies still surrounding the use of RBC transfusion in the critically ill patient. ***(CHEST 2007; 131:1583–1590)***

Key words: critically ill; RBC; risk; transfusion

Abbreviations: CI = confidence interval; DPG = diphosphoglycerate; pHi = intramucosal pH; TRICC = Transfusion Requirements in Critical Care

Historically, RBC transfusions have been viewed as a safe and effective means of improving oxygen delivery to tissues. Beginning in the early 1980s, transfusion practice began to come under systematic scrutiny.[1–3] Initially, primary concerns related to the risks of transfusion-related infection. While advances in transfusion medicine have greatly decreased the risk of viral transmission during blood transfusion, other concerns now drive the debate over transfusion practice and have continued the reexamination of the approach to RBC transfusion. The examination and debate over RBC transfusion risks over the last 2 decades have led to a more critical examination of transfusion benefits. These issues are particularly important in the critically ill patient population. This review will examine some of the important controversies still surrounding the use of RBC transfusion in the critically ill patient, including patients with cardiac disease, severe sepsis, and septic shock.

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Transfusion Practice in the Critically Ill

Anemia is very common in the critically ill; almost 95% of patients admitted to the ICU have a hemoglobin level below normal by ICU day 3.[4,5] As a consequence of this anemia, critically ill patients receive a large number of RBC transfusions. Two cross-sectional studies[6,7] conducted in Europe and the United States observed that RBC transfusions were administered in approximately 40% of all patients studied. On average, critically ill patients received almost 5 U of RBCs. This has changed little over the past decade despite the scrutiny of transfusion practice.[4]

The best evidence available regarding the efficacy of RBC transfusion among critically ill patients is from a randomized controlled trial, the Transfusion Requirements in Critical Care (TRICC) trial, conducted by the Canadian Critical Care Trials Group.[8] In this study, a liberal transfusion strategy (hemoglobin 100 to 120 g/L, with a transfusion trigger of 100 g/L) was compared to a restrictive transfusion strategy (hemoglobin 70 to 90 g/L, with a transfusion trigger of 70 g/L) in a general medical and surgical critical care population. Patients who were euvolemic after initial treatment who had a hemoglobin concentration < 90 g/L within 72 h were enrolled. The TRICC trial[8] documented an overall nonsignificant trend toward decreased 30-day mortality in the restrictive group; however, there was a significant decrease in mortality in the restrictive group among patients who were less acutely ill (APACHE [acute

physiology and chronic health evaluation] II scores < 20) and among patients who were < 55 years of age. Patients in the restrictive group received 54% less RBC units than those in the liberal group. Based on the results of the study, the authors[8] recommended that critically ill patients receive allogeneic RBC units when hemoglobin concentrations fall < 70 g/L and maintained at hemoglobin concentrations from 70 to 90 g/L. The diversity of patients enrolled in the trial and the consistency of the results suggest that the conclusions may be generalized to most critical care patients, with the possible exception of patients with active coronary ischemic syndromes.

Since the publication of the TRICC trial,[8] Carson et al[9] performed a systematic review of the literature to document all of the clinical trial evidence examining transfusion triggers. They identified 10 randomized clinical trials of adequate methodologic quality in which different RBC transfusion triggers were evaluated. Included were a total of 1,780 surgery, trauma, and ICU patients enrolled in trials conducted over the past 40 years. The transfusion triggers evaluated in these trials varied from 70 to 100 g/L. Data on mortality or hospital length of stay were only available in six of these trials. Conservative transfusion triggers were not associated with an increase in mortality; on average, mortality was one fifth lower (relative risk, 0.80; 95% confidence interval [CI], 0.63 to 1.02) with conservative compared with liberal transfusion triggers. Likewise, cardiac morbidity and length of hospital stay did not appear to be adversely affected by the lower use of RBC transfusions. From the 1,780 patients, 892 patients (50%) had cardiovascular disease. Using metaanalytic techniques, there were no differences in the combined odds of death or cardiac events using restrictive strategies as compared to more liberal approaches. There were insufficient data on potentially relevant clinical outcomes such as stroke, thromboembolism, multiorgan failure, delirium, infection, or delayed wound healing to perform any pooled analysis. Carson and colleagues[9] concluded there were insufficient data to address the full range of risks and benefits associated with different transfusion thresholds, particularly in patients with coexisting disease. They also noted that their metaanalysis was dominated by a single trial: the TRICC trial,[8] which enrolled 838 patients and was the only individual trial identified that was adequately powered to evaluate the impact of different transfusion strategies on mortality and morbidity.

The observational studies,[6,7] in combination with the TRICC trial,[8] have raised questions regarding the validity of the historical assumption that RBC transfusion was beneficial for critically ill patients with anemia. Few studies have attempted to determine whether clinical practice has changed following the publication of the TRICC trial. Hébert and colleagues[10] reported the results of a repeat of a 1993 survey of Canadian critical care physicians to examine transfusion practice in critically ill patients. There were important changes observed between responses to the 2002 and 1993 surveys of transfusion practice. A threshold of 70 g/L was adopted 34% of the time in 2002, as compared to 15% of the time in 1993 ($p < 0.001$). Thresholds > 100 g/L were reported in 6% of all responses in 2002 as compared to 29% in 1993 ($p < 0.0001$). Indeed, 85% of physicians stated that they had modified their approach to transfusion following the publication of the TRICC. However, there still remains variation in RBC transfusion practice patterns.[6,7] Despite the apparent change in attitudes of Canadian critical care physicians, we are unsure if these attitudes prevail elsewhere. In addition, the survey demonstrated persistence of practice variations.

To date, there are no convincing data to support the routine use of RBC transfusion to treat anemia in hemodynamically stable critically ill patients without evidence of acute bleeding. The data available would suggest that, in the absence of acute bleeding, hemoglobin levels of 70 to 90 g/L are well tolerated by most critically ill patients and that a transfusion threshold of 70 g/L is appropriate. There is still some controversy as to what the appropriate transfusion threshold should be for critically ill patients with acute ischemic cardiac disease or in the early resuscitation of the septic patient.

Transfusion Practice in Patients With Septic Shock

Recently, a study published by Rivers and colleagues[11] documented that the use of early goal-directed care based on hemodynamic variables and a mixed central venous saturation decreased mortality from 46.5% in the control group to 30.5% in the goal-directed therapy group ($p = 0.009$) in patients identified in the first 6 h of septic shock. As one of the many interventions in patients with early septic shock, hematocrit concentrations were increased $> 30\%$ if the central venous saturations fell to $< 70\%$. As a consequence of goal-directed therapy, 64% of patients as compared to 18.5% of the control group received RBC transfusions in the first 6 h of care ($p < 0.0001$).

There are significant differences in patient populations, as well as many aspects of the conduct and scope of both the early goal-directed care study[11] and the TRICC trial.[8] The early goal-directed ther-

apy trial[11] used a decrease in mixed central venous oxygen saturation, a measure of ongoing oxygen debt, to initiate a therapeutic algorithm that included fluid resuscitation, inotropic support, vasopressor support, and RBC transfusions. In this early resuscitation trial,[11] this diagnostic measure accompanied by a series of interventions improved mortality and morbidity in patients with early septic shock. In contrast, the TRICC trial[8] compared two different transfusion strategies in a wide variety of resuscitated critically ill patients. Both trials raise important concerns in how best to transfuse and resuscitate critically ill patients with septic shock as well as other patient populations. For instance, given the complexity of care provided in the early goal-directed therapy trial,[11] it is unclear how much benefit was derived from a higher transfusion trigger, if any, as compared to other interventions within the algorithm. At this juncture, it would be prudent and sensible to adopt aspects of both trials while awaiting further research.

Transfusion Practice in Patients With Cardiac Disease

A number of risk factors for adverse outcomes associated with anemia have been identified in clinical practice guidelines[1,2,12] and reviews.[3,13,14] Anemia is believed to be less well tolerated in older patients, in the severely ill, and in patients with clinical conditions such as coronary, cerebrovascular or respiratory disease. However, the clinical evidence confirming that these factors are independently associated with an increased risk of adverse outcome is lacking. One small case-control study[15] following high-risk vascular surgery suggested an increase in postoperative cardiac events with increasing severity of anemia. In perioperative[16] and critically ill patients,[17] two large cohort studies have documented that increasing degrees of anemia were associated with a disproportionate increase in mortality rate in the subgroup of patients with cardiac disease. In 1958 Jehovah's Witness patients,[16] the adjusted odds of death increased from 2.3 (95% CI, 1.4 to 4.0) to 12.3 (95% CI, 2.5 to 62.1) as preoperative hemoglobin concentrations declined from the range of 100 to 109 g/L to 60 to 69 g/L in patients with cardiac disease. A significant increase in mortality in noncardiac patients was not observed at comparable levels of anemia. In a separate study[17] of critically ill patients, patients with cardiac disease and hemoglobin concentrations < 95 g/L also had a trend toward an increased mortality (55% vs 42%, $p = 0.09$) as compared to anemic patients with other diagnoses. Although both cohort studies were retrospective in nature and may not have controlled for a number of important confounders, available studies suggest that anemia increases the risk of death in patients with significant cardiac disease.

Two additional observational studies have explored the clinical consequences of anemia in patients with acute coronary syndromes or an acute myocardial infarction. Wu et al[18] used Medicare records in a retrospective study of 78,974 patients > 65 years old who were hospitalized with a primary diagnosis of acute myocardial infarction. The authors then categorized patients according to their admitting hematocrit. Although anemia defined in the study[18] as a hematocrit $< 39\%$ was present in nearly half the patients, only 3,680 patients received an RBC transfusion. Lower hospital admission hematocrit values were associated with increased 30-day mortality, with a mortality rate approaching 50% among patients with a hematocrit $\leq 27\%$ who did not receive an RBC transfusion. This study was among the first to demonstrate that RBC transfusion may be beneficial in patients with acute myocardial infarction. However, a number of potential biases severely limited any inferences made from this study. Specific concerns include a very low rate of exposure to RBCs, limited statistical adjustments made in the multivariable analysis, an analysis based on the admitting hematocrit rather than the hematocrit value associated with the transfusion, no consideration for the time dependent use of RBCs, and residual confounding because the use of RBCs are intimately linked to hematocrit values (confounding by indication). Moreover, the observed benefits of RBC transfusion did not persist for patients with admitting hematocrit levels between 30.1% and 33% in a secondary analysis that removed patients who died within 2 days of hospital admission. Despite these limitations, the authors and an accompanying editorial stated there was sufficient evidence from this publication to recommend the transfusion of RBCs below a hematocrit of 33% in elderly patients following an acute myocardial infarction.

The second study by Rao and colleagues[19] attempted to overcome the limitations of the study by Wu et al[18] by using detailed and accurate prospectively collected data, by focusing on a patient population that required aggressive interventions and a greater exposure to blood products, and by using a number of multivariable statistical techniques that might better adjust for the influence of many baseline characteristics as well as time. In their analysis,[19] they noted that RBC transfusions were not associated with improved survival when nadir hematocrit values were in the range of 20% or 25% and were clearly associated with worsened outcomes when values were $> 30\%$. Despite superior methods, some limitations still remain. The study by Rao et al[19] only

had 2,400 patients (10%) who received RBC transfusions, a small number of exposed individuals given an average mortality of 4%. Indeed, an overall mortality difference as large as 2% may not have been detected, and larger differences would have been missed in some of the strata, as suggested by the disproportionate high odd ratios at higher hematocrit levels.

Importantly, over and above apparent differences, both studies[18,19] consistently demonstrate that patients who receive RBCs at a higher hematocrit appear to be harmed by the transfusions. At hematocrit values $< 30\%$, it is possible that the interpretation given by the authors represent aspects of the true effects, especially since there are many differences between studies. Wu et al[18] derived observations from a wide population of all elderly patients who had an acute myocardial infarction, whereas Rao and colleagues[19] only included younger individuals who required aggressive interventional management. It is plausible that a higher transfusion threshold would benefit elderly patients because of the greater degree of diffuse vascular disease, the presence of additional comorbid illnesses, and the inability to augment cardiac output as a means of compensation for anemia. However, younger patients may derive less benefit from RBC transfusions because of widespread use of aggressive revascularization procedures, statins, new antiplatelet agents, and other therapies that have been shown to save lives. In addition to more elaborate treatment for the primary lesion, collateral blood flow is either adequate or treated as part of cardiovascular management strategy. It is also possible that younger patients can better adapt to anemia. If this interpretation holds, clinicians should consider adopting a higher transfusion strategy in all elderly patients while allowing patients who are aggressively treated for their acute coronary syndromes to be treated according to a more restrictive approach to transfusions. It is also plausible that there is limited incremental benefit of RBC transfusion in patients following a myocardial infarction with a hematocrit $> 20\%$ or a hemoglobin concentration > 70 g/L as suggested by the findings of Rao et al.[19] Ideally, further evidence from randomized controlled trials would provide the needed evidence to determine optimal transfusion strategies in this high-risk patient population.

Potential Reasons for the Apparent Lack of Benefit of RBC Transfusions

Two plausible explanations have been suggested to explain the apparent lack of benefit from RBC transfusions. The first explanation is that the adverse clinical consequences of RBC transfusion results from the effects of leukocytes contained in the transfused blood. The second explanation is that the adverse clinical consequences of RBC transfusion result from prolonged RBC storage (*ie*, transfusion of "old" RBCs).

Several studies[20,21] have suggested that blood transfusions depress immune function in a recipient. Evidence of transfusion-associated immune suppression emerged following observations that blood transfusions improve renal allograft survival,[22] as well as increased ICU[23] and postoperative[24] infections. A randomized controlled trial[25] undertaken to examine infections in cardiovascular surgical patients found an approximate 4.2% absolute decrease in mortality but no decrease in infections in patients receiving leukoreduced blood, as compared to patients receiving buffy coat depleted blood. A second trial[26] conducted by the same investigators designed to evaluate mortality documented a similar decrease in 30-day mortality rate in this same patient population. These investigators[26] postulated that depressed immunity following blood transfusions predisposed high-risk cardiovascular surgical patients to multiple organ failure and ultimately resulted in higher mortality. However, metaanalyses and reviews[27,28] of the randomized trials do not provide convincing evidence for or against the potential role of leukoreduction in decreasing mortality or postoperative infections. Hébert and colleagues[29] conducted a study of 14,786 patients before and after universal leukoreduction in patients undergoing cardiac surgery, repair of a hip fracture, or who required intensive care following a surgical intervention. In this study,[29] the authors documented a 1% decrease in mortality rate associated with the implementation of universal leukoreduction without observed changes in serious infections. At this juncture, evidence would suggest that, at most, removal of leukocytes from RBC transfusions may have a small but potentially important effect on clinical outcomes following critical illness. The overall cost-effectiveness of universal leukoreduction has yet to be proven, especially in lower-risk populations. In addition, studies[30] suggest that the incremental benefits provided by leukoreduction may not be mediated through immunomodulation but rather through decreased stimulation of the inflammatory cascade.

In 1992, Marik and Sibbald[31] first demonstrated the potential harm from prolonged RBC storage by detecting an association between a fall in gastric intramucosal pH (pHi), an indicator of poor flow and oxygenation of the bowel, and transfusion of RBCs stored for > 15 days. This seminal study[31] stimulated a number of investigators to question whether old RBCs are effective oxygen carriers. In asking

whether prolonged RBC storage affects function, one is led to review how shelf life was established for this blood product. Indeed, the inability to define the optimum and minimum transfusion thresholds and the inability to reliably measure tissue oxygenation have made it difficult to study and determine the efficacy of different RBC products. As a consequence, the determination of shelf life for RBCs has been based on the maintenance corpuscular integrity and posttransfusion 24-h survival.[32]

A number of changes to the corpuscule and cytosol occur over time. Several reviews[32–36] have summarized the large volume of literature characterizing biochemical and corpuscular changes to RBCs during storage, collectively referred to as the storage lesion. From these reviews, it is evident that there are few data on the clinical consequences of transfusing old stored RBC products.[33] Traditionally, the storage lesion has been restricted to changes occurring in the RBCs rather than bioreactive substances (see below). During storage, RBCs undergo a predictable change in morphology, evolving from biconcave discs to deformed spheroechinocytes. These corpuscular changes are associated with a number of biochemical and biomechanical changes, including a depletion of adenosine triphosphate[37–39] and 2,3-diphosphoglycerate (DPG),[38–41] membrane phospholipid vesiculation[42–44] and loss, protein oxidation[36,45] and lipid peroxidation of RBC membrane,[46] and loss of deformability.[47,48] These corpuscular changes may contribute to adverse clinical consequences as a result of altered or diminished oxygen transport. For instance, the loss of the biconcave disk and associated cellular deformability will impair the ability of the 8 μm RBC to navigate the microcirculation with capillaries diameters of 3 to 8 μm. The RBC storage changes also increase RBC-endothelial interactions,[49] which are further increased by endotoxins and inflammatory cytokines.[50,51] The loss of deformability and interactions with vascular endothelium compromise microvascular flow of stored RBCs,[52] and critically ill patients would be expected to be vulnerable.[33] Even if able to navigate the microcirculation, the unloading of oxygen to the tissues may be impaired by the well-documented depletion of 2,3-DPG in the stored RBCs. It has been repeatedly demonstrated in man and nonhuman primates that following transfusion of DPG-depleted RBCs, systemic DPG levels, as well as the oxygen-hemoglobin dissociation curve values (a measure of oxyhemoglobin affinity indicated by the oxygen tension at 50% hemoglobin saturation), fall significantly and then regenerate at a variable rate taking up to 24 h to several days.[41,53] Based on these observations, it has been speculated that transfusion of large amounts of stored RBCs may have an adverse clinical consequence on oxygen delivery in patients whose balance is compromised.[54–57] However, this hypothesis has not been tested in large controlled clinical trials.

During RBC storage, there are a number of other time-dependent changes also occurring within the storage medium, such as a progressive fall in pH, an increase in plasma potassium and release of free hemoglobin from lysed RBCs.[58] The clinical consequences of transfusing these storage byproducts are probably limited (except in neonates), given the recipient's capacity to buffer, dilute, or remove these substances. There is also a generation of cytokines and other bioreactive substances,[59] including histamine,[60] complement,[61,62] lipid,[63] and cytokines,[64] accumulating in the storage media. Clinical consequences, again unknown, would be mediated through stimulation of proinflammatory pathways.

There are also a number of reports[65–69] suggesting that disease processes, such as sepsis, also impair RBC deformability. The combination of significant systemic microcirculatory dysfunction[70,71] and the decrease in RBC deformability may dramatically affect tissue oxygen delivery in sepsis and septic shock.[65–68] In this setting, transfusion of poorly deformable 2,3-DPG-depleted stored RBCs could potentially exacerbate underlying microcirculatory dysfunction, further impairing tissue perfusion. Therefore, the available evidence suggests that transfusions of stored RBCs may have adverse effects on microcirculatory flow and oxygen utilization.

Retrospective clinical studies have documented an association between prolonged storage times and adverse clinical outcomes including mortality,[72] pneumonia,[73] serious infections,[74] and length of stay[75,76] in many patient populations including multiple trauma victims, critically ill patients, and patients undergoing cardiac surgical procedures. Martin et al[75] observed a statistically significant association between the transfusion of aged blood (> 14 days old) and increased length of ICU stay ($p = 0.003$) in 698 critically ill patients. In patients receiving a transfusion, aged RBCs was the only predictor of length of stay ($p < 0.0001$). In survivors, from this analysis, only the median age of blood was predictive of length of stay ($p < 0.0001$). Purdy et al[72] demonstrated a negative correlation ($r = -0.73$) between the proportion of RBC units with older RBCs and survival in patients admitted to the ICU with a diagnosis of severe sepsis ($n = 31$). Unfortunately, all retrospective studies evaluating prolonged RBC storage will invariably be subject to the confounding influences of factors, such as the number of RBC units transfused and the mixture of storage times from the multiple units transfused throughout a hospital stay, as well as patient factors

including severity of illness. Inferences related to the clinical consequences of transfusing RBCs with a storage time < 8 days were limited by a small sample size and clinically important imbalances in baseline characteristics.

Two randomized controlled trials in adults have been reported. Walsh and colleagues[77] evaluated changes in gastric pHi, a measures of gastric perfusion, in 22 critically ill patients receiving mechanical ventilation who required an RBC transfusion. In this study,[77] the authors were not able to detect any adverse consequences on pHi and changes in the arterial-gastric mucosal carbon dioxide gap with a storage time > 20 days as compared to patients receiving RBCs < 5 days. These results contradicted earlier observations in a before and after study conducted by Marik and Sibbald,[31] who documented an inverse relationship between the age of transfused RBCs and gastric pHi ($r = -0.71$; $p < 0.001$). However, it should be noted that patients in the study by Walsh et al[77] received leukodepleted RBCs.

A summarization is as follows: (1) there is strong laboratory evidence suggesting that prolonged RBC storage may be deleterious; (2) observational studies report a number of associations between prolonged storage and adverse clinical outcomes, such as mortality and organ failure; however, (3) only two small adult trials have been published assessing clinical consequences of prolonged RBC storage. Given the importance of the question and limited evidence in humans, a definitive clinical trial is necessary to answer this question. If the age of transfused RBCs is in fact important, it would have major ramifications on the already limited blood supply. At this juncture, high-quality clinical evidence is not available.

Clinical Recommendations

Despite the frequent use of RBC transfusions, the TRICC trial[8] remains the only large randomized trial that has examined RBC transfusion in the critical care setting. Given the lack of demonstrated clinical efficacy of RBC transfusion in critically ill patients, in the absence of active bleeding, and the results of the TRICC trial,[8] we recommend a transfusion trigger of 70 g/L in most critically ill patients, including patients with a history of cardiac disease and beyond 6 h of septic shock. However, in early septic shock (< 6 h), a higher trigger may be indicated (*eg*, from 80 to 100 g/dL), particularly if there is evidence of inadequate oxygen delivery (*eg*, low mixed venous saturation) after fluid resuscitation (Table 1). Similarly a transfusion trigger from 80 to 100 g/L would seem reasonable for patients with acute coronary syndromes until further evidence becomes available. In addition, clinicians should only administer 1 U of RBCs at a time and remeasure hemoglobin concentrations after each RBC unit is transfused. We should also note that the TRICC trial[8] does not provide sufficient evidence to determine optimal transfusion practice in other clinical settings or patients populations such as postoperative care and in critically ill children. Finally, most transfusion practice guidelines[78,79] published prior to the completion of the TRICC trial are now dated and need to have expert opinion informed by solid evidence in diverse clinical settings. In the next several years, several randomized trials will provide additional evidence in support of bedside decision making.

Table 1—*Transfusion Recommendations*

Variables	Transfusion Trigger, g/L*	Goal, g/L
General critically ill (no acute bleeding)	70	70–90
Critically ill with septic shock (> 6 h)	70	70–90
Critically ill with septic shock (< 6 h)	80–100	100
Critically ill with chronic cardiac disease	70	70–90
Critically ill with acute cardiac disease	80–100	100

*Administer 1 U of RBCs at a time and remeasure hemoglobin concentrations.

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