

PACKED RED BLOOD CELL TRANSFUSION IN THE INTENSIVE CARE UNIT: LIMITATIONS AND CONSEQUENCES

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- **OBJECTIVE** *To review the literature on the limitations and consequences of packed red blood cell transfusions, with particular attention to critically ill patients.*
- **METHODS** *The PubMed database of the National Library of Medicine was searched to find published articles on the indications, clinical utility, limitations, and consequences of red blood cell transfusion, especially in critically ill patients.*
- **RESULTS** *Several dozen papers were reviewed, including case series, meta-analyses, and retrospective and prospective studies evaluating the physiological effects, clinical efficacy, and consequences and complications of transfusion of packed red blood cells. Most available data indicate that packed red blood cells have a very limited ability to augment oxygen delivery to tissues. In addition, the overwhelming preponderance of data accumulated in the past decade indicate that patients receiving such transfusions have significantly poorer outcomes than do patients not receiving such transfusions, as measured by a variety of parameters including, but not limited to, death and infection.*
- **CONCLUSIONS** *According to the available data, transfusion of packed red blood cells should be reserved only for situations in which clear physiological indicators for transfusion are present. (American Journal of Critical Care. 2007;16:39-49)*

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Even though it was not widely practiced until well into the 20th century, transfusion of blood or blood products has been a source of great interest for centuries. Although the story is now widely discredited, the earliest blood transfusion is said to have occurred in 1492, when the blood of 3 young boys was allegedly transfused into the dying Pope Innocent VIII. In 1665, British physician Richard Lower reported the first successful dog-to-dog transfusions, and, in 1667, Jean-Baptiste Denis reported successful sheep-to-human transfusions in France. The first well-documented

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and successful human-to-human transfusion was performed in 1818 by James Blundell, a British obstetrician.

Transfusion of blood and blood components remains an extremely common practice in the United States. The American Association of Blood Banks reports that in 2001 nearly 29 million units of blood components were transfused, including nearly 14 million units of packed red blood cells (PRBCs).¹

Transfusion of PRBCs is a common practice in the critical care setting. In 1995, Corwin et al² reported that 85% of critically ill patients who remained in the intensive care unit (ICU) longer than 1 week received blood transfusions. The mean volume of PRBCs transfused was 9.5 units per patient. More recently, researchers in the CRIT study³ reported an overall transfusion rate of 44% among patients in the ICU.

Complications of blood transfusions such as transfusion reactions and the transmission of a variety of infectious agents long have been recognized. The widespread and sometimes indiscriminate use of PRBC transfusion has continued, despite a growing body of literature documenting its limitations and describing a broad array of complications associated with its use. In this article we review data addressing these limitations and complications, with particular attention to critical care patients.

Methods

The published literature was searched by using the PubMed database of the National Library of Medicine. To evaluate the effect of PRBC transfusion in different populations of critically ill patients, we selected articles that represented original research (prospective or, more commonly, retrospective in nature) for inclusion in the review.

The overall transfusion rate among ICU patients is 44%.

Background

Data indicate that as many as 95% of patients have a lower than normal hemoglobin level by day 3 of their ICU stay.⁴ The causes of this anemia are varied and include blood loss due to the primary underlying abnormality (eg, gastrointestinal bleeding), impaired erythrocyte production, and iatrogenic blood loss due to phlebotomy. The significance of the role of phlebotomy in the development of anemia in ICU patients is underappreciated. Results of a 1986 study indicated that ICU patients lost an average of 65 mL of blood

daily as a result of phlebotomy.⁵ Mean total blood loss per patient was 762 mL per ICU stay (944 mL if an arterial catheter was in place).

Subsequent studies have shown a slight decrease in the amount of blood taken from patients in the ICU, probably due to increased cognizance of the severity of the problem and the institution of blood conservation strategies in the ICU.^{6,7} However, these studies indicated that approximately 41 mL per day of blood loss could still be attributed to phlebotomy in patients in the ICU.

Ninety-five percent of critical care patients will have a lower than normal hemoglobin by ICU day 3.

Complications such as infections, immunosuppression, impairment of microcirculatory blood flow, 2,3-diphosphoglycerate deficiency, and an array of biochemical and physiological derangements including hypocalcemia, coagulopathy, hyperkalemia, and hypothermia are associated with the use of PRBCs. Some of these complications are a result of inherent properties of the blood products being transfused; others are a consequence of the storage of the red blood cells.

Historically, infection associated with PRBC transfusion has been attributed more often to occult infection in the donor than to contamination of the blood during collection and storage. Numerous studies published in recent years, however, have documented secondary bacterial infection in patients receiving PRBC transfusions, and these studies are reviewed in detail in the following paragraphs.

PRBC transfusion results in a variety of immunomodulatory effects, often referred to as transfusion-associated immunomodulation. Numerous components of blood have been implicated as agents of transfusion-associated immunomodulation. Recent reviews^{8,9} of the immunomodulatory effects of blood provide extensive details on this topic. In support of earlier observations, in 1997 Opelz et al¹⁰ demonstrated a clear benefit of red cell transfusions on renal allograft survival in transplant recipients. With regard to the effect of transfusion on tumor recurrence and outcomes in cancer patients, meta-analyses have not yielded an answer to the question of whether transfusion increases the risk of death or tumor progression in these patients.^{11,12}

The effect of storage on PRBCs includes decreased levels of 2,3-diphosphoglycerate with a resultant increase in oxygen affinity and a decrease in the ability

of hemoglobin to offload oxygen. Morphological changes in erythrocytes may result in increased fragility, decreased viability, and decreased deformability of the cells as well as the release of a number of substances resulting in such adverse systemic responses as fever, cellular injury, alterations in regional and global blood flow, and organ dysfunction. Transfusion with PRBCs that have been stored for long periods is associated with poorer oxygen delivery than is transfusion with fresher cells.¹³⁻¹⁵ Evidence also suggests that the transfusion of older blood (stored >14 days) is an independent risk factor for the development of multiple organ failure.¹⁶

Increased red blood cell storage results in reduced red blood cell function and impaired oxygen delivery.

Two prospective studies^{7,17} of outcomes in ICU patients showed a higher mortality rate in patients receiving PRBCs than in those not receiving PRBCs, even when adjusted for acuity and other factors. In a 1999 study of transfusion requirements in critical care (TRICC) conducted by the Canadian Critical Care Trials Group, patients in ICUs were randomized to 1 of 2 transfusion groups: liberal (transfusion when hemoglobin level was <100 g/L to a target of 100-120 g/L) or restricted (transfusion when hemoglobin was <70 g/L, target 70-90 g/L).¹⁷ Hospital mortality was lower in the restrictive group, and 30-day mortality was lower among patients who had Acute Physiology and Chronic Health Evaluation (APACHE) II scores of 20 or less or who were younger than age 55. In sicker or older patients, outcome parameters did not differ between the 2 groups. These results suggested that a more restrictive transfusion strategy was safe in the ICU population and might be beneficial for some patients. In an observational study of more than 3500 patients published in 2002, Vincent et al⁷ showed a higher mortality in ICU patients receiving PRBC transfusion than in patients not receiving PRBC transfusion, with an odds ratio of death of 1.37 for the transfusion group.

Indications for Transfusion

Despite the widespread use of PRBC transfusions for a variety of reasons, the number of indications and scenarios in which such transfusions are appropriate is actually quite limited. In 1992, the American College of Physicians published a series of guidelines titled "Practice Strategies for Elective Red Blood Cell Transfusions."²¹⁸ Among the key points of these guidelines

Table 1 Summary of studies evaluating the safety of restrictive red blood cell transfusion strategies

Reference	Year	Population	Safety demonstrated?
Hebert et al ¹⁷	1999	Mixed	Yes
Hebert et al ^{19*}	2001	Cardiac	Yes
McIntyre et al ^{20*}	2004	Trauma	Yes
Earley et al ²¹	2006	Trauma	Yes

*Subgroup analysis of data reported by Hebert et al.¹⁷

were the avoidance of an empiric transfusion threshold and the appropriateness under certain circumstances of single-unit transfusion. The use of PRBC transfusion was specifically considered appropriate in patients with acute anemia whose symptoms were related to blood loss and were refractory to crystalloid infusions, as well as in patients with chronic anemia in whom nontransfusion therapies (eg, iron replacement, erythropoietin) had not been effective.

Specifically discouraged was the use of transfusion to enhance the general sense of well-being of the patient, to promote wound healing, as a prophylactic measure in the absence of signs and symptoms, or to expand intravascular volume in the absence of evidence of inadequacy in oxygen-carrying capacity or oxygen delivery. Support for the avoidance of a numerical "transfusion trigger" can be found in the results of the TRICC trial, with its findings of either equivalence or, in some groups, better outcomes when a restrictive transfusion strategy was used.¹⁷ A summary of published articles assessing the safety of restrictive transfusion strategies is shown in Table 1.

Transfusion and Oxygen Delivery

One of the primary therapeutic goals in treating various shock states and sepsis is to increase oxygen delivery to meet previously unmet tissue needs. One of the techniques often used to achieve this end is the transfusion of PRBCs with the intention of increasing oxygen-carrying capacity and, by extension, oxygen delivery. However, despite the theoretical basis for this intervention, the preponderance of evidence in published reports suggests that blood transfusions given to patients with sepsis may not help increase oxygenation deficits in organ systems.

In a 1990 paper, Dietrich et al²² evaluated critically ill patients in shock who received a transfusion after volume resuscitation. Although transfusion increased oxygen delivery, neither oxygen consumption nor lactic acidosis improved in these subjects. In

another article published the same year, Conrad et al²³ were able to show an increase in oxygen consumption in association with PRBC transfusion, but only in patients with low oxygen extraction ratios.

Using intramucosal pH measured by gastric mucosal tonometry as a marker for tissue oxygenation, Silverman and Tuma²⁴ compared the effectiveness of dobutamine administration with the effectiveness of transfusion in increasing this parameter. Although dobutamine administration significantly increased a low baseline intramucosal pH, transfusion with PRBCs failed to have any effect on intramucosal pH in the patients evaluated.

Marik and Sibbald's 1993 study¹⁴ of oxygen delivery failed to show a beneficial effect of red cell transfusion on measured systemic oxygen uptake in patients with sepsis. They concluded that poorly deformable cells cause microcirculatory occlusions, and further postulated that these occlusions lead to tissue ischemia. They measured hemodynamics, oxygenation, and gastric tonometry immediately after transfusion, and at 3 and 6 hours after transfusion. Hemoglobin and arterial lactate concentrations were measured at each time point. Marik and Sibbald reported an increase in calculated (but not measured) oxygen uptake at 6 hours after transfusion. They also unexpectedly found a decrease in gastric intramucosal pH after transfusion of cells that were stored for more than 15 days, reflecting an inadequacy of splanchnic oxygenation.

Transfusions in septic patients do not improve oxygen deficits in organ systems.

In a 1997 study, Fitzgerald et al¹³ found that red blood cell transfusions were not effective in maintaining tissue oxygen delivery in patients with sepsis. The researchers examined storage time of packed cells, changes that occur to blood that has been banked, and the microcirculatory changes associated with sepsis in an animal model. They were unable to improve tissue oxygenation. They found that storing animal red cells in citrate dextrose adenine-1 for more than 21 days diminished the effectiveness of this treatment and did not acutely improve tissue oxygenation. They did show that transfusion with fresher cells, stored for less than 3 days in citrate dextrose adenine-1, was accompanied by an immediate increase in systemic oxygen uptake. Impaired deformability of cells stored for longer periods, and/or the trapping of such poorly deformable cells in capillaries, thereby impeding passage and delivery, were postulated as explanations for these findings.

More recently, Mazza et al²⁵ measured mixed venous oxygen saturation and lactate levels in patients with the systemic inflammatory response syndrome (SIRS) or sepsis before and after transfusion with PRBCs. Hemoglobin levels before and after transfusion were 81.4 and 94 g/L, respectively. The investigators were unable to demonstrate a significant improvement in either lactate level or mixed venous oxygen saturation, even in the subset of patients who had hemoglobin levels less than 80 g/L.

Guidelines²⁶ published as part of the Surviving Sepsis Campaign have endorsed the use of PRBCs in the treatment of patients with sepsis who show evidence of inadequate oxygen delivery to tissues under certain circumstances. This recommendation is primarily based on data published by Rivers et al,²⁷ who evaluated an algorithmic approach to patients in septic shock. PRBC transfusion (up to a hematocrit of 0.30) was one of the interventions included in this algorithm, which included a goal of achieving a mixed venous oxygen saturation of 70% in study subjects. Patients achieving this goal had better outcomes than did patients who did not reach the goal. The specific effect of transfusion was not evaluated in this study, however, as the study was designed to assess the overall algorithm rather than its component parts.

Infection and Blood Transfusion

It has been more than a decade since the question of an increased risk of bacterial infections in patients receiving PRBCs appeared in the literature. In that interval, numerous articles have been published demonstrating this association in diverse populations of critically ill patients.

Taylor et al²⁸ assessed 1717 patients admitted to a 40-bed medical-surgical-trauma ICU. Nosocomial infection rates were compared among 3 groups: the entire cohort, the patients who received a transfusion, and the patients who did not receive a transfusion. The infection rate in the transfusion group was 15.38% versus 2.92% for the nontransfusion group. A dose-response pattern also was apparent. The more blood the patients received, the greater the risk of infection. For each unit of blood received, the odds of a nosocomial infection developing were increased by a factor of 1.5. Overall, infection was 6 times more likely to develop in the transfusion group than in the nontransfusion group.

Claridge et al²⁹ also demonstrated a connection between infections and transfusions, this time in trauma patients. In that study, 1593 consecutive adult patients admitted to a level I trauma center during a 3-year period were analyzed. The infection rate in patients who received at least 1 unit of PRBCs was 33% versus 7.6%

in patients who did not receive a transfusion. Claridge et al also reported a strong linear correlation between number of units transfused and the incidence of infection.

Hill et al³⁰ evaluated the association between blood transfusion and the incidence of postoperative bacterial infection. Their meta-analysis of 20 peer-reviewed articles showed that blood transfusion is associated with a greater risk of postoperative bacterial infection in surgical patients than in patients who did not receive blood during or after elective surgery. After analysis of the subset of trauma patients, the authors concluded that this population is especially at risk for infection after blood transfusion. In their study they allude to the combination of immunosuppressive effects of transfusion and the inflammation and tissue injury following trauma as “a significant and often overlooked risk factor” unique to trauma patients receiving transfusions of allogeneic packed cells.

The greater the number of red blood cell transfusions, the greater the risk of infection.

In a 2005 prospective observational study, Shorr et al³¹ looked at the relationship between PRBC transfusion and the development of ICU-acquired bloodstream infection. The study population comprised 4892 patients in 284 adult ICUs across the United States. The patients were screened for bloodstream infection at the time of ICU admission and 48 hours after admission. A total of 3.3% of the study population had an ICU-acquired bloodstream infection. Three variables were independently associated with diagnosis of a new bloodstream infection when a multivariate analysis adjusting for severity of illness, primary diagnosis, use of mechanical ventilation, placement of central venous catheters, and ICU length of stay was completed. The 3 variables were baseline treatment with cephalosporins, higher sequential organ failure assessment score on ICU days 3 to 4, and PRBC transfusion. This study differs from the previously mentioned studies in that it focused more on everyday critical care processes known to cause infections, such as hand hygiene, use of antibiotics, use of mechanical ventilation, presence of central catheters, and aseptic technique variables associated with catheter insertion, than on the patient's diagnosis or a particular population of patients.

Using a logistic regression analysis, El-Masri et al³² determined that the number of units of PRBC transfused, along with the number of central venous catheters

inserted and the use of chest tubes, were a surrogate marker for injury severity and a predictive factor for the development of bloodstream infection in trauma patients.

In 2 recent studies,^{33,34} researchers found an increased rate of infection in cardiac surgical patients receiving PRBC transfusion. Neither fresh-frozen plasma nor platelets were associated with an increased risk of infection, and in fact some evidence indicated that these blood components may partially attenuate the increased risk of infection associated with PRBCs.³⁴ As in the studies by Taylor et al²⁸ and Claridge et al,²⁹ a correlation between the number of units of PRBCs transfused and the risk of bloodstream infection has been demonstrated in cardiac surgical patients.³⁴

Transfusion in Cardiac Disease

Anemia has long been thought to be detrimental to patients with heart disease, especially those with ischemic heart disease. Based primarily on theoretical considerations, conventional wisdom has guided the common practice of maintaining the hemoglobin level of cardiac patients at a level of at least 80 g/L and often 100 g/L. Although evidence suggests that lower baseline hemoglobin levels are associated with poorer outcomes in patients with ischemic heart disease, it does not necessarily follow that increasing the hemoglobin level through transfusion of PRBCs is beneficial. Recent data, in fact, suggest that such interventions may have a detrimental effect on outcome in these patients.

In their 1999 paper comparing a liberal versus a restrictive transfusion strategy in ICU patients, Hebert et al¹⁷ demonstrated a higher incidence of pulmonary edema and myocardial infarction among patients in the liberal transfusion group. In a subsequent subset analysis of patients with cardiac disease included in the previously mentioned trial (357 total cardiac patients, 257 with ischemic heart disease), Hebert et al¹⁹ showed that the patients in the liberal transfusion arm had a higher incidence of organ dysfunction. No differences in mortality could be identified at any point (30 days, 60 days, ICU or hospital).

Using a Medicare database of more than 78 000 patients, Wu et al³⁵ reported on mortality rates for patients more than 65 years old with acute myocardial infarction who received PRBC transfusion. Transfusions were associated with a lower mortality rate in elderly cardiac patients if the patients' admission hematocrit was 0.30 or lower, although the reliance on an administrative database rather than clinical records has led to some criticism of these findings.³⁶

Rao et al³⁶ performed a meta-analysis of data collected as part of 3 major international trials (GUSTO IIb, PURSUIT, and PARAGON) involving patients with

acute coronary syndrome. More than 24 000 patients were enrolled in these trials, and 2401 received PRBC transfusion for anemia or bleeding that developed during their hospitalization. Thirty-day mortality, myocardial infarction, and death/myocardial infarction as a composite end point were all higher among patients who received transfusions, even when adjusted for the patient's age and comorbid diseases.

Patients with acute coronary syndrome who receive transfusions have worse outcomes.

Yang et al³⁷ recently reported on transfusion and outcomes among patients experiencing acute coronary syndromes not associated with ST-segment elevation. More than 74 000 cardiac patients who did not undergo coronary artery bypass surgery were evaluated. Patients receiving PRBC transfusions were older and had more comorbid diseases (eg, renal insufficiency) than did patients not receiving transfusions. However, even when adjusted for these factors, patients receiving PRBCs had a significantly greater risk of death alone and death or reinfarction as a combined outcome measure than did patients not receiving blood.

Transfusion of PRBCs also has been implicated as an independent predictor of mortality in patients undergoing cardiac surgery. In a 2002 study,³⁸ the researchers evaluated mortality in patients undergoing first-time cardiac surgery. Of 1915 patients evaluated, 649 received a PRBC transfusion at some point during their hospitalization. The researchers reported that patients in the transfusion group were older, smaller, more often female, and had more comorbid diseases than patients who did not receive a transfusion. However, even when adjusted for comorbid diseases and other risk factors, the transfusion group had a 70% increase in the risk of mortality compared with the nontransfusion group.

These findings were confirmed and expanded on by Koch et al,³⁹ who evaluated outcomes in nearly 12 000 cardiac surgical patients treated during a 7-year period. Of these, 48.6% received PRBCs during their hospitalization. Koch et al identified a significant association between PRBC transfusion and every perioperative morbidity they assessed: renal failure, prolonged ventilatory support, serious infection, cardiac complications, and neurological events. They also reported an incremental increase in the risk of each adverse outcome with each unit of blood transfused.

In addition to acute complications of PRBC transfusion, Koch et al⁴⁰ also have reported on long-term sequelae of such therapy. Six- to 12-month follow-ups of patients undergoing cardiothoracic surgery showed that postoperative functional status was incrementally worse the more PRBCs the patient had received. Worse postoperative status also was associated with platelet transfusion in that study.

Although the mechanisms for the apparently worse outcomes in cardiac patients receiving PRBCs are not yet fully elucidated, the evidence is accumulating that such therapy appears to be an independent risk factor for worse outcomes. In light of the growing body of data as presented here, it would seem prudent to reserve such interventions for situations with a clear indication.

Transfusions and the Lungs

The relationship between transfusions and pulmonary function is complex. The entity known as transfusion-related lung injury is well recognized and has been reviewed elsewhere.⁴¹ In recent years, numerous investigators have evaluated the relationship between transfusions and pulmonary function with regard to the need for mechanical ventilation, weaning from mechanical ventilation, and any possible association with acute respiratory distress syndrome (ARDS).

Although it has long been suggested that giving transfusions to anemic patients may facilitate weaning from mechanical ventilation, the data evaluating this hypothesis are very limited. In a 1999 case series, Schonhofer et al⁴² reported on 5 patients referred to their regional weaning center after unsuccessful attempts at liberation from mechanical ventilation at outside hospitals. These patients were given transfusions that increased the mean hemoglobin level from 87 g/L to a mean of 120 g/L, and all were successfully weaned off mechanical ventilation. The authors concluded that correction of anemia by transfusion of PRBCs was a significant factor in weaning these patients. The small number of patients, absence of any comparison or control group, and the fact that successful weaning was accomplished at a weaning center, however, does not seem to justify such a specific conclusion.

Data from the TRICC trial, in contrast, failed to support such a conclusion.⁴³ A total of 713 patients in that study received mechanical ventilation, 357 in the restrictive transfusion group and 356 in the liberal transfusion group. No differences in duration of mechanical ventilation or extubation success were identified in these patients. Vamvakas and Carven⁴⁴ have suggested that PRBC transfusion may specifically be responsible for a prolonged need for mechanical ventilation. A group of 416 patients undergoing open heart surgery

were evaluated for the number of days of ventilation required following their operation, as well as the volumes of PRBCs, platelets, and plasma transfused. The volume of PRBCs, but not the volumes of platelets or plasma, was associated with the need for mechanical ventilation beyond the first postoperative day.

Two recent studies^{45,46} have established a specific association between ARDS and other pulmonary morbidities and transfusion of PRBCs. In a 7-year review of more than 5000 patients with moderate lung injury, Croce et al⁴⁵ identified any transfusion of PRBCs as an independent risk factor for the development of ARDS. They also found that PRBC transfusion was associated with the development of ventilator-associated pneumonia and death. Gong et al⁴⁶ reported on risks for the development of ARDS and mortality. PRBC transfusion was a risk factor for ARDS, with an odds ratio of 2.19, and a risk factor for mortality in ARDS, with an odds ratio of 1.10 per unit of blood transfused.

Transfusion and Trauma

Not surprisingly, a substantial proportion of all blood transfused in the United States, 10% to 15%, is used in the care of trauma patients. Blood transfusion is used in 8% to 55% of trauma patients.^{47,48} In the past few years, the effect of transfusion on outcomes in these patients has been evaluated in several studies.^{20,21,49-54}

Malone et al⁴⁹ studied outcomes in a cohort of more than 15 000 patients admitted to a level I trauma center. The use of blood transfusion was an independent predictor of mortality, need for ICU admission, ICU length of stay, and hospital length of stay. Patients receiving blood were 3 times more likely to die and 3 times more likely to be admitted to the ICU than patients not receiving blood.

In 2005, Robinson et al⁵⁰ reported on a study of transfusion in patients with blunt hepatic and splenic injuries. After shock and injury severity were controlled for, transfusion was identified as an independent risk factor for death among all patients and among patients treated nonoperatively. The risk of death increased with each unit of blood transfused. Hospital stays were also longer among patients receiving transfusions.

Dunne et al⁵¹ assessed the incidence of systemic inflammatory response syndrome (SIRS) among trauma patients receiving transfusions. Data on approximately 7600 patients were evaluated. The investigators found that transfusion and volume of transfusion were associated with the development of SIRS. A multinomial regression analysis indicated that transfusion was an independent risk factor not only for SIRS but for mortality and ICU admission as well.

In one of the rare prospective studies in this area, Silverboard et al⁵² recently evaluated the incidence of

ARDS and mortality in patients with major trauma who received PRBC transfusion. A total of 102 consecutive patients were divided into 3 groups on the basis of the number of units of PRBCs they received in the first 24 hours (0-5, 6-10, or >10). In a multivariate analysis, these researchers found a significant association between the amount of blood transfused and the development of ARDS, even when adjusted for such factors as severity of illness, type of trauma, and base deficit. Patients receiving more blood also had a significantly higher mortality rate.

Dunne et al⁵³ recently evaluated the effect of transfusion on outcome in combat casualties. They found PRBC transfusion to be independently associated with higher rates of infection and need for ICU admission. These findings are particularly interesting because the patients studied were especially young and healthy at baseline.

A restrictive transfusion strategy is safe and beneficial in trauma victims.

Looking at this question conversely, McIntyre et al²⁰ analyzed data from the TRICC trial, comparing outcomes in trauma patients who had been randomized to liberal and restrictive transfusion groups. No differences in outcome parameters (mortality, multiple organ dysfunction, length of stay in the ICU or the hospital) were identified. Although no advantage could be attributed to the more restrictive strategy, the findings suggested that such an approach is safe in trauma patients admitted to the ICU.

In a 2006 study, Earley et al²¹ reported on the effect of the implementation of an anemia management program in trauma patients. Under this strategy, patients in hemodynamically stable condition received a transfusion only if their hemoglobin levels decreased to less than 70 g/L. Despite a significant reduction in the amount of blood transfused on average, the length of stay, the mortality rate, and the incidence of myocardial infarction did not differ from the period before implementation of this program. However, after institution of the anemia management program, the incidence of ventilator-associated pneumonia decreased significantly. These results support the conclusion that a restrictive transfusion strategy is safe and possibly beneficial in trauma patients.

PRBC transfusion also has been associated with worse outcomes in burn patients. In a study published in 2006 involving 666 patients with major burns treated at

Table 2 Summary of main articles on clinical effects of red blood cell transfusions

Category	Reference	Year	Clinical effect
Infection	Taylor et al ²⁸	2002	Increased nosocomial infection
	Claridge et al ²⁹	2002	Increased overall infection
	Hill et al ³⁰	2003	Increased postoperative infection
	Shorr et al ³¹	2005	Increased bloodstream infection
	El-Masri et al ³²	2005	Increased infection
	Banbury et al ³⁴	2006	Increased bloodstream infection
Cardiac disease	Hebert et al ¹⁹	2001	Increased organ dysfunction
	Wu et al ³⁵	2001	Decreased mortality
	Rao et al ³⁶	2004	Increased mortality, myocardial infarction
	Yang et al ³⁷	2005	Increased mortality, combined mortality/reinfarction
Cardiac surgery	Engoren et al ³⁸	2002	Increased mortality
	Koch et al ³⁹	2006	Increased renal failure, ventilator dependence, infection, cardiac complications, neurological events
Pulmonary	Schonhofer et al ⁴²	1999	Successful weaning
	Hebert et al ⁴³	2001	No difference in weaning
	Vamvakas and Carven ⁴⁴	2002	Prolonged ventilation
	Croce et al ⁴⁵	2005	Increased acute respiratory distress syndrome, death
	Gong et al ⁴⁶	2005	Increased acute respiratory distress syndrome, death due to acute respiratory distress syndrome
Trauma	Malone et al ⁴⁹	2003	Increased mortality, length of stay
	Dunne et al ⁵¹	2004	Increased rates of systemic inflammatory response syndrome, death
	Robinson et al ⁵⁰	2005	Increased mortality, length of stay
	Silverboard et al ⁵²	2005	Increased mortality, acute respiratory distress syndrome
	Palmieri et al ⁵⁴	2006	Increased infection, mortality
	Dunne et al ⁵³	2006	Increased infection, admission to intensive care unit

21 burn centers, the use of PRBCs was associated with increased infection rates and higher mortality, even when the results were adjusted for severity of burns.⁵⁴

Conclusion

It is prudent to be cautious about adopting the attitude “where there’s smoke, there’s fire.” Many of the studies reviewed are open to criticism of their methods, particularly with regard to the fact that most are retrospective analyses. Nevertheless, near unanimity is apparent in the results of recent studies of outcomes in patients receiving PRBC transfusions. With rare exception, recent studies indicate that critically ill patients who receive PRBC transfusions have worse outcomes as measured by a variety of parameters, including mortality, infections, organ failure, and pulmonary

complications (Table 2). Even in cardiac patients, in whom it long has been assumed that hemoglobin must be maintained at a relatively high level, accumulating data indicate that liberal transfusion in patients with cardiac disease has a detrimental effect on outcome.

Overall, critically ill patients who received red blood cell transfusions had worse outcomes.

Overall, these studies urge a reevaluation of common practices regarding transfusion of PRBCs. Although both clear and relative indications for transfusion remain, a growing body of data now indicate

that many situations that historically might have prompted transfusion of PRBCs should no longer do so. In situations in which transfusion is deemed to be warranted, the number of units of PRBCs transfused should be minimized. In the era of evidence-based practice, interventions based on theoretical considerations and anecdotal experience, especially when contradicted by the best available data, should be avoided.

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CE Test Test ID A0716013: **Packed Red Blood Cell Transfusion in the Intensive Care Unit: Limitations and Consequences.** *Learning objectives:* 1. Examine data regarding critical care patients and packed red blood cell transfusion. 2. Identify circumstances in which transfusions are necessary. 3. Discuss the consequences of routine packed red blood cell transfusions in critically ill patients.

- When was the first well-documented human-to-human transfusion performed?**
 - 1492, when the blood of 3 young boys was transfused into the dying Pope Innocent VIII.
 - 1665, performed by British physician Richard Lower
 - 1667, performed by Jean-Baptiste Denis
 - 1818, performed by James Blundell, a British obstetrician
- How many units of blood components were transfused in 2001 according to the American Association of Blood Banks?**
 - 9 million
 - 14 million
 - 29 million
 - 44 million
- What kind of study is presented in this article?**
 - A prospective review of patients receiving blood transfusions.
 - A random study of patients who received blood compared with those who did not receive blood
 - A review of data addressing potential limitations and complications of blood transfusion
 - A concurrent review of patients in the emergency department who had complications following blood transfusions
- What are 3 causes of anemia in patients in the intensive care unit (ICU)?**
 - Vitamin B₁₂ deficiency, iron deficiency, thalassemia
 - Primary underlying abnormality, impaired erythrocyte production, and iatrogenic loss due to phlebotomy
 - Vitamin B₁₂ deficiency, impaired erythrocyte production, and iatrogenic loss due to phlebotomy
 - Impaired erythrocyte production, iatrogenic loss due to phlebotomy, iron deficiency
- According to studies cited in the article, what amount of blood loss per day can be attributed to phlebotomy in patients in the ICU?**
 - 14 mL
 - 26 mL
 - 41 mL
 - 57 mL
- Which of the following is an independent risk factor for developing multiple organ failure?**
 - Transfusion of blood stored > 21 days
 - Transfusion of blood stored > 14 days
 - Transfusion of blood stored > 7 days
 - Transfusion of blood stored > 24 hours
- Which of the following is a contraindication for transfusion of packed red blood cells (PRBCs)?**
 - Acute anemia with symptoms of blood loss
 - Acute anemia in patients resistant to crystalloids
 - Chronic anemia in patients in whom nontransfusion therapies have not been effective
 - Empiric transfusion threshold of hematocrit < 28%
- Which of the following statements is true?**
 - The preponderance of published reports suggest that blood transfusions given to patients with sepsis may not help to increase oxygenation deficits in organ systems.
 - A study by Marik and Sibbald (1993) showed a beneficial effect of red cell transfusion on measured systemic oxygen intake in patients with sepsis.
 - The 1997 study by Fitzgerald and colleagues showed that red blood cell transfusions are effective for maintaining oxygen delivery in patients with sepsis.
 - Mazza and colleagues demonstrated a significant improvement in both lactate level and mixed venous oxygen saturation in patients with systemic inflammatory response syndrome or sepsis who received blood transfusions.
- Which of the following statements is true?**
 - The more blood a patient receives, the greater the risk of infection.
 - Trauma and nontrauma patients show no difference in rate of infection after blood transfusion.
 - Packed red blood cells, fresh frozen plasma, and platelets increase the risk of infection in cardiac surgery patients
 - Cardiac patients require a hemoglobin of 100 g/L.
- Croce and colleagues identified any transfusion of PRBCs as an independent risk factor for development of which of the following?**
 - Pneumothorax
 - Chronic obstructive pulmonary disease
 - Acute respiratory distress syndrome
 - Community-acquired pneumonia
- What was the difference in mortality rate between trauma patients receiving blood and those not receiving blood?**
 - Death was 6 times more likely for patients receiving blood.
 - Death was 3 times more likely for patients receiving blood.
 - Death was 1.5 times more likely for patients receiving blood.
 - There was no difference in mortality rate.
- Which of the following conclusions can be drawn from this article?**
 - PRBCs are always safe to administer.
 - There is no relationship between PRBC administration and pulmonary complications.
 - Liberal transfusion in patients with cardiac disease has a positive effect on outcome.
 - If necessary, the number of PRBCs should be minimized.

Test Answers: Mark only one box for your answer to each question. You may photocopy this form.

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