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BLOOD TRANSFUSION AND SEPSIS

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Septic shock is a common reason for admission to the intensive care unit (ICU). Despite recent medical advancements, mortality from sepsis remains around 40% [1] and can be as high as 85% in severe septic shock [2]. Since severe sepsis and septic shock result in significant oxygen delivery (DO_2) and extraction impairments, anemia may have serious clinical consequences in this population. The severe hemodynamic alterations require the administration of fluids, vasoactive drugs and frequently red blood cell (RBC) transfusions to maintain oxygen delivery. However, RBC transfusions may adversely affect immune function [3, 4], and potentially worsen the microvascular defects caused by infection. Recently, a large multicenter trial evaluating transfusion requirements in critical care (TRICC) concluded that a restrictive approach to RBC transfusion was at least as safe as a more liberal approach. Results from the trial were consistent with RBC transfusions either causing harm or being of limited benefit. In this chapter, we will review the potential benefits and risks of anemia and RBC transfusion in the critical care setting. We will also review the TRICC trial in the context of patients with severe sepsis and septic shock.

OXYGEN TRANSPORT, ANEMIA AND SEPSIS

The amount of oxygen delivered, either to the whole body or to specific organs, is the product of blood flow and arterial oxygen content. For the whole body, DO_2 is the product of cardiac output and arterial oxygen content [5-7]. Although anemia decreases arterial oxygen content, a number of adaptive mechanisms are initiated as a means of attempting to maintain DO_2.

These include increased cardiac output as a result of reduced blood viscosity and increased sympathetic output; redistribution of blood flow toward the cerebral and coronary circulation; and, an increase in 2,3-diphosphoglycerate (2,3-DPG) levels making it easier for hemoglobin to unload oxygen in peripheral tissue beds. Hébert and colleagues reviewed the evidence supporting the different adaptive mechanisms in response to anemia (Table 1)[5].

Inference	Quality of evidence
Oxyhemoglobin dissociation curve	
Anemia shifts the oxyhemoglobin curve to the right because of increased 2,3-DPG levels	Ci
Anemia causes clinically significant rightward shifts in the oxyhemoglobin curve because of the Bohr effect	Civ
The shift in the oxyhemoglobin curve has been clearly established in many forms of anemia (excluding hemoglobinopathies)	Cii
The shift in the oxyhemoglobin curve has been clearly established in a number of human diseases	Civ
Cardiac Output	
Cardiac output increases with increasing degrees of normovolemic anemia provided that blood volume is adequate	Ci
Increased cardiac output in normovolemic anemia is a result of increased stroke volume	Ci
The contribution of increased heart rate to the increase in cardiac output following normovolemic anemia is variable	Ci
Other hemodynamic alterations	
Changes in blood viscosity result in many of the hemodynamic changes in normovolemic anemia	Ci
Normovolemic anemia is accompanied by increased sympathetic activity	Ci
Normovolemic anemia causes increased myocardial contractility	Cii
Normovolemic anemia causes a decrease in systemic vascular resistance	Ci
Normovolemic anemia results in a redistribution of cardiac output toward the heart and brain and away from the splanchnic circulation	Ci
Maximum global O_2 delivery occurs at hemoglobin concentrations ([Hb]) of 100-110 g/l	Ciii
Global O_2 delivery declines above and below [Hb] of 100-160 g/l	Ci
Coronary and cerebral blood flow	
Coronary and cerebral blood flow is increased during anemia	Ci
Coronary artery disease in the presence of moderate degrees on anemia ([Hb] < 90 g/l) results in impaired left ventricle contractility or ischemia	Ci
Moderate anemia does not aggravate cerebral ischemia in patients with cerebrovascular disease	Ci

Note: 2,3-DPG=2,3-diphosphoglycerate.

Table 1. *Inferences drawn from the literature addressing physiologic mechanisms in anemia. Adapted from* [5]

However, it is unclear if and to what degree the complex effects of infection and inflammation may interfere with adaptive physiologic mechanisms initiated during anemia. During sepsis, the production of bacterial toxins and many of the cytokines released as a consequence of the host inflammatory responses result in increased cardiac output, impaired left ventricular contractility, decreased afterload from arterial vasodilatation and increased venous capacitance resulting in decreased preload [8-16]. Following adequate volume resuscitation, both anemia and sepsis result in decreased afterload and increased cardiac output but result in divergent effects on contractility and preload, decreased in sepsis and increased in anemia.

It is possible that the decreased contractility observed in sepsis may impair the increase in cardiac output required to maintain DO_2 in anemic patients. At this juncture, there are few laboratory studies examining the combined effects of anemia and sepsis on myocardial function. The interaction between sepsis and anemia may also modulate adaptive responses in the peripheral vasculature, particularly related to changes in the distribution of blood flow between organs [17]. Again, both pathologic processes result in the preferential redistribution of blood flow from the splanchnic circulation towards the brain and heart. However, the combined effects may not be similar to their independent effects.

Overwhelming infections and host immune responses not only modify the delivery of oxygen but have a number of clinically important effects on oxygen utilization. Indeed, sepsis results in increased basal metabolic rates and is also postulated to cause defects in microvascular flow and cellular respirations [18,19]. Studies using intra-vital microscopy suggest capillary occlusion occurs during sepsis [18]. The increase in inter-capillary area may result in increased diffusing distances and potentially cause cellular hypoxia [18,20,21]. A number of studies have also suggested that infection or inflammation as a consequence of infection impairs the ability to generate ATP through cellular respiration [22].

Normovolemic anemia or hemodilution may in fact improve the body's ability to deliver oxygen to the tissues through abnormal microvasculature beds in sepsis but will certainly have little or no effect on oxygen utilization if the predominant effect is an impairment of cellular respiration.

OXYGEN TRANSPORT, RBC TRANSFUSION AND SEPSIS

Over the past 30 years, the prevailing dogma in critical care has been to maintain DO_2 in the normal range and possibly to aim to maintain beyond normal values. Since hemoglobin is the principal oxygen carrier in blood,

RBC transfusion is potentially the most efficient method of augmenting DO_2; however, there are well established and theoretical risks to transfusion [23, 24]. There are a number of controversial issues surrounding oxygen kinetics which include the determination of optimal DO_2 and the ability to detect and optimally treat an oxygen debt in sepsis [25-27]. RBC transfusions have also been reported to result in clinically important immune suppression. There may be adverse clinical effects from the prolonged RBC storage time. These competing risks and benefits complicate any determination of optimal transfusion practice in critically ill patients with severe sepsis and septic shock.

In critical care, many opinion leaders have long advocated maintaining elevated hemoglobin concentrations as an adjunct in targeting oxygen transport to supranormal values [28-30]. The underlying rationale was based on a theory that disease processes, such as sepsis and acute respiratory distress syndrome (ARDS), induce tissue hypoxia by producing an abnormally elevated anaerobic threshold. Below this threshold or critical level of DO_2, O_2 consumption decreases as DO_2 decreases. This abnormal linear relationship is often referred to as 'pathologic supply dependence'. The resultant tissue hypoxia may eventually contribute to the evolution of irreversible multiple system organ failure (MOF) followed by death. Two prospective studies [25,31] have also documented a significant association between mortality and the finding of pathologic supply dependence.

Few studies, however, have examined the role of hemoglobin and red cell transfusions as a means of documenting and potentially alleviating supply dependency [32-37]. Ronco and colleagues [32,34] using red cell administration concluded that there was a pathologic dependence of oxygen consumption (VO_2) on DO_2 in ARDS. While systematically reviewing the literature, we identified 14 clinical studies evaluating the impact of RBC transfusions on oxygen kinetics. All studies measured DO_2 delivery and VO_2 before and after the transfusion of a pre-specified number of allogeneic RBC units. DO_2 uniformly increased but VO_2 was observed to change in only five of the studies (Table 2). Using blood transfusions, similar findings were noted in patients with sepsis [35]. There are no randomized clinical trials which examine the role of red cell transfusions in critically ill patients with potential 'pathologic supply dependence'.

In a study by Heyland et al. [38], the effect of interventions to achieve supraphysiologic values of cardiac index, DO_2 and VO_2 in critically ill patients were systematically reviewed. Mortality rates in this patient population were not significantly altered by these interventions; however, potential benefit was noted in patients in which therapy was initiated pre-operatively. The inferences drawn from this review may be limited by the methodologic limitations of the included studies. Six randomized open-

labeled clinical trials [24,28,39-42] evaluated therapeutic interventions other than red cells to augment DO_2. These clinical trials involved the implementation of rigorous protocols using volume expansion with crystalloid and inotropic agents [24,28,40-42] or prostaglandin E_1 [39]. All but one [39] concluded that increasing DO_2 improves survival from sepsis [24], critical illness [42] and high risk surgery [28,40,41].

Concerns with all of these studies include small numbers, complex interventions, biased selection, over interpretation of subgroup analyses and a lack of blinded evaluations of outcomes. In the randomized trials that reported hemoglobin concentrations, transfusion triggers were set very high to maintain hemoglobin concentrations greater than 120 g/1 [23].

The oxygen kinetics literature thus still has a number of unanswered questions. The identification of critical levels of DO_2 and, more importantly, optimal levels of DO_2 in various clinical conditions have not been well elucidated. From the overall results of the TRICC trial, transfused RBCs may be the best means of achieving optimal DO_2.

A prospective study which examined the effect of RBC transfusions in twenty-three septic patients had very different results [43] (Figure 1). The transfusion of 3 units of blood did not increase the oxygen uptake as measured by indirect calorimetry for up to 6 hours. A surprising result was a paradoxical decrease in splanchnic oxygen availability as measured by gastric tonometry after the transfusion. The decrease in gastric intramucosal pH (pHi) was inversely related to the age of the transfusion unit. The authors attributed the decrease to poorly deformable transfused red blood cells which caused microcirculatory ischemia. Presently unknown is whether or not a blood transfusion would improve DO_2 after 6 hours since the deformability of transfused RBCs can recover if given time [44,45].

RBC TRANSFUSION AS A CAUSE OF INFECTION

RBC transfusions may cause infections through direct transmission of viruses, bacteria or parasites or through indirect effects on the recipient's immune system. Although the cause of one of the most important epidemics of this century, the risk of transfusion-related viral infections has diminished greatly in developed nations as a consequence of improved collection procedures and testing of the donated blood [46]. The risk of bacterial contamination per unit transfused ranges from 1:100,000 and 1:150,000 for hepatitis B and C, respectively and 1:1,000,000 for human immunodeficiency virus (HIV) (Canadian Blood Services, personal communication, 2000). While the contamination of RBC transfusions by bacteria is quite rare, it is a much more frequent occurrence in platelet transfusions.

Study	Patients	No. of Patients	RBC Dose	HgB	Do_2	Vo_2	Lactate	Comments
Ronco et al [32] (1990)	PCP pneumonia	5	1.5 U	Yes	Yes	Yes	NA	All patients had lactate at baseline. Thermodilution used for DO_2 and Vo_2 measurements.
Fenwick, et al [34] (1990)	ARDS	24	1.5 U	Yes Yes	Yes Yes	No No	No Yes	Normal lactate group (n=1) was compared with high lactate group (n=13). Thermodilution catheter used for all measurements. Significant increases in Vo_2 in response to transfusion in high lactate group.
Ronco, et al [105] (1991)	ARDS	17	1.5 U	Yes	Yes	No	NA	Normal lactate group (n=7) was compared with high lactate group (n=10). No relationship between DO_2 and Vo_2 directly measured with expired gases.
Shah, et al [106] (1982)	Posttrauma	8	1 or 2 U	Yes	Yes	Yes	NA	Thermodilution used for DO_2 and Vo_2 measurements.
Steffes, et al [107] (1991)	Post-operative + Posttrauma	21	1-2 U	Yes	Yes	Yes	No	27 measurements sets in 21 patients. Thermodilution used for DO_2 and Vo_2 measurements. Increased lactate levels did not predict Vo_2 response.
Babineau, et al [108] (1992)	Post-operative	31	328±9 ml	Yes	Yes	No	NA	32 of 33 transfusions were single units. Thermodilution used for DO_2 and Vo_2 measurements. 58% of transfusions did not increase Vo_2.
Gilbert, et al [35] (1988)	Septic	17	20 g/L	Yes	Yes	No	No	33 measurement sets in 31 patients. 10 of 17 patients had increased lactate levels. Vo_2 increased significantly in high group only.

Dietrich, et al [37] (1990)	Medical shock (septic/cardiac)	32	577 ml	Yes	Yes	No	No	36 measurement sets in 32 patients. No change in Vo_2 after transfusion. Thermodilution used for DO_2 and Vo_2 measurements.
Conrad, et al [33] (1990)	Septic shock	19	30 g/L	Yes	Yes	No	No	Normal lactate group (n=8) compared with high lactate group (n=11). No increase in Vo_2 with transfusion in either group. Thermodilution used for DO_2 and Vo_2 measurements.
Marik, et al [43] (1993)	Septic	23	3 U	Yes	Yes	No	No	DO_2 measured independently of Vo_2. Using gastric tonometry, patients receiving old RBCs developed evidence of gastric ischemia.
Lorento, et al [109] (1993)	Septic	16	2 U	Yes	Yes	No	NA	Dobutamine significantly increased VO_2; RBCs did not. Thermodilution used for DO_2 and Vo_2 measurements.
Mink, et al [110] (1990)	Septic shock (2 mo - 6 yrs)	8	8-10 ml/kg x 1-2 h	Yes	Yes	No	NA	In pediatric patients, VO_2 did not increase with RBCs. Thermodilution used for DO_2 and Vo_2 measurements.
Lucking, et al [111] (1990)	Septic shock (4 mo - 15 yrs)	7	10-15 ml/kg x 1-3 h	Yes	Yes	Yes	NA	8 measurement sets in 7 patients. Thermodilution used for DO_2 and Vo_2 measurements.

Table 2. *Studies examining oxygen delivery (DO_2), oxygen consumption (VO_2) and lactate before and after RBC transfusion*

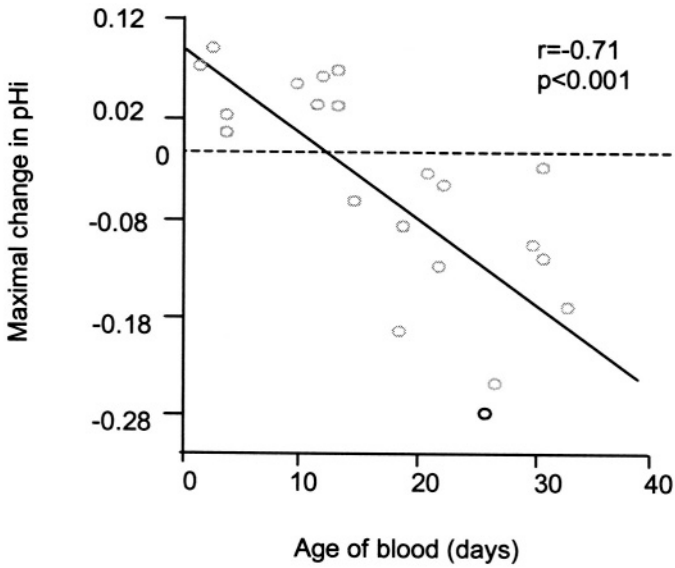

***Figure 1:** Relationship of gastric intramucosal pH with increasing age of red blood cells (from [43])*

The immunosuppressive effects of allogeneic blood transfusions were first reported in the early 1970s. Opelz et al. [47] reported improved renal allograft survival in patients who had received multiple blood transfusions. Many laboratory studies have suggested that the immune suppression is primarily mediated by the white cells remaining in transfused RBCs. Altered host immune responses following allogeneic red cell transfusions may also predispose critically ill transfusion recipients to nosocomial infections [53,56-62] and increased rates of MOF [63,64] which may ultimately result in higher mortality rates. However, studies examining postoperative infections following transfusions have not been able to establish a causal association [65,66] due to weak study design and the lack of independence between allogeneic RBC transfusions and the potential complication.

Despite very compelling laboratory studies, observational and randomized controlled clinical trials have documented contradictory findings. We identified eight randomized controlled clinical trials evaluating the immune consequences of red cell transfusions, contrasting either rates of cancer recurrence (n=2) or postoperative infections (n=6). Investigators compared either leukocyte-depleted [62,67-70] or autologous [56,71] transfusions to allogeneic RBCs (Figure 2).

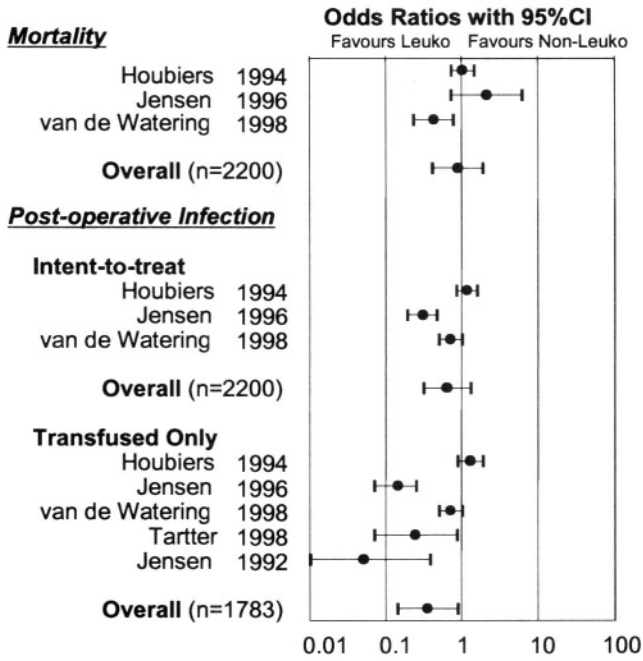

***Figure 2**: Post-operative infection in the included studies*

Contradictory conclusions were drawn from the six RCTs examining postoperative infections. Two of the six studies [70,71] did not find any significant difference in the rates of infection among patients having undergone colorectal surgery. Houbiers et al. [70] found a higher rate of postoperative infections in patients receiving leukodepleted as opposed to allogeneic RBCs (42% versus 36%, $p>0.05$). The four remaining studies [56,62,68,69] documented clinically important decreases in postoperative infections in patients receiving leukodepleted allogeneic RBCs as compared to standard allogeneic RBC products. In a recent study, Jensen and colleagues [69] demonstrated that the rates of wound infections and intra-abdominal abscesses were significantly lower in patients receiving allogeneic RBCs compared to the untransfused groups (12% vs 1%, $p<0.0001$). The frequency of pneumonia was also lower in patients receiving leukodepleted RBCs (3%) or no transfusions (3%) compared to patients receiving buffy-coated leuko-depleted allogeneic transfusions (23%, $p<0.001$).

In summary, the six randomized controlled trials reached divergent conclusions concerning the risks of postoperative infections attributed to

allogeneic red cell transfusions. A recent meta-analysis [72] combined the results from these trials and was unable to detect clinically important increases mortality and postoperative infections. Since the publication of the meta-analysis, van de Watering and colleagues have published another clinical trial in patients undergoing cardiovascular surgical interventions and observed a decrease in 30-day mortality from 7.8% in patients receiving buffy coat-depleted red cells compared to 3.6% and 3.3% (p=0.015) in patients receiving either fresh-filtered or stored-filtered RBCs, respectively [4]. Although the study was well conducted, the allogeneic RBC transfusion rates in the control group were on average 5.4 RBC units, well in excess of North American norms suggesting that the study results may have limited generalizability. In addition, the number of events were small, suggesting that the mortality estimates might be quite unstable.

To better understand the results of this study in the context of the rest of the literature, we have added the results of this new clinical trial to the meta-analysis by McAllister et al. [72]. In doing so, the relative risk for all-cause mortality was 1.05 (95% confidence interval ranging from 0.88 to 1.25) and 1.10 (95% confidence interval ranging from 0.85 to 1.43) for post-operative infections. In summary, despite convincing laboratory evidence, the clinical significance of the immunosuppressive effects of allogeneic RBC transfusions have not been clearly established [3].

RBC TRANSFUSIONS AS A CAUSE OF MICROCIRCULATORY DYSFUNCTION IN SEPSIS

A few recent reviews have summarized a large volume of literature characterizing well-defined biochemical and corpuscular changes to RBCs during storage, collectively referred to as the storage lesion [73-75]. From these reviews, it is evident that there are few data on the clinical consequences of transfusing old stored RBC product. Traditionally, the storage lesion has been restricted to changes occurring in the RBC rather than bioreactive substances as described by the media. Corpuscular changes include a depletion of ATP and 2,3-DPG, membrane vesiculation [76-78], lipid peroxidation of RBC membrane [79] and loss of deformability [80-82].

Depletion of 2,3-DPG is well described and has become an accepted occurrence during storage but its clinical relevance is debated. It has been repeatedly demonstrated in man and non-human primates that following transfusion of DPG-depleted RBCs, systemic DPG levels, as well as the p50 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 hours to several days [83,84]. The potential

consequences of transfusing older stored RBCs on DO_2 has not been adequately studied yet has led some clinicians to advocate the use of fresh blood in certain patients, such as those massively transfused. Under these circumstances, it has been speculated that transfusion of large amounts of stored blood low in 2,3-DPG may have an adverse clinical consequence on DO_2 in patients whose balance is precarious [85-88].

During RBC storage, there is a progressive fall in pH, an increase in plasma potassium and release of free hemoglobin from lysed RBCs [89]. The immediate clinical consequences of transfusing these storage by-products are probably limited (except in neonates) given the recipients capacity to buffer, dilute or remove these substances. However, their long-term effects are not known. In addition, there is generation of cytokines and other bioreactive substances [90], including histamine [91], complement [92,93], lipid [94], and cytokines [95], which have been found in the storage media and which may have deleterious effects when transfused.

There are no randomized clinical trials evaluating the clinical consequences of transfusing these bioreactive substances. The only prospective study in this area was designed to test the difference in gastric ischemic episodes between septic and nonseptic patients. Marik and colleagues [43] demonstrated an association between a fall in gastric pHi and transfusion of RBCs stored for greater than 15 days. Three retrospective clinical studies tested the association between the age of transfused blood and length of stay in the ICU [96] or mortality [97]. Martin et al. [96] 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 median age of blood was predictive of length of stay ($p<0.0001$). Purdy et al. [97] demonstrated a negative correlation ($r=-0.73$) between the proportion of RBC units of a given age transfused to survivors and increasing age of RBCs in patients admitted to the ICU with a diagnosis of severe sepsis (n=31). Purdy et al. also noted that these latter units were more likely to be older. A recently published study evaluating the effect of length of RBC storage on postoperative pneumonia in 416 consecutive patients undergoing coronary artery bypass grafting noted an adjusted increase of 1% in the risk of postoperative pneumonia per day of average increase in the length of storage of RBCs ($p<0.005$) in transfused patients [98]. Each of these three studies also noted that patients receiving a large number of RBC units had a higher mortality.

SEPSIS, SEPTIC SHOCK AND THE TRICC TRIAL RESULTS

We recently completed and published the results of TRICC, a large multicenter clinical trial. The study was designed to determine whether a restrictive and a liberal transfusion strategy were equivalent in usual clinical ICU practice. We reasoned that if both transfusion strategies were found to be equivalent, then a lower threshold should be recommended in critically ill patients. Eight hundred and thirty-eight patients who: 1) were expected to stay more than 24 hours; 2) had a hemoglobin concentration less than or equal to 9.0 g/dl within 72 hours of ICU admission; and 3) were considered volume resuscitated or normovolemic by the attending staff were included in the study. Once randomized, a study patient's hemoglobin level was maintained using allogeneic red cell transfusions as required. Patients allocated to the restrictive strategy had their hemoglobin levels maintained between 7.0 and 9.0 g/dl, with a transfusion trigger at 7.0 g/dl. Patients allocated to the liberal transfusion strategy had their hemoglobin levels maintained between 10.0 and 12.0 g/dl, with a transfusion trigger at 10.0 g/dl. Blinding of treatment allocation was not feasible.

Average hemoglobin concentrations (8.5 ± 0.72 vs 10.7 ± 0.73 g/dl, $p<0.01$) and RBC units transfused (2.6 ± 4.1 vs. 5.6± 5.3 RBC units, $p<0.01$) were significantly lower in the restrictive as compared to the liberal group. Overall, 30-day mortality tended to be lower in the restrictive transfusion group (18.7 vs 23.3, $p = 0.11$). However, 30-day mortality rates were significantly decreased (8.7 vs 16.1%, $p=0.03$) in patients who were less acutely ill (APACHE II score < 20) and less than 55 years of age (5.7 and 13.0%, respectively, $p = 0.02$) but not in patients with significant cardiac disease (22.9 vs 20.5%, $p = 0.69$). Hospital mortality was significantly lower in the restrictive group (22.3 vs 28.1%, $p=0.05$). Other mortality rates, including ICU mortality (13.9 vs 16.2%, $p =0.29$) and 60-day mortality (22.8 vs 26.5%, $p =0.23$), were not significantly different but were always lower in absolute terms in the restrictive group. The multiple organ dysfunction score, modified to include mortality, was significantly less in the restrictive group overall (10.7±7.5 vs 11.8±7.7, $p = 0.03$). Therefore, in the TRICC trial, a trend towards decreased 30 day mortality was observed in patients treated according to a restrictive RBC transfusion strategy as compared to a more liberal approach to RBC transfusion. The significant differences noted in hospital mortality and in several subgroups, the increased rates of cardiac complications, and increased rates of combined organ dysfunction and mortality all favored the restrictive strategy. Thus, the use of an allogeneic red cell transfusion threshold as low as 7.0 g/dl combined with maintenance of hemoglobin concentrations in a low range was not only equivalent, but

possibly superior, to a more liberal transfusion strategy in volume resuscitated critically ill patients.

Can the TRICC trial results be applied to patients sepsis and septic shock? In general, we suggest that the answer is yes because more than a third of all patients were admitted with an infection. In addition, all primary and secondary analyses conducted demonstrated that a restrictive policy was either equivalent or superior to a more liberal policy.

ALTERNATIVES TO RBC TRANSFUSION

Corwin et al. have reported that at least 30% of the transfusion requirement for patients in an ICU is due to blood sampling and testing [99]. A restricted blood testing policy with the elimination of routine laboratory tests will reduce the amount of blood transfused in critically ill patients. The routine use of pediatric sampling tubes can reduce the blood loss due to testing [100]. The use of pulse oximetry can reduce the need for blood gases. Furthermore, the practice of discarding the drawback blood from arterial sampling lines should be altered which can help reduce the amount of iatrogenic blood loss in critically ill patients. The use of new blood conservation systems along with in-line monitoring systems may further reduce the blood loss due to testing thus further reducing transfusion requirements. Erythropoietin (EPO), a hormone that stimulates the formation of RBCs in the bone marrow, may be used clinically to decrease transfusion needs by increasing endogenous erythrocyte production. A recently completed trial in 160 critically ill patients demonstrated that [101] EPO in high doses decreased transfusion requirements by 45% ($p<0.002$) with higher discharge hematocrits (35.1 vs 31.6, $p<0.01$). A larger trial is underway to assess whether a lower dose is effective and confirm that EPO is safe and possibly improves patient outcomes. All of these strategies may complement a restrictive transfusion strategy. Cell salvage, a non pharmacological intervention, may be useful in a small number of postoperative ICU patients while others, such as pre-operative autologous donation, have no place in this setting [102]. Finally, other pharmacological agents such as antifibrinolytics have limited usefulness in critically ill patients [103].

CONCLUSION AND RECOMMENDATIONS

The TRICC trial [104] demonstrated that a transfusion trigger of 7.0 g/dl and maintenance of hemoglobin concentrations between 7.0 and 9.0 g/dl was at worst equivalent and very likely superior to the more liberal use of red cells.

A restrictive strategy is truly a superior therapy because clinical outcomes are superior, transfusions are decreased by 54% and costs are minimized. Given conflicting evidence, the optimal transfusion policy for septic patients is not known. The increased demands imposed by sepsis along with its impairment of the normal adaptive process to anemia would suggest that severely infected patients should have a more liberal transfusion practice as compared to nonseptic patients. The potential problems with allogeneic blood products however limits one's enthusiasm for an aggressive transfusion practice. Thus, the best approach would be to limit the need to transfuse but to transfuse the best product available if a transfusion is required. We anxiously await the results of further trials with EPO, different RBC products, and other studies to confirm the results observed in the TRICC trial.

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