Red Blood Cell Transfusion in Sepsis: A Review

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Abstract
Sepsis is very common and lethal. Sepsis is the leading cause of death in non-coronary Intensive Care Units, and the tenth leading cause of death overall. Red blood cell transfusion is one of the most commonly used interventions in the ICU to treat severe anemia, which often occurs in sepsis. Several problems were documented with RBC transfusions and will be reviewed, such as infection, pulmonary complications such as TRALI and Transfusion-Associated Circulatory Overload (TACO), Transfusion-Related Immunomodulation (TRIM) and multiorgan failure, and increased mortality. Most of these complications are partially explained by volume of the unit of blood as well as pathogenic factors of stored RBCs related to 2,3 BPG concentration, inflammatory mediators, nitric oxide, ATP concentration and RBC rheology, and RBC adhesion characteristics. These same factors are present in RBCs of septic patients as well. Until better evidence is available, a “restrictive” strategy of RBC transfusion (transfuse when Hb < 7 g/dL) is recommended except in acute hemorrhage, or in patients with acute myocardial ischemia when a hemoglobin trigger of 8 g/dL is reasonable.

Keywords: Sepsis; Red blood cells; RBC; Transfusion

Introduction
In the United States, approximately 750,000 cases of sepsis occur each year, of which at least 225,000 are fatal. One study evaluating the epidemiology of sepsis between 1979 and 2000 demonstrated an 8.7% increase in the annual incidence of sepsis. The cost of management of one septic patient has been estimated at $50,000, amounting to annual costs of approximately $17 billion. Sepsis is the leading cause of death in non-coronary Intensive Care Units (ICUs), and the tenth leading cause of death overall. Organ failure occurs in about one third of patients with sepsis and severe sepsis is associated with an estimated mortality rate of 30-50%. Seventy percent of patients with three or more organ failures (classified as severe sepsis or septic shock) die [1-8].

Red blood cell transfusion is one of the most commonly used interventions in the ICU to treat severe anemia, which often occurs in sepsis. In the United States, more than 14 million units of Packed Red Blood Cells (RBCs) are administered annually, many of which are administered in the ICU [9]. Approximately 40 to 80% of RBC transfusions in the ICU are not given for bleeding, but rather for low hemoglobin levels, for a decrease in physiological reserve, or for alterations in tissue perfusion [10,11]. In addition, RBC transfusion is recommended as part of early goal-directed therapy for patients with severe sepsis [12]. This review will focus on RBC properties, complications of RBC transfusions in the critically ill patient with emphasis on the septic patient, mechanisms of transfusion-associated complications, clinical evidence about transfusion in sepsis, and finishing with current guidelines and recommendations.

RBC Transfusion
For decades, it was considered that a hemoglobin concentration of 10 g/dl, or a hematocrit of 30%, represented the lowest level acceptable, thereby providing a standard and convenient “transfusion trigger” [13]. An understanding of the physiology of anemia and oxygen delivery is required to understand such considerations. Tissue oxygen delivery (DO2) is the product of tissue blood flow and arterial oxygen content. In turn, tissue blood flow is determined by cardiac output and regional vasoregulation, and arterial oxygen content depends on hemoglobin concentration and its percentage saturation. Oxygen flow increases as the hemoglobin falls to a level termed the “optimal hematocrit”, at which point DO2 is highest at the lowest energy cost to the individual. This occurs around a hematocrit of 30% [14]. Decreases in hematocrit from this “optimal” level must be compensated by active increases in cardiac output to maintain DO2. For instance, Cardiac output peaks at 180% of control at a hematocrit of around 20%. Below this “optimal” level, the maintenance of tissue oxygen consumption (VO2) and aerobic metabolism at decreasing levels of DO2 is principally provided by increased oxygen extraction. In the critical care environment, there have been several studies examining the interrelationship between hematocrit, DO2 and VO2. Shoemaker et al. [15] and Boyd et al. [16] initially defined the optimal hematocrit at around 30% since, below this level, oxygen delivery and consumption were decreased in critically ill patients and mortality was increased. Above this level, there was no change in these variables or outcome. This line of reasoning led to the common practice of maintaining this “10/30 rule” as the transfusion triggers.

Complications of RBC transfusion (Table 1)

Transfusion-related acute lung injury (TRALI): TRALI is defined as Acute Lung Injury (ALI) that occurs within 6 h of transfusion (may happen up to 72 hours) and is not related to other risk factors for ALI or Acute Respiratory Distress Syndrome (ARDS) [17,18]. ALI and ARDS were defined by the North American-European Consensus Conference in 1994 as acute hypoxemia (PaO2/FIO2 ≤ 300 mm Hg for ALI or < 200 for ARDS), bilateral pulmonary infiltrates on chest radiograph, and no evidence of left atrial hypertension [19]. TRALI is the most common cause of major morbidity and mortality after transfusion [18,20]. The risk of TRALI is estimated at 1 case per 5,000 units PRBCs. The estimated mortality rate for TRALI is 5-8% [21]. The leading hypothesis of pathogenesis is a “two hit” hypothesis, with the first

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hit being the clinical condition of the patient resulting in pulmonary endothelial activation and Polymorphonuclear (PMN) sequestration, and the second event is the transfusion of a biologic response modifier (including anti-granulocyte antibodies, lipids, and CD 40 ligand) that activates these adherent PMNs resulting in endothelial damage, capillary leak, and TRALI [22,23]. Sepsis has been shown to be a risk factor for the development of TRALI [24]. Management is supportive.

**Transfusion-associated circulatory overload (TACO):** TACO is the development of fluid overload and pulmonary edema secondary to transfusion. It also happens during or within few hours of transfusion. Patients develop hypoxemia, tachypnea, tachycardia, and develop bilateral infiltrates on CXR. TACO is the second most common cause of transfusion-related morbidity and mortality as reported in the United States [25]. TACO could be difficult to distinguish from TRALI. TACO is hydrostatic pulmonary edema—a pressure phenomenon, whereas TRALI is a phenomenon of increased permeability. A marker of heart distention can be helpful in differentiating, such as B-type natriuretic peptide [26]. An echocardiogram or more invasive means to measure heart pressures could aid in differentiation as well. Sepsis itself could lead to myocardial dysfunction, possibly secondary to the effect of inflammatory mediators on the myocardium [27]. However, it is unknown whether this higher prevalence of myocardial dysfunction in sepsis is associated with a higher incidence of TACO in sepsis as well.

**Transfusion-related immunomodulation (TRIM):** TRIM is defined as immunosuppression secondary to allogenic blood transfusion. The mechanism of immunosuppression seems to involve donor allogeneic leukocytes [28], leading to increased risk of nosocomial infections, morbidity, mortality and tumor recurrences in the recipient [29,30]. Leukoreduction in an attempt to decrease or abolish this immunomodulation secondary to allogenic blood transfusion has shown conflicting results [29,31-35]. It thus seems clear that allogenic blood transfusion induces immunosuppression in the host, however, the role of leukoreduction in preventing or alleviating this complication remains uncertain.

**Hemolytic transfusion reactions:** Hemolytic Transfusion Reactions result from interactions between antibodies in the recipient’s plasma and surface antigens on donor RBCs. There are immediate or delayed reactions.

**Immediate reactions:** Immediate hemolytic transfusion reactions are typically the result of ABO incompatibility. Incompatibility between donor RBC antigens and recipient plasma antibodies produces an antigen–antibody complex causing complement activation, intravascular hemolysis and thus destruction of the transfused blood. Symptoms start very soon after starting the transfusion. They include headache, chest and flank pain, nausea and vomiting, fever, chills, flushing, urticaria, shortness of breath, hypotension, hemoglobinuria and disseminated intravascular coagulation. The transfusion should be stopped immediately and patient should be treated emergently and mainly with supportive therapy. The most common causes of this complication are clerical and labeling errors [36,37].

**Delayed reactions:** In delayed hemolytic transfusion reactions, the donor RBC antigen–plasma antibody interactions are usually the result of incompatibility with minor blood groups such as Rhesus and Kidd. This results in extravascular hemolysis that typically happens 3 days to 3 weeks later. The patient presents with reduction in hematocrit despite transfusion, jaundice (unconjugated hyperbilirubinemia) and a positive direct antiglobulin (Coomb’s) test. In general, no treatment is required except monitoring the anemia and transfusion if needed [36,37].

**Non hemolytic febrile reactions:** Fever is the hallmark of this reaction, in addition to fatigue, malaise, myalgias, chills, and rarely hypotension, vomiting and shortness of breath. This is a relatively benign reaction that results from donor leukocyte antigens reacting to antibodies present in the recipient’s plasma forming a leukocyte antigen–antibody complex that binds complement and results in the release of IL-1, IL-6 and TNFα. Management involves slowing the transfusion and in rare cases stopping it, as well as prescribing antipyretics [36,37].

**Transfusion-related infections:** Bacterial and viral contaminations are infrequent these days. RBCs are stored at 4°C. This makes contamination with Gram-negative bacteria such as Pseudomonas species more likely as they proliferate rapidly at this temperature. Pre-transfusion testing of donated blood (for hepatitis B, hepatitis C, HIV 1 and 2, human T cell lymphotrophic virus, syphilis and cytomegalovirus) has significantly reduced transfusion-related viral infections [37,38].

**Transfusion-related allergic reactions:** Transfusion-related allergic reactions may result in pruritis, urticaria, and fever. These reactions are usually mediated by Ig-E in response to foreign proteins in donor plasma. The transfusion should be stopped and anti-histamines administered. Anaphylaxis is rare, and treatment is the same as for any anaphylactic reaction.

**Electrolyte abnormalities:** Hyperkalemia and Hypocalcemia are the major potential electrolyte abnormalities, and the incidence of these electrolyte abnormalities increases with the number of units transfused. The potassium concentration of plasma increases in stored blood. This is in part due to red blood cell membrane Na⁺–K⁺ ATPase inactivation [39,40]. Hyperkalemia is more common in patients with acute kidney injury or in renal failure.

Stored blood is anticoagulated with citrate, which binds calcium. Each RBC unit contains approximately 3 g of citrate. This is usually prevented by hepatic metabolism unless the patient is hypothermic, or has liver disease [41]. Plasma potassium and calcium concentrations should be monitored in patients who require transfusions, particularly with multiple units transfused, renal insufficiency or liver disease.

**Mechanisms for Transfusion-Associated Complications**

RBCs are stored up to 42 days. Several changes occur to the RBCs during storage that could contribute to the complications and adverse events discussed above.

**2,3 Bisphosphoglycerate (2,3 BPG) concentration**

The concentration of 2,3 BPG affects the oxygen-hemoglobin...
dissociation and thus the ability of the RBC to deliver oxygen to the tissues. The longer the RBC unit is stored, the lower the levels of 2,3 BPG are, leading to a left shift in the oxygen-hemoglobin dissociation curve and thus less oxygen delivered to the tissues. However, there is evidence that 2,3 BPG concentrations return back to normal levels within 6 to 24 hours of transfusion [42,43].

Inflammatory mediators

Storing RBC can lead to increase levels of cytokines, lipids and other inflammatory mediators, thus inducing a profound inflammatory reaction in the recipient. This has been shown to increase with duration of RBC unit storage time [44-47].

Adenosine Triphosphate (ATP) and RBC viability and deformability

The concentration of ATP in RBCs falls gradually during storage. As a result, the capacity of RBCs to phosphorylate glucose is impaired, and their viability is lost [43,48]. Stored RBCs also show a progressive increase in rigidity, leading to loss of rheologic capability and deformability of the RBC, which in turn leads to the RBCs unable to pass freely through capillaries (worsening microcirculatory dysfunction of sepsis). This loss of deformability correlates as well with the loss of ATP [49]. The RBC is shaped as a biconcave disc with an 8-micron diameter, so it needs to deform to be able to pass through the capillaries of the microcirculation (mean diameter, 3–8 microns). With ATP deprivation during storage, a sequence of morphologic changes occurs in the RBC leading to spherocytosis and rigidity. Several experiments have shown that RBC deformability is decreased in sepsis [50-53]. The mechanisms resulting in the decreases of RBC deformability during storage are similar to those implicated in sepsis.

RBC adhesion

In vitro and in vivo animal and human studies have shown that exposure of RBCs to endotoxin and inflammatory cytokines increases RBC adhesion to microvascular endothelium, and that this RBC adhesion increases with storage time [54-56]. Transfusion of adhesive RBCs may thus compromise tissue blood flow, especially in states of compromised microcirculatory flow, like sepsis.

Nitric oxide

Nitric oxide functions as a potent vasodilator. When nitric oxide binds to hemoglobin, through a series of reactions, S-nitrosohemoglobin (SNO-Hb) is formed in RBCs. SNO-Hb is a vasodilator that is released binds to hemoglobin, through a series of reactions, S-nitrosohemoglobin (SNO-Hb) is formed in RBCs. SNO-Hb is a vasodilator that is released.

Potassium leakage

As discussed above, the potassium concentration of plasma increases in stored blood, due to RBC membrane Na+-K+-ATPase inactivation and passive leakage of potassium out of the RBC. Loss of one unit of blood through bleeding results in a loss of 1.5 meq of potassium, whereas transfusion of one RBC unit of RBC can provide approximately 10 meq of potassium, leading to a net gain of 8.5 meq [60]. However, the risk of hyperkalemia from RBC transfusion is more pronounced in patients with acute kidney injury or in renal failure.

Anemia and RBC Physiology in Sepsis and Critical Illness (Table 2)

Forty to 50% of septic and other critically ill patients require blood transfusion during their ICU stay [61]. By day two in the ICU, nearly 95% of patients are anemic [62]. This section will focus on the pathogenesis of anemia in septic and ICU patients.

Phlebotomy and bleeding

Phlebotomy can contribute to up to 2 units of blood loss per day in ICU patients, particularly the sicker and septic patients. Phlebotomy accounts for up to 20% of total blood loss [63,64]. Bleeding is a common cause of anemia in the ICU accounting for up to 20% of blood loss, whether overt (like GI bleeding, surgery, trauma, procedures, etc) or occult bleeding [65].

RBC destruction

This is a less common cause of blood loss in the ICU, but worth mentioning. This could be from intravascular causes such as Disseminated Intravascular Coagulation (DIC), Thrombotic Thrombocytopenic Purpura (TTP), endovascular devices, and prostheses; immune mediated (e.g hemolytic transfusion reactions, drug-induced (e.g penicillin’s, cephalosporin’s, sulfas, and quinines).

Abnormal iron metabolism

Inflammatory cytokines, such as produced in sepsis, play a major role in alterations in iron metabolism, leading to decrease serum iron levels [66]. These inflammatory cytokines (TNF-a, IL-1β, and IL-6) also increase iron storage by the reticuloendothelial system, limiting the availability of iron for erythropoiesis [67]. Anti-inflamaritory cytokines, like IL-10, also play a role in iron metabolism by increasing heme degradation and iron storage in monocytes and, thus, contributing to iron retention in the reticuloendothelial system [68].

Erythropoiesis

Serum erythropoietin is the growth factor responsible for erythropoiesis, and it is produced in the kidneys. Erythropoietin levels below those expected for the degree of anemia have been demonstrated in septic and critically ill patients [69,70]. There is evidence that inflammatory cytokines have play an inhibitory role on erythropoietin production as well as a direct inhibitory effect on erythroid progenitor cell production in the bone marrow [71-75].

Inflammation and sepsis

In addition to their significant contribution to all of the above pathogenic mechanisms in anemia, inflammatory mediators play other important roles in anemia of sepsis. The proinflammatory cytokines decrease erythrocyte survival time (79, 80). In sepsis, functional and structural changes are found in erythrocytes. These changes are very similar to the changes that are present in naturally aged populations of erythrocytes, including decreased red blood cell deformability and antioxidant activity, decreased hemoglobin content, and increase in oxidatively modified lipids and proteins [76-78]. Oxidative stress and free radicals that develop from inflammation in sepsis can also trigger RBC apoptosis by opening Ca²⁺ channels [79]. In addition, hypersplenism due to infection can increase the sequestration and

| Table 2: Causes of Anemia in Sepsis. |
|-------------------------------------|
| Phlebotomy                          |
| Bleeding                            |
| RBC destruction                     |
| Abnormal Iron Metabolism            |
| Abnormal Erythropoiesis             |
| Infections                         |
| Inflammation                       |

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Clinical Evidence for Transfusion in Sepsis

The mean number of RBC transfusions per ICU patient is about 5 units with the average pre-transfusion hemoglobin being 8.5 g/dl [82]. It has also been shown most transfusions are given for low hemoglobin level with less than one in five patients being transfused for active bleeding [83]. Approximately 40-50% of patients admitted to the ICU are transfused at least 1 RBC unit. Several studies have shown that RBC transfusion in sepsis did not improve oxygen delivery, oxygen consumption, mixed venous oxygen saturation or lactate levels [84-86].

This suggests that RBC transfusions in sepsis are not associated with an improvement in tissue oxygenation in spite of a significant increase in Hemoglobin levels. The clinical evidence will be reviewed for different time periods: after the first 6 hours of developing sepsis; and within 6 hours of severe sepsis.

Sepsis beyond the initial 6 hours

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 [87]. It is not stated in this trial whether RBC transfusion is given in the first 6 hours or afterwards in septic subpopulation, nonetheless, this trial is the basis for further transfusion trials and recommendations in septic as well as other critically ill patients. In this study, a liberal transfusion strategy (hemoglobin 10 to 12 g/dL, with a transfusion trigger of 10 g/dL) was compared to a restrictive transfusion strategy (hemoglobin 7 to 9 g/dL, with a transfusion trigger of 7 g/dL) in a general medical and surgical critical care population. Patients who were euvolemic after initial treatment who had a hemoglobin concentration < 9 g/dL within 72 h were enrolled. The TRICC trial 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 II scores < 20) and among younger patients (< 55 years of age). Patients in the restrictive group received 54% less RBC units than those in the liberal group [87]. 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 including septic patients, with the possible exception of patients with acute coronary syndromes. Nonetheless, recent evidence supports a restrictive transfusion at a slightly higher hemoglobin concentration (< 8 g/dL) in patients with acute coronary syndromes [88]. In a recent analysis by the Cochrane database of 19 trials involving a total of 6264 patients, restrictive transfusion strategies were associated with a statistically significant reduction in hospital mortality (RR 0.77, 95% CI 0.62-0.95) but not 30 day mortality (RR 0.85, 95% CI 0.70 to 1.03) [89]. The authors concluded that the existing evidence supports the use of restrictive transfusion triggers in most patients including those with pre-existing cardiovascular disease. In addition, the effects of restrictive transfusion triggers in high risk groups such as acute coronary syndrome need to be tested in further large clinical trials [89].

Within 6 hours of severe sepsis

Guidelines published as part of the Surviving Sepsis Campaign [12] have endorsed use of RBCs in the treatment of patients with severe sepsis who show evidence of hypoperfusion. This recommendation is primarily based on data published by Rivers et al. [90] who evaluated a bundle approach to patients in severe sepsis. Red blood cell transfusion to obtain a hematocrit of 30% is included in this bundle for patients with a central venous oxygen saturation < 70%. Patients achieving this goal had better outcomes than patients who did not reach the goal. The specific effect of transfusion was not evaluated in this study, however, as the investigation was designed to assess the overall bundle rather than its component parts. Using Near Infrared Spectroscopy (NIRS) or Sidestream Dark Field (SDF), several investigators have reported that microcirculation is markedly altered in sepsis, that these alterations are more severe in nonsurvivors than in survivors, that persistent microvascular alterations are associated with development of multiple organ failure and death, and that microvascular alterations are the most sensitive and specific predictor of outcome in septic patients [91-97].

The effects of RBC transfusion on the microcirculation in sepsis could be numerous. Several studies have demonstrated that RBC rheology is impaired (increased aggregation, decreased deformability, alterations of RBC shape) in recipient RBCs in septic patients [80,90,100]. RBC can also act as oxygen sensor, which can modulate tissue oxygen flow variables – by the release of the vasodilators, nitric oxide [101,102] or ATP [103]. This release of vasodilators from RBCs during hypoxia could be impaired during storage and/or sepsis. Storage of RBCs decreases levels of 2,3-diphosphoglycerate and Adenosine Triphosphate (ATP) levels with a resultant increase in oxygen affinity and a decrease in the ability of hemoglobin to offload oxygen. Morphological changes in erythrocytes occur during storage which may result in increased fragility, decreased viability, and decreased deformability of red blood cells. A release of a number of substances occurs during storage resulting in such adverse systemic responses as fever, cellular injury, alterations in regional and global blood flow, and organ dysfunction.

In a general critically ill population, using NIRS, muscle tissue oxygenation, oxygen consumption and microvascular reactivity were globally unaltered by leukoreduced RBC transfusion in a study by Creteur et al. [104]. However, muscle oxygen consumption and microvascular reactivity improved following transfusion in patients with alterations of these variables at baseline [104]. In severe sepsis patient requiring leukoreduced RBC transfusion, using SDF, Sakr et al. showed that the sublingual microcirculation was globally unaltered, however, it improved in patients with altered capillary perfusion at baseline [105]. Using SDF and NIRS, Sadaka et al. [106] looked at patients that got non-leukoreduced RBCs for a hemoglobin <7.0, or for a hemoglobin between 7.0 and 9.0 with either lactic acidosis or central venous oxygen saturation < 70%. Sadaka et al. [106] showed that muscle tissue oxygen consumption, microvascular reactivity, and sublingual microcirculation were globally unaltered by RBC transfusion in septic patients. However, muscle oxygen consumption improved in patients with low baseline and deteriorated in patients with preserved baseline. Future research with larger samples is needed to further examine the association between RBC transfusion and outcomes of patients resuscitated early in severe sepsis, with an emphasis on elucidating the potential contribution of microvascular factors.

Recommendations and Guidelines

The most recent guidelines were put together by American College of Critical Care Medicine of the Society of Critical Care Medicine and the Eastern Association for the Surgery of Trauma Practice Management

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Sepsis Beyond The Initial 6 HOURS

RBC transfusion is indicated for patients with evidence of hemorrhagic shock. A "restrictive" strategy of RBC transfusion (transfuse when Hb < 7 g/dL) is recommended in hemodynamically unstable anemia. In the absence of acute hemorrhage, RBC transfusion should be given as single units. Consider transfusion if Hb < 7 g/dL in patients with stable cardiac disease. There is no benefit of a "liberal" transfusion strategy (when Hb < 10 g/dL) in patients with stable cardiac disease.

RBC transfusion may be beneficial in patients with acute myocardial ischemia who are anemic (Hb<8g/dL).

Within 6 Hours of Severe Sepsis

Transfuse RBC when Hb < 10 g/dL to achieve ScvO2 >70% (only after CVP of 8-12 mmHg and MAP >65mmHg are achieved).

Table 3: Guidelines for RBC Transfusion in Sepsis.

Workgroup in 2009 [82] and still stand today. For the septic patient, the guidelines state that there are insufficient data to support Level 1 recommendations on this topic and that the transfusion needs for each septic patient must be assessed individually since optimal transfusion triggers in sepsis patients are not known and there is no clear evidence that blood transfusion increases tissue oxygenation. However, the recommendations for the generally critical ill patient apply to the septic patient beyond the first 6 hours as well based on the existing evidence. Please refer to Table 3 for details. In summary, A "restrictive" strategy of RBC transfusion (transfuse when Hb < 7 g/dL) is as effective as a "liberal" transfusion strategy (transfuse when Hb < 10 g/dL) in critically ill patients with hemodynamically stable anemia, except possibly in patients with acute myocardial ischemia. Evidence supports RBC transfusion at a slightly higher hemoglobin concentration (< 8 g/dL) in patients with acute myocardial ischemia, until further evidence is available. For severely septic patients within the first 6 hours, the recommendation is to transfuse when Hb < 10 g/dL to get ScvO2 >70%, until evidence becomes available that is examining the association between RBC transfusion and outcomes of patients resuscitated early in severe sepsis.

Conclusion

Red blood cell transfusion is one of the most commonly used interventions in the ICU to treat severe anemia, which often occurs in sepsis. Several problems were documented with RBC transfusions, such as infection, pulmonary complications such as TRALI and transfusion-related circulatory overload. Transfusion-related cytokine release (TRIM) and multiorgan failure, and associated costs of care. French ICU Group for Severe Sepsis. JAMA 274: 227-242.

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