Published in final edited form as:

Crit Care Nurs Clin North Am. 2017 September ; 29(3): 331–340. doi:10.1016/j.cnc.2017.04.003.

Balance between the pro-inflammatory and anti-inflammatory immune responses with blood transfusion in sepsis

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Keywords

Leukocyte reduction; Immune suppression; Cytokines; Sepsis; Inflammation; Blood transfusion

INTRODUCTION

In the United States, 13.6 million units of blood are donated and 21 million blood products are transfused annually (1). For much of the last century, blood transfusion has been viewed as having clinical benefits. More recently, however, allogenic transfusion has come under increased scrutiny. Initially, transfusion related infections were the major concern. With modern blood banking techniques, the risk of a major infection risk (per unit of blood; e.g., human immunodeficiency virus, hepatitis B and C) is low, ranging from 1:220,000 to 1:800,000 (2). Issues surrounding blood transfusion are particularly important in the critically ill. Up to 95% of patients admitted to the ICU have anemia of critical illness by the third hospital day (3). Blood product transfusion occurs in nearly 45% of patients in the intensive care setting. In patients with an ICU length of stay greater than one week, the proportion of patients transfused increases to 85% (4, 5). Recent findings suggest blood transfusion in critically ill patients is associated with worse outcomes, including higher morbidity and mortality. It remains uncertain whether blood transfusion compounds an immunosuppressive environment such as that observed in sepsis, which is a leading cause of mortality in the ICU.

Sepsis, the systemic inflammatory response syndrome in the setting of a severe infection, is responsible for more than 150,000 deaths in the United States annually (6–8). This condition

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is characterized by an early robust inflammatory response with a concomitant state of persistent immunosuppression (9–11). With improved treatment algorithms, mortality within the first 3 days of sepsis has been reduced. However, more than 70% of deaths in sepsis occur after the early inflammatory response. Deaths during the immunosuppressive phase are typically due to failure to control the primary infection or acquisition of nosocomial infections (10). In a postmortem study, 80% of patients had unresolved septic foci at time of death (12), highlighting the prevalence of an immunosuppressive state and the lack of ability for bacterial clearance.

While blood transfusions are prevalent among ICU patients, the criteria for optimal management of anemia during sepsis are not clearly defined. Administration of blood products can influence the host immune response during sepsis. Understanding these alterations is critical to improving patient outcomes (13). This review aims to discuss recent literature on the associated inflammatory responses that occur with blood transfusion and to provide an analysis of alterations in key inflammatory pathways in response to transfusion in a sepsis population.

Immunomodulation from blood transfusion

The effects of blood transfusion on the immune system involve both augmentation and suppression of the immune response, a condition called transfusion-related immune modulation (TRIM). Clinically, the immunosuppressive effects of allogenic blood transfusion were first recognized in prolonged graft survival in solid organ transplants in humans and animals (14, 15). The immunosuppressive effect of transfusion is further supported by increased rates of tumor recurrence after surgical resection and increased postoperative infection rates (16, 17). Further, allogeneic blood transfusions were used therapeutically to reduce renal allograft rejection prior to the availability of effective immunosuppressant drugs (17).

Leukocytes—Leukocytes present in the blood components and the related expansion of class I and class II HLA antigens distributed on leukocytes are thought to mediate TRIM. Potential cells that can play a role during TRIM are summarized in Table 1. These mechanisms include suppression of cytotoxic cell and monocyte activity, release of immunosuppressive prostaglandins, inhibition of interleukin-2 (IL-2) production, and increased suppressor T-cell activity (17–19). Other mechanisms are increased IL-10 and IL-4 secretion (20, 21). *In vitro* assays have demonstrated decreased IL-2 secretion (22), modulates natural killer (NK) cell activity (17, 18), and delayed-type hypersensitivity responses (23). To prevent or abrogate these immunosuppressive effects and mechanisms, autologous blood or leukoreduced allogenic blood can be used (24, 25). This process reduces leukocyte numbers by 3 logs. The goal of leukoreduction is to avoid the accumulation of bioactive substances implicated in TRIM (summarized in Table 2), thereby reducing post-transfusion infections, preventing febrile transfusion reactions, and decreasing HLA alloimmunization and platelet refractoriness in the recipient.

Nonpolar lipids and lysophosphatidylcholines—In addition to residual leukocytes, pRBC units also contain non-polar lipids and pro-inflammatory lysophosphatidylcholines

(lyso-PCs) (25, 26). Lyso-PCs can increase NK and T cells activity, act as NK cell chemoattractants, induce dendritic cell maturation, and stimulate the production of pro-inflammatory cytokines (25, 27–29). Immune suppressive eicosanoids (prostaglandins and thromboxanes) also accumulate in pRBCs (30). Altogether, the presence of these substances results in additional immunomodulation in a transfused patient.

Erythrocytes—Erythrocyte storage may contribute to the negative immune modulating consequences of blood transfusion. Transfusion of RBCs stored for greater than two weeks is associated with increased rates of nosocomial infections, multisystem organ failure, and mortality (31, 32). With increased storage time, RBCs undergo alterations in pH, lactate, nitric oxide, ATP, and 2,3-diphosphoglycerate (33, 34). These alterations have been associated with adverse processes including thrombosis, lung injury, and immunomodulation (35). Stored RBC units have increased levels of IL-1, keratinocyte chemoattractant, macrophage inflammatory protein 1 α , and macrophage inflammatory protein 2 as compared to fresh RBCs (36). In a murine model, Belizaire *et al.* demonstrated that washing aged RBCs reduced pro-inflammatory cytokine concentrations after storage such that when transfused, the systemic inflammatory response in the recipient was attenuated (36). This finding suggests that washing stored RBCs may improve outcomes in critically ill patients requiring transfusion.

Microparticles—Microparticles (MPs) are small vesicles derived from the cell membrane, ranging from 0.3 μ M to 1.0 μ M, that retain the surface markers of the parent cell and can modulate the immune system (37). MPs are formed from erythrocytes during morphologic transformation in over time (38). They can then exert their biologic effect via receptor interaction with target cells or direct transfer of their contents (39). In mice, it was demonstrated that resuscitation with RBC-derived MPs resulted in increased pulmonary congestion, thickening of alveolar walls, and neutrophil recruitment (40). Further, increased neutrophil priming and activation following administration of RBC-derived MPs was observed (40). Recent research has demonstrated that acid sphingomyelinase (Asm) activity in RBCs is associated with MP formation and treatment of RBCs with amitriptyline, an Asm inhibitor, inhibited MP formation during RBC storage. This treatment was associated with reduced lung inflammation following blood transfusion in a murine model (41). Together, these data demonstrate the significant contribution of RBC-derived MPs to immunomodulation after transfusion.

Host Immune Response in Sepsis

Sepsis refers to the systemic inflammatory response that occurs due to severe infection (42). Traditionally, research was focused on blunting the initial hyperinflammatory “cytokine storm.” However, the majority of septic deaths occur during the protracted immunosuppressive phase due to unresolved septic foci or acquisition of nosocomial infections from opportunistic pathogens (12, 43, 44). Tissue harvested from spleens or lungs of septic patients had significantly reduced cytokine production, increased expression of inhibitory molecule expression, expansion of T regulatory cell and myeloid-derived suppressor cell populations. These findings highlight the immunosuppressive state that occurs in sepsis. Studies have demonstrated a significant increase in positive blood cultures

due to opportunistic bacteria in late stages of sepsis such as *Pseudomonas*, *Candida*, *Acinetobacter*, *Enterococcus*, depicting the severity of the depressed immune response (44). While some patients may die during the acute hyper-inflammatory phase, new therapies and treatments are also directed towards ameliorating the immunosuppressive phase during sepsis.

Blood Transfusion in Sepsis

Transfusion goals—In the ICU, blood transfusion is prevalent among patients with sepsis. As described above, blood transfusion has immune modulating effects. Consequently, understanding the goals of transfusion in sepsis and which patients benefit the most from transfusion is of critical importance. The 2012 Surviving Sepsis Campaign guidelines recommend a target hemoglobin concentration of 7–9 g/dL (45). These recommendations are based on the findings of the Transfusion Requirements in Critical Care Trial that demonstrated a hemoglobin of 7–9 g/dL was not associated with increased mortality in comparison with a hemoglobin of 10–12 g/dL (46). Despite these recommendations, Reade *et al.* demonstrated that actual clinical practice is variable for blood transfusion in critical care settings (47). This variability further highlights the need to understand the risks of transfusion in critically ill patients to deliver effective care to patients with sepsis.

Patient Mortality—Studies have examined whether blood transfusion increases patient mortality. To discuss this effect, an examination of both the sepsis and non-sepsis critically ill literature is necessary. Of note, blood transfusion itself is a marker for severity of illness, complicating the ability to assess mortality following transfusion. In addition, there is a positive correlation between number of transfusion units and mortality.

Findings that show blood transfusions increase mortality involve hip or cardiac surgery or intensive care following trauma or surgery. In a retrospective review, Hebert *et al.* demonstrated that patient mortality increased with transfusion in comparison with that of without transfusion (48). However, this increased mortality was reduced with leukoreduction (48). Furthermore, through an analysis of data from five cardiac-surgery randomized controlled trials, Vamvakas *et al.* reported that increased short term mortality (up to 3 months following transfusion) was observed in patients receiving transfusion (19). However, others have suggested that there is no difference in mortality in surgical patients (49). Further randomized control studies are necessary to address the effect of blood transfusions on the mortality of patients with sepsis.

Effect on immune mediators—The literature of the effects of blood transfusion on immune mediators in critical illness in patients covers both animal and human studies. An initial report regarding transfusion in septic rats indicates that blood transfusion exacerbates sepsis-induced immunosuppression (50). Transfusion during sepsis resulted in the downregulation of blood TNF- α , and IFN- γ levels, as well as an impaired cellular immune response through decreased CD4 populations (51).

Similar immunosuppressive effects have been observed in humans. It was reported that patients receiving blood transfusions had a 70% reduction in IL-2, TNF- α , and IFN- γ (52). These researchers reported alterations in cytokine profiles and reductions in cytotoxic cells,

which will contribute to decreased resistance to bacterial infection. More recently, Torrance et al. found that anti-inflammatory mediators, IL-10 and IL-27, which suppress the Th17 pro-inflammatory response, were elevated in critically ill polytrauma patients receiving an immediate blood transfusion (53). These initial alterations were observed less than 2 hours following transfusion. Further, they observed a direct correlation between the number of transfused units and IL-10 levels. In contrast, the pro-inflammatory mediator TNF- α had a less significant increase. Greater reductions in IFN- γ and Th17 transcription factors were also observed. Altogether, this points to the immunosuppressive nature of the response in critically ill patients.

Infection—The potential for TRIM to aggravate the aberrant immune response in sepsis and increase infectious complications is of significant concern. As described above, blood transfusion can negatively alter the T and NK cell function which can result in increased susceptibility to nosocomial infection. This effect is supported by increased rates of bacterial infection following surgery and blood transfusion (54, 55). Further, a multivariate analysis suggests that blood transfusion is an independent risk factor for infection, but that the risk is reduced with leukoreduced blood (55–59). Houbiers *et al.* demonstrated a dose response associated between the number of transfused RBC units and the incidence of postoperative infection, including pneumonia, urinary tract infection, infected hematomas, and septicemia (60). In 2015, Torrance *et al.* concluded that blood transfusion exacerbates the immunosuppressive response in critically ill polytrauma patients, noting an increased susceptibility to infections that was independent of the injury severity score (53).

CONCLUSION

Blood transfusion in critically ill patients, including those with sepsis, remains a complex issue due to the prevalence of transfusion and associated consequences in this patient population. Through our review of the literature, we conclude that blood product transfusion may exacerbate the primarily immunosuppressive response of sepsis. Therefore, nurses and other patient care providers must be diligent in recognizing and managing a worsening immune status. For example, monitoring the absolute lymphocyte count may be one simple way to detect a worsening immune status (61) as an absolute lymphocyte count of 0.6 cells per μ l or less at four days after a diagnosis of sepsis has been observed to be associated with the occurrence of secondary infections and mortality (62). Additionally, caregivers should take advantage of flow cytometry to monitor patients' immune status (13). For example, blood cytokine levels, immune cell enumeration and activation can play a role in the assessment of the immune status of persons who receive blood transfusions (61). This type of monitoring may be instrumental in reducing morbidity and mortality in persons with sepsis.

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Key Points

- Blood transfusion in critically ill patients, including those with sepsis, remains a complex issue due to the prevalence of transfusion and associated consequences in this patient population.
- Nurses and other patient care providers must be diligent in recognizing and managing a worsening immune status.
- Health care providers should take advantage of flow cytometry to monitor patients' immune status; for example, blood cytokine levels, immune cell enumeration and activation can play a role in the assessment of the immune status of persons who receive blood transfusions.

Table 1**Immune Cells**

Cell Type	Function
Leukocytes/White blood cells	Cells of the immune system including neutrophils, lymphocytes, monocytes, basophils, and eosinophils
Myeloid cells	Lineage of cells that produce neutrophils, monocytes, basophils, eosinophils, erythrocytes, and platelets
Dendritic cells	Antigen presenting cells that initiate the adaptive immune response
Monocytes/Macrophages	Monocytes are circulating cells that differentiate into macrophages, which migrate to peripheral tissues and organs to eliminate potential threatening organisms or cells by phagocytosis
Neutrophils	Phagocytic cells that are part of the innate immune response which contain granules with microbicidal enzymes
Lymphocytes	T and B cells that function as part of the adaptive immune system determining the specificity of immunity
B cells	Lymphocytes responsible for humoral immunity that once activated become antibody-secreting plasma cells
Cytotoxic T cells	CD8 positive T cells that directly mediate pathogen clearance
T helper cells	CD4 positive T cells that produce cytokines that activate B cells, cytotoxic T cells, and macrophages
• T1 helper cells	Produce IL-2 that stimulates growth of T cells and IFN- γ , which activates macrophages
• T2 helper cells	Produce IL-4 and IL-5 that stimulates growth of B cells and differentiation to plasma cells
• T17 helper cells	Produce IL-17 that enhances migration of neutrophils in an inflammatory response and stimulates mucosal immunity
Regulatory or suppressor T cells	Inhibit T helper and T cytotoxic cells
Natural killer cells	Function as part of the innate immune system to kill virus-infected cells and produces IFN- γ to activate macrophages

Table 2**Regulatory Proteins of Immune Response**

Cytokines	Subtype	Function
Interferon-gamma (IFN- γ)		Produced by T helper cells to activate and enhance elimination of pathogens by macrophages
Interleukins		Cytokines that mediate cellular functions of the immune system
	IL-1	Proinflammatory cytokine produced by macrophages and acts on the hypothalamus to induce fevers during infection
	IL-2	T cell growth factor produced by T helper cells to activate both regulatory and effector T cells
	IL-4	Produced by T helper cells to cause proliferation of B cells and production of specific antibodies
	IL-6	Proinflammatory cytokine produced by macrophages and induces production of acute phase proteins
	IL-7	Stimulates stem cells to differentiate into T and B cells
	IL-10	Produced by T2 helper cells to inhibit activation of T1 helper cells
	IL-12	Produced by macrophages to increase the number of T1 helper cells
	IL-17	Produced by T17 helper cells stimulating the migration of neutrophils to the site of inflammation
	IL-27	Pro- and anti-inflammatory effects on T helper cells
Tumor necrosis factor-alpha (TNF- α)		Proinflammatory cytokine produced by macrophages which activates neutrophils and enhances migration by increasing production of adhesion molecules