Published in final edited form as:

Crit Care Nurs Clin North Am. 2012 September ; 24(3): 403–418. doi:10.1016/j.ccell.2012.06.005.

Pulmonary Complications of Transfused Blood Components

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Keywords

Blood component transfusion; Blood transfusion; Red blood cell transfusion; Acute lung injury; Pulmonary edema; Critical care

INTRODUCTION

Transfusion is common in critically ill patients, with up to 44% of patients admitted to an intensive care unit (ICU) in the United States receiving a transfusion.¹ Red blood cell transfusions are given most commonly due to anemia in both bleeding and nonbleeding patients, whereas platelets or plasma should be utilized primarily in bleeding patients, or before surgeries or procedures in which microvascular bleeding complications are probable because of quantitative or qualitative platelet abnormalities or coagulation imbalances.¹

Three transfusion complications are responsible for the majority of morbidity and mortality associated with transfused blood components in hospitalized patients. The respiratory complications associated with these pathophysiologic processes are discussed, including definitions, diagnosis, mechanism, incidence, risk factors, clinical management, and strategies for prevention. In addition, this article explores how different patient populations and different blood components differentially affect the risk of these deadly transfusion complications. Lastly, the article discusses how health care providers can risk-stratify individual patients or patient populations to determine whether a given transfusion is more likely to benefit or harm the patient based on the transfusion indication, risk, and expected result.

The “terrible T’s” refer to transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and transfusion-related immunomodulation (TRIM). These transfusion complications primarily damage the lung, leading to respiratory failure. In addition, these potential complications are not commonly addressed during consent for blood components, but lead to significant patient morbidity and mortality, especially in critically ill and postoperative patient populations. TRALI is the most extensively studied of these three conditions; therefore a description of this condition is more extensive than that of TACO or TRIM.

TRALI

The consensus conference definition of TRALI is new acute lung injury occurring during or within 6 hours after a transfusion, with a clear temporal relationship to the transfusion.² TRALI has become the leading cause of transfusion-related mortality in most of the

industrialized world.^{3–7} In 1983, Popovsky and colleagues from the Mayo Clinic described five cases of noncardiogenic pulmonary edema after transfusion of packed red blood cells (PRBCs) or whole blood and coined the term TRALI to describe this syndrome.⁸

Diagnosis of TRALI

In 2004, the National Heart, Lung, and Blood Institute convened a working group to identify a common clinical definition to promote research in TRALI. The diagnosis must satisfy the criteria for acute lung injury (ALI), including (1) acute onset, (2) hypoxemic lung disease with (3) bilateral infiltrates on frontal chest radiograph, and (4) no evidence of left atrial hypertension (Table 1).⁹ If an arterial blood gas is not available, an oxygen saturation (SPO₂) of 90% or less meets the acute hypoxemia criterion when a patient is breathing room air at sea level.²

In addition to meeting the standard criteria for ALI, TRALI requires further criteria (see Table 1). A patient must develop ALI during or within 6 hours of transfusion and no ALI may be present before transfusion. If alternative ALI risk factors exist (ie, sepsis, trauma, aspiration), TRALI can still be diagnosed if the clinical course of the patient suggests that ALI resulted mechanistically from the transfusion alone or a synergistic relationship between the transfusion and the underlying risk factor. If the temporal relationship between the transfusion and ALI (within 6 hours) is considered coincidental to the development of ALI from an alternate risk factor, a diagnosis of TRALI should not be used.² Laboratory findings are not included as diagnostic criteria for TRALI; however, transient acute leukopenia, leukocyte antigen–antibody match between donor and recipient (HLA class I or II, anti-granulocyte or anti-monocyte), or increased neutrophil priming activity in the plasma of blood products have been described and support the diagnosis of TRALI.²

Differentiating TRALI from Other Pulmonary-Related Transfusion Complications

The differential diagnosis for patients who develop respiratory distress during or within a few hours after transfusion include TRALI, TACO, an anaphylactic transfusion reaction, and transfusion of contaminated (bacteria) blood products. Differentiating these four syndromes is difficult due to similarities in their clinical presentation. Pulmonary complications of TRIM are delayed, so this transfusion complication is not considered in the context of an acute onset.

Differentiating TRALI (permeability pulmonary edema) from TACO (hydrostatic pulmonary edema) is difficult in the setting of underlying heart failure, renal failure, massive transfusion, or resuscitation.¹⁰ In both syndromes the acute onset of pulmonary edema results in severe dyspnea, tachypnea, and worsening or new hypoxemia. Transient neutropenia may support the diagnosis of TRALI due to neutrophil sequestration in the lung, but if not present it does not rule out TRALI.¹¹ TRALI is more commonly associated with relative hypotension while TACO results in relative hypertension from pre-transfusion to post-transfusion. Clinical factors differentiating TACO from TRALI include distended neck veins, S3 on cardiac examination, and peripheral edema consistent with volume overload. A chest radiograph with septal lines, cephalisation, and an enlarged vascular pedicle (>65 mm) is more consistent with TACO. The most important clinical determinant of TACO is the rapid resolution time of the patient's pulmonary edema after successfully reducing pulmonary capillary pressures through diuresis. Antibody testing of the implicated blood components lacks sensitivity for TRALI because non-antibody-mediated mechanisms are common. However, testing is still recommended and may be helpful if antibody levels are detected.

Unlike TRALI and TACO, anaphylactic transfusion reactions usually present with bronchospasm rather than pulmonary edema. As a result, wheezing rather than crackles are heard during pulmonary auscultation and a clear chest radiograph rather than new infiltrates will accompany the respiratory distress. Similar to TRALI, fever and vasodilatory shock is common with anaphylaxis, but erythema and edema with associated urticaria over the head, neck, and trunk is more consistent with anaphylaxis.¹² Lastly, the transfusion of contaminated PRBCs or platelet concentrates may result in transfusion-related bacterial sepsis that manifests as septic shock and acute lung injury. Transfusion-related bacterial sepsis must be considered if septic shock is the overriding clinical presentation, and culturing the component bags is essential for diagnosis.¹²

Mechanism of TRALI

Multiple animal studies as well as epidemiologic and translational observations in humans with TRALI support a two-event mechanism. First, the pulmonary vascular endothelium is activated resulting in neutrophil “priming” and adhesion within the pulmonary microvasculature. Many different clinical states can trigger this “first event” (ie, sepsis, surgery, trauma, systemic inflammatory state). These primed, sequestered neutrophils are hyperactive and easily activated by a “second event.” Identified triggers in blood components known to induce a “second event” and subsequent TRALI in humans and animals include donor antibodies to recipient leukocyte antigens, bioactive lipids, soluble CD40-ligand, microparticles, and others.^{13,14} Animals develop TRALI after transfusion of blood components with high concentrations of known TRALI mediators (second event) only when administered lipopolysaccharide (first event) before transfusion.^{15,16} In rare situations, a “first event” is not required because certain antibody–antigen interactions (most commonly HNA-3a, an anti-neutrophil antibody) from blood components alone have enough activation energy to trigger the whole chain of events.¹⁷

Multiple disease processes are capable of activating the pulmonary vascular endothelium and inducing adherence of neutrophils.¹⁷ The higher incidence of TRALI in ICU patients (8%), as compared to a mixed population of hospitalized patients (0.16%) at the same institution, is likely a result of the “primed” state induced by critical illness.^{18,19}

The Incidence of TRALI is Variable and Underreported

The reported incidence of TRALI is extremely variable and highly dependent on the inflammatory state and characteristics of the patient population studied.^{20,21} Retrospective “look-back” studies suggest that TRALI is grossly under-recognized, so the incidence reported in studies utilizing passive surveillance underestimates the true incidence.^{22,23} Only recently have prospective surveillance studies of transfused critically ill and operative patients recognized the alarming incidence of TRALI in the critically ill.^{18,24–27} In the ICU, 37% to 44% of patients receive blood products, with the incidence rising to 85% in patients in the ICU for 7 days or longer.^{1,28} Recent prospective observational trials demonstrate that 5% to 8% of all transfused patient admitted to a medical and surgical ICU develop TRALI. The incidence of TRALI is 2.4% in cardiac surgery and 1.3% in patient undergoing liver transplantation, but rises to 29% in transfused patients with chronic liver disease who are actively bleeding from varices.^{24,27,29}

Evaluation of Risk for TRALI

When evaluating TRALI risk, two questions should be asked: what is the inflammatory state of the patient and what type and volume of planned blood component exposure is planned?

TRALI risk is highly dependent on the pretransfusion clinical state of the patient and the amount of exposure to blood components. In addition, different types of blood components

carry different risks that are independent of the patient's clinical state. Therefore, both patient-specific and transfusion-specific factors need to be considered when determining the patient-specific risk versus benefit for each planned unit of transfused blood component.

TRALI is common in critically ill patients—The presence of multiple clinical risk factors for acute lung injury (ALI) increase the susceptibility to the subsequent development of TRALI.^{30–32} Common risk factors for ALI include sepsis, trauma, aspiration, heavy alcohol use, mechanical ventilation, massive transfusion, and pneumonia.^{14,24} More specifically, transfusion is an independent risk factor, in a dose-dependent manner, for the subsequent development of TRALI in patients with these preexisting ALI risk factors.^{30,33–37} Consistent with the “two-event” mechanism, transfusion appears to act synergistically with other diagnoses that predispose patients to ALI. Two large prospective trials performed in the United States (n = 901) and Europe (n = 2024) demonstrate a TRALI incidence of 8% and 5% respectively. In these studies, sepsis and emergent surgery were strong independent risk factors for the development of TRALI. In addition, a cohort study of 225 patients admitted to an ICU due to gastrointestinal bleeding revealed a TRALI incidence of 29% in bleeding patients with chronic liver disease. In critically ill patients receiving massive transfusion the incidence of ALI is 21% to 45%, though these studies do not report the number of cases that were temporally related to transfusion (within 6 hours).^{30,32,35} Collectively, these studies confirm the extraordinary high and variable incidence of TRALI in critically ill patients (Fig. 1).

TRALI can occur after the transfusion of any blood component—TRALI has been described after transfusion of most blood components including leukoreduced and non-leukoreduced PRBCs; plasma (fresh frozen, FP24, and thawed) from female multiparous, never pregnant, and male donors; platelets (apheresed, random donor or whole blood-derived); and a few case reports after transfusion of intravenous immunoglobulin (IVIG), cryoprecipitate, bone marrow stem cells, and transfused granulocytes.^{38–41}

TRALI is more common after transfusion of plasma-containing blood products—Surveillance data are skewed toward severe cases of TRALI in which the diagnosis is clear and other possible etiologic risk factors for ALI are uncommonly present. It is known that antibody-mediated TRALI is more common in these instances, and as a result high-plasma-containing blood components such as platelets and plasma (fresh frozen or FP24) are more commonly implicated in these passive surveillance studies. A report from the Red Cross TRALI surveillance system implicates plasma as the etiologic agent in 75% of cases and 63% of deaths from TRALI.⁴² An examination of reported TRALI fatalities to the United States Food and Drug Administration (FDA) implicated plasma in 50% of deaths reported.⁴³

In critically ill patients, epidemiologic studies reporting an association between massive transfusion and the development of ALI failed to control for plasma that is universally administered as part of a massive transfusion protocol.^{30–32} Plasma administration has emerged as an independent risk factor for TRALI in trauma, medical and surgical ICU populations.^{18,33,37,44–46} In most of these studies, high-plasma containing blood products (fresh frozen plasma [FFP] and platelets), not PRBCs, were associated with TRALI.^{18,33,44,46,47}

Management of TRALI

When TRALI is diagnosed, the management is similar to the management of ALI from other causes. This includes supportive care that entails optimization of mechanical ventilator parameters (low tidal volume) to avoid further injury to the lung while reducing pulmonary

venous pressures with diuretics in patients without shock.^{25,48} A restrictive transfusion strategy should be employed because transfusions in patients with existing ALI worsen outcomes.³⁵

TRALI Prognosis

Mortality rates vary based on the patient population studied and are highly dependent on the relative health of the individual before the lung injury. In single-center studies TRALI-associated mortality was 6% to 13%.^{19,49} National reporting systems likely overestimate the mortality rate in the general population owing to reporting bias for cases resulting in death, but underestimate the mortality risk in the ICU because these cases are rarely reported and tend to result in higher mortality rates. Hemovigilance data from Great Britain (SHOT), Quebec, and France reported TRALI mortality rates of 9%, 9.5%, and 15%, respectively.^{50,51} In a nonselect group of critically ill patients the TRALI mortality is 41% to 53% while it is 92% in gastrointestinal bleeding patients with chronic liver disease. Cardiac surgery patients have an in-hospital TRALI mortality of 13% while the rate is 29% in liver transplantation.^{29,52}

Prevention: Transfuse Safer Blood Components

Multiple attempts have been attempted to remove TRALI-causing mediators from stored blood components in an attempt to make the components we transfuse less likely to cause TRALI. These large-scale strategies have had variable effects and are discussed in the text that follows.

Leukoreduction and TRALI risk—Residual leukocytes contaminating stored PRBCs can theoretically potentiate TRALI by increasing the amount of lipids and inflammatory cytokines (IL-6, IL-8, TNF- α) that accumulate during storage.^{53,54} These substances may act as a second hit when transfused into a patient with endothelial activation and/or primed neutrophils resulting in TRALI.^{53,55,56} As a result of epidemiologic studies demonstrating an association between leukoreduction and improved outcomes, universal leukoreduction was adopted in most industrialized nations. Unfortunately, the majority of before and after studies as well as subsequent randomized controlled trials (RCTs) have failed to demonstrate a reduction in TRALI from leukoreduction.^{57–59} Prestorage leukoreduction may reduce the accumulation of some of the biologically active mediators associated with storage, but does not significantly alter TRALI risk.

Age of blood and TRALI risk—Storage of RBCs results in a number of morphological and biochemical alterations known as the RBC storage lesion.⁶⁰ During routine storage of cellular components, a variety of neutrophil priming substances accumulate. Multiple epidemiologic studies have shown an association between increasing age of red blood cells and increased morbidity, mortality in trauma, medical and surgical ICU patients.^{61–64} Age of blood was shown to be an independent risk factor for mortality in trauma after the institution of leukoreduction.^{65,66} A recent small RCT demonstrated no difference in the changes in oxygenation in intubated patients after transfusion of 1 unit of fresh (4 day) versus old (27 day) PRBCs.⁶⁷ However, until the results from large multicenter clinical trials that are currently underway are available, the effect of storage duration on TRALI risk and outcome remains undefined.

Antibodies in high-plasma-containing blood components and TRALI risk

The majority of severe TRALI cases are associated with alloantibodies to leukocytes.^{6,19,42,49,68,69} High-plasma-containing blood components such as plasma (FFP or FP24) and platelets contain different types and concentrations of alloantibodies depending on the donor. In women reporting three or more pregnancies, 40% have presence of

antibodies to either HLA class I, HLA class II, or granulocytes in donated plasma-containing components.⁷⁰ Several studies have demonstrated the clinical significance of female gender and multiparity of donor plasma and platelets on the recipient risk of developing antibody-mediated TRALI.^{42,71,72} As a result, similar to the leukoreduction story, the majority of countries have transitioned to a male- and/or nonpregnant female-only donor policy for platelets and plasma. In addition, some countries have initiated antibody testing and other production techniques to reduce antibody contamination.^{73,74} Fortunately, this blood banking strategy has reduced reported TRALI incidence and mortality in most before-and-after studies.^{75–77}

In addition, a promising solvent/detergent process used for creating plasma removes antibodies and potentially other neutrophil-activating mediators. It is widely used in Europe, but has yet to receive FDA approval for use in the United States.⁷⁸ No TRALI cases have been reported to date using this process, and this plasma product has been demonstrated to be effective in reversing coagulopathic states.^{76,78,79}

Prevention: Risk-Stratify Patients and Adjust Transfusion Strategy

The first step in preventing TRALI is educating practitioners regarding patient-specific risks while simultaneously enforcing the appropriate use of blood components. In the critically ill, one RCT has reported a significant decrease in the development of pulmonary edema by decreasing red blood cell transfusion thresholds.⁸⁰ In addition, transfusion of PRBCs rarely results in an improvement in oxygen utilization (the ultimate goal) at current PRBC transfusion thresholds (hemoglobin 8–10 mg/dL) in critically ill patients with sepsis.^{25,81} Therefore the risk versus benefit of each unit of PRBC transfused should be weighed heavily in the critically ill (Fig. 2). More restrictive plasma administration may have a potentially larger benefit because plasma is utilized inappropriately in 45% of hospitalized patients and 48% of critically ill patients.^{82,83} In addition, current guideline use lacks level I evidence, and in many instances evidence suggests that plasma administration in bleeding patients or before minor procedures to correct coagulopathy lacks clinical benefit.^{82,84–89} Ongoing clinical trials will be informative with regard to the risk-to-benefit ratio of preprocedural plasma in patients with coagulopathy.⁹⁰

TACO

The FDA has reported TACO to be the second most common cause of transfusion-related mortality in the United States.^{91,92} TACO is defined as pulmonary edema that develops in response to elevated pulmonary capillary hydrostatic pressures precipitated from the transfusion of blood components.¹⁰ TACO usually develops within 2 hours of transfusion and can occur with any blood component because the volume, speed of transfusion, and oncotic properties of the transfused component are likely more important than type.¹⁰ Initially, TACO is difficult to differentiate from TRALI because both lead to pulmonary edema and respiratory failure, but after a successful reduction in pulmonary capillary hydrostatic pressures with diuresis or dialysis pulmonary edema should resolve rapidly in patients with TACO. Other clues suggesting the diagnosis of TACO versus TRALI include peritransfusion hypertension, clinical clues to elevated left atrial hypertension, and lack of fever or leukopenia.^{93,94} The use of brain natriuretic peptides to differentiate TRALI from TACO is controversial, but can be helpful at extremes.^{95,96}

TACO is more common in critically ill patients, with an incidence of 6% in prospective studies, but the hospital mortality is significantly lower than TRALI at 8%.⁹⁷ The incidence is variable in other patient populations ranging from 1% to 8%.^{47,93,98} TACO is also grossly under-recognized and underreported.^{96,97} Risk factors include left ventricular dysfunction, plasma transfusion, and rate of transfusion.^{91,92} Pretransfusion diuresis has not been

demonstrated to be beneficial.⁹¹ Clinical management includes reducing pulmonary capillary hydrostatic pressures with volume removal and/or a reduction in left ventricular afterload. Positive pressure ventilation is often needed to support the patient, which can also be beneficial in reducing pulmonary capillary hydrostatic pressures through left ventricular preload and afterload reduction.

Prevention of TACO requires recognition of at risk patients (left ventricular dysfunction and/or preexisting volume overload) and a determination that transfusion is truly indicated. Plasma is a common cause of TACO and often transfused in critically ill patients against guideline recommendation.^{82,83} In high-risk patients in whom transfusion is clearly indicated, consider slowing the infusion rate and monitoring for hypoxemia.

TRIM

TRIM refers to the immunomodulatory effects of transfused blood components and the risk of subsequent infection to the transfused patient associated with this phenomenon. Early cohort studies demonstrated reductions in kidney transplant rejection and increased cancer recurrence associated with PRBC transfusion, leading to investigation of the immunomodulatory effect of PRBCs.^{99,100} The mechanisms of immunomodulation are multifactorial, complex, and incompletely understood.^{99,100} Since these early associations, multiple cohort studies have demonstrated a dose-dependent association between PRBC transfusion and the subsequent development of infection.^{99,100} This association has yet to be confirmed in clinical trials, but the epidemiologic evidence is intriguing. Pulmonary complications result primarily from nosocomial pneumonia (including ventilator-associated pneumonia), which is the most deadly of the common infections associated with PRBC transfusion, but any infection causing severe sepsis can also lead to pulmonary complications from ALI and subsequent respiratory failure.^{101–103}

Diagnosis can be inferred but not proven in patients developing a nosocomial or postoperative infection after they had been transfused PRBCs. Management is specific to the infectious source and includes antibiotics and source control. It is not possible to delineate the prognostic differences between infections developed in the setting of TRIM versus infections unrelated to transfusion because currently there is no method by which to differentiate etiology.⁹⁹ The patient population that bears the greatest risk are those undergoing cardiac surgery, as the effect of TRIM in other patient populations has been inconsistent in cohort studies.¹⁰⁴

Currently it is debateable whether leukoreduction or age of blood reduces the infectious risk of PRBCs, but clinical trials are underway.^{99,105–108} At present, the best strategy for prevention is to limit PRBC transfusion in critical care patients to clinical situations in which patients exhibit delivery-dependent tissue hypoxia or have the risk of developing this condition based on clinical course. Initiation of a restrictive PRBC transfusion protocol has demonstrated a reduced incidence of ventilator-associated pneumonia in one study.¹⁰⁹

SUMMARY

In summary, the “terrible T’s” of TRALI, TACO, and TRIM are all potentially fatal complications of blood transfusion. The mechanisms are multifactorial and complex, involving both transfusion-specific and patient-specific factors. Epidemiologic evidence suggests that these complications are more common in critically ill patients independent of the amount and type of transfused blood components transfused. Therefore, practitioners must be vigilant with respect to blood components in these patient populations. Transfused blood components should be administered only after careful consideration of the patient’s unique risk of a transfusion complication versus the physiologic benefit of the planned

transfused blood component. Blood components should be treated like pharmaceuticals, with continued refinement of the product in response to common and deadly side effects, and large multicenter trials performed to demonstrate efficacy. In the meantime, with regard to transfusion, less is often more.

Acknowledgments

This work was supported by grant no. K24 HL089223 from the National Institutes of Health.

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KEY POINTS

- There are potentially fatal complications of blood transfusion involving both transfusion-specific and patient-specific factors.
- Transfused blood components should be administered only after careful consideration of the patient's unique risk of a transfusion complication versus the physiologic benefit of the planned transfused blood component.
- Blood components should be treated like pharmaceuticals, with continued refinement of the product in response to common and deadly side effects and large multicenter trials performed to demonstrate efficacy. In the meantime, with regard to transfusion, less is often more.

Transfusion-Related Acute Lung Injury (TRALI) in the critically ill

- Associated most commonly with platelets and plasma
- Pre-existing inflammatory state increases risk (i.e. sepsis)
- TRALI is common in critically ill patients (5-8% of transfused ICU patients)
- Mortality of TRALI is 30-50% in ICU patients
- Antibody mediated (Anti-HLA I or II, anti-neutrophil) vs. non immune mediated

Fig. 1.

Definition and risk factors for TRALI. TRALI is defined as ALI that develops within 6 hours of a transfused blood component and has a high mortality in ICU patients. TRALI is commonly due to plasma-containing blood components and is prevalent in ICU patients due to both antibody-mediated and non-antibody-mediated mechanisms.

RBC Transfusion in Critically ill

Risk vs. Benefit

Fig. 2.

Weighing the risk vs. benefit of PRBC transfusion in the critically ill. Practitioners should weigh the pulmonary risks of PRBC transfusion against the physiologic benefit in critically ill patients. Reversing delivery dependent tissue hypoxia is a clear indication for PRBC transfusion. Other reasons for transfusion should be weighed against the most common and serious complications of PRBC transfusion in this patient population including TRALI, TACO, and TRIM.

Table 1

Diagnostic criteria for transfusion-related acute lung injury (TRALI)

Consensus definition of ALI	
Timing:	Acute in onset
Hypoxemia:	$P_{aO_2}/F_{iO_2} < 300$ OR $SpO_2 < 90\%$ at sea level on room air
Chest radiograph:	Bilateral infiltrates seen on frontal chest radiograph
Edema not purely hydrostatic	No clinical evidence of left atrial hypertension
Consensus definition of TRALI (ALI diagnosis + three criteria below)	
1. Onset of signs or symptoms ≤ 6 h after transfusion	
2. ALI not present before transfusion	
3. Alternative ALI risk factors may be present; clinical course should determine whether the ALI is mechanistically related to the transfusion.	
Transient leukopenia, fever, hypotension may be present (not required).	