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Transfusion Related Acute Lung Injury: A comprehensive review with a focus on the critically ill

Abulhassan Ali, [1] Faris Abu Za'nouneh, [1] Collin Clarke, [1] Shunsuke Kondo,[1] Christian John S Capirig, [1] Ehab G Daoud [2]

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Abstract

Transfusion-related acute lung injury (TRALI) is a severe, life-threatening complication of blood products transfusion characterized by acute hypoxemia and non-cardiogenic pulmonary edema, typically within six hours following transfusion of blood products. It is a highly morbid complication in critically ill patients, particularly those with pre-existing lung injury or systemic inflammation. TRALI remains frequently under-reported due to diagnostic challenges, mainly attributable to the absence of validated confirmatory tests, resulting in diagnostic uncertainty, delayed recognition, and unfavorable clinical outcomes.

The present review represents an extensive literature search for evidence related to the diagnostic utility of novel biomarkers, including interleukin-8, soluble intracellular adhesion molecules, and a review of existing data on management strategies in the critical care setting, including the role of mechanical ventilation, non-invasive ventilation, and the potential roles of immunomodulatory therapies. Through a focused lens on critically ill populations, this review aims to clarify the current TRALI diagnosis and management landscape while highlighting areas for ongoing investigation.

Keywords: Transfusion-related acute lung injury (TRALI), biomarker, mechanical ventilation, critically ill.

Authors:

1. MD, John A. Burns School of Medicine, University of Hawai'i, Hawaii, USA
2. MD, FACP, FCCP. Associate professor of Medicine, John A Burns School of Medicine, University of Hawai'i, Hawaii, USA

Corresponding author: vpc051@gmail.com
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Introduction

Transfusion-Related Acute Lung Injury (TRALI) is a severe, life-threatening complication of blood transfusion characterized by acute hypoxemia and non-cardiogenic pulmonary edema. TRALI typically develops within six hours following transfusion and is one of the leading causes of transfusion-related morbidity and mortality. [1] TRALI has an estimated incidence of 1 in 5,000 transfusions, although this figure is likely underreported due to diagnostic challenges.

Over the past two decades, significant strides have been taken to refine the definition of TRALI, with increasing literature in the critical care community documenting the dose-dependent relationship between transfusion and the development of acute lung injury (ALI) in the critically ill patients; however, TRALI still proves to be a diagnostic challenge, with no clear gold-standard in the diagnosis, apart from the temporal nature of clinical decompensation relative to transfusions. [2] Understanding TRALI, its pathophysiology, diagnostic challenges, and future direction of diagnostic testing is vital for enhancing transfusion safety and patient outcomes, particularly in the critical care setting.

This review aims to provide an in-depth understanding of TRALI, particularly in the critical care setting, and highlights the challenges in diagnosis, the potential diagnostic utility of novel biomarkers, and current management strategies.

History

TRALI was first recognized in the early 1950s by Barnard et. al, [3] who described a syndromic pattern of respiratory failure occurring hours after transfusions of blood products. It was not until the 1980s that systematic studies began elucidating its characteristics, and the term TRALI was coined. The establishment of the Canadian Consensus Conference in 2004 [4] provided a formal definition and diagnostic criteria, standardizing the identification of TRALI cases. Evolving changes in diagnostic awareness have improved the recognition and reporting of TRALI, with implementation of transfusion practices aimed toward reducing incidence and subsequent morbidity and mortality. These changes include screening protocols to exclude leukocyte antibody containing donors and the selective use of male plasma and nulliparous female donor products. However, despite these measures, TRALI remains a complex condition to manage due to diagnostic difficulty, unpredictable clinical nature, and high morbidity and mortality, particularly in the critical care setting.

Epidemiology

TRALI is one of the leading causes of transfusion-associated mortality, with incidence rates varying between 1 in 5000 to 1 in 10000 transfusions of blood products, with a reported fatality rate of 21%, [5] and is identified by the American Society of Hematology (ASH) as one of the most lethal transfusion reactions. TRALI has been associated with infusions of leuko-depleted and non-leuko-depleted red blood cells, platelets, and fresh frozen plasma. [4]

The incidence of TRALI following transfusions of different blood products is variable, dependent on the characteristics and baseline inflammatory state of the studied patient population. However, TRALI has been theorized to form an independent synergistic risk factor in conjunction with predisposing conditions for the subsequent development of acute lung injury (ALI) in critically ill patients and thus carries an elevated risk of mortality in the inpatient setting ranging between 5 to 25%, [6] and increasingly more fatal in critically ill patients, with mortality rates between 25 to 40%. [7]

TRALI Underreporting

TRALI is significantly underreported, with an estimated true incidence exceeding the frequently reported 1 in 5,000 to 1 in 10,000 transfusions. [8-10] The incidence recorded in passive surveillance reports probably understates the true incidence, particularly in critically ill patients, as retrospective studies indicate that TRALI is highly underreported. [4,11] This underreporting stem from low clinical awareness, diagnostic overlap with Acute Respiratory Distress Syndrome (ARDS) and Transfusion Associated Circulatory Overload (TACO), and the lack of specific biomarkers. Even when consensus criteria are applied, many cases remain unreported.

Risk Factors

Several patient-related risk factors have been identified for TRALI (Table 1), including liver disease, hematologic malignancies, sepsis, and trauma. Patients with liver disease are at increased risk due to the presence of cytokines and other inflammatory mediators. Those with hematologic malignancies often have underlying immune dysregulation, making them more susceptible to TRALI. The systemic inflammatory response in sepsis can predispose patients to TRALI, and the inflammatory response associated with trauma can also increase the risk. These conditions contribute to systemic inflammation and prime pulmonary neutrophils, fulfilling the first “hit” in the two-hit model for

TRALI development. [7,12,13]

Blood product-related risk factors include plasma from multiparous female donors and the presence of leukocyte antibodies in transfused blood. Multiparous female donors are more likely to have leukocyte antibodies, which can trigger TRALI. These antibodies bind to recipient leukocytes, leading to neutrophil activation and lung injury. Identifying these risk factors has led to the implementation of preventive measures in transfusion practices, such as screening blood donors for leukocyte antibodies and preferentially using plasma from male donors or nulliparous female donors. Donor-related risk stems from transfusing plasma-rich products from multiparous female donors, in whom alloimmunization leads to anti-HLA or anti-HNA antibodies; this significantly raises TRALI risk compared to male donors. [14]

Other risk factors for TRALI include the type and volume of blood products transfused, the duration of blood product storage, and the presence of bioactive lipids and cytokines in the transfused blood. Plasma-rich blood products, such as platelets and fresh frozen plasma, have been associated with the highest risk of TRALI. [15] Additionally, the storage of blood products can lead to the accumulation of bioactive lipids and cytokines, which can activate neutrophils and other immune cells upon transfusion. ARDS. [19]

Table 1: Risk Factors for Transfusion-Related Acute Lung Injury (TRALI).

Category	Risk Factors
Patient-related	• Liver disease • Hematologic malignancies • Sepsis • Trauma • Major surgery (especially liver transplantation) • Burns • Chronic alcohol consumption
Blood product-related	• Plasma from multiparous female donors • Presence of leukocyte antibodies
Type and volume of transfusion	• Plasma-rich blood products • Large volumes of transfusion
Storage duration	• Accumulation of bioactive lipids • Accumulation of cytokines

Pathophysiology

The pathophysiology of TRALI is commonly described by the two-hit hypothesis. The first hit consists of a neutrophil-priming event secondary to a predisposing inflammatory condition, such as infection, recent surgery, or underlying systemic disease, which primes the pulmonary endothelium and promotes the sequestration of neutrophils within the pulmonary microvasculature. [8] The second hit occurs when transfused biologically active mediators, including donor-derived antibodies, cytokines, or bioactive lipids, activate these primed neutrophils. This activation triggers the release of proteases and reactive oxygen species, resulting in endothelial injury, increased capillary permeability, and the development of non-cardiogenic pulmonary edema, manifesting as acute lung injury, hypoxemia, and ultimately TRALI. [16]

Immune-mediated TRALI primarily involves donor antibodies directed against recipient human leukocyte antigens (HLA) or human neutrophil antigens (HNA). [11] These antibodies bind to recipient leukocytes, triggering an inflammatory cascade characterized by complement activation, neutrophil degranulation, and endothelial disruption, culminating in alveolar edema and impaired gas exchange. In contrast, non-immune TRALI arises from the accumulation of proinflammatory mediators, such as bioactive lipids and soluble CD40 ligand, during the storage of cellular blood components. [17] These substances can prime neutrophils independently of alloantibody interactions and elicit a similar pattern of endothelial injury and pulmonary capillary leak upon transfusion. [18]

Once activated, neutrophils adhere to the pulmonary endothelium via upregulation of adhesion molecules, including CD11b/CD18 integrins, and release cytotoxic mediators such as myeloperoxidase, elastase, and reactive oxygen species. [19] This process leads to disruption of intercellular junctions, detachment of endothelial cells, and loss of alveolar-capillary barrier integrity. Consequently, protein-rich fluid leaks into the alveolar spaces, resulting in pulmonary edema, impaired gas exchange, and severe hypoxemia. Histopathologic findings typically reveal neutrophil infiltration, capillary congestion, and diffuse alveolar damage consistent with acute lung injury. [20] Collectively, these mechanisms underscore the central role of neutrophil-mediated endothelial injury as the final common pathway driving TRALI pathogenesis.

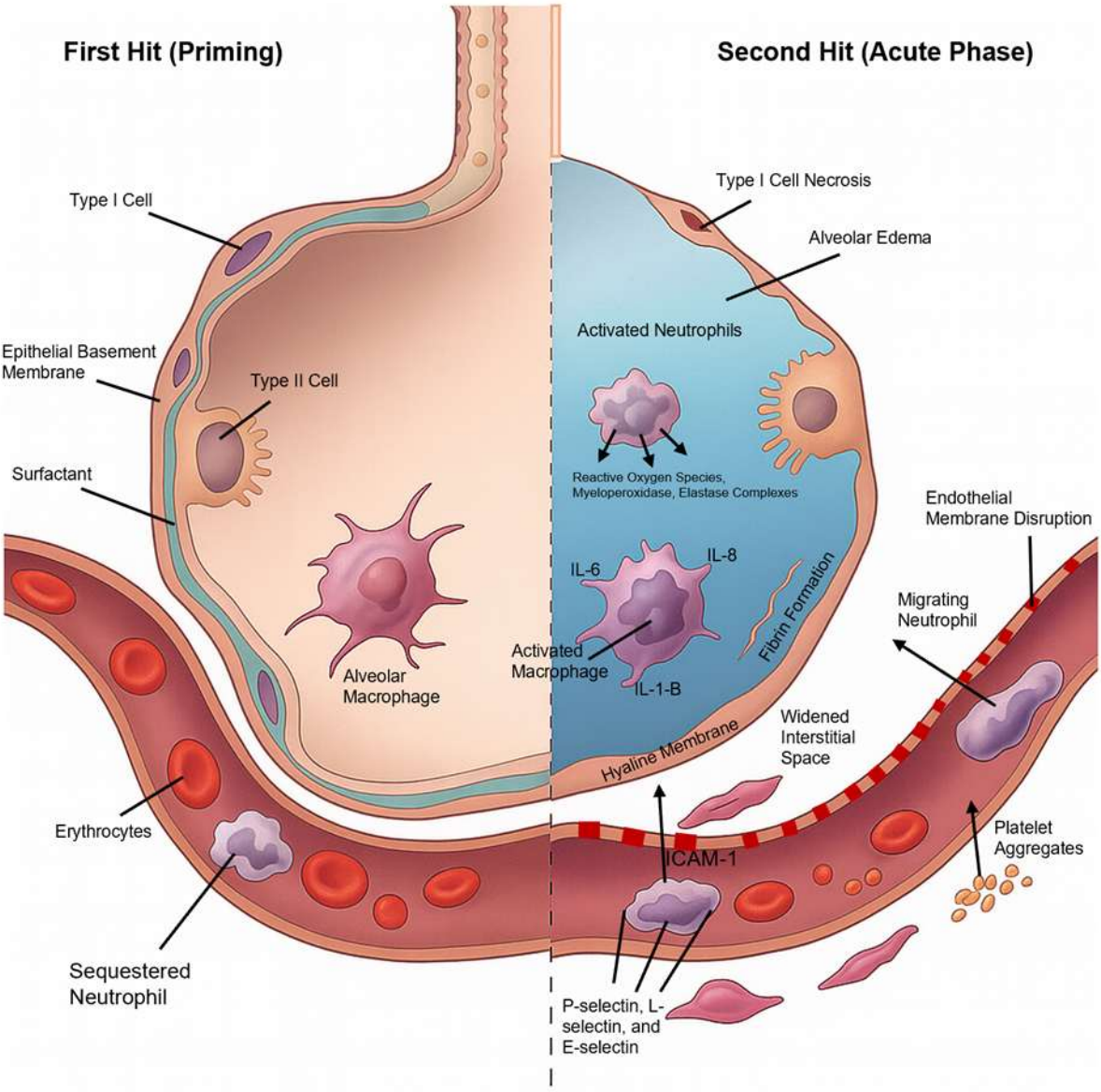

Figure 1: Pathophysiology of TRALI, demonstrating the two-hit hypothesis, including the priming-phase, and neutrophil sequestration within the pulmonary-alveolar capillaries, and the acute inflammatory phase within the alveolar-capillary membranes.

Diagnosis

TRALI typically presents with an acute onset of respiratory distress, hypoxemia, and bilateral pulmonary infiltrates on chest radiography, without evidence of circulatory overload (Table 2). Fever and hypotension can also occur, complicating the clinical picture. The rapid development of these symptoms often necessitates immediate medical attention and intervention. The clinical presentation of TRALI is similar to other forms of acute lung injury.

Differentiation from TACO hinges on the absence of elevated BNP or NT-proBNP, lack of jugular venous distension, cardiomegaly, and pleural effusions (Table 3); features more characteristic of TACO. Though not always present, hypotension or transient leukopenia are suggestive of TRALI. [21,22] Bedside lung ultrasound may show diffuse B-lines in the context of normal inferior vena cava diameter and preserved cardiac function, supporting a TRALI diagnosis. In contrast, TACO usually presents with IVC distension and pleural effusions, markers of circulatory volume overload. [22,23] TRALI is diagnosed clinically by the acute onset of hypoxemic respiratory failure, defined by PaO_2:FiO_2 ratio ≤ 300 or SpO_2 < 90% on room air, with new bilateral lung infiltrates appearing during, or within 6 hours of transfusion, without evidence of circulatory overload. [23]

Accurate diagnosis of TRALI requires careful assessment of the clinical presentation and exclusion of other potential causes of acute lung injury, such as ARDS and TACO. The

absence of specific laboratory tests further complicates the diagnostic process, underscoring the importance of clinical acumen and a thorough understanding of the diagnostic criteria.

Differentiating TRALI from TACO

The differential diagnosis of acute lung injury following transfusion of blood products includes TRALI, transfusion-associated circulatory overload (TACO), and anaphylaxis, with the latter becoming increasingly uncommon due to commonly performed blood-typing practices.

Differentiating TRALI (non-cardiogenic pulmonary edema) and TACO (hydrostatic pulmonary edema) is difficult, particularly in critically ill patients with numerous comorbidities such as advanced heart failure and renal failure, which may obscure the clinical picture. Factors that may suggest TRALI are transient neutropenia, due to sequestration of neutrophils within the lungs, though the absence of this does not rule out TRALI. [26] As outlined in Table 3, TACO may be differentiated clinically from TRALI by clinical signs and symptoms of volume overload, due to the development of hydrostatic pulmonary edema following blood product transfusion, which includes jugular venous distension, edema, hypertension, and elevated CVP. Crepitations are non-specific as both TRALI and TACO lead to alveolar edema. In addition, chest x-ray findings are non-specific as both TRALI and TACO may present with bilateral pulmonary infiltrates on a chest x-ray;. In some cases, pleural effusions are present, which may be more indicative of TACO. [27] One of the most important diagnostic factors of TACO is the rapid clinical improvement following diuretics with off-loading of the pulmonary capillaries, whereas, there is no role for diuretics in the management of TRALI. [28]

Table 2: Diagnostic criteria for TRALI as established by the NHLBI working group, Canadian consensus conference, Revised Delphi panel, and the American Society of Hematology (ASH).

Organization	Diagnostic Criteria
NHLBI Working Group (2005) [24]	For patients without ALI risk factors: Acute onset of lung injury, hypoxemia ($PaO_2/FiO_2 \leq 300$ or $SpO_2 < 90\%$ on room air), bilateral infiltrates on chest X-ray, and no evidence of circulatory overload. For patients with ALI risk factors: A new episode of ALI occurring within 6 hours post-transfusion, requiring clinical assessment to determine if transfusion was the primary cause.
Canadian Consensus Conference (2004) [4]	No preexisting lung injury before transfusion, development of ALI within 6 hours of transfusion, and absence of a clear temporal relationship to another ALI risk factor. If another risk factor is present but transfusion may have contributed, the case is categorized as "Possible TRALI."
Revised Delphi Panel Definition (2019) [25]	TRALI is classified into Type I (patients without ARDS risk factors) and Type II (patients with ARDS risk factors or mild existing ARDS). Diagnosis requires acute onset hypoxemia ($PaO_2/FiO_2 \leq 300$ or $SpO_2 < 90\%$ on room air), bilateral pulmonary edema on imaging, and absence of left atrial hypertension.
American Society of Hematology (ASH) Guidelines [1]	TRALI presents as acute lung injury occurring during or within 6 hours of transfusion. Key features include hypoxemia, bilateral pulmonary infiltrates, and absence of an alternative risk factor for ALI. If an alternative risk factor exists, the case may be classified as "Possible TRALI."

ALI: Acute lung injury, ARDS: Acute respiratory distress syndrome, TRALI: Transfusion-related acute lung injury

Table 3: Differentiating the clinical syndromes, diagnostic, and expected treatment response for TRALI and TACO

Feature	TRALI (Transfusion-Related Acute Lung Injury)	TACO (Transfusion-Associated Circulatory Overload)
Presentation	Non-cardiogenic pulmonary edema	Cardiogenic pulmonary edema
Time of Onset	Within 6 hours of transfusion	Within 12 hours of transfusion
Mechanism	Neutrophil activation causing increased capillary permeability (two-hit hypothesis)	Volume overload; hydrostatic pulmonary edema due to rapid/high-volume transfusion
Symptoms and Clinical Signs	Acute dyspnea, hypoxemia, hypotension, fever may be present	Acute dyspnea with signs of volume overload: hypertension, elevated CVP, peripheral edema
Laboratory Findings	Neutropenia or leukopenia (5-35% of cases); BNP is usually normal or low	Elevated brain natriuretic peptide (BNP); possible troponin elevation
Imaging Findings (Chest X-Ray)	Bilateral pulmonary infiltrates; not associated with cardiomegaly or pleural effusion	Bilateral pulmonary infiltrates; may have cardiomegaly and pleural effusions
Treatment Response	Supportive care (oxygen, mechanical ventilation if needed); does not improve with diuretics	Responsive to diuretics and fluid restriction; may require temporary oxygen and ventilatory support
Prognosis	Higher short-term mortality; typically resolves within 48–96 hours	Lower mortality; clinical resolution typically within 48–72 hours with diuresis

Diagnostic challenges and future areas of improvement

Current diagnostic challenges include distinguishing TRALI from other causes of acute lung injury, such as TACO and ARDS. The absence of specific laboratory tests or biomarkers for TRALI further complicates diagnosis. Clinicians must rely on clinical judgment, patient history, and exclusion of other potential causes to accurately diagnose TRALI. The overlap in clinical presentation and the lack of definitive diagnostic markers make it difficult to establish a precise diagnosis in many cases. Emerging biomarkers and advanced imaging techniques, such as lung ultrasound, may enhance TRALI diagnosis.

Research efforts are ongoing to identify novel biomarkers and develop new diagnostic tools for TRALI. Promising candidates include markers of endothelial injury, neutrophil activation, and inflammatory mediators. Emerging evidence shows that several biomarkers may enhance TRALI diagnosis. Soluble intercellular adhesion molecule-1 (sICAM-1) is a marker of endothelial injury that has been studied to aid in the diagnosis of various conditions that involve increased vascular permeability. Levels of sICAM-1 in both the plasma and pulmonary edema fluid have been shown to be higher in patients with acute lung injury compared to patients with hydrostatic pulmonary edema. [29] Clara cell secretory protein (CC16), an anti-inflammatory protein secreted by epithelial respiratory cells, has been shown to be decreased in patients with acute lung injury compared to patients with cardiogenic pulmonary edema. [30] In 2016, Roubinian et al. [31] found that interleukin-8 (IL-8) was the most accurate biomarker in the diagnosis of TRALI, and interleukin-10 (IL-10) was the most valuable biomarker in differentiating the various pulmonary transfusion reactions from one another. These biomarkers can provide additional diagnostic information and help differentiate TRALI from other conditions. Future research should focus on validating these biomarkers in clinical settings and integrating them into diagnostic protocols. The development of point-of-care diagnostic tests could significantly improve the rapid and accurate diagnosis of TRALI.

The use of molecular and genetic techniques has the potential to revolutionize TRALI diagnosis. Studies have suggested

that specific genetic polymorphisms may be associated with an increased risk of TRALI, suggesting that genetic screening could help identify at-risk patients and donors. For example, donor samples containing human neutrophil antigen-3a (HNA-3a) have been shown to be associated with severe cases of TRALI. [32] Additionally, advances in proteomics and metabolomics could lead to the discovery of novel biomarkers and provide deeper insights into the pathophysiology of TRALI.

TRALI in the Intensive Care Unit

Transfusion-related acute lung injury (TRALI) remains a critical complication in the intensive care setting due to the high frequency of transfusions and the vulnerability of critically ill patients. Patients in the ICU often require multiple blood products, including red blood cells, platelets, and fresh frozen plasma, which increases their exposure to immune and non-immune mediators that precipitate lung injury. The "two-hit" hypothesis is particularly relevant in this environment, were predisposing factors such as sepsis, major surgery, trauma, or systemic inflammation prime pulmonary neutrophils as the first hit. Transfused biologically active substances, including anti-leukocyte antibodies and bioactive lipids, then serve as the second hit, triggering capillary leak and non-cardiogenic pulmonary edema. [24] Cardiac surgery patients experience a similarly high incidence of TRALI, with one prospective cohort reporting rates comparable to other critically ill populations, [33] which underscores the importance of recognizing this frequently underdiagnosed entity in diverse ICU populations.

The morbidity and mortality associated with TRALI in critically ill patients are substantial. Compared with transfused controls, TRALI patients exhibit significantly higher in-hospital mortality, prolonged mechanical ventilation requirements, and extended ICU lengths of stay. [34] This was noted in a large, nested case-control study; whereby the mortality rate among TRALI patients was 17% and increased to 42% in those with pre-existing acute lung injury, highlighting the compounding effect of transfusion-induced injury in patients with baseline pulmonary dysfunction. [12,35]

The diagnostic challenge posed by TRALI, which presents similarly to acute respiratory distress syndrome, volume overload, and ventilator-associated pneumonia, can delay recognition and appropriate treatment, thereby worsening outcomes. In addition, emerging evidence indicates that transfusion practices in critical care are often liberal, with a substantial proportion of transfusions potentially avoidable. Machine learning analyses of large ICU datasets have estimated that adopting more restrictive transfusion strategies could modestly reduce ICU mortality, including cases attributable to TRALI. [3]

Management of TRALI in the ICU is primarily supportive and requires coordinated multidisciplinary care. Immediate cessation of transfusion is the first critical intervention. Respiratory support, including supplemental oxygen and mechanical ventilation with lung-protective strategies, is often necessary. Hemodynamic management may involve cautious fluid administration and vasopressor therapy, as aggressive diuresis is contraindicated in non-cardiogenic pulmonary edema. [36] Preventive strategies are increasingly emphasized and include universal leukoreduction of blood products, preferential use of plasma from male donors to mitigate anti-HLA antibody exposure, and improved hemovigilance systems to enhance recognition and reporting. Given the high risk in critically ill populations, education of ICU teams regarding prompt diagnosis and adherence to evidence-based transfusion thresholds remains essential to reduce the incidence and adverse outcomes associated with TRALI.

Role of non-invasive and invasive mechanical ventilation in TRALI

Advanced respiratory support is a critical component of TRALI management in the intensive care setting. Most patients with moderate to severe TRALI require supplemental oxygen, and approximately 70–80% necessitate invasive mechanical ventilation due to the rapid onset of hypoxemia and respiratory failure. High-flow oxygen therapy (HFOT) and non-invasive positive pressure ventilation (NPPV) have been used in selected patients with milder presentations or as bridging strategies during recovery. Observational studies indicate that while HFOT and NPPV may reduce the need for intubation in general acute hypoxemic respiratory failure, their effectiveness in potentially reducing intubation rates or mechanical-ventilator free days in TRALI is less well-defined due to a lack of dedicated trials in TRALI patients, with data limited to pediatric case reports. [37]

Non-invasive respiratory support, including HFOT and NPPV, may be a consideration for patients with less severe hypoxemia and preserved mental status. HFOT can deliver up to 60 – 80 liters per minute of heated, humidified oxygen with a low level of positive end-expiratory pressure that improves alveolar recruitment and reduces work of breathing. Although no TRALI-specific randomized controlled trials exist; evidence extrapolated from broader hypoxemic respiratory failure populations with non-cardiogenic pulmonary edema and acute respiratory distress syndrome (ARDS) supports the hypothesis that HFOT reduces intubation rates and improves

oxygenation compared with standard oxygen therapy. In a meta-analysis including over 1,800 patients with acute respiratory failure, HFOT reduced the risk of escalation to invasive ventilation by approximately 15%. [38] Ultimately, more studies are necessary to aid in defining the role of HFOT and NPPV in the management of patients with TRALI in the critical care setting.

Mechanical ventilation remains the primary modality for the majority of TRALI patients with severe hypoxemia or respiratory distress. Observational data indicate that 78% of patients diagnosed with TRALI require intubation, with most needing ventilatory support for a median of 48 hours. [39] Lung-protective ventilation strategies using low tidal volumes, low driving pressures, and moderate positive end-expiratory pressure are recommended to minimize ventilator-associated lung injury, similar to established ARDS protocols. While no prospective studies have defined optimal ventilator settings specific to TRALI, adherence to supportive measures, including lung-protective ventilation; as utilized in the management of non-cardiogenic pulmonary edema in the setting of ARDS, correlates with improved oxygenation and shorter duration of mechanical ventilation in patients with TRALI. [15,34,36] Most patients can be weaned relatively quickly, with successful extubation occurring within 72 hours in most cases, provided the underlying inflammatory response resolves. Early transition to spontaneous breathing trials and careful fluid management are critical to facilitate liberation from ventilatory support and reduce ICU length of stay.

Management of TRALI

The management of TRALI involves immediate cessation of the transfusion and supportive care. Key management strategies include administering supplemental oxygen to maintain adequate oxygenation, providing ventilatory support in severe cases of hypoxemia or respiratory distress, and managing hypotension to ensure adequate perfusion. Supportive care remains the mainstay of TRALI management. [40] This includes oxygen therapy, mechanical ventilation, hemodynamic support, and judicious use of fluids. Diuretics are contraindicated in TRALI as the condition is not due to fluid overload. They are not beneficial and may cause harm due to exacerbation of hypotension.[13,36] Similarly, there is limited data supporting the efficacy of steroids in the treatment of TRALI. Animal studies have shown that methylprednisolone can decrease systemic inflammatory markers but fail to reduce pulmonary edema or prevent lung injury. [41]

Given the lack of effective treatment measures for TRALI; prevention is key. Preventative measures including screening blood donors for leukocyte antibodies and using plasma from male donors or nulliparous female donors. These strategies can reduce the risk of TRALI and improve transfusion safety. [1] Studies have found that a minimum of 80% of TRALI cases can be attributed to the presence of donor antibodies; [42] thus, screening for these antibodies can be transformative in reducing the incidence of TRALI. Additionally, implementing stringent transfusion protocols and monitoring patients closely for early signs of TRALI can help mitigate the severity of the condition. Education and training of healthcare professionals on the recognition and management of TRALI are essential for improving patient outcomes.

Several novel therapies in the treatment of TRALI are being investigated, with one of the most promising being IL-10 therapy. In murine models, IL-10 levels are reduced in subjects that develop TRALI, and IL-10 knockout mice exhibit increased susceptibility to the condition. [43] The administration of IL-10 in mice not only appeared to prevent the development of TRALI completely but was also an effective rescue therapy in animals that developed symptoms of TRALI. [44] Although administration of IL-10 in humans has been demonstrated to be safe with only minimal side effects, its effects may impair the host immune system and cause harm. [44,45] More studies, particularly those with human subjects, are needed to validate the efficacy and safety of IL-10 in the treatment of TRALI.

Role of Immunologic Agents and Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) has demonstrated a dual role in TRALI. On one hand, preclinical studies have shown that IVIG administration significantly attenuates TRALI severity in animal models. For instance, in a murine model of anti-MHC class I-mediated TRALI, IVIG therapy administered prophylactically, or shortly after antibody exposure, markedly reduced lung inflammation and improved survival by inhibiting neutrophil-mediated oxidative damage. [46] Additional studies confirm that IVIG modulates immune cell activation and prevents the cytokine storm and endothelial injury characteristic of TRALI. [47,48]

However, clinical reports also suggest that IVIG itself may occasionally act as a trigger for TRALI. [49] Several case reports describe acute lung injury following IVIG infusions, potentially linked to the presence of leukocyte-reactive antibodies in specific IVIG-lots or high-dose rapid administration. [48,50,51] This rare but serious complication underscores the need for rigorous screening of IVIG preparations and cautious administration, particularly in patients with underlying inflammatory states.

One known "first-hit" risk factor for TRALI is C-reactive protein (CRP), an acute-phase reactant raised in inflammatory states. [23,52] In TRALI, a CRP inhibitor has been created and shows promise in lowering the inflammatory response. [38] Complement targets, osteopontin targets, NET disruption, and TLR4 (endothelial LPS receptor) blocking are additional possible immunologic treatment approaches. [23,42,53]

Both receiver and blood product variables have been shown to contribute to the development of TRALI in bovine models. When injected with supernatant from stored but not fresh blood, eighty percent (80%) of "sick" sheep (i.e., sheep initially infused with LPS) developed TRALI in contrast to "healthy" sheep (i.e., sheep infused with saline). [54] Additionally, compared to stored platelets, stored RBCs caused more severe harm, indicating that the effects of storage lesions vary depending on the kind of blood component. The transfusion of fresher red blood cells may reduce the incidence of TRALI, according to the existing hypotheses, although there is limited supportive data. [55]

Prognosis

Later investigations showed that TRALI may not always resolve as quickly, even if early findings by Popovsky et al. favorably characterized recovery of hypoxemia within 48 hours through supportive care. [9,12,17,56] In contrast with ARDS, the lung injury in TRALI is typically temporary, with around 80% of individuals showing clinical recovery in 48 to 96 hours. A subset of patients may experience a prolonged clinical course and potentially death. According to one prospective study, patients with TRALI and possible TRALI experienced tachypnea, hypotension, prolonged hypoxemia, fever, and tachycardia in comparison to transfused controls. Of these patients, 78% needed mechanical ventilation, 25% required vasopressors, and 17% of patients ultimately expired. [39]

Additionally, patients with TRALI and possible TRALI had extended hospitalizations, more days spent in the intensive care unit (ICU), and longer durations of mechanical ventilation. TRALI outcomes can be severe, even with supportive care, necessitating lung-protective ventilation and conservative fluid management. Between fiscal years 2012 and 2016, TRALI-related deaths accounted for 34% of all transfusion-related deaths reported to the FDA, making them the primary cause of transfusion-related deaths before and throughout the early deployment of mitigation techniques. However, between 2016 and 2020, this percentage fell to 21% of FDA-reported transfusion-related deaths, trailing only TACO (34%), which accounted for 87%. [5]

Prevention

Should we adjust our transfusion strategy in the critically ill?

Unfortunately, with the unpredictable and highly morbid risk that TRALI presents in the critically ill, transfusion strategy and the need for risk stratification prior to transfusion have become an emerging necessity in the critical care setting. An essential step in preventing TRALI is educating providers on the importance of appropriate use of blood products and the patient-specific risk factors for TRALI. One RCT demonstrated a significant reduction in the development of pulmonary edema by reducing transfusion thresholds, without adverse impact on patients in the ICU. [57] In addition, there is substantial existing controversy regarding transfusion goals and thresholds for transfusions in the critical care setting, with data to support that transfusion of packed red blood cells rarely results in improved tissue oxygen delivery and oxygen utilization at hemoglobin transfusion thresholds greater than 7mg/dL in non-bleeding critically ill patients. [57] Furthermore, there is supportive data that RBC transfusions in non-bleeding patients do not improve delivery of oxygen (DO_2), or tissue perfusion. [58,59] The paradigm has shifted to a restrictive transfusion approach with the American College of Chest Physicians strongly recommending a transfusion goal of 7mg/dL, with the exception of acute coronary syndrome. [60]

More data is needed to determine the most appropriate threshold in various clinical settings; however, a risk-benefit analysis should be conducted prior to transfusion of blood products. This is particularly relevant to the administration of plasma-containing blood products, as plasma is widely utilized inappropriately, with estimates of up to 48% of plasma transfusions in the critical-care setting being inappropriate and not otherwise indicated. [61,62] More clinical trials are critical to better define guidance for transfusion strategies in the critical care setting to balance the risks of TRALI and TACO with the benefits of blood-product transfusion.

Conclusion

TRALI remains a significant challenge in the critical care setting. While substantial progress has been made in understanding its pathophysiologic mechanisms, development of standardized diagnostic criteria, and implementation of preventative measures; diagnostic challenges persist. Future research should focus on identifying specific biomarkers and developing advanced diagnostic tools, which may enhance TRALI diagnosis and patient outcomes. In conjunction with implementing evidence-based practices, transfusion safety can be enhanced

by improving understanding of TRALI and the ability to make a rapid, accurate diagnosis, thereby reducing the risk of morbidity and mortality, particularly in critically ill populations.

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