Review Article

The history of transfusion related acute lung injury: how we got to where we are today

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Abstract: Transfusion-related acute lung injury (TRALI) is a serious and acute complication of blood transfusion, manifesting as non-cardiogenic pulmonary edema requiring respiratory support, and often, mechanical ventilation. TRALI typically occurs during or after the transfusion of high plasma volume blood components, but can occur with any blood component in susceptible recipients due to the passive transfusion of donor anti-leukocyte antibodies or biological response modifiers that accumulate in stored blood products. Once the leading cause of transfusion associated mortality, TRALI incidence has declined significantly following the implementation of prevention measures. Broader understanding of the pathogenesis demonstrated that a significant proportion of cases occur consequently to anti-leukocyte antibodies in the plasma of multiparous female donors. Thus, exclusion of these high-risk donors with the use of male-only, never-pregnant female, or antibody-negative tested female donors resulted in a substantial decline of TRALI in participating countries, internationally. Although effective, these measures have not completely eradicated the risk of TRALI, which remains the second leading cause of transfusion-related death. TRALI is not only challenging to differentiate from transfusion-associated circulatory overload (TACO), but continues to go under-reported, altogether highlighting the opportunity for further research into these remaining cases. We provide a review on the evolution of TRALI, including its defining criteria, pathophysiology, mitigation strategies, and promising new therapeutic modalities. TRALI is an excellent example of how improved understanding of a disease process can translate into effective prevention measures through a combination of research and hemovigilance reporting.

Keywords: Acute respiratory distress syndrome (ARDS); hemovigilance; transfusion-associated circulatory overload (TACO); transfusion reaction; transfusion-related acute lung injury (TRALI)

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Introduction

Transfusion-related acute lung injury (TRALI) is defined clinically by the acute onset of hypoxemia and non-cardiogenic pulmonary edema. Cases suggestive of TRALI were first described in the literature more than 70 years ago although it wasn't until three decades later when the term TRALI emerged. The European Haemovigilance Network (EHN), the Canadian Consensus Conference (CCC), the National Heart, Lung, and Blood Institute (NHLBI), and the National Healthcare Safety Network (NHSN) all developed similar early clinical definitions of TRALI. A more recent re-definition has been suggested, however, to better align with the updated clinical definition

of acute respiratory distress syndrome (ARDS) (1). TRALI is potentially fatal, and prior to the introduction of risk-mitigation strategies, it was the leading cause of transfusion-related morbidity and mortality. Even with the success of these risk-mitigation strategies, TRALI cases continue to occur, highlighting our incomplete understanding of its pathogenesis. It is currently understood that TRALI is caused by the transfusion of blood products containing either anti-leukocyte antibodies or biological response modifiers (BRMs). However, the precise underlying cellular mechanisms remain uncertain. There are no specific treatments for TRALI, with supplemental oxygen and mechanical ventilation being the principal management strategies. Laboratory and animal models have provided insight into how TRALI develops with potential for new treatment modalities. This review explores how our understanding of TRALI has developed over time. It describes the evolution of clinical definitions, differential diagnoses, incidence rates, pathogenesis, prevention and mitigation measures, clinical management, prognosis, the current limitations, and steps for the future.

Evolution of TRALI case definition

In 1951, Bernard *et al.* described a TRALI-like syndrome occurring within hours of blood Transfusion (2,3). The term TRALI, however, was not coined until 1983 when Popovs*k*y *et al.* described similar clinical findings of marked respiratory distress, hypoxemia, hypotension, fever, and bilateral pulmonary edema in five patients all developing within 4 hours of transfusion (4). This was further characterized in 1985 following an analysis of 36 patients (5). In their analysis, if known causes of acute respiratory distress (ARD), acute left ventricular dysfunction, circulatory overload, pulmonary aspiration or infection were suspected, patients were eliminated from the study. The minimum TRALI acceptance criteria for the study was radiographic evidence of pulmonary infiltrates that developed subsequently to the transfusion. Granulocyte and human leukocyte antigen (HLA) antibodies were detected in the serum of 89% of the blood donors with an HLA donor antibody/recipient antigen concordance in 59% of cases. These findings were consistent with many subsequent reports, suggesting that TRALI is, at least in part, the result of passive transfusion of donor antibodies resulting in a donor antibody-patient antigen interaction (3,5).

Through the EHN [now the International Haemovigilance Network (IHN)] in 2003, a Working Party on Definitions of Adverse Events was established to develop a TRALI definition that would facilitate data comparison between hemovigilance schemes of participating European countries (6,7). The definition shared criteria with the original description, including ARD within six hours of transfusion, no evidence of circulatory overload, and radiographic evidence of bilateral pulmonary infiltrates (6).

Shortly after, the CCC commenced in April 2004, sponsored by Canadian Blood Services and Héma-Québec with support from the International Society of Blood Transfusion (ISBT) Biomedical Excellence for Safer Transfusion (BEST) subcommittee, with the intent of standardizing the case definition and facilitating better understanding of the epidemiology, pathogenesis, management, and prevention of TRALI (8,9) (*Table 1*). The CCC defined TRALI as a new episode of acute lung injury (ALI) occurring during or within 6 hours of transfusion, that is not temporally related to a competing ALI etiology including direct (i.e., aspiration, pneumonia, pulmonary contusion, near drowning) and indirect (i.e., severe sepsis/shock, disseminated intravascular coagulation, burn injury, trauma, cardiopulmonary bypass, drug overdose) causes of lung injury (8,9,12). This definition maintained consistency with the 1994 American-European Consensus Conference (AECC) ALI definition, the international pulmonary and critical care standard at the time (13). The definition also included hypoxemia and chest radiograph abnormalities suggestive of alveolar or interstitial disease (i.e., bilateral infiltrates) in the absence of evidence of circulatory overload. Hypoxemia was defined as a ratio of the partial pressure of arterial oxygen to the fractional inspired oxygen concentration (PaO_2/FiO_2) ≤300 mmHg or percent oxygen saturation (SpO_2) <90% on room air. In a setting where the pulse oximetry measurement was unavailable, other clinical evidence of hypoxemia could be used. Lack of clinical evidence of circulatory overload included no evidence of left atrial hypertension (LAH) as determined by pulmonary capillary wedge pressure (PCWP) <18 mmHg, jugular venous distention, muffled breath sounds, S3 gallop on auscultation, orthostatic dyspnea, and/or increased central venous pressure (CVP). For cases in which ALI is temporally related to transfusion, but a non-transfusion ALI risk factor is also present, the term possible TRALI (pTRALI) was suggested.

The NHLBI Working Group on TRALI published a concurrent definition in 2005 (10). This definition was essentially identical in sharing the foundation of hypoxemia as defined by a PaO_2/FiO_2 ≤300 mmHg, regardless of

Table 1 The evolution of TRALI defining criteria

Definition	Diagnostic criteria of TRALI	Sub-definition with criteria
Popovsky *et al.*, 1983 (4)	(I) Marked respiratory distress, hypoxemia, hypotension, fever, and bilateral pulmonary edema following transfusion	None
	(II) Occurs within 4 hours of transfusion	
	(III) Radiographic evidence of pulmonary infiltrates	
	(IV) Absence of known causes of ARD, acute left ventricular dysfunction, circulatory overload, pulmonary aspiration, or infection	
European Haemovigilance Network Working party on Definitions of Adverse Events, 2003 (6)	(I) Occurrence of acute respiratory distress during or within 6 hours of transfusion	None
	(II) No signs of circulatory overload	
	(III) Radiographic evidence of bilateral pulmonary infiltrates	
Canadian Consensus Conference, 2004 (9)	(I) Defined by:	Possible TRALI
	(i) Acute onset	(I) Same criteria mentioned above
	(ii) Hypoxemia (PaO_2/FiO_2 ≤300 mmHg or SpO_2 <90% on room air or other clinical evidence of hypoxemia)	(II) In the presence of an alternative risk factor for ALI
	(iii) Bilateral infiltrates on chest radiograph	
	(iv) No evidence of LAH and/or CVP <18 mmHg	
	(II) No existing ALI before transfusion	
	(III) During or within 6 hours of transfusion	
	(IV) No temporal relationship to an alternative risk factor for ALI	
National Heart, Lung, and Blood Institute Working Party on TRALI, 2005 (10)	New ALI temporally associated with transfusion in a patient without ALI risk factors other than transfusion. ALI is defined as:	Indeterminate
	(I) Acute onset during or within 6 hours after the end of transfusion of one or more plasma-containing products	Cases with another recognized ALI risk factor
	(II) No evidence of LAH	(I) By assessing the patient's clinical course, the new ALI is either:
	(i) Pulmonary artery occlusion pressure ≤18 mmHg when measured	(i) TRALI, and the new ALI is inferred to be mechanistically related to the transfusion or with/without the risk factor
	(ii) A lack of clinical evidence of LAH	(ii) Not TRALI, and the new ALI is mechanistically related to the alternative ALI risk factor alone
	(III) Chest radiograph: bilateral infiltrates seen on frontal chest radiograph	
	(IV) Hypoxemia	
	(i) PaO_2/FiO_2 ≤300 mmHg	
	(ii) SpO_2 <90% on room air	

Table 1 *(continued)*

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Definition	Diagnostic Criteria of TRALI	Sub-definition with criteria
Centers for Disease Control and Prevention, National Health Safety Network, 2009/2018 (11)	(I) No evidence of ALI prior to transfusion (II) ALI onset during or within 6 hours of cessation of transfusion (III) Hypoxemia defined by any of these methods: i. PaO_2/FiO_2 ≤300 mmHg ii. SpO_2 <90% on room air iii. Other clinical evidence (IV) Radiographic evidence of bilateral infiltrates (V) No evidence of LAH (i.e., circulatory overload) Definition requires I, II, III (either i, ii, or iii), IV, and V	None
Consensus re-definition, 2019 (1)	TRALI type I (I) No risk factors for ARDS (II) Acute onset (III) Hypoxemia (PaO_2/FiO_2 ≤300 mmHg or SpO_2 <90% on room air) (IV) Clear evidence of bilateral pulmonary edema on imaging (i.e., chest radiograph, chest CT, or ultrasound) (V) No evidence of LAH or if LAH is present, it is judged to not be the main contributor to the hypoxemia (VI) Onset during or within 6 hours of transfusion (VII) No temporal relationship to an alternative risk factor for ARDS	TRALI type II (I) Has risk factors for ARDS or mild ARDS* (II) Findings as described for TRALI type I (III) Stable respiratory status in the 12 hours before transfusion

*, has risk factors for ARDS (but no diagnosis of ARDS) or have mild ARDS but with respiratory deterioration as a result of transfusion. TRALI, transfusion-associated lung injury; ARD, acute respiratory distress; PaO_2, partial pressure arterial oxygen; FiO_2, fraction inspired oxygen; ALI, acute lung injury; LAH, left atrial hypertension; CVP, central venous pressure; SpO_2, percent oxygen saturation; ARDS, acute respiratory distress syndrome; CT, computed tomography.

positive end-expiratory pressure level, or by SpO_2 <90% on room air and bilateral infiltrates on chest radiograph. It also required pulmonary artery occlusion pressure ≤18 mmHg when measured or lack of clinical evidence of LAH. Cases whereby ALI occurred in a patient with another recognized ALI risk factor were designated as "indeterminate".

In March 2009, the NHSN Biovigilance Component Hemovigilance Module Surveillance Protocol was established to implement national surveillance of transfusion-associated adverse events in the United States (US), through the US Centers for Disease Control and Prevention (CDC). TRALI was defined as acute hypoxemia with a PaO_2/FiO_2 of ≤300 mmHg (or SpO_2 <90% on room air or other clinical evidence) combined with a chest radiograph showing bilateral infiltrates in the absence of LAH (i.e., circulatory overload) and no temporal relationship to an alternative risk factor for ALI during or within 6 hours of transfusion. The NHSN protocol offered both severity and imputability categorizations, which have undergone minor revisions since inception. The most recent version (v2.8) based definite *vs.* possible TRALI on the absence or presence of alternative ALI risk factors, respectively (11).

In 2012, with rising concerns regarding the validity of

the 1994 AECC ALI definition, a panel convened through a European Society of Intensive Care Medicine initiative to develop the Berlin Definition of ARDS, altogether dropping the ALI terminology (14). This defined ARDS as (I) occurring within one week of a known clinical insult or new or worsening respiratory symptoms; (II) bilateral chest opacities on imaging not fully explained by effusions, lobar/lung collapse, or nodules; (III) respiratory failure not fully explained by cardiac failure or fluid overload; and (IV) oxygenation status (i.e., mild, moderate, and severe).

Since the CCC in 2004, considerable amounts of new information became available from published studies and hemovigilance data, including the Berlin ARDS definition, prompting re-visitation of the TRALI definition by a panel of experts in 2019 (1). Notably, interval studies investigating pTRALI found evidence against transfusion being important in its development leading to its reclassification as a distinct entity from TRALI (15). Cases of pTRALI were not linked to anti-HLA antibodies (i.e., not associated with female donor products) and were not shown to increase with the number of units received (13,15). Thus, evidence supported that using plasma from male donors did not reduce the incidence of pTRALI (16). Ultimately, recognizing that risk factors for ARDS may also serve as TRALI risk factors in the context of a pre-transfusion inflammatory state, led to abandonment of the term pTRALI. Instead, subcategorization of the definition was suggested: TRALI type I (without an ARDS risk factor) and TRALI type II (with an ARDS risk factor or with existing mild ARDS) (*Table 1*). Changes to the 2004 definition included the use of additional diagnostic imaging modalities to evaluate pulmonary edema [i.e., computed tomography (CT) scan, ultrasound]. Additionally, the new definition addressed the declining use of invasive techniques (i.e., pulmonary artery catheters) to measure PCWP, and non-invasive diagnostic imaging techniques were included to rule out LAH. Interestingly, the authors also described that the presence of LAH does not definitively exclude TRALI if it is judged not to be a main contributor to the hypoxemia. Furthermore, in line with the Berlin definition, slight modifications were made to the previous ARDS risk factors. Pulmonary vasculitis and specification of aspiration of gastric contents were included as causes of direct lung injury, while causes of indirect lung injury were amended to include non-pulmonary sepsis, pancreatitis, severe burns, non-cardiogenic shock, and major trauma. The previous risk factor of cardiac surgery was removed as these patients may be exposed to several ARDS risk factors, and studies failed to consistently demonstrate the role cardiac surgery plays as an independent risk factor (1). For cases with ARDS risk factors, the classification of TRALI type II is reserved for those patients who do not demonstrate respiratory deterioration 12 hours prior to transfusion but subsequently show deterioration following transfusion, while meeting TRALI type I criteria.

Incidence

The incidence of TRALI is not definitively known. Although estimation is largely reliant on passive surveillance, published studies using active surveillance have contributed to our knowledge on its incidence (17). Nevertheless, it is understood that TRALI is likely under-recognized and under-reported.

Early literature suggested widely varying TRALI rates from 1 in 500 to 1 in 100,000 per plasma-containing blood component or between 0.08% and 15% of patients receiving a blood transfusion (18,19). Prospective studies, however, observed higher incidence rates (20). Vossoughi *et al.* studied TRALI rates per component from 2007 to 2017. From 2007 to 2013, the rates per component were estimated at 2.57, 2.72, and 1.50 per 100,000 components transfused for plasma, platelets, and red blood cells (RBCs), respectively (12). However, with improved hemovigilance reporting systems in place and the implementation of TRALI mitigation strategies in the US, incidence rates have declined. More recent reports following implementation of mitigation strategies from North America suggest that the incidence rates range from 1 in ~64,000 to 1 in ~200,000 per unit transfused (21,22). Broken down by component type, the same study by Vossoughi *et al.* demonstrated TRALI rates from 2014–2017 of approximately 0.41, 1.31, and 0.93 per 100,000 transfused plasma, platelets, and RBC components, respectively (12). Similarly, TRALI incidence rates per product type were evaluated in Australia (23). Their reported incidence rates from 2006 to 2019 were approximately 1 in 13,000, 1 in 42,000, and 1 in 21,000 per transfused plasma, RBC, and platelet components, respectively. However, following risk-reduction strategies, cases dropped significantly with 5 TRALI and 4 possible TRALI cases observed since 2012, and subsequently, an absence of reported cases from 2016 to 2018. European and United Kingdom (UK) literature also reported varying rates from 1 in 7,000 to 1 in 375,000 per unit transfused (24-29). In particular, UK hemovigilance data from 2005 to 2006 post-mitigation implementation suggested incidence rates

of 3.2 and 5.8 per million plasma and platelet components transfused, respectively (25). Meanwhile, German hemovigilance data from 2010 described rates as low as 0 per million for transfused plasma and platelet components and 0.22 per million for transfused RBC components (26). Although not able to definitively rationalize the lower TRALI rates in Germany compared to other nations, the authors suggested contributing factors including voluntary antibody testing of half of apheresis platelet donors as well as increased TRALI awareness which has led to more frequent testing of these donors and subsequently to a selective reduction of high-risk donors (26). The impact of mitigation and prevention strategies on the incidence of TRALI will be detailed later in this article.

Pathogenesis

In their early studies, Popovs*ky et al.* observed an absence of anti-leukocyte antibodies in patients who developed TRALI but noted the presence of these antibodies in the serum of donors (5). Thus, they suggested that passive transfer of antibodies is a factor in the pathogenesis of TRALI. Furthermore, they showed that implicated donors were typically multiparous females, highlighting the association between parity and the induction of HLA antibodies (4,5). Thereafter, several publications in the 1980s suggested that complement activation leads to ALI through aggregation of polymorphonuclear (PMN) cells, ultimately resulting in interstitial and alveolar edema (30-32). This was evidenced in the lung histology of both fatal cases and mouse models, demonstrating PMN infiltration into the pulmonary microvasculature and alveolar edema (33,34). Additionally, it was postulated that the associated endothelial damage was a result of metabolic by-products, superoxide radicals, and proteases produced following granulocyte or complement activation by the transfused antibodies.

Later understanding of TRALI prompted the hypothesis in 2003 that, like ARDS, TRALI may result from a "two-hit" phenomenon (35-37). This was largely based on observations that passive transfusion of cognate antibodies did not cause TRALI in every recipient (15,38-40). The first event or "first hit" occurs as a result of the patient's underlying clinical condition (i.e., sepsis, trauma, cardiopulmonary bypass), or administration of lipopolysaccharide (LPS) in experimental models, creating a pro-inflammatory state which activates the pulmonary endothelial cells (41). This was further evidenced through studies demonstrating the association between increased plasma interleukin (IL)-8, a pro-inflammatory cytokine, and TRALI development (16,42). The inflammatory state activates the pulmonary vascular endothelium, which results in increased intercellular adhesion molecule 1 (ICAM-1) expression by the endothelial cells with chemokine release. Chemokines recruit and prime PMNs, leading to adherence of the sequestered PMNs to the endothelial surface (6,41). Subsequently, these adhered PMNs undergo cytoskeletal changes forming rigid cells that cannot transverse the pulmonary microcirculation (24,35,43). These shape conformations increase pulmonary transit times and delay apoptosis, precipitating the inflammatory response (44).

The "second hit" occurs through passive transfusion of biologic substances (i.e., antibodies, BRMs, cytokines) that activate the primed PMNs. Activated PMNs degranulate to release pro-inflammatory mediators, cytotoxic reactive oxygen species, and toxic enzymes (i.e., elastase) which damage the endothelium, cause capillary leakage, and pulmonary edema (35-37,45). This two-hit model incorporates antibody-mediated and non-antibody mediated mechanisms of PMN activation (41,46).

The antibody-mediated mechanism, as previously mentioned, is due to the passive transfusion of anti-leukocyte [i.e., anti-HLA and/or anti-human neutrophil antigen (HNA)] antibodies acquired during pregnancy, transfusion, or transplantation. Numerous animal models have successfully reproduced both anti-HLA- and anti-HNA-mediated mechanisms of TRALI (45). The relative occurrence of HLA and HNA antibodies implicated in TRALI, however, differs among hemovigilance reporting systems (45). Although HNAs are expressed mainly on PMNs, they can be found on other cells and tissues. HNA-3, for example, is expressed on lymphocytes, platelets, and endothelial cells, among others while HNA-4 and -5 are both expressed on monocytes/macrophages and lymphocytes (47,48). HLA class I antigens are also expressed on endothelial cells. Transfused HNA and HLA class I antibodies bind to their cognate antigens on primed PMNs which results in the classic TRALI reaction (49). Research has shown, though, that direct endothelial binding and dysfunction by HNA-3a can also lead to TRALI (50). This alternative pathogenesis to TRALI development may support how TRALI develops in severely neutropenic patients or in mouse models following neutrophil depletion (50-53). Additionally, mouse models have described the interaction of anti-HNA-3a antibodies with a trimolecular complex comprising of choline transporter-like protein-2, endothelial von Willebrand factor, and CD11b/CD18

on the surface of PMNs, resulting in PMN activation and agglutination via CD11b/CD18 signal transduction. This interaction may then promote TRALI-associated endothelial leakage (50). Kopko *et al.* further noted that HLA class II antibodies are also implicated in TRALI, despite not being expressed on PMNs (54). Of interest, though, studies have demonstrated that expression of HLA Class II on PMNs can be induced through exposure to macrophage colony-stimulating factor (MCSF), granulocyte-MCSF (GMCSF), LPS, or cytokines (41). Kelher *et al.* demonstrated this with a rat model, whereby priming with the aforementioned-agonists resulted in OX6 major histocompatibility complex (MHC) class II expression on PMNs and subsequent development of anti-OX6-mediated TRALI (55). Additional studies demonstrated that transfused HLA class II antibodies activate monocytes expressing the cognate class II antigens, which are then stimulated to secrete pro-inflammatory cytokines [e.g., IL-8, tumor necrosis factor (TNF)-α, leukotriene B4] (56,57). These cytokines can then either directly increase endothelial permeability or indirectly activate primed PMNs accumulated in the pulmonary vasculature. Direct activation of pulmonary endothelium via LPS and HLA class I antibodies leading to enhanced expression of TLR4 (LPS receptor) and ICAM-1 along the endothelial surface, increasing PMN transmigration, has also been reported as a TRALI mechanism (58). Furthermore, the specific role of macrophages in TRALI induction has been studied (59,60). Macrophages secrete osteopontin, an important matricellular protein with multiple biological functions, including its role as a pro-inflammatory cytokine able to act as a pulmonary PMN chemoattractant (60).

Interestingly, several published reports have suggested the role of mitochondrial damage-associated molecular patterns (MtDAMPs) in the development of antibody-mediated TRALI (61,62). MtDAMPs are generated and elevated in stored blood products. A recent murine model demonstrated that intravenous injections of mitochondria, prior to injection with a monoclonal anti-MHC class I antibody, resulted in a TRALI-like picture with increased lung wet/dry ratio, temperature loss, and lung neutrophil accumulation, altogether suggesting mitochondria may act as a first hit in antibody-mediated TRALI (63).

In a subset of TRALI cases, anti-leukocyte antibodies are not detected. This mechanism suggests that primed PMNs are activated by something other than antibodies in the donor product. BRMs, which include bioactive lipids (BALs, e.g., lysophosphatidylcholines, arachidonic acid, and hydroxyeicosatetraenoic acids), soluble CD40 ligand (sCD40L), IL-8, and extracellular vesicles (EVs) that accumulate during storage (such that older cellular blood products contain higher concentrations), have been suggested (64). BALs, structurally similar to platelet activating factor (PAF), have been imputed to activate PMNs through a G-protein-coupled receptor on the PMN surface, whereas sCD40L is thought to cause activation through the CD40 receptor on PMNs and endothelium, each resulting in release of pro-inflammatory cytokines (16,18,65,66). Cellular products undergo physical and chemical changes during storage. However, although animal models have clearly associated product storage with TRALI, human reports continue to be controversial (64,67,68).

Mouse models have also demonstrated a significant role that activated platelets play in TRALI development (69). Activated platelets induce EVs which may become more numerous and injurious with longer platelet storage (70). Animal studies have suggested that both platelet depletion and pretreatment with aspirin prevents TRALI (69). Nevertheless, the importance and critical relevance of recipient platelets in TRALI development is conflicting in the literature (71,72). Given the associated increased risk of TRALI with longer stored platelets, human clinical studies sought to evaluate this. In one study, 18 healthy male volunteers were subjected to an experimental "first hit" (i.e., LPS) and experienced no changes in TRALI pathways after transfusing 2- and 7-day stored autologous platelet concentrates (68). Further delving into the role of platelet types in the development of pulmonary transfusion reactions, another study compared the pulmonary safety of conventional platelet concentrates to pathogen-reduced (PR) platelets (73). The primary outcome was the need for treatment-emergent assisted mechanical ventilation (TEAMV) of any type (i.e., intubation, tight-fitting mask with positive inspiratory pressure, loose-fitting mask, nasal cannula) for any indication following transfusion (73). In the large cohort of hematology-oncology patients, the investigators found that although there was reduced TEAMV in the PR platelet cohort, there was no difference in pulmonary adverse events (i.e., TRALI, ARDS) or mortality between the two types of platelets.

The role of complement in TRALI development has also been investigated (74). Complement is notably elevated in TRALI patients, and investigators found that *in vitro* complement activation was critical for murine antibody-mediated TRALI induction, correlating with increased macrophage trafficking from lungs to blood in an Fc-dependent manner and dependent on C5 complement.

The investigators further noted high levels of complement activation in human TRALI patient plasma, which correlated with neutrophil extracellular traps (NETs). NETs are composed of decondensed chromatin combined with granular proteins in the presence of activated PMNs, and function to trap pathogens (75).

In 2007, a threshold model was established serving to expand upon the current "two-hit" hypothesis of priming and activation (76). Although the PMN is the agreed upon major player in TRALI, it is unclear how many substances the PMN must encounter or which threshold must be overcome to incur lung damage (6,76). The threshold model sought to explain the heterogeneity in TRALI severity, whereby PMNs in a less severe TRALI reaction (i.e., requiring only non-invasive supplemental oxygen supportive care) may undergo a lower level of activation compared to those of a more severe reaction (i.e., requiring mechanical ventilation) (77).

It is important to mention that there have been a few reports describing cases of TRALI in which antibodies are present in the recipient rather than in the donor product (78-80). Typically, this has involved multiparous females and has been termed reverse or inverted TRALI. The antibodies in these cases bind to cognate antigens on the transfused PMNs where they induce PMN priming, pulmonary sequestration, and subsequent development of TRALI (6). This, however, has largely been addressed through pre-storage leukodepletion in many countries. Nonetheless, the potential for reverse TRALI remains, when provoked by soluble proteins in the product. During storage, PMN surface protein CD177 complexes with proteinase 3 in plasma or in the supernatant of RBC components, which binds to activated endothelial cells (81). In the presence of antibodies to CD177 or proteinase 3 in the recipient, binding of the CD177/proteinase 3 complex to activated endothelial cells causes release of reactive oxygen species and apoptosis, and has been shown to precipitate a TRALI-type reaction (81).

Transfusion-associated circulatory overload (TACO), an important differential diagnosis

Distinguishing TRALI from other conditions that may present with ARD in association with blood transfusion can be challenging. TACO is an important respiratory transfusion reaction that must be differentiated from TRALI. While both present with acute pulmonary edema during or within hours of a transfusion, unlike TRALI, TACO is of cardiogenic origin (82). TACO is defined as an acute or worsening respiratory compromise and/or evidence of pulmonary edema, demonstrated through clinical physical examination and/or radiographic chest imaging and/or other non-invasive assessments of cardiac function, during or up to 12 hours after transfusion (83). The ISBT published this most updated definition in 2019 in collaboration with the IHN and AABB. TACO typically presents with signs and symptoms of new cardiovascular system changes and/or evidence of fluid overload including tachycardia, hypertension, jugular venous distension, elevation of the brain natriuretic peptide (BNP) levels, a positive fluid balance, and responsiveness to diuretic treatment (*Table 2*) (11). Regarding BNP, some investigators have reported significant overlap of BNP values between TACO and TRALI, concluding that it is of limited value in distinguishing the two entities in critically ill patients (84). Elevation of the N-terminal prohormone BNP (NT-proBNP) has also been associated with TACO, though one recent study showed no association between NT-proBNP and TACO, instead noting that levels of another biomarker, syndecan-1, were increased in TACO (85). Echocardiography can be a helpful tool. As in other etiologies of volume overload, echocardiography may show left atrial enlargement, ventricular dilation, and a reduced ejection fraction. The pulmonary edema itself is a differentiating feature. Transudative edema is found in TACO while exudative edema in seen in TRALI. Notably, though, evidence of pulmonary edema is only required in the diagnostic criteria for TRALI (8). Although, not a diagnostic criterion, new onset fever is commonly seen in TRALI, and while fever is less common in TACO, it can be seen in up to one-third of cases (86).

As noted above, newer surveillance TRALI definitions allow for its diagnosis even in the presence of underlying ARDS risk factors or existing mild ARDS (TRALI type II), provided that the respiratory status is stable in the 12 hours preceding transfusion with an acute deterioration after the transfusion. Risk factors for TACO, however, are typically those risks for volume overload, including heart failure, renal failure, and extremes of age. Differentiating TACO and TRALI, while identifying those at risk is imperative because as TRALI incidence has declined with mitigation measures, TACO has become the leading cause of transfusion associated mortality (87).

Finally, another differential diagnosis for respiratory distress in association with transfusion includes transfusion-associated dyspnea (TAD) (11). TAD is considered when respiratory distress occurs within 24 hours of transfusion,

Table 2 Diagnostic comparison of TRALI, TACO, and TAD

Diagnostic parameter	TRALI	TACO	TAD
Recipient risk factors	Inflammatory state, "first hit"	Congestive heart failure, renal failure, extremes of age	None, however pediatric patients may be more susceptible
Donor factors	Multiparity, prior blood transfusion, transplantation	None	None
Blood component involved	Typically high plasma volume blood products (i.e., plasma, apheresis-derived platelets) and less commonly platelets and RBCs	All products	All products
Onset of symptoms	Acute, during or within 6 hours of transfusion	Acute, during or within 12 hours of transfusion	Acute, during or within 24 hours of transfusion
Hypoxia/respiratory distress	(I) PaO_2/FiO_2 less than or equal to 300 mmHg (II) Oxygen saturation less than 90% on room air (III) Other clinical evidence	Present (dyspnea, tachypnea, cyanosis and decreased oxygen saturation values)	Acute respiratory distress where allergic, TRALI, or TACO reactions are not applicable
Chest imaging	Radiographic evidence of bilateral infiltrates and/or consistent with pulmonary edema	Radiographic evidence of bilateral infiltrates and/or consistent with pulmonary edema	No defining feature
Vital signs			
Temperature	Fever	Fever uncommon may be present in ~1/3 of patients	No definitive change
Blood pressure	Hypotension	Hypertension	No definitive change
Heart rate	Tachycardia	Tachycardia	No definitive change
Pulmonary edema	Exudate	Transudate	Possible
Laboratory criteria	None	Elevated BNP	None
Mechanism of action	(I) Priming and sequestration of PMN cells (II) Activation of PMN cells through transfusion of anti-leukocyte antibodies or BRMs (III) Macrophage secretion of osteopontin (IV) Pulmonary endothelial activation by LPS and HLA class I antibodies (V) NET formation (VI) Damaged pulmonary endothelium and leaky capillaries (VII) Pulmonary edema	(I) Fluid accumulation in pulmonary vasculature (II) Hydrostatic pulmonary pressure increased (III) Pulmonary edema	Unknown
Treatment	Supportive with or without mechanical ventilation	Diuretics	Supportive, no response to diuretics

Adapted from van den Akker *et al.* (8), *American Journal of Clinical Pathology*, 2021;156(4), p. 531. TRALI, transfusion-related acute lung injury; TACO, transfusion-associated circulatory overload; TAD, transfusion-associated dyspnea; RBCs, red blood cells; PaO_2, partial pressure arterial oxygen; FiO_2, fraction of inspired oxygen; BNP, brain natriuretic peptide; PMN, polymorphonuclear; BRM, biological response modifier; LPS, lipopolysaccharide; HLA, human leukocyte antigen; NET, neutrophil extracellular traps.

evidence for underlying ARDS is lacking, and the respiratory event fails to meet the criteria for TACO or TRALI. In contrast to TRALI and TACO, published cases of TAD are usually milder; however, more severe or even fatal cases have been reported to hemovigilance surveillance systems (88,89).

Prevention and mitigation

With improved understanding, successful mitigation and prevention strategies have been implemented to reduce the incidence and mortality of TRALI.

Since its commencement in 1996, the UK Serious Hazards of Transfusion (SHOT) hemovigilance collaborative has included TRALI as a reportable adverse event. A review of TRALI cases reported to SHOT between 1996 and 2002, a time when TRALI was the leading cause of transfusion-attributed mortality, revealed important findings (90). The review demonstrated that not only was the rate of TRALI five- to seven-fold greater following transfusion of high plasma volume products (i.e., plasma, platelets re-suspended in plasma) compared to low plasma volume products (i.e., RBCs, cryoprecipitate), but also that TRALI from high plasma volume products was associated with leukocyte antibody-positive female donors (90,91). As a result, in October 2003, the National Blood Services in the UK implemented a policy to minimize transfusion of high plasma volume products from female donors (90). Following this policy, a reduction in TRALI reports was observed from 36 cases in 2003 to 10 in 2006 (25).

In the US, TRALI was also credited as the most frequent cause of transfusion-related death reported to the Food and Drug Administration (FDA) between October 2003 and September 2005, contributing to mortality in approximately 1 in 220,000 transfusion recipients (91). To address this, the Association for the Advancement of Blood and Biotherapies (AABB; formerly, the American Association of Blood Banks), issued TRALI mitigation recommendations and strategies through a series of bulletins. In 2005, AABB Bulletin #05-09 sought to promote further research into the true incidence and pathophysiology behind TRALI (92). This bulletin also included the first recommendations in the US for blood centers to evaluate a person's eligibility to donate with consideration to defer those whose products had been implicated in TRALI. A concurrent interim supplement to the AABB *Standards for Blood Banks and Transfusion Services* (23rd edition) was also published stating, "Donors implicated in TRALI or associated with multiple events of TRALI shall be evaluated regarding their continued eligibility to donate" (92,93).

After the first AABB bulletin, Eder *et al.* published a review of fatal cases of TRALI reported to the American Red Cross (ARC) from 2003 to 2005. The findings mirrored those in the UK with the majority of cases associated with plasma and apheresis-derived platelet components and with leukocyte antibody-positive female donors involved in 75% of fatalities (94). In November 2006, an AABB TRALI working group was formed which proposed additional recommendations in bulletin #06-07 to further reduce the risks of TRALI (91). The recommendations included: (I) blood centers should minimize the preparation of high plasma volume products from donors known to be, or at risk of being, leukocyte-alloimmunized; (II) transfusion services should implement evidence-based practices to minimize unnecessary transfusion; and (III) continued monitoring of TRALI incidence and TRALI-related mortality (91). Mitigation strategies included the use of male donors or never-pregnant females for high plasma volume-containing products intended for transfusion while reserving remaining female donations for further manufacture, or performing leukocyte antibody testing on intended female donors (91). These AABB recommendations were to be implemented by November 2007 for plasma components and whole blood and by November 2008 for platelet components. It was also acknowledged in the bulletin that although FDA-licensed solvent/detergent (S/D)-treated plasma and platelet additive solution (PAS) were unavailable in the US at that time, they had been available in other countries, particularly S/D plasma which was available in Europe since 1992. These strategies could potentially mitigate TRALI risk, given their methods of production (i.e., donor plasma pooling and antibody dilution in the former and donor plasma replacement by additive solution in the latter). Although, PAS may reduce approximately two-thirds of the initial plasma volume in platelets, it is unclear whether this reduction has a substantial impact on the incidence of antibody-mediated TRALI (95). Of interest, the UK had been using S/D plasma as therapeutic apheresis replacement fluid for the treatment of thrombotic thrombocytopenic purpura (TTP) since 2004 as an additional TRALI and variant Creutzfeldt-Jakob disease (vCJD) mitigation strategy (25).

The November 2007 AABB Bulletin, #07-03, published the results of a survey investigating the status of those mitigation recommendations made two years prior (96). The survey found that 86% of responding blood centers or

blood banks in the US had at least partially implemented TRALI risk reduction strategies for plasma, including the use of male donors for plasma intended for transfusion, with or without HLA antibody testing. Conversely, 70% of respondents had not yet begun implementing risk reduction methods for platelets (96).

Subsequent AABB surveys were conducted to again assess the degree to which TRALI mitigation measures had been implemented (97). By September 2009, plasma and platelet measures had been implemented in 98% and 87% of responding institutions, respectively (97). Difficulties were reportedly met with AB group plasma donors. A 2012 survey of 10 large US blood centers reported that while 100% of supplied group O, A, and B plasma were from male, never-pregnant female, or HLA antibody-negative female donors, only 70% of AB group plasma donors met these criteria (97). Despite challenges with AB plasma, since the implementation of these strategies, several sources demonstrated that TRALI rates in the US had declined. In 2008, the ARC successfully achieved a 95% male donor pool for their transfusable plasma components. From 2006 to 2008, they reported an 80% reduction in TRALI cases associated with their products (98). Additionally, a dual center study prospectively looked at TRALI cases from 2006 to 2009 as mitigation strategies were being implemented (16). The strategies including plasma from all male donors (Mayo Clinic) and plasma from male and never-pregnant female donors [University of California, San Francisco (UCSF)] which occurred in 2007 to 2008. Concurrently, reduction of platelets from previously pregnant females (UCSF) and use of predominantly male platelet donors (Mayo) was partially implemented by 2008. The study demonstrated that from 2006 to 2009, TRALI incidence decreased by 68%. Finally, according to the 2011 report of transfusion-related fatalities reported to the FDA, there was an 83% decline in TRALI-related fatalities attributed to plasma from 23 deaths in 2006 to 4 deaths in both 2010 and 2011 (99). The ARC experienced a similar decline in reported TRALI-related fatalities, from 6 in 2006 to none in 2008 (97).

Internationally, similar trends in TRALI incidence have been observed. An international survey was conducted in 2012 to investigate the international experience of conducting risk mitigation measures to lower the incidence of TRALI and whether they were effective (100). As expected, responses varied. While most countries reported exclusive use of non-transfused male plasma donors (i.e., Australia, Canada, Ireland, Italy, Netherlands) in TRALI risk mitigation, some countries expanded this to non-transfused, non-multiparous females donors (i.e., France, Germany), while others hadn't changed donor restrictions at all (i.e., China, Mexico). Furthermore, there were countries that used some S/D plasma, while others used exclusively S/D plasma (i.e., Ireland, Finland, France). Like plasma, platelet donors also varied widely between countries; some using male-only donors, while many countries included never-pregnant or antibody-negative female donors. The use of PAS in place of plasma and PR platelet products was highly variable both between countries and within those with decentralized blood systems. Anti-HLA and anti-HNA antibody-screening protocols for plasma-rich products ranged from only testing donors implemented in suspected TRALI reactions (i.e., Australia, Canada) to screening all female donors for antibodies (i.e., Japan), each using their own testing platforms, including Luminex solid phase testing (Luminex, Austin, TX, USA) and enzyme-linked immunosorbent assay (ELISA) testing. Additionally, many countries reported no antibody screening performed. The effectiveness of these risk reduction strategies have been published by numerous countries. For example, in Germany, risk mitigation measures were implemented in 2008 to 2009 which restricted plasma collections from male, never-pregnant female, or in some cases HLA antibody-negative female donors (26). The number of immune-mediated TRALI cases showed a continuous decrease from 35 in 2006/2007 to 24 in 2008/2009 and 1 in 2010. During the same period, however, the annual number of non-immune-mediated TRALI cases did not change. The Canadian Blood Services implemented similar TRALI mitigation strategies from 2007 to 2008 (101). Since the CCC definition of TRALI in 2004, an increase in reported cases was noted, likely due to an increased awareness. However, following implementation of prevention strategies, a subsequent decline was observed, most notably for plasma-associated cases. A Dutch study also demonstrated a reduction of TRALI cases by 33% following introduction of male-only plasma for transfusion in 2007 (29). Further supporting the success of the mitigation measures, TRALI rates in Australia declined with their use of plasma exclusively from male donors in 2012 and male platelet apheresis donors in 2016 (23). As mentioned previously, the UK was early in implementing TRALI risk reduction measures based on SHOT-reported data with the benefit of decline of TRALI cases.

In 2013, the aforementioned mitigation strategies were published in the 29th edition of the AABB *Standards* to apply

to all plasma units collected after April 1, 2014. *Standard* 5.4.1.2 read, "*plasma and whole blood for allogeneic transfusions shall be from males, females who have not been pregnant, or females who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies*" (102). Additionally, in 2013, S/D plasma received FDA approval in the US and was established to be in conformance to the *Standards* concerning TRALI prevention as a medical alternative for plasma. Testing of S/D plasma provided by one manufacturer (Octapharma, Langenfeld, Germany) demonstrated that no HLA class I or II antibodies were detected in 20 batches of the product, hypothesized to be due to dilution of antibodies through pooling of plasma prior to treatment (103,104). International studies have also supported the benefits of S/D plasma in TRALI prevention. An analysis of cases reported to the French Hemovigilance Network Database from 2007 to 2008, demonstrated that TRALI was implicated in 1 per 31,000 units of fresh frozen plasma (FFP) while no incidence was attributed to the transfusion of S/D plasma (105). However, rare reports have documented that although S/D plasma may lower the incidence of TRALI, the risk is not eliminated (106,107). A Dutch multicenter study compared TRALI cases between FFP and S/D plasma transfusions in the critical care setting. The study, using active surveillance, showed that although TRALI incidence was reduced with S/D plasma (0.45% risk per unit) compared to FFP (0.85% risk per unit), TRALI can still occur with S/D plasma (17).

Management and prognosis

Despite the evolution of definitions and mitigation strategies, TRALI remains a clinical diagnosis with supportive care being the mainstay in management. Immediate management includes supplemental oxygenation and hemodynamic support (i.e., vasopressors). Extracorporeal membrane oxygenation (ECMO) can offer hemodynamic and oxygenation support when needed; however, it is only available at specialized centers (108). Some form of respiratory support, either non-invasive or invasive mechanical ventilator support, is required in almost all cases (109).

Beneficial use of glucocorticoids for ARDS treatment has not been established (110,111). In applying the "two-hit" pathophysiology of antibody-mediated TRALI to a mouse model, methylprednisolone was also not shown to prevent the development of lung injury (112).

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator, which has been shown to reduce the extent to which ECMO is required in persistent pulmonary hypertension of newborns (113). Although guidelines recommend against its use in ARDS due to a lack of mortality benefit and an association with renal dysfunction, there is limited literature describing iNO use in TRALI (114). One case report detailed the use of iNO in TRALI, suggesting its use prevented the need for ECMO (115).

Many novel therapies are being investigated targeting the TRALI inflammatory response but remain to be studied in human trials. Studies have shown that IL-10 levels are low in both murine TRALI models and TRALI patients, but not in TACO, thus suggesting a role for IL-10 therapeutic agents in TRALI management (42,74,116-118). C-reactive protein (CRP), an acute phase reactant elevated in inflammation, is a known "first-hit" risk factor for TRALI (74,119,120). A CRP inhibitor has been developed and may play a promising role in reducing the inflammatory response in TRALI (117,121). The role of intravenous immunoglobulin (IVIg) has also been studied in animal models with success in preventing the onset of TRALI, as well as reducing lung damage (122). However, conflicting reports have described TRALI development after IVIg administration, potentially due to the presence of anti-leukocyte antibodies in the IVIg formulation (41,123). Thus, the benefit of IVIg remains to be further studied. Additional potential immunologic therapeutic strategies include complement targets, osteopontin targets, NET disruption, and TLR4 (endothelial LPS receptor) blockade (41,58,74,108,117).

Ovine models demonstrated that both recipient and blood product factors contribute to the development of TRALI. The majority (80%) of "sick" sheep (i.e., sheep first infused with LPS) developed TRALI when infused with supernatant from stored but not fresh blood compared with "healthy" sheep (i.e., sheep infused with saline). Furthermore, stored RBCs induced a more severe injury than stored platelets, suggesting that outcomes associated with storage lesions are unique to each blood product type. The investigators hypothesized that transfusion of fresher RBCs may minimize TRALI risk (124,125).

A role for antiplatelet agents in TRALI has been suggested with inconclusive efficacy. In one study, platelet depletion and aspirin pre-treatment were seemingly protective against TRALI development in LPS-primed mice infused with anti-MHC class I antibodies (69). These finding were replicated in later papers (75,126). The protective effect of antiplatelet agents was thought to be secondary to the reduction of platelet and PMN

sequestration in the lungs. Other studies, however, have failed to demonstrate this protective effect in critically ill patients (127).

Finally, as TRALI is not associated with volume overload, diuretics are not effective, or indicated, in its management.

While early reports by Popovsky *et al.* favorably described resolution of hypoxemia within 48 hours through supportive management, later studies demonstrated that TRALI may not always resolve so quickly (5,128-130). Unlike ARDS, the lung injury in TRALI is usually transient with clinical improvement seen in ~80% of cases within 48 to 96 hours (109). The remaining subset of cases can experience a protracted course, some with a fatal outcome. One prospective study demonstrated that compared to transfused controls, patients with TRALI and pTRALI had tachypnea, hypotension, prolonged hypoxemia, fever, and tachycardia, of which 78% required mechanical ventilation, 25% required vasopressors, and 17% died (131). Furthermore, those with TRALI and pTRALI showed increased duration of mechanical ventilation, more intensive care unit (ICU) days, and longer hospital stays. Despite supportive care, including measures used in ARDS management (e.g., lung protective ventilation, appropriate use of neuromuscular blocking agents, prone positioning, and conservative fluid management), TRALI outcomes may be fatal. TRALI-related fatalities were the leading cause of transfusion related deaths reported to the FDA prior to/during early implementation of mitigation strategies, comprising 34% of reported deaths between fiscal years 2012 to 2016 (132). Between 2016 and 2020, however, this number dropped to 21% of transfusion-related deaths reported to the FDA, behind TACO (34%) (87).

Limitations and the next steps

While we aim to provide a comprehensive understanding of TRALI with a look into how that understanding has shaped mitigation measures to reduce incidence, we recognize that there are still limitations preventing the complete eradication of these potentially severe transfusion complications. With the use of male-only, never-pregnant female, or leukocyte antibody-negative female donors for high plasma volume components intended for transfusion, there have been successful reductions of the overall incidence of cases and associated fatalities, internationally. TRALI, however, occurs from a combination of patient and donor factors, with current prevention strategies focusing on the donor aspect of antibody transfer. Therefore, as stated in the German study by Funk *et al.* and reiterated by Fung and Tung, these selective measures have little to no effect on the non-antibody mediated cases of TRALI, leaving non-antibody mediated mechanisms to be further investigated (26,133).

Conclusions

As a broader understanding of the risks and pathophysiology of TRALI has been established, the definition has been refined allowing for improvements in reporting and case surveillance via hemovigilance programs. Improved reporting has provided the opportunity to observe the outcomes of mitigation strategy implementation, with global reductions of TRALI cases as well as TRALI-associated mortality. Additionally, research has not only contributed to better understanding of TRALI, but has also inspired the development of novel therapeutic agents which hold promise for successful treatment of TRALI beyond supportive care in the future. Finally, although improved reporting of TRALI is imperative, the importance of reporting all adverse events to improve patient safety and to minimize associated morbidity and mortality should be emphasized. Such reporting will aid in identifying trends in new emerging adverse events as described eloquently by the NHSN (11).

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://aob.amegroups.com/article/view/10.21037/aob-23-39/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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