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Transfusion-related Acute Lung Injury: 36 Years of Progress (1985–2021)

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Abstract

The term transfusion-related acute lung injury (TRALI) was coined in 1985 to describe acute respiratory distress syndrome (ARDS) after transfusion, when another ARDS risk factor was absent; TRALI cases were mostly associated with donor leukocyte antibody. In 2001, plasma from multiparous donors was implicated in TRALI in a randomized controlled trial in Sweden. In 2003 and in many years thereafter, the U.S. Food and Drug Administration reported that TRALI was the leading cause of death from transfusion in the United States. In 2003, the United Kingdom was the first among many countries to successfully reduce TRALI using male-predominant plasma. These successes are to be celebrated. Nevertheless, questions remain about the mechanisms of non-antibody TRALI, the role of blood products in the development of ARDS in patients receiving massive transfusion, the causes of unusual TRALI cases, and how to reduce inaccurate diagnoses of TRALI in clinical practice. Regarding the latter, a study in 2013–2015 at 169 U.S. hospitals found that many TRALI diagnoses did not meet clinical definitions. In 2019, a consensus panel established a more precise terminology for clinical diagnosis: TRALI type I and TRALI type II are cases where transfusion is the likely cause, and ARDS are cases where transfusion is not the likely cause. For accurate diagnosis using these clinical definitions, critical care or pulmonary expertise is needed to distinguish between permeability versus hydrostatic pulmonary edema, to determine whether an ARDS risk factor is present, and, if so, to determine whether respiratory function was stable within the 12 hours before transfusion.

Keywords: transfusion-related acute lung injury; transfusion reaction; pulmonary edema; blood transfusion; respiratory distress syndrome

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The Curious Story of Donor Antibodies and Transfusion-related Acute Lung Injury

The term transfusion-related acute lung injury (TRALI) was coined in 1985 (1) (Figure 1). This condition had been described by many different names. Unifying them under one name that states the mechanism—the acute lung injury is related to the transfusion—facilitated diagnosis and enabled research. Why is this review written 36 years later? The reason is that we now understand clinical TRALI enough to define the condition correctly and in more detail. Although intensivists have replaced the term "acute lung injury" with acute respiratory distress syndrome (ARDS) according to the 2012 Berlin definition (2), the familiar term "TRALI" has been retained for transfusion-related ARDS. TRALI was first defined as noncardiogenic ARDS after transfusion in patients without other known causes of ARDS (1). In their 2-year prospective study at an academic center, the investigators studied TRALI in both medical and surgical

patients, both intraoperatively and postoperatively, and found that most of the 36 patients who developed TRALI received donor leukocyte antibodies. Since then, other investigators have conducted retrospective reviews of patients who also received plasma from an implicated donor in TRALI cases (3, 4) and surprisingly found that most other recipients did not develop TRALI, even though they received cognate antibodies—that is, the donor antibodies matched the recipient's antigens.

These intriguing findings raised questions. For example, why did not all recipients of cognate antibody develop TRALI? Can TRALI be completely prevented? What causes non-antibody TRALI? Because there is no diagnostic laboratory test, how is TRALI defined when the patient has another risk factor for ARDS? Some of these questions have been answered (5), but the answers have been refined and new questions continue to be raised.

According to PubMed (January 1985 through November 28, 2021), 1,191 original articles and reviews on TRALI have been published, including experimental as well as clinical studies of TRALI. This review focuses primarily on changes in nomenclature that improved diagnosis, key clinical studies that led to a decrease in TRALI, and clinical questions that remain to be answered. A timeline in the history of TRALI since 1985 is shown in Figure 1.

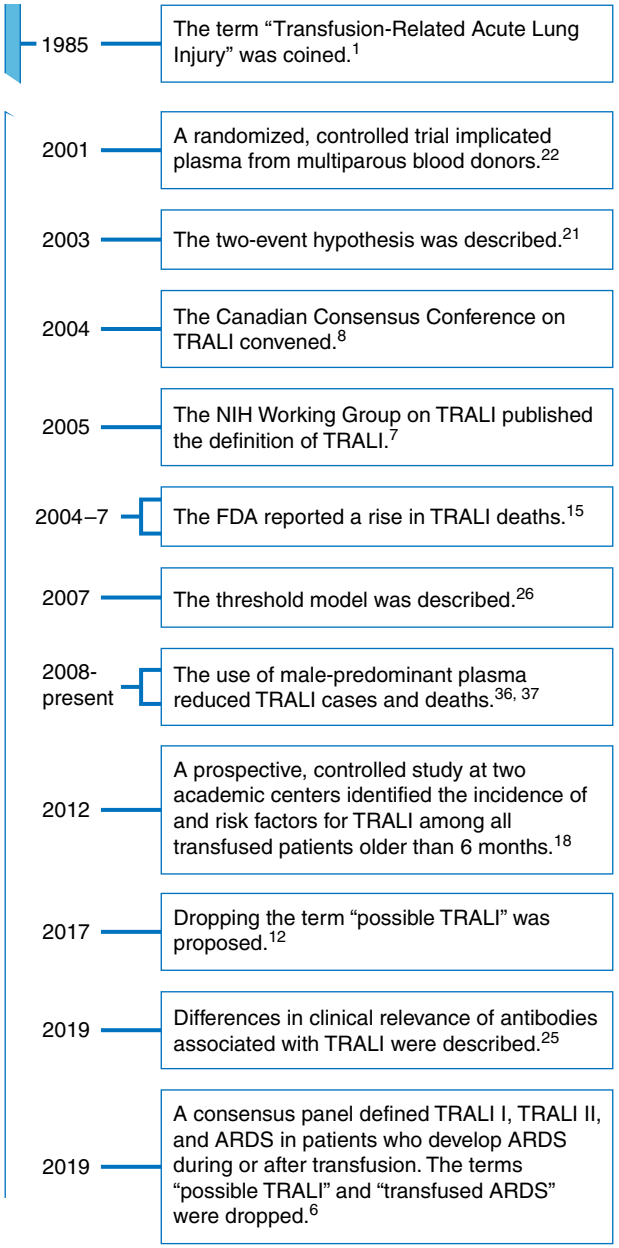

Figure 1. Timeline history of transfusion-related acute lung injury (TRALI). ARDS = acute respiratory distress syndrome; FDA = U.S. Food and Drug Administration; NIH = National Institutes of Health.

Clinical Definitions

Because there is no specific laboratory test for TRALI, current diagnosis is still based on criteria that depend on clinical information, such as whether the patient has another ARDS risk factor, and if so, whether the patient's respiratory status was stable in the 12 hours before transfusion (6) (Table 1).

1. The patient does not have another ARDS risk factor: The nomenclature has been updated from TRALI to TRALI type I (6). As background, the National Heart, Lung, and Blood Institute TRALI Working Group defined TRALI as acute lung injury during or within 6 hours of transfusion in the absence of another risk factor for ARDS (7), and the Group's definition was presented at the Canadian Consensus Conference (8) (Figure 1). In 2019, a consensus panel updated the previous diagnosis of TRALI to TRALI type I (6) (Table 1).
2. The patient does have another ARDS risk factor, but the patient's respiratory function was stable in the 12 hours before transfusion: The new nomenclature is TRALI type II (6). In such cases, the ARDS risk factor was present but did not worsen the patient's respiratory function, and the transfusion precipitated ARDS. The transfusion likely caused the ARDS (Table 1).
3. The patient does have another ARDS risk factor, and the patient's respiratory function was already worsening in the 12 hours before transfusion: Because the ARDS risk factor likely caused ARDS rather than the transfusion (Table 2), the nomenclature for this condition has been updated from possible TRALI to ARDS (6) (Table 1).

Table 1. Differential diagnosis of acute respiratory distress syndrome during or within 6 hours after transfusion

	Presence of an ARDS Risk Factor	Respiratory Function within 12 h before Transfusion	Likely Cause of the ARDS during or within 6 h after the End of Transfusion
TRALI, type I	No	Stable	Transfusion
TRALI, type II	Yes	Stable	Transfusion
ARDS	Yes	Worsening	ARDS risk factor

Definition of abbreviations: ARDS = acute respiratory distress syndrome; FI_{O_2} = fraction of inspired oxygen; P/F = Pa_{O_2}/FI_{O_2}; Pa_{O_2} = arterial oxygen tension/pressure; TRALI = transfusion-related acute lung injury.
TRALI type I indicates patients who develop ARDS during or within 6 hours of transfusion and have no risk factors for ARDS (6). The transfusion likely caused the ARDS. TRALI type II indicates patients who have risk factors for ARDS (e.g., sepsis) but who have not been diagnosed with ARDS or who have existing mild ARDS (P/F of 200–300); their respiratory status was stable in the 12 hours before transfusion, and ARDS developed during or within 6 hours after transfusion. The transfusion likely caused the ARDS. Patients with ARDS are those who have ARDS risk factors (e.g., sepsis), and their respiratory function was already worsening in the 12 hours before transfusion. Their ARDS risk factor likely caused the ARDS.

As background, in the past, it was difficult to classify transfused patients who had another ARDS risk factor. To address this difficulty, the Canadian Consensus Conference in 2004 provided the term possible TRALI, which refers to cases in which another ARDS risk factor in addition to transfusion is present (8). ARDS risk factors include conditions that cause direct or indirect injury to the lungs (9). Subsequent substantial evidence did not support transfusion as a risk factor in possible TRALI cases (10, 11), and replacing the term possible TRALI with "transfused ARDS" was considered (12) (Figure 1). However, the term transfused ARDS was still ambiguous, because it might imply that transfusion was the cause. To clarify these ambiguities, a consensus panel recommended in 2019 that these cases be classified as ARDS (6). Thus, the ambiguous terms possible TRALI and transfused ARDS are no longer recommended (6) (Figure 1).

Differential Diagnosis

TRALI can be confused with transfusion-associated circulatory overload (TACO), and the definitions for both were updated in 2019 (6, 13). TRALI is transfusion-related ARDS, which is an increased permeability pulmonary edema; TACO is transfusion-associated hydrostatic pulmonary edema due to heart failure and/or intravascular volume overload. Details regarding how to distinguish between permeability versus hydrostatic pulmonary edema are well known to critical care specialists, pulmonologists, and cardiologists (9, 14). However, especially for patients with TACO who are not monitored in intensive care, the diagnosis may be difficult.

In the U.S. Food and Drug Administration Fiscal Year 2019 report, TRALI and TACO represented the leading causes of transfusion-associated death (15). In practice, when TRALI cannot be distinguished from TACO even by the best intensivists, these cases are categorized as TRALI/TACO, and criteria for this condition have been published (6, 13). Proposed diagnostic tests to differentiate these two conditions, such as N-Terminal-proB-type Natriuretic Peptide (NT-proBNP), will require prospective clinical studies to test predictive utility (16).

In another condition, hematopoietic stem cell transplantation, TRALI is one of many possible causes of ARDS (17). In a large controlled study of TRALI, hematopoietic stem cell transplant and hematologic malignancy were not risk factors for TRALI when the multivariate analysis was controlled for other risk factors (18).

Finally, and importantly, even though rare after the introduction of bacterial screening, bacteria in the blood product can also cause ARDS after transfusion. The sepsis can be fatal if undetected, so when infection is recognized, the patient must be promptly treated with antibiotics. Components not yet transfused from the same donation must be promptly quarantined by the blood bank and not transfused to other patients (19).

Clinical Course

In a prospective, controlled study of TRALI and possible TRALI, clinical course has been described (20). Patients with TRALI developed fever, tachycardia, tachypnea, hypotension, and prolonged hypoxemia. Mechanical ventilation was required to treat the acute respiratory failure in 78% of cases, and 25% required initiation of vasopressors; 15 of 89 patients with TRALI (17%) died (20), a rate higher than in other common transfusion reactions. Patients with TRALI had evidence of more systemic inflammation, with increases in circulating neutrophils and a decrease in platelets compared with control subjects. Treatment of TRALI is the same as the treatment of ARDS and focuses on supportive care, including lung-protective ventilation and a fluid conservative approach once shock has resolved (9).

Substantial Evidence That Possible TRALI Is Not Likely Transfusion-mediated

The 2019 consensus panel (6) dropped the term possible TRALI and added the term ARDS. The evidence that possible TRALI is not likely transfusion-mediated has been summarized as follows (12). Unlike TRALI case rates, possible TRALI case rates were not higher in recipients of anti-human leukocyte antigen (HLA)–positive versus anti-HLA–negative plasma-rich components (8). Unlike TRALI cases, increasing number of units received did not increase the risk of possible TRALI (11). Unlike TRALI cases, receipt of plasma or whole blood from female donors was not a risk factor for possible TRALI (11). Unlike TRALI cases, the male predominant plasma strategy did not decrease the incidence of possible TRALI cases when not combined with TRALI cases (18). Unlike TRALI cases, mortality in possible TRALI cases was not lower than that observed in ARDS (20). Because TRALI and

Table 2. Risk of transfusion versus other acute respiratory distress syndrome (ARDS) risk factors in causing ARDS

Risk Factor	Risk of ARDS
Pneumonia requiring ICU care	12% of patients with the risk factor
Septic shock	47% of patients with the risk factor
Sepsis syndrome without hypotension	29% of patients with the risk factor
Aspiration of gastric contents	15–36% of patients with the risk factor
Near drowning	33% of patients with the risk factor
Disseminated intravascular coagulation	22% of patients with the risk factor
Drug overdose requiring ICU care	9% of patients with the risk factor
Fracture of long bones or pelvis	5–11% of patients with the risk factor
Transfusion after male-predominant plasma had been implemented	
UK reported cases in 2005–2006 (38)	0.00032% per unit of plasma, 0.00058% per unit of platelets;
U.S. active surveillance study in 2009 (18)	0.00081% per unit (all units)

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ICU = intensive care unit. Transfusion-related acute lung injury cases are rare, especially after male-predominant plasma was implemented (3–8 cases per million units transfused), whereas ARDS due to other risk factors is much more common (5–47 cases per hundred patients with the risk factor). Thus, in a transfused patient who has an alternate ARDS risk factor, the cause of the ARDS is much more likely the alternate ARDS risk factor rather than the transfusion. (Adapted by permission from Reference 7.)

possible TRALI are distinct conditions, analyses and interpretations of data from studies that combined TRALI and possible TRALI groups may have limitations.

Mitigation of Risk Factors

In 2003, it was proposed that TRALI is a two-hit phenomenon (Figure 1), with predisposing factors in the patient comprising the first hit and transfusion factors comprising the second hit (21). As expected, the risk is highest when both patient and transfusion factors are present, and, indeed, both sets of risk factors were found by multivariate analysis in a prospective controlled study of all transfused patients over 6 months of age at two academic centers (18) (Figure 1).

In terms of patient risk factors, inflammation before transfusion, as indicated by elevated concentrations of plasma IL-8 (interleukin 8), was associated with increased risk (18, 21). Other patient factors are those known to be associated with increased risk for ARDS (18). In terms of mitigation of patient risk factors, reduction in patient risk factors, including inflammation, chronic alcohol abuse, and smoking, are challenging to achieve, but physicians can control peak airway pressure in mechanically ventilated patients and reduce positive fluid balance (9, 18).

In terms of transfusion risk factors, receipt of plasma from female donors is a risk. In 2001, evidence was shown in a double-blind, crossover, randomized controlled trial in Sweden (22) (Figure 1), in which 105 intensive care patients were closely monitored with respect to pulmonary function after transfusion of plasma from multiparous donors versus from nonimmunized donors (no transfusion or pregnancy). The incidence of HLA antibodies in female donors with zero, one to two, and three or more pregnancies have been reported to be 7.8%, 14.6%, and 26.3%, respectively (23). Transfusion of maternal blood was similarly a risk for TRALI in pediatric patients undergoing spinal surgery (24). Mitigation of TRALI by reducing transfusion of donor leukocyte antibody is described below.

Which leukocyte antibodies are clinically relevant? The risk is now known to be higher if the patient receives larger amounts of donor plasma containing stronger anti-HLA class II cognate antibody and/or granulocyte antibody (18). An expert review (Figure 1) pointed out that the leukocyte antibodies that cause TRALI are granulocyte antibodies and HLA class II antibodies; rarely, HLA class I antibodies alone can cause TRALI if they are strong and agglutinate leukocytes *in vitro* (25). In contrast, transfusion of leukocyte antibody (10) and transfusion of plasma from female donors (11) were not associated with a higher incidence of possible TRALI, further suggesting that possible TRALI is not transfusion-mediated (12).

The curious question at the beginning of this review was why many previous recipients of leukocyte antibody did not develop TRALI (3–5). Data now support the concept that the combined patient and transfusion risk factors must reach a threshold before TRALI develops (25, 26) (Figure 1). The patient may not have had inflammation or other patient risk factors (18). The patient may not have received cognate antibody. The cognate antibody received may have been weak, as measured quantitatively by mean fluorescence intensity (MFI) for HLA antibodies, or the quantity of cognate antibody received may have been small, as measured by MFI times the volume of plasma transfused (18). Cognate HLA class I antibodies received may not have been strong (low MFI) and were unable to agglutinate neutrophils (25).

Pathophysiology

A two-hit model of neutrophil-mediated proinflammatory endothelial activation and pulmonary endothelial damage that requires adherence and chemokine release has been carefully described (21, 27).

Inflammation is commonly an important first hit in the pathogenesis of TRALI. Lung pathology in fatal TRALI cases (28) and in experimental models (29) has revealed the prominent presence of neutrophils in lung capillaries. In transfusion recipients, increased pretransfusion IL-8 was associated with greater risk for TRALI (18, 21). Inflammation in the lungs was found in transfused cardiac surgery patients (30). Cytokines, chemokines, and cell-derived particles in the supernatant of red blood cell units may cause a proinflammatory response in the recipient (31).

Transfusion of donor antibodies has been found to be the important risk factor in controlled clinical studies and is a well-established cause of TRALI (18, 25, 32, 33). Direct endothelial damage by complement-fixing antibodies may lead to a neutrophil response. Activated platelets are also important contributors to lung pathology (34) and can induce the formation of neutrophil extracellular traps (NETs) (35). NETs are composed of decondensed chromatin decorated with granular proteins that function to trap extracellular pathogens and, in one study, have been detected in the lungs and plasma of patients with TRALI (35). These findings indicate that NETs may contribute to lung endothelial injury in TRALI in humans. In addition, one study

found that post-transfusion complement activation increases in human TRALI, and the increase may facilitate NET release and pulmonary endothelial injury (36).

The pathophysiology of TRALI is complex. The contributions of other immune inflammatory mediators and cells have been found in experimental studies (37), such as bioactive lipids that accumulate in stored platelets (38) and macrophages (39). A complete review of experimental studies is beyond the scope of this review, which is focused primarily on clinical studies.

Remarkable Progress in the Prevention of TRALI

The incidence of TRALI has decreased in many countries because of the switch to plasma from male-predominant donors, the United Kingdom being the first country to start this proactive action in late 2003 (40) (Figure 1). TRALI decreased in the United Kingdom after the implementation of male-predominant plasma and platelets, the risk of highly likely/probable TRALI due to fresh frozen plasma falling from 15.5 per million units issued during 1999 through 2004 to 3.2 per million during 2005 through 2006 ($P = 0.0079$) and from 14.0 per million to 5.8 per million for platelets (41). In the United Kingdom, 100% of hospitals participate in reporting to Serious Hazards of Transfusion; even though the reporting is comprehensive, TRALI is now a rare cause of death, and TACO is much more important (42). TRALI has decreased (43) in other countries that used male-predominant plasma or solvent-detergent plasma that is pooled from multiple donors and thus dilutes donor antibodies (Figure 2). One case of TRALI was reported after transfusion of solvent-detergent plasma, but the footnote below Table 2 in the article stated that the expert panel could not rule out TACO (44).

The reported incidence of a disease is almost always higher—and perhaps also more accurate—with active surveillance than with passive reporting, because cases are less likely to be missed. Thus, it is worth noting that a prospective study with active surveillance also showed a decrease in TRALI after the switch to male-predominant plasma transfusion. Figure 3 shows that the rate of TRALI decreased by two-thirds (18). Significant underreporting was unlikely in this study (18), because all inpatients and outpatients older than 6 months were prospectively monitored for hypoxemia ($Pa_{O_2}/F_{I_{O_2}} < 300$ mm Hg) within 12 hours after issue of any blood component from the blood bank by 24/7 electronic surveillance of arterial blood gas results and blood bank records in the hospital laboratory information system.

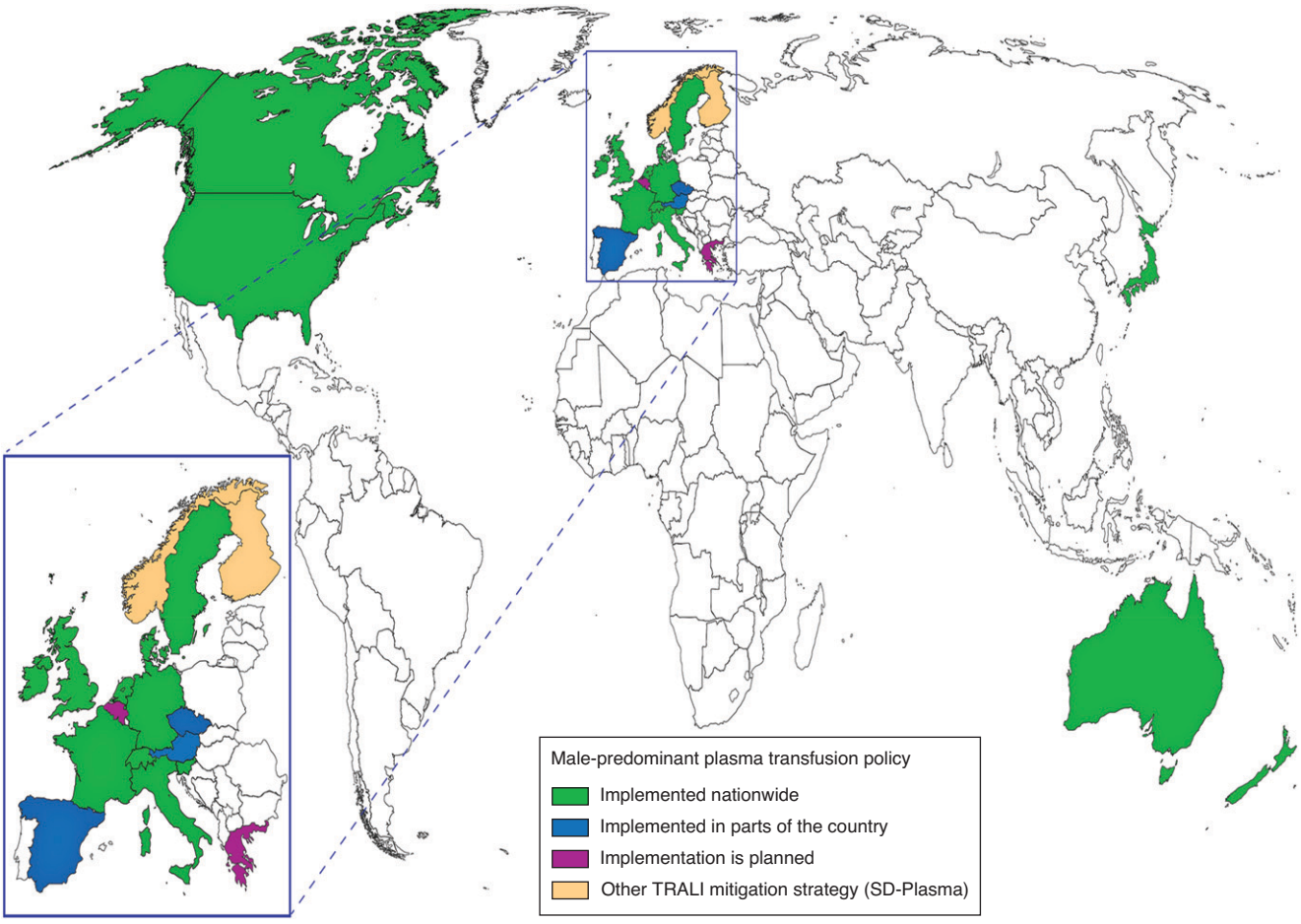

Figure 2. Transfusion-related acute lung injury (TRALI) mitigation strategies for plasma transfusions that have been adopted by different countries by 2015 (adapted by permission from Reference 43). SD = solvent-detergent.

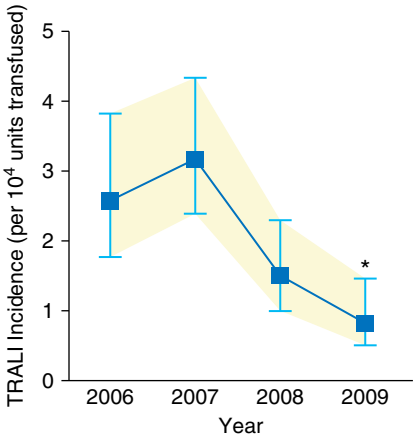

Figure 3. Transfusion-related acute lung injury (TRALI) incidence by year in a prospective study at two academic medical centers (2006–2009) (18). Reduction of high-risk plasma was implemented from 2007 to 2008. In 2006, neither center had started TRALI mitigation. In 2009, both centers had completed TRALI mitigation. The annual TRALI incidence decreased from 2.57 (95% confidence interval [CI], 1.72–3.86) per 10,000 units transfused (23 cases/89,321 units) in 2006 to 0.81 (95% CI, 0.44–1.49) per 10,000 units transfused (10 cases/123,731 units) in 2009. *$P < 0.002$.

Remaining Questions

Questions remain, including whether blood products are the cause of ARDS after massive transfusion in injured patients, what are the causes of non-antibody TRALI, and how to improve accuracy of diagnosis in clinical practice.

Role of Transfusion in Trauma Patients Who Develop ARDS after Transfusion

Massive transfusion has long been considered a risk factor for ARDS. In the past, microaggregates in blood transfusions were believed to be the cause of ARDS after massive transfusion, but investigators were unable to demonstrate an advantage to the use of micropore filtration in preventing ARDS (45). We now know that donor leukocyte antibody is likely the risk factor for ARDS, when large volumes of plasma from female donors are transfused (18). When male-predominant plasma is used, whether massive transfusion should remain an ARDS risk factor may need to be revisited in future studies.

After the switch to transfusion of male-predominant plasma, it seemed likely that transfusion should play a reduced role in ARDS associated with injury and hemorrhage. In support of this prediction, in two reports (46, 47), acute crystalloid exposure, but not blood products, was found to be a risk factor for lung edema in injured patients. When one total blood volume is lost (when 10 units of red blood cells are transfused to an adult), replacement with crystalloid infusion without plasma predictably lowers the patient's plasma albumin, which reduces protein osmotic pressure and can increase extravascular tissue fluid.

Studies of TRALI cases without ARDS risk factors found most TRALI cases to be antibody-mediated (1, 48). However, in a study in which the TRALI group included patients with hemorrhagic shock (18), curiously, only half of the TRALI cases were antibody-mediated. Possible explanations are higher cutoffs for positive antibody tests in this study or that the shock caused the ARDS in non-antibody cases in this study.

Non–Antibody-mediated TRALI

Another important question is what are the causes of non-antibody TRALI in humans? Biologic response modifiers in blood products were suggested to be causes of TRALI in humans, but evidence has not been found in two reviews (48–50). Further human studies did not find that 35-day-old stored red blood cells or lipids that accumulate in stored blood products cause TRALI (51–53).

Antibody-mediated TRALI can be missed. Red blood cell units have been implicated in TRALI (15). Unlike male-predominant plasma, red blood cell units are donated by both males and females, and some of these apparently non-antibody TRALI cases could perhaps be due to strong antibody in red blood cell units from female donors.

The Berlin list (2) is a short list of the most common ARDS risk factors. Many other causes of ARDS have been identified, and pulmonary reactions to new therapies such as novel immunotherapies continue to emerge; thus it is possible that some of what is now termed non-antibody TRALI may be ARDS (5).

Other TRALI Cases

Reverse TRALI cases continue to be reported and may be lethal (54). It is a condition where the antibodies are in the recipient, especially in multiparous recipients, instead of being in donor blood. The recipient antibodies are directed at transfused donor leukocytes. Also, acute lung injury after exchange transfusion in two newborns with glucose-6-phosphate dehydrogenase deficiency has been reported (55).

Inaccuracy of Diagnoses in Practice

In contrast to clinical research studies focused on TRALI, in everyday practice the diagnosis of TRALI is often not accurate. In one study, medical chart retrospective review from 2013 to 2015 at 169 U.S. hospitals found that many potential TRALI cases identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes did not meet clinical definitions (56). The key skills required for the diagnosis of TRALI using current definitions (6) are the ability to identify ARDS risk factors, the ability to distinguish between increased permeability pulmonary edema (TRALI) versus hydrostatic pulmonary edema (TACO), and the ability to determine whether pulmonary function was deteriorating in the 12 hours before transfusion in a patient with an ARDS risk factor. Critical care and pulmonary physicians have the skills to make these decisions and are invaluable as consultants to assist in the differential diagnosis of pulmonary edema after transfusion.

The successful mitigation of TRALI by using safer plasma blood products is a major triumph in the field. However, not all countries have implemented TRALI mitigation (43) (Figure 2). The 2019 new definitions (6) need to be widely implemented, and questions remain to be answered. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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