A consensus redefinition of transfusion-related acute lung injury

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BACKGROUND: Transfusion-related acute lung injury (TRALI) is a serious complication of blood transfusion and is among the leading causes of transfusion-related morbidity and mortality in most developed countries. In the past decade, the pathophysiology of this potentially life-threatening syndrome has been increasingly elucidated, large cohort studies have identified associated patient conditions and transfusion risk factors, and preventive strategies have been successfully implemented. These new insights provide a rationale for updating the 2004 consensus definition of TRALI.

STUDY DESIGN AND METHODS: An international expert panel used the Delphi methodology to develop a redefinition of TRALI by modifying and updating the 2004 definition. Additionally, the panel reviewed issues related to TRALI nomenclature, patient conditions associated with acute respiratory distress syndrome (ARDS) and TRALI, TRALI pathophysiology, and standardization of reporting of TRALI cases.

RESULTS: In the redefinition, the term "possible TRALI" has been dropped. The terminology of TRALI Type I (without an ARDS risk factor) and TRALI Type II (with an ARDS risk factor or with mild existing ARDS) is proposed. Cases with an ARDS risk factor that meet ARDS diagnostic criteria and where respiratory deterioration over the 12 hours before transfusion implicates the risk factor as causative should be classified as ARDS. TRALI remains a clinical diagnosis and does not require detection of cognate white blood cell antibodies.

CONCLUSIONS: Clinicians should report all cases of posttransfusion pulmonary edema to the transfusion service so that further investigation can allow for classification of such cases as TRALI (Type I or Type II), ARDS, transfusion-associated circulatory overload (TACO), or TRALI or TACO cannot distinguish or an alternate diagnosis.

ABBREVIATIONS: ARDS = acute respiratory distress syndrome; BNP = brain natriuretic peptide; CCC = Canadian Consensus Conference; GIFT = granulocyte immunofluorescence test; ISBT = International Society for Blood Transfusion; LAH = left atrial hypertension; LPS = lipopolysaccharide; PEEP = positive end-expiratory pressure; P/F = PaO2/FiO2; pTRALI = possible TRALI; TACO = transfusion-associated circulatory overload; TAD = transfusion-associated dyspnea.

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In 2004, Canadian Blood Services convened a (Canadian) Consensus Conference (CCC) on transfusion-related acute lung injury (TRALI).[1] The outcome of the CCC was to formulate a standardized definition of TRALI to facilitate research on its epidemiology, pathophysiology, and risk mitigation (i.e., prevention) as well as to provide a framework for decisions about appropriate case investigation and donor testing. The CCC defined two entities: TRALI and possible TRALI (pTRALI). The latter category was established for patients with a clinical syndrome that met the TRALI definition but who concurrently had a risk factor for the acute respiratory distress syndrome (ARDS). These two categories were created to explore whether they represented separate groups from epidemiologic and/or pathophysiologic perspectives and, through ongoing research, to determine whether pTRALI cases were due to transfusion versus a nontransfusion ARDS risk factor.

Considerable information from prospective and retrospective research studies and from hemovigilance (HV) systems has accumulated in the 14 years since the CCC.[2] For the most part, these studies and/or hemovigilance summaries have reported their data using the CCC definitions, although a careful reading of the literature reveals that certain aspects of the definitions were applied differently. For example, studies have not been uniform in how they distinguished TRALI from pTRALI and, due to small numbers of cases, some studies have reported these outcomes in aggregate rather than separately.[3]

Several groups have synthesized this accumulated information and made recommendations for and against changes in the definitions of TRALI and pTRALI.[4–8] Several of the authors of these publications decided that a substantial contribution could be made if a more stringent and inclusive review process was undertaken. Another motivation for this effort was the recognition that pulmonary medicine experts had redefined acute lung injury (ALI) and ARDS at a 2012 consensus conference in Berlin (referred to as the Berlin definition), but the transfusion medicine field had yet to incorporate this information in its consideration of TRALI.[9]

A panel of experts was convened and agreed that the current TRALI definition no longer encompassed all current knowledge on the subject and decided to reconsider the definition of TRALI including criteria for diagnosis, clinical findings, timing of onset, and relationship to ARDS risk factors. In addition, the panel broadened out its review to include issues related to TRALI nomenclature, conditions associated with ARDS and TRALI, TRALI pathophysiology, differential diagnosis (e.g., distinguishing TRALI from transfusion-associated circulatory overload [TACO]), and standardization of the reporting of TRALI case data both in research and in hemovigilance settings. This article reports the results of the panel's work and identifies areas for further inquiry.

MATERIALS AND METHODS

The TRALI redefinition and other TRALI-related recommendations proposed in this article resulted from application of Delphi panel method, a method used to achieve expert consensus.[10] It represents a structured process to collect knowledge by defining a problem, selecting a panel of experts, developing questions to resolve using open-ended questionnaires, and performing controlled assessment and feedback until consensus is established.

The TRALI Delphi panel consisted of 10 international experts. Most were academics and clinicians who had conducted and published TRALI related research or policy articles. The panel included two hemovigilance experts: one recommended by AABB and one by the International Society for Blood Transfusion (ISBT) based on their TRALI expertise. The panel co-chairs (AV and SK) drafted the first round of questions (Appendix S1) sent to the panel. Responses were then collated anonymously by a panel secretary (AP) and summarized and discussed on a conference call. This gave rise to the co-chairs generating a second round of questions, some of which reexamined first round questions for which there was not yet consensus (Appendix S1). In total two Delphi rounds took place. Several subsequent teleconferences and e-mail exchanges were held to discuss issues and obtain consensus.

RESULTS

TRALI redefinition and proposed new nomenclature

The 2004 CCC definitions introduced the term pTRALI for patients who fulfilled the clinical criteria for TRALI in the presence of an ARDS risk factor. The use of the word "possible" was intended to indicate that it was unclear whether the ARDS risk factor or the transfusion was causing the ALI (Table 1).[1] Thus, application of this definition resulted in cases where an ARDS risk factor was present being excluded as TRALI cases and also resulted in cases of ARDS being classified as pTRALI.[11]

Clinical and preclinical studies have shown that an inflammatory "first hit" is almost always present before TRALI onset,[12] and some clinical studies have identified ARDS risk factors that may also be TRALI risk factors (see below).[13–16] Analysis of these data led our panel to recommend dropping the pTRALI terminology and, instead, using clinical criteria and clinical judgment to classify such patients as either having TRALI or having ARDS. This approach is similar to one originally proposed by the NHLBI Working Group on TRALI.[17] Additionally, we propose that TRALI be further subclassified into two categories: TRALI Type I (without an ARDS risk factor) and TRALI Type II (with an ARDS risk factor or with existing mild ARDS; Tables 2 and 3). For a case to be classified as TRALI Type II, the case must meet three conditions: 1) fulfill the same clinical criteria as TRALI Type I (see Table 2, TRALI Type I, Section a); 2) the onset of posttransfusion pulmonary edema occurred in the presence of an ARDS risk factor or mild ARDS; and 3) there has been a stable pulmonary status (e.g., based on PaO_2/FiO_2 [i.e., P/F] ratio) in the 12 hours before transfusion. Cases that meet the first two criteria but did not meet the third

TABLE 1. 2004 CCC definition of TRALI and possible TRALI

1. TRALI	a. i. Acute onset	
	ii. Hypoxemia	Research setting: P/F ≤ 300 or SpO_2 < 90% on room air Nonresearch setting: P/F ≤ 300 or SpO_2 < 90% on room air or other clinical evidence of hypoxemia
	iii. Bilateral infiltrates on chest radiograph	
	iv. No evidence of LAH and/or central venous pressure <18 mmHg	
	b. No existing ALI before transfusion	
	c. During or within 6 hr of transfusion	
	d. No temporal relationship to an alternative risk factor for ALI	
2. Possible TRALI	a. As mentioned above	
	b. In the presence of an alternative risk factor for ALI	

criterion should be classified as ARDS unless the case lacks documentation that the P/F ratio is less than 300. In this latter circumstance, the case should be classified as transfusion-associated dyspnea (TAD).

Harmonization of the new TRALI definition with the Berlin ARDS definition

The 1994 American European Consensus Criteria (AECC)[18] for diagnosing ALI or ARDS was updated by pulmonary medicine experts in 2012.[19] In this updated definition (i.e., the Berlin definition), the term ALI was dropped and replaced by mild ARDS. Nevertheless, because TRALI terminology is entrenched in transfusion medicine and hemovigilance systems worldwide, we propose retaining the term TRALI and not changing it to TR-ARDS.

Our new definition is aligned with most of the Berlin criteria. First, we slightly altered the 2004 CCC list of ARDS risk factors to more closely parallel those in the Berlin definition with some minor deviations (Table 4), based on the premise that the Berlin list was vetted and approved by numerous ARDS experts but did not fully consider the transfusion setting. Specifically, consistent with the 2004 CCC, we agree that multiple (massive) transfusions should not exclude a case as TRALI Type I; however, if a multiply transfused patient had an ARDS risk factor, the case would be further evaluated and then classified as TRALI Type II, ARDS, or TAD (as discussed above and below). Second, in line with the Berlin definition, we revised the diagnostic criteria for bilateral pulmonary edema and left atrial hypertension (LAH) by including use of additional diagnostic imaging modalities such as chest CT scan or lung ultrasound (Table 2). Given the declining use of pulmonary artery catheters, the pulmonary artery wedge pressure criterion was removed from the LAH criterion. Also, because hydrostatic pulmonary edema in the form of cardiac failure or fluid overload may coexist with ARDS, the new TRALI definition recognizes that even though some degree of LAH may be present, a case may still be classified as TRALI. This requires a determination of whether the main driver of respiratory deterioration is inflammatory lung edema (e.g., TRALI or ARDS) or hydrostatic

TABLE 2. New consensus TRALI definition

TRALI Type I—Patients who have no risk factors for ARDS and meet the following criteria:

- a. i. Acute onset
  - ii. Hypoxemia (P/F ≤ 300* or SpO_2 < 90% on room air)
  - iii. Clear evidence of bilateral pulmonary edema on imaging (e.g., chest radiograph, chest CT, or ultrasound)
  - iv. No evidence of LAH† or, if LAH is present, it is judged to not be the main contributor to the hypoxemia
- b. Onset during or within 6 hr of transfusion‡
- c. No temporal relationship to an alternative risk factor for ARDS

TRALI Type II—Patients who have risk factors for ARDS (but who have not been diagnosed with ARDS) or who have existing mild ARDS (P/F of 200-300), but whose respiratory status deteriorates§ and is judged to be due to transfusion based on:

- a. Findings as described in categories *a and b* of TRALI Type I, and
- b. Stable respiratory status in the 12 hr before transfusion

* If altitude is higher than 1000 m, the correction factor should be calculated as follows: [(P/F) × (barometric pressure/760)].

† Use objective evaluation when LAH is suspected (imaging, e.g., echocardiography, or invasive measurement using, e.g., pulmonary artery catheter).

‡ Onset of pulmonary symptoms (e.g., hypoxemia—lower P/F ratio or SpO_2) should be within 6 hours of end of transfusion. The additional findings needed to diagnose TRALI (pulmonary edema on a lung imaging study and determination of lack of substantial LAH) would ideally be available at the same time but could be documented up to 24 hours after TRALI onset.

§ Use P/F ratio deterioration along with other respiratory parameters and clinical judgment to determine progression from mild to moderate or severe ARDS. See conversion table in Appendix S2 to convert nasal O_2 supplementation to FiO_2.

TABLE 3. Classification of pulmonary edema not fulfilling TRALI criteria*

- ARDS: Patients who have risk factors for ARDS, and deteriorate not due to transfusion, but as a consequence of the already present ARDS risk factors.
  a. Onset of ARDS within 6 hr after transfusion but respiratory status was deteriorating in the 12 hr before transfusion
  b. Existing ARDS of any severity that further deteriorates after transfusion where respiratory status was already deteriorating in the 12 hr before transfusion
- TRALI/TACO cannot be distinguished: Patients in whom TRALI cannot be distinguished from TACO or in whom both conditions occur simultaneously
  a. Clinical findings compatible with TRALI and with TACO and/or lack of data to establish whether or not significant LAH is present

* If pulmonary edema occurs greater than 6 hours after the transfusion, and is clinically suspicious for temporal association with transfusion, the case should be classified as TAD as is currently done in many hemovigilance systems.

lung edema (e.g., CHF or TACO). When available, objective criteria such as echocardiography and/or invasive measurement such as pulmonary artery wedge pressure should be used; however, clinical judgment may also be required.[21] In some cases, biomarkers (brain natriuretic peptide [BNP] or NT-proBNP) at onset of pulmonary symptoms may be useful: when low (BNP < 300 pg/mL or NT-proBNP < 2000 pg/mL), they can rule out TACO or when high (NT-proBNP posttransfusion/pretransfusion ratio > 1.5), they may suggest TACO.[22,23] However, since in critically ill patients and severe TRALI cases these biomarkers are always elevated due to hypoxic vasoconstriction, NT-proBNP is only likely to be useful in the general patient population and in cases with mild pulmonary symptoms.[24]

We determined that the Berlin criterion of using ventilator support (e.g., at least 5 cmH_2O positive end-expiratory pressure [PEEP] treatment) as a necessary criterion to diagnose ARDS is not applicable for diagnosing TRALI. The Berlin PEEP criterion was mainly developed to eliminate the effect of conditions such as atelectasis on a reduced P/F ratio. The application of PEEP is mostly performed in an intensive care setting, which for the general ARDS population is fine. However, since TRALI may develop on the ward as a mild lung injury in which only supplemental oxygen is needed, the PEEP criterion is unnecessarily restrictive.

TABLE 4. ARDS risk factors according to the Berlin definition (with slight modification due to consideration of the transfusion setting)*

Direct
Pneumonia
Aspiration of gastric contents
Inhalational injury
Pulmonary contusion
Pulmonary vasculitis
Drowning
Indirect
Nonpulmonary sepsis
Major trauma†
Pancreatitis
Severe burns
Noncardiogenic shock*
Drug overdose

* Multiple (massive) transfusion is included in the Berlin definition of ARDS risk factors; however, we have removed it from this list because we recommend that ARDS occurring during or within 6 hours after multiple transfusions be classified as TRALI, provided no other ARDS risk factors (as listed in this table) are present. One example of a case scenario of multiple (massive) transfusion that fits the criteria for TRALI Type I is acute gastrointestinal bleeding without trauma or any other ARDS risk factors.

† Major trauma is defined as multiple fractures (two or more major long bones, an unstable pelvic fracture, or one major long bone and a major pelvic fracture).[20] An alternate definition proposed by the Panel is an injury severity score of greater than 15.

Posttransfusion time frame for TRALI occurrence

There was unanimous consensus that the time frame in which TRALI could occur should not change from the original definition, that is, within 6 hours after transfusion. This recommendation is based on the current universal practice in hemovigilance systems and the lack of robust data supporting change. In addition, data from the earlier years of the UK SHOT program where a 24-hour time frame had been used indicated that there were no additional verified cases when using this longer time frame.[25] The 6-hour time frame refers to the occurrence of respiratory compromise or hypoxemia. The additional findings needed to diagnose TRALI (pulmonary edema on lung imaging and determination of lack of significant LAH) would ideally be available at the same time but could be documented up to 24 hours after TRALI onset.[26,27]

Diagnosis of TRALI Type II

Accumulated evidence indicates that an inflammatory underlying condition may serve as first hit in the onset of TRALI.[12] Based on preclinical and clinical observations, the presence of a first hit increases the likelihood of developing TRALI after a transfusion. Although in experimental settings this mechanism has been confirmed by several groups, the translation to the clinical setting remains challenging[7,28–38] as it is possible that the underlying condition itself rather than the transfusion is causative for pulmonary edema. To accommodate this uncertainty and based on expert consensus and only a low level of published evidence, the panel recommends that a patient with an ARDS risk factor who shows no respiratory deterioration in the 12 hours before transfusion and who then deteriorates after transfusion be classified as having TRALI and further subclassified as TRALI Type II. Although changes in respiratory status (particularly with regard to oxygenation)

are often best determined using the P/F ratio [see Appendix S2]), it is recommended that the full clinical picture be evaluated when determining the transfusion recipient's respiratory status (e.g., markers of oxygenation, respiratory rate, work of breathing, respiratory support requirements). Many factors can modify the P/F ratio without meaningfully impacting the patient's actual respiratory status. Examples of such circumstances may include prone positioning, neuromuscular paralysis, PEEP titration, or inversed-ratio ventilation. Similarly, the implementation of these respiratory support maneuvers may signal a decline in respiratory status despite stable P/F ratio measurements. In these circumstances, clinical judgment should accompany the use of the P/F ratio in determining the transfusion recipient's respiratory status. Therefore, we recommend that expert panels evaluating reported TRALI cases should include physicians with understanding of mechanical ventilation and respiratory medicine. A further proposed expansion of the TRALI definition is based on the premise that a progression of mild ARDS to severe ARDS may be due to transfusion and recognizes that such cases should be classified as TRALI; that is, in contrast to the 2004 CCC, mild pretransfusion ALI (i.e., mild ARDS) does not rule out a subsequent diagnosis of TRALI.

We recommend that a patient who develops ARDS within 6 hours of transfusion in the presence of respiratory deterioration in the 12 hours before transfusion be classified as ARDS. Tabulating these cases separately in hemovigilance systems to distinguish them from ARDS without transfusion would allow for future research to ascertain whether transfusion may have contributed to causation in some of these cases. Potential hemovigilance system terminology could be: 1) ARDS with apparent incidental transfusion or 2) ARDS temporally related to transfusion.

Patient conditions and transfusion risk factors associated with TRALI

Based on large TRALI cohort studies, conditions associated with TRALI have been identified. TRALI is thought to involve a "two-hit" pathophysiology in which the first hit is the underlying condition of the patient (e.g., a proinflammatory condition) and the "second hit" is the transfusion.[12] Human data show that higher concentrations of interleukin (IL)-8 in the patient's pretransfusion plasma is an independent risk factor for TRALI.[39] That is, inflammation from any cause is the first hit in humans and physiologically results in priming of neutrophils and/or other effector cells. This may explain why critically ill and injured patients are especially at risk for TRALI. Based on preclinical and clinical studies, specific underlying conditions that result in monocyte, neutrophil, and/or endothelial activation or priming and which thereby may increase the risk of ARDS after a blood transfusion have been identified.[28,35–37,40–42]

The panel decided that evaluating conditions associated with TRALI required a critical literature appraisal which was performed by five panel members (PT, SK, DK, ML, and AV). Identified patient conditions previously associated with TRALI, pTRALI, and ARDS are summarized in Table 5. The complexity in diagnosing TRALI in the presence of an ARDS risk factor is that first or second hits alone, if strong enough, can cause ARDS. For example, higher doses of first hits such as lipopolysaccharide (LPS) in animal models or sepsis in patients can cause ARDS. Similarly, second hits alone, if strong enough, can cause ARDS. For example, transfusion of strong (mean fluorescence intensity [MFI] > 1500, see below) HLA Class II antibody can cause TRALI in a healthy subject.[49–52] These observations resulted in the establishment of the TRALI threshold model.[53]

Although any inflammatory condition probably could serve as a first hit in TRALI, we limit our discussion below

TABLE 5. Conditions historically associated with TRALI and ARDS

I. Conditions historically associated with TRALI and pTRALI that are also major ARDS risk factors in the Berlin definition (Table 4)*
- Sepsis†
- Noncardiogenic shock‡
- Massive transfusion§

II. Conditions historically associated with TRALI (or both TRALI and ARDS) but not listed as major ARDS risk factors in the Berlin definition (Table 4)*
- Cardiac surgery[13,43]
- Increased pretransfusion plasma IL-8[39]
- Mechanical ventilation with peak airway pressure >30 cm H_2O[39]
- Chronic alcohol abuse[39]
- Current smoker[39]
- Positive fluid balance[39]
- Higher APACHE II score[14,16]
- Increased age[13]
- End-stage liver disease[15]
- Postpartum hemorrhage[44]
- Liver transplantation surgery[39,45]
- Thrombotic microangiopathy[44]
- Surgery requiring multiple transfusions[46]
- Hematologic malignancy[16,43,44]

NB: The conditions listed in this table are not diagnostic criteria for TRALI Type I and II.

* Of note, most patient conditions associated with TRALI have not been consistently found across all studies. The variability of findings may be explained by differences in study design including type of patient population, differing case mixes of TRALI and pTRALI[13–16,55] prospective versus retrospective, and passive versus active reporting.

† Sepsis: For analysis purposes, several studies combined TRALI and pTRALI cases.[14,16,55]

‡ Noncardiogenic shock: In one study in which noncardiogenic shock was shown to be a TRALI risk factor, the definition of noncardiogenic shock excluded cardiogenic and septic shock while including hemorrhagic shock, intensive care unit patients on vasopressors for hypotension associated with sedation, and a category of "other" shock for shock that could not be classified into established categories.[39]

§ Historically, before the 2004 CCC, massive transfusion was associated with ARDS. This finding is partially explained by its strong association with TRALI. Studies performed before implementation of plasma TRALI risk mitigation strategies have shown that massive transfusion may serve as a second hit for antibody-mediated TRALI or as a first hit when the transfusions were given before the 6-hour time frame.[16]

to those conditions identified in large clinical cohort studies of TRALI and pTRALI. Knowledge of these conditions should alert the clinician to clinical scenarios in which TRALI is more likely to occur. Table 5 provides a concise summary of these data but should not be used for TRALI diagnosis; importantly, criteria for diagnosis are provided in Tables 2–4.

Patient conditions associated with TRALI (first hit)

Animal data show that priming is generally necessary for the development of TRALI.[29,31,34–36,41] Multiple investigators have shown that proinflammatory endothelial activation is responsible for the first hit in TRALI[39,43] and have used LPS for pulmonary endothelial activation.[30,34,48,53,54] Inflammation may also be initiated through activation of transfusion-induced coagulopathy.[47] Detailed in vitro experimentation has determined that LPS induces the synthesis and release of chemokines (e.g., IL-8, growth-related oncogene-α [GROα], and epithelial neutrophil activating factor-78 [ENA-78]) from human pulmonary endothelial cells, and these chemokines induced polymorphonuclear leukocyte (PMN) priming and firm adherence, whereas immunoprecipitation of these chemokines inhibited PMN-mediated endothelial cell destruction.[30] In both antibody- and non–antibody-mediated TRALI models, the LPS first hit resulted in a higher likelihood to induce TRALI. In large clinical cohort studies, it has been shown that the presence of sepsis before transfusion resulted in an increased risk of developing TRALI.[14,16,55]

Transfusions can also cause inflammation in the human lung and thus serve as the first hit.[47] As the supernatants of stored red blood cells (RBCs)[35,56] and platelets (PLTs)[29,36] are inflammatory, it is not surprising that transfusion of stored blood products causes inflammation. It has been shown that massive transfusion (first hit) in the 48 hours before onset of pulmonary edema resulted in an increased risk of developing ARDS after transfusion, after a subsequent transfusion of additional blood units (second hit).[16]

Mechanical ventilation causes lung inflammation in mice[40,57] and in humans.[58] In patients with ARDS, mortality was greater when the plateau airway pressure was greater than 30 cm H_2O.[59] Thus, it is not surprising that TRALI risk was also associated with pretransfusion peak airway pressure of more than 30 cm H_2O.[39] Chronic alcohol abuse and current smoking are other existing patient inflammatory conditions identified as TRALI risk factors in multivariate analysis after controlling for transfusion and other patient risk factors.[39] Larger positive fluid balance plays a role as it increases hydrostatic pressure and thus lowers the threshold for developing pulmonary edema. Also, it can be hypothesized that once pulmonary vascular permeability is increased during TRALI, higher amounts of fluids will increase the leakage gradient and worsen pulmonary edema. Indeed, larger positive fluid balance was found to be a risk factor for TRALI[39] and was found to be present in approximately one-third of ARDS patients.[60]

Certain clinical conditions and/or scenarios are associated with multiple TRALI risk factors (e.g., inflammation; multiple transfusions that may contain white blood cell [WBC] antibodies; lung injury induced by mechanical ventilation; see Table 5). Major trauma can present with multiple TRALI risk factors including shock, lung contusion, and (massive) transfusion, all of which induce inflammation. Cardiac surgery patients may be exposed to several risk factors: for example, inflammation, peak airway pressure of more than 30 mm H_2O while on a ventilator, and receipt of many transfusions. In one study, TRALI was observed postoperatively in 2.4% of cardiac surgery patients.[13] When cardiac surgery parameters were separated in a multivariate model, time on pump was an independent TRALI risk factor, which can be explained by the neutrophil-priming capacity of the cardiopulmonary bypass circuit. In another cohort study, cardiac surgery was not a significant independent TRALI risk factor (odds ratio, 0.921; 95% confidence interval, 0.239-3.6; p = 0.91) when added to a multivariate model that included known TRALI risk factors.[39]

Hematologic malignancy is another condition with multiple TRALI risk factors (e.g., inflammation, multiple transfusions),[16,43] although in one study, it remained an independent risk factor after correction for multiple transfusions.[16] Other clinical conditions requiring multiple transfusions and associated with increased TRALI risk include intensive care unit patients admitted with gastrointestinal bleeding, abdominal aortic surgery,[46,61] postpartum hemorrhage,[44] stem cell transplantation,[44] and thrombotic microangiopathy.[44]

TABLE 6. Transfusion risk factors for TRALI

- Cognate HLA Class II antibody[39,42,48,53,71]
- Cognate HNA antibody[30]
- Granulocyte antibody positive by GIFT[39]
- Cognate anti-HLA Class I that activates cells as shown, for example, by granulocyte aggregation in vitro[71] or at least by a positive by GIFT result
- Higher volume of female plasma[39]

Transfusion risk factors (second hit)

Greater number of transfusions

Patients receiving large numbers of blood units have long been observed to be at higher risk for ARDS. In a TRALI cohort study, the number of transfusions of any blood or blood component within 6 hours before TRALI was found to be an independent TRALI risk factor; however, multivariate modeling found that this risk was attributable to two specific measurements: the total amount of strong cognate HLA Class II antibody (MFI > 1500, using a microbead-based assay on the Luminex platform) and the total volume of plasma containing granulocyte-binding antibody (i.e., granulocyte immunofluorescence test [GIFT]-positive plasma).[39]

High-volume plasma products from female donors

Plasma from female donors that contains WBC antibodies is an important TRALI risk factor[39,62,63] and reports from the

United Kingdom,[64] France,[44] Germany,[65] the Netherlands,[66] and the United States[67] have documented that a risk mitigation strategy of providing male-only or male-predominant plasma reduces TRALI incidence. With regard to female plasma as a pTRALI risk factor and the effect of plasma risk mitigation on pTRALI, the panel noted that the data are inconclusive, with some studies showing an association or a mitigation effect[14,16,55,61,68] and others not.[13,14,39,69,70] The explanation for these discordant findings is not completely clear but could be due to interstudy differences in the criteria used to classify cases as pTRALI (including whether or not the 2004 CCC list of ALI risk factors was applied with or without modification), differences in analysis method, or perhaps other factors unique to particular recipient populations.[14,39,44,55,61,68,70]

HNA antibodies and cognate HLA Class II antibodies

Historically, TRALI was attributed primarily to human leukocyte antigen (HLA) Class I and human neutrophil antigen (HNA) antibodies. HLA Class II antibodies associated with TRALI were first described until 2001 when solid-phase tests for HLA Class II antibodies became more widely available.[42] Since then, cognate HLA Class II antibodies have been documented to often be the causative second hit.[14,71] In contrast, cognate HLA Class I antibodies were found to have much less of an association with TRALI,[71] except when they cause granulocyte aggregation in the granulocyte agglutination test.[71] HNA antibodies have been implicated as second hits while other granulocyte-binding antibodies detected by GIFT or granulocyte agglutination test, but without a clear specificity to a known neutrophil antigen, may play a role.[71]

The cognate antibody strength and the volume of plasma containing the antibody are contributing factors. Transfusion of larger volumes of HNA antibody and larger volumes of strong (e.g., MFI > 1500) cognate HLA Class II antibodies increase the risk for TRALI, when analyzed by multivariate analysis controlling for patient risk factors.[39] Plasma-rich products (e.g., fresh-frozen plasma) were associated with higher risk than RBC units in an international study conducted before a male-predominant plasma transfusion strategy was in widespread use.[72] Table 6 summarizes these transfusion risk factors.

Other factors potentially impacting on diagnosis

Presence of cognate WBC antibodies

There are currently no biomarkers available to diagnose TRALI. The panel affirmed that TRALI should remain a clinical diagnosis and that the presence of cognate WBC antibodies should not be a criterion for diagnosis since other mechanisms (e.g., proinflammatory mediators accumulating in cellular blood products) may cause TRALI. The panel also noted that the results of an immunologic case workup of recipient and donors may take weeks to months; thus, the presence or absence of antibodies does not help the bedside physician in diagnosing TRALI. Conversely, the panel recognizes that the presence of cognate WBC antibodies is important for understanding pathophysiology and for evaluating risk mitigation strategies (including eligibility of the WBC antibody–positive donor for future donations) and therefore recommends that such information be collected and reported by hemovigilance systems.[73]

Designating cases as TRALI and TACO cannot be distinguished

Transfusion-associated circulatory overload and TRALI are both characterized by respiratory distress due to onset of pulmonary edema within 6 hours of transfusion. However, the primary mechanism of the pulmonary edema is different. In TRALI, the primary physiologic abnormality resulting in pulmonary edema is an increase in capillary permeability, while in TACO, edema is believed to result primarily from increased capillary hydrostatic pressure (nonpermeability edema).

To differentiate between TRALI and TACO it is essential to know whether there is increased hydrostatic pressure in the lung capillaries. In the past, the gold standard was the measurement of the pulmonary capillary wedge pressure using a pulmonary artery catheter. However, pulmonary artery catheter utilization has become increasingly obsolete in clinical practice as it did not improve outcome in critically ill patients. For this reason, the Berlin definition dropped the pulmonary capillary wedge pressure criterion in excluding circulatory overload; instead, laboratory assays (e.g., BNP), ultrasound, and clinical variables such as fluid balance are used to evaluate the role of circulatory overload in the onset of respiratory distress. The published ISBT diagnostic criteria for TACO, which have recently undergone revision and field validation also include tachycardia and increased blood pressure.[74] In addition to these indirect criteria, our panel suggests that the use of an objective criterion such as echocardiography to differentiate between TRALI and TACO would be helpful in cases in which the clinician has ordered such testing.

Based on experience from research studies that involved extraction of clinical data for review by an expert panel, there are cases in which data are insufficient to distinguish whether the diagnosis should be TRALI, TACO, or both. To accommodate such cases that are missing critical clinical data, the panel has added the classification "TRALI/TACO cannot be distinguished" (Table 3). This category can also be used in situations in which distinguishing between TRALI and TACO is not possible even though relatively complete data have been provided or when TRALI and TACO occur concurrently at the same time in the same patient.

Finally, transfusion-transmitted bacterial infection[75] or an anaphylactic reaction should be considered in the differential diagnosis of posttransfusion pulmonary edema.[76] Table 7 summarizes the features of this classification scheme.

Immunologic workup of involved donors

Donors involved in a TRALI case (either Type I or Type II) should be screened for the presence of HLA Class I and II

and HNA antibodies and the transfusion recipient for the cognate antigen(s); in contrast, our recommendation is that this is not necessary for cases of ARDS or other categories in our classification scheme. For further in-depth discussion, we refer the reader to the ISBT consensus paper for immunologic workup of TRALI cases as well as to the 2004 CCC recommendations.[1,77]

Improvement in reporting

The panel reached consensus that: 1) clinical services should report all cases of posttransfusion (within 6 hr) pulmonary edema to the transfusion service even if ARDS risk factors were present and the clinician believed the case to be ARDS and 2) the transfusion service should further investigate cases by working with the clinician to review relevant data and then to classify the case. Of note, surveys of clinical case reporting indicated that when some ARDS risk factors were present (e.g., sepsis), clinicians neglected to report these cases of posttransfusion pulmonary edema to the transfusion service.[11,38,78] However, since some such cases could now be classified as TRALI Type II based on careful evaluation, it is important these cases be reported.

Opinions varied as to how to best: 1) structure a case reporting form and whether it should be the same for routine hemovigilance reporting versus clinical research studies and 2) establish the necessary dialogue between clinicians and transfusion medicine specialists. The appropriate administrative structure to review and classify cases needs to be determined both at the level of individual hospitals and in hemovigilance systems. At the hospital level, responsibility could rest with the transfusion service or with a broader multidisciplinary committee (e.g., hemotherapy committee, transfusion committee). In addition to clinical information, the panel believes that the initial reporting should include the type of component(s) transfused, their volume, and the interval over which each unit was infused in the 6 hours before pulmonary edema onset.

Characterization of transfusion reactions reported to hemovigilance systems includes comparing the case findings to diagnostic criteria (i.e., diagnosing the case), grading the reaction severity, and assigning an imputability as to whether the signs and symptoms were related to transfusion rather than another cause. One reason that imputability is necessary is because case reporting does not always include all of the needed clinical and laboratory data to accurately assess the role of transfusion.

Past use of the term "possible TRALI" created ambiguity with the inherent confusion related to an interpretation of what the term "possible" was referring to: was it how well the signs and symptoms matched the reaction definition (i.e., the symptoms were related to transfusion but the symptom complex did not clearly meet the definition of TRALI) versus imputability (i.e., the likelihood of the suspected reaction to be transfusion related). Most commonly, the term possible

TABLE 7. Comparison table to assist with pulmonary reaction classification

	TRALI Type I	TRALI Type II	ARDS	TRALI/TACO	TACO	TAD
Hypoxemia	Present	Present	Present	Present	May be present but not required	May be present but not required
Imaging evidence of pulmonary edema	Documented	Documented	Documented	Documented	May be present but not required	May be present but not required
Onset within 6 hr	Yes	Yes	Yes	Yes	Yes*	No*
ARDS risk factors	None	Yes—with stable or improving respiratory function in prior 12 hr	Yes—with *worsening* respiratory function in prior 12 hr	None, or if present, with stable or improving respiratory function in prior 12 hr	Not applicable	Not applicable
LAH†	None/mild	None/mild	None/mild	Present or not evaluable	Present	May be present but not required

* Some definitions of TACO allow onset up to 12 hours posttransfusion. However, our current recommendation is that 6 hours be used. If pulmonary edema occurs greater than 6 hours following the transfusion and is clinically suspicious for a temporal association with transfusion, the case should be classified as TAD as is currently done in many hemovigilance systems.

† LAH is difficult to assess. When LAH is suspected, we recommend using objective evaluation to determine if it is present. Objective criteria include imaging (e.g., echocardiography) or invasive measurement (e.g., pulmonary artery catheter pressure measurement). However, clinical judgment is often required and, if this is needed, should be used for case classification as follows: TRALI and/or TACO = respiratory insufficiency at least partially explained by hydrostatic lung edema resulting from cardiac failure or fluid overload or unable to fully assess the contribution of hydrostatic lung edema resulting from cardiac failure or fluid overload; TACO = respiratory insufficiency explained by hydrostatic lung edema resulting from cardiac failure or fluid overload.

TRALI referred to imputability; that is, ARDS risk factors were also present at the time of the suspected transfusion reaction. The newly proposed nomenclature will eliminate this ambiguity. Although cases can be reported as suspected TRALI or suspected ARDS, we recommend that cases should be reported simply and without ambiguity as posttransfusion pulmonary edema. Transfusion medicine specialists would then conduct a more extensive investigation and would classify a case as TRALI (Type I or II), ARDS, TACO, TRALI/TACO cannot be distinguished, TAD, or place the case into another category or would rule out a transfusion reaction completely.

We recognize that this detailed classification system differs from current hemovigilance practice as it includes a larger number of categories and also incorporates some of the imputability assessment into those categories. Given that this approach is new, we recommend that its feasibility be evaluated by hemovigilance experts, perhaps by prospectively evaluating the feasibility of achieving accurate classification using the redefinition compared to using the current TRALI definition.

Currently, for cases classified as TRALI, the detection of donor WBC antibodies (HLA or HNA) that correspond to recipient cognate antigens is not always a hemovigilance system reporting requirement. However, the collection of such information is important to better identify those TRALI reactions that have a serologic basis versus those not associated with WBC antibodies. For research purposes it may also be valuable to collect additional information about the WBC antibodies (e.g., detection method and titer) although the panel recognizes that this may be difficult.

FUTURE RESEARCH DIRECTIONS

Several areas in which future research is needed are:

- To establish how the new definition and/or classification scheme can be operationalized in hemovigilance systems including a consideration of how best to gather the necessary clinical information.
- To reexamine whether currently reported TRALI risk factors and predisposing clinical conditions can be verified and, specifically, to investigate whether transfusion is a risk factor separately for TRALI Type I or Type II. This is necessary as the current associations were found using the previous definitions and need to be reevaluated using the new classification system. Further, since existing data were obtained before TRALI risk mitigation for plasma-associated and PLT-associated TRALI, it is possible that clinical and transfusion factors that were previously associated with TRALI may no longer be.
- To evaluate the role of transfusion in the onset of ARDS in the setting of trauma given the frequent coexistence of tissue damage and hemorrhagic shock.
- To investigate if posttransfusion progression from mild to moderate or from moderate to severe ARDS has a transfusion-related mechanism.
- To further explore TRALI pathophysiologic mechanisms (from RBCs and PLTs and including non–antibody-mediated TRALI) with the goal of developing an intervention to lower the risk of TRALI after RBC transfusion.
- To develop TRALI and TACO criteria for the neonatal and pediatric setting as this proposed definition has been developed only for adults developing transfusion-related pulmonary complications.

CONCLUSIONS

Evidence accumulated over the past decade has resulted in the need to update and modify the 2004 CCC definition of TRALI. Clinicians should be encouraged to report all cases of posttransfusion pulmonary edema to the transfusion service so that further investigation (either conducted jointly by the transfusion service and the clinical team or through a hemovigilance system) can allow for classification of such cases as TRALI (Type I or Type II), ARDS, TACO, TRALI/TACO, TAD, or an alternate diagnosis.

We encourage transfusion medicine organizations, hemovigilance systems, and critical care societies to strongly consider adopting these definitions. We hope that a consensus classification scheme can be agreed upon so that standardized uniform definitions can be applied as rigorously as possible to generate data that can be compared across research studies and hemovigilance systems. At a minimum, future TRALI publications should clearly indicate very specifically what definition and/or classification scheme is used.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1. Delphi method - round 1 and round 2 questions
Appendix S2. Conversion tables.