

Transfusion-Associated Circulatory Overload and Transfusion-Related Acute Lung Injury

A Review of Underreported Entities With Current Updates

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ABSTRACT

Objectives: To review the new current diagnostic criteria of transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) from the literature while highlighting distinguishing features. We provide comprehensive understanding of the importance of hemovigilance and its role in appropriately identifying and reporting these potentially fatal transfusion reactions.

Methods: A review of the English language literature was performed to analyze TACO and TRALI while providing further understanding of the rationale behind the historical underrecognition and underreporting.

Results: Our review demonstrates the new 2018 and 2019 case definitions for TACO and TRALI, respectively. With more comprehensive diagnostic strategies, adverse transfusion events can be better recognized from mimicking events and underlying disease. In addition, there are mitigation strategies in place to help prevent complications of blood product transfusion, with emphasis on the prevention of TACO and TRALI.

Conclusions: TACO and TRALI are potentially fatal adverse complications of blood transfusion. Both have been historically underrecognized and underreported due to poor defining criteria and overlapping symptomatology. Developing a thorough clinical understanding between these two entities can improve hemovigilance reporting and can contribute to risk factor identification and preventative measures.

Key Points

- We demonstrate the current diagnostic guidelines for transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI).
- We outline the rationale of why TACO and TRALI continue to be underrecognized and therefore underreported.
- We describe current and theoretical mitigation strategies to help prevent complications of blood product transfusion, with emphasis on the prevention of TACO and TRALI.

Hemovigilance is the set of procedures in place to gather information about unexpected or undesirable events resulting from blood collection or transfusion to prevent occurrence and recurrence.¹ Both national (United States Biovigilance Network) and international (International Haemovigilance Network [IHN] Database) hemovigilance programs exist to implement these procedures and track adverse events.¹ Investigation into a presumptive transfusion reaction involves a combinational workup by the clinical team, blood bank personnel, and transfusion medicine physician. The workup includes early sign/symptom recognition with immediate transfusion cessation by the clinician and prompt notification to the blood bank. Common clinical signs and symptoms include fever (increase in 1°C), chills, respiratory distress, hypo/hypertension, skin manifestations (redness, edema, urticaria), hemoglobinuria, nausea/vomiting, oliguria/anuria, or anaphylaxis. A standard laboratory workup soon follows with clerical checks (bag, label, patient sample), repeat ABO testing on posttransfusion samples, visual checks of the physical product unit, and

direct antiglobulin test, with all results subsequently reported to the medical director.² The medical director and/or transfusion medicine physician will then further investigate the workup, provide a transfusion reaction classification, and, if warranted, provide recommendations for subsequent transfusions. Despite these hemovigilance systems, adverse transfusion reactions continue to be underreported.¹⁻⁵

The underreporting and underrecognition of transfusion reactions are often a consequence of multiple factors, including lack of understanding (and therefore lack of recognition) among clinicians, temporal relationships contributing to missed delayed reactions, and difficult sign recognition in noncommunicative patients.⁶ Furthermore, in critically ill patients, these adverse effects may be difficult to definitively identify due to frequent overlaps with underlying disease symptomatology. In pediatric populations, due to their different biochemical and physical makeup to that of adults, the response to blood transfusion and transfusion reactions will differ as well. In fact, studies comparing transfusion reaction rates of pediatric and adult patients have shown significantly higher reaction rates in pediatric populations.^{7,8} Reaction types also have been shown to differ between age groups, with most adverse transfusion reactions in pediatric populations comprising allergic, febrile nonhemolytic, and acute hemolytic transfusion reactions, while adult populations show allergic reactions in addition to higher rates of delayed serologic reactions, delayed hemolytic transfusion reactions, and transfusion-associated circulatory overload (TACO).⁷ Consistent with hemovigilance data, both patient populations demonstrate higher rates of reactions to RBC and platelet unit transfusions.^{7,8}

When reporting transfusion reactions, the subclassifications include acute hemolytic, anaphylactic, septic, febrile, delayed hemolytic, delayed serologic, TACO, and transfusion-related acute lung injury (TRALI) reactions, among others. Most notably, TACO and TRALI are not only historically underreported but are the two leading causes of transfusion-related fatalities and morbidity in developed countries.⁹ In fact, according to the US Food and Drug Administration (FDA), during the combined 2014 and 2018 fiscal years (FYs), TACO was the leading cause of reported transfusion-related fatalities (32%), with TRALI and possible TRALI comprising the second leading cause of transfusion-related death (26%).⁹

Although TACO and TRALI may closely mimic one another at presentation, differentiation is of the utmost importance as the treatment and prevention differ greatly **Table 1**. Over the past couple decades, many classification systems and definitions have been established, with continuous redefinition and modification as we acquire

new medical knowledge. With the 2018 and 2019 modifications and updated proposals for TACO and TRALI, respectively, we provide an up-to-date review of the etiology, pathogenesis, and current diagnostic criteria from the current literature to emphasize the importance of reporting while providing aid in distinguishing these reactions in the clinical setting.

Transfusion-Associated Circulatory Overload

TACO is the development of acute respiratory distress in the form of pulmonary edema, which occurs in temporal association with a prior blood product transfusion. The case definition for what constitutes TACO has continuously evolved over decades to provide a standardized definition to establish treatment, prevent occurrences, and help distinguish it from other pulmonary complications of transfusion like TRALI. Recent case definitions include the National Healthcare Safety Network (NHSN) Biovigilance Component Hemovigilance Module, provided by the Centers for Disease Control and Prevention, as well as the 2011 case definition established by the International Society of Blood Transfusion (ISBT) in collaboration with the IHN. The former was created to implement national surveillance of transfusion-associated adverse events, with each event classified through combinational criteria, including definition of event, severity, and imputability.¹⁰ The most recent version (2018) defines TACO as a new onset or exacerbation of respiratory symptoms within 6 hours of transfusion cessation. The symptoms must include three or more of the following: (1) acute respiratory distress, manifested by cough, dyspnea, orthopnea, and tachypnea; (2) elevated brain natriuretic peptide (BNP); (3) elevated central venous pressure; (4) evidence of left heart failure; (5) evidence of positive fluid balance; and/or (6) radiographic evidence of pulmonary edema.¹⁰

The ISBT provides an alternative definition of TACO. The aforementioned 2011 case definition by the collaborated efforts of the ISBT with the IHN, although comprehensive, was determined inadequate as many cases called TACO by clinicians and hemovigilance systems were still not accepted based on 2011 ISBT criteria.¹¹ Therefore, experts of the ISBT, IHN, and AABB (formerly American Association of Blood Banks) collaborated once more to develop a 2018 revised TACO definition.^{11,12} The revised 2018 criteria define TACO as the onset of respiratory symptoms within 12 hours of blood product transfusion. This is a modification of the 2011 definition, which limited the criterion to

Table 1
Comparison of TACO and TRALI Characteristics^a

Feature	TACO	TRALI
Risk factors		
Patient	Heart failure, renal failure, extremes of age	Prime: Sepsis, surgery, massive transfusion Transfusion: Plasma containing products (FFP, platelets, RBC, cryo, IVIG)
Donor	NA	Multiparity, prior blood transfusion, transplant
Product	All products	Immune mediated: Fresh-frozen plasma, platelet concentrates Non-immune mediated: Platelet and erythrocyte concentrates
Proposed mechanism of action		
Mechanism of action	Fluid accumulation in pulmonary vasculature Increased hydrostatic pressure Extravasation of fluid into alveoli and tissues	“Two-hit” hypothesis: 1. Prime through systemic inflammation 2. Transfusion of anti-HLA/HNA antibodies or BALs
Vital signs		
Temperature	Often unchanged; one-third can show new fever onset	Fever common
Blood pressure	Hypertension	Hypotension
Heart rate	Tachycardia	Tachycardia
Widened pulse pressure	Yes	No
Chest auscultation	Rales, crackles	Rales, crackles
Diagnosis		
Pulmonary edema fluid	Transudate	Exudate
Chest imaging	Diffuse bilateral infiltrates, Kerley B lines, peribronchial cuffing, ± pleural fluid	Diffuse bilateral infiltrates, no pleural fluid
Fluid balance	Positive	Balanced/unchanged
Weight change	Increased	Unchanged
Diuretic response	Significant	Minimal to none
BNP	>1,200 pg/mL	<200 pg/mL
Transient WBC drop	Unknown	Possible
Treatment ^b	Diuretics (furosemide)	Immune-mediated: Ventilatory support Non-immune-mediated: Oxygen support

BAL, biologically active lipid; BNP, brain natriuretic peptide; cryo, cryoprecipitate; FFP, fresh-frozen plasma; HLA, human leukocyte antigen; HNA, human neutrophil antigen; IVIG, intravenous immune globulin; NA, not applicable; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

^aAdapted from transfusion-associated circulatory overload definition (2018).¹¹

^bTreatment is based on severity. Severe hypoxemia may require intubation and ventilation (more commonly seen in severe immune-mediated TRALI).

within 6 hours of transfusion completion.¹³ The patient must have either acute/worsening respiratory compromise or acute/worsening pulmonary edema to classify as having TACO. This may be determined on clinical physical examination, radiographic chest imaging, other noninvasive assessments of cardiac function, or a combination. These suggestive methods of assessment have been revised from the sole frontal chest radiograph of the 2011 definition. Cardiovascular system changes have also been revised from tachycardia and increased blood pressure in 2011 to any cardiovascular system changes not explained by the patient’s underlying clinical condition, including tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette, peripheral edema, or any combination of symptoms. The next criterion of fluid overload may include positive fluid balance or clinical improvement following diuresis. Finally, the case definition includes

supportive utilization of a relevant biomarker (ie, BNP, N-terminal pro-BNP), as did the 2011 definition, but with additional information. The biomarker should be above the age group–specific reference range and greater than 1.5 times the pretransfusion value, similar to the AABB BNP recommendations.^{12,14} **Table 2** shows a comparison of the past and current TACO case definitions. Caution with the use of BNP and other biomarkers as differentiating diagnostic measures between TACO, TRALI, and other pulmonary manifestations is warranted, as they may be significantly elevated in critically ill patients.^{15,16}

Pathogenesis

The development of pulmonary edema in circulatory overload associated with blood product transfusion shows a similar pathogenesis to those of other

Table 2

Comparison of TACO Case Definitions, Past and Present^{10,12}

2011 ISBT/IHN TACO Definition	2018 ISBT/IHN/AABB TACO Definition	2018 NHSN (CDC) TACO Definition
TACO Within 6 hours of completion of transfusion	TACO Onset during or up to 12 hours after transfusion	TACO definitive New onset of exacerbation within 6 hours of cessation of transfusion
I. Acute respiratory distress, acute or worsening pulmonary edema on frontal chest radiograph	I. Acute or worsening respiratory compromise* or evidence of acute or worsening pulmonary edema* (based on clinical physical exam, radiographic chest imaging, and/or other noninvasive cardiac function assessment)	I. Acute respiratory distress (dyspnea, orthopnea, cough)
II. Tachycardia, increased blood pressure	II. Development of cardiovascular changes not explained by the patient's underlying condition^ (tachycardia, hypertension, JVD, enlarged cardiac silhouette, and/or peripheral edema)	II. Elevated BNP
III. Evidence of positive fluid balance	III. Evidence of fluid overload^ (positive fluid balance or clinical improvement following diuresis)	III. Elevated CVP
IV. Elevated BNP	IV. Supportive result of relevant biomarker^ (BNP, NT-proBNP) above the age-specific range and greater than 1.5 times the pretransfusion level	IV. Evidence of positive fluid balance
i. Supportive of TACO but not a criterion	Characterized by at least 1 required (*) criterion and a total of 3 or more criteria (required and additional (^))	V. Radiographic evidence of pulmonary edema
Characterized by any 4 or more of the above criteria		Requires 3 or more of the above criteria
		Probable: NA Possible: NA

BNP, brain natriuretic peptide; CDC, Centers for Disease Control and Prevention; CVP, central venous pressure; IHN, International Haemovigilance Network; ISBT, International Society of Blood Transfusion; JVD, jugular venous distention; LAH, left atrial hypertension; NA, not applicable; NHSN, National Healthcare Safety Network; NT-proBNP, N-terminal pro-brain natriuretic peptide; TACO, transfusion-associated circulatory overload.

nontransfusion causes of acute cardiogenic pulmonary edema. Circulatory overload manifests when increased intravascular pressure forces fluid into the pulmonary vasculature. This increased pressure leads to transudate fluid extravasation into interstitial spaces and alveoli, thus causing pulmonary edema.¹⁷ TACO, however, is unique to other forms of circulatory overload as a new-onset fever has been observed in one-third of patients, perhaps arguing against a purely volume-overloaded pathogenesis.¹⁸ In fact, fever-associated TACO reactions were studied by Parmar et al¹⁸ to analyze associations with patient or product age. The analysis, however, revealed that 38% of patients with TACO developed new-onset fever without any statistically significant associations to older products or advanced patient age identified. To support this nonpurely cardiogenic pathogenesis, significant decreases in TACO incidences have been observed with the implementation of leukoreduction techniques.¹⁹ To better explain these unique phenomena, alternative hypotheses have been suggested, including immune TRALI-like mechanism (discussed later), in which transfusion may promote an inflammatory process and subsequently evoke pulmonary capillary leakage, contributing to development

of pulmonary edema.^{18,19} Evidence to support this may be found in the association between cardiac patients and fever development, for example, in post-myocardial infarction (MI) fever (Dressler syndrome). Furthermore, the febrile stage in the period following a MI has been linked to the inflammatory response following MI-induced cardiac tissue damage, through the increase of proinflammatory cytokines (interleukin [IL] 6, C-reactive protein [CRP]) and neurohormones (BNP).²⁰ Extensive cytokine profiles and their roles in TACO have been further investigated to perhaps explain these alternative hypotheses. Roubinian et al²¹ found that IL-6 was elevated posttransfusion in patients with TACO, whereas IL-8, another proinflammatory cytokine, was not elevated pre- or posttransfusion in patients with TACO. IL-10, an anti-inflammatory cytokine, was also found to be elevated both pre- and posttransfusion.^{15,21} These findings were nearly inverted when studied in patients with TRALI. Although only IL-6 was found to be elevated, perhaps it is the role of this proinflammatory agent that contributes to the development of fever in a subset of patients with TACO. Overall, the pathogenesis of TACO is incompletely understood and remains an area to be further investigated.

Risk Factors

TACO is observed in those who have risk factors and sensitivity to intravascular fluid volume fluctuation. According to a 2013 retrospective review, risk factors for the development of TACO include those with a history of heart failure (41%), renal dysfunction (44%), and age greater than 70 years (65%).¹⁸ In addition to volume-sensitive risk factors, however, studies have shown that extremes of age, number of blood products transfused, and fluid balance per hour all increase a patient's risk of developing TACO.¹²⁻²⁵ A recent prospective review in 2018 found similar risk factors as above for the development of TACO, including congestive heart failure, cardiomegaly, pretransfusion diuretic use, hypertension, acute kidney injury, chronic kidney disease, recent surgery, and emergency surgery.²⁶

Incidence

The true incidence of TACO is difficult to quantify as a result of underrecognition, underreporting, and underrepresentation in the literature.^{3,4} The reliance on passive (voluntary) reporting by clinical teams to the transfusion medicine service greatly underestimates the incidences, as there is approximately a 100-fold higher incidence identified with active reporting hemovigilance systems.^{12,25} The underreporting of these pulmonary manifestations is thought to be a result of the multifactorial diagnostic criteria of clinical, radiographic, and laboratory evidence. In addition, as TACO may present with mild respiratory distress that resolves following diuresis, these reactions may not be reported as such.²⁷ Much like development of a fever during a blood transfusion can be a source of confusion between febrile nonhemolytic transfusion reactions and fever due to underlying disease, the same can be said for hypertension in the setting of TACO, further emphasizing cause for underrecognition. With acknowledgment of underreporting, National Blood Collection and Utilization Surveys from 2011 to 2015 have estimated the current incidence of TACO at approximately 1 in every 9,000 to 13,000 transfusions.²⁸ In addition, the incidence of developing TACO varies among patient populations. In fact, TACO incidence is estimated to occur between 1% and 12% in low- and high-risk populations, respectively.²⁹

Mitigation Strategies

The preliminary task in TACO prevention is the identification of individuals at risk for developing circulatory overload. Specifically, this relies on clinicians identifying high-risk patients and informing the hospital blood bank or transfusion medicine service. As mentioned previously,

those with underlying congestive heart failure, pulmonary disease, renal disease, and extremes of age or those receiving large numbers of blood products should warrant attention toward a high-risk transfusion. Once at-risk patients are identified and transfusion is deemed necessary, multiple steps can be taken to prevent the development of TACO, including slower transfusion rates, one unit infused at a time, washing with volume reduction of cellular blood components, preemptive diuretics, and advanced supervision.^{30,31} In fact, as of April 1, 2016, AABB-accredited hospital transfusion services/blood banks are required to have a policy regarding the transfusion of blood products to patients clinically deemed high risk of developing TACO, which includes one or multiple of the recommendations above.^{31,32} Studies on transfusion rates have shown that rapid, high-volume transfusions are associated with increases in pulmonary capillary wedge pressure (PCWP) posttransfusion compared with pretransfusion.³³ Therefore, in patients who are volume sensitive, this can produce rapid volume changes and pose an imminent threat. Thus, slowing the rate of transfusion and transfusing only one unit at a time allow for better pulmonary hemodynamic adjustments and ultimately safer blood product transfusions. In addition, transfusing one unit grants the opportunity to assess a patient's response to a single unit specifically when one transfusion is sufficient to provide clinical response. In avoiding unnecessary transfusion, the risks of the procedure are avoided and smaller blood volumes are transfused in positive fluid-balanced patients.

Washing with volume reduction through split or aliquoted units is commonly used for neonates, infants, and those who cannot withstand large-volume transfusion, may be implemented in patients at high risk for TACO. Volume reduction ultimately minimizes the volume introduced into the intravascular circulation.

The use of preemptive diuretics, commonly furosemide, has been studied in adult and neonate populations. Gupta et al³⁴ looked at PCWP pre- and post-RBC transfusion in adult patients with severe anemia. Despite the nearly obsolete usage of PCWP in practice, the study found statistically significant increases of PCWP in the group without pretreatment with 40 mg furosemide.³⁴ Another study of preterm infants also identified a small significant increase in the fraction of inspired oxygen (FiO₂) levels posttransfusion in patients without furosemide pretreatment compared with those with pretreatment.³⁵ Additional studies, however, experienced less consistent findings. For example, Pendergrast et al³⁶ encountered a similar roadblock to that experienced in true clinical practice with inconsistencies in chart documentation

pertaining to fluid balance and transfusion rates. This deemed the safe administration and effectiveness of preventing TACO by pretransfusion diuretic administration unclear. As furosemide is available in oral (PO) (slow-acting) and intravenous (IV) (rapid-acting) formulations, it has been suggested to provide each drug formulation based on the patient's risk status. With a 5- to 30-minute onset of action, the IV route has been suggested to benefit high-risk individuals (history of TACO, history of congestive heart failure, diastolic/systolic left ventricular dysfunction, positive fluid balance, renal dysfunction, acute MI within prior 4 weeks, or patients requiring plasma transfusions), whereas administration via the PO route with an onset of 30 to 60 minutes should be provided to lower-risk patients (aged >60 years without high-risk symptoms) before transfusion.³⁰

Finally, advanced supervision by a sufficiently trained medical professional is crucial. Skilled professionals are able to promptly identify changes in blood pressure, pulse pressure, and mean arterial pressure as well as noncardiac symptoms of fever or respiratory distress. Patients can present as early as 15 minutes into the blood product transfusion and up to 12 hours following completion. When TACO presents, vigilant monitoring can lead to immediate cessation of the transfusion and prompt therapeutic intervention.

Transfusion-Related Acute Lung Injury

TRALI is an acute transfusion reaction during or following the transfusion of plasma, plasma-containing products (RBCs, platelets, cryoprecipitate), or products prepared from large pools of plasma (IV immunoglobulin). Multiple clinical definitions have been established to standardize the definition and defining criteria of TRALI. Similar to TACO, the most recent NHSN Biovigilance Component Hemovigilance Module provides a definition of TRALI based on five criteria: (1) no evidence of acute lung injury (ALI) before transfusion; (2) ALI onset during or within 6 hours of cessation of transfusion; (3) hypoxemia, defined as the partial pressure of oxygen (PaO_2)/ FiO_2 less than or equal to 300 mm Hg, O_2 saturation less than 90%, or other clinical evidence; (4) radiographic evidence of bilateral pulmonary infiltrates; and (5) no evidence of left atrial hypertension.^{3,10}

In 2004, the Canadian Blood Services held the Canadian Consensus Conference (CCC) on TRALI to better facilitate understanding about the epidemiology, pathogenesis,

management, prevention, and research of the disease.^{37,38} At that time, the international experts of the CCC provided case definitions of TRALI and possible TRALI, in which possible TRALI was defined when ALI was temporally related to the transfusion with the presence of an ALI risk factor.³⁷ In 2012, however, acute respiratory disease syndrome (ARDS) experts (European Society of Intensive Care Medicine, American Thoracic Society, Society of Critical Care Medicine) redefined ARDS (and dropped ALI terminology) with the development of the Berlin classification.³⁹ Following this redefinition of ARDS, in 2019 came a reconsideration of the current TRALI definition to better encompass the more current knowledge on the subject.¹⁶ Retained from the previous definition, TRALI presents as an acute onset of hypoxemic respiratory distress during or within 6 hours of a blood product transfusion. The hypoxemic state is defined as $\text{PaO}_2/\text{FiO}_2$ less than or equal to 300 mm Hg or O_2 saturation less than 90% on room air. In addition, on imaging there must be clear evidence of bilateral pulmonary edema with either no evidence of left atrial hypertension (LAH) or LAH present that is determined not to be the main contributor to the hypoxemia. These last two criteria were modified from the 2004 definition to parallel the Berlin definition, with the suggestion of using additional imaging modalities, such as computed tomography (CT) scan or ultrasound, concurrently with the traditional chest radiograph to identify pulmonary edema.^{16,39} In addition, with decreasing usage in practice, the use of PCWP to determine LAH was dropped. With the new understanding of ARDS, new nomenclature was proposed to reflect this. The nomenclature change suggested removal of the "possible" TRALI terminology with the introduction of two new TRALI categories: TRALI type I and TRALI type II. TRALI type I is classified as above, in the absence of an ARDS risk factor. The latter, TRALI type II, is in place to better address the new ARDS Berlin criteria within the clinical context of TRALI. To classify as having TRALI type II, a patient must fulfill the same clinical criteria as TRALI type I but with posttransfusion pulmonary edema occurring in the presence of ARDS risk factors or mild ARDS, with stable pulmonary status 12 hours before transfusion.¹⁶ In light of the Berlin definition, ARDS risk factors are subcategorized into direct and indirect. Direct risk factors include pneumonia, aspiration of gastric contents, inhalation injury, pulmonary contusion, pulmonary vasculitis, and drowning, whereas indirect factors include nonpulmonary sepsis, major trauma, pancreatitis, severe burns, noncardiogenic shock, chronic alcohol abuse, and drug overdose.^{16,39} Although multiple transfusions were

also included in the Berlin definition as an indirect risk factor, it was determined in 2019 that in the absence of other ARDS risk factors, when ARDS occurs during or within 6 hours of a transfusion, the prior multiple transfusions may have provoked the ARDS (ie, first hit) and therefore should be classified as TRALI.^{16,39} Any patient with risk factors who developed ARDS within 6 hours of transfusion but demonstrated pulmonary deterioration 12 hours before transfusion should then be classified as having ARDS. Clinical judgment should always accompany the above criteria as TRALI remains a clinical diagnosis. The above case definitions are summarized in **Table 3**.

Pathogenesis

Whether the presence of ARDS risk factors exists or not, the pathogenesis of the illness may develop as a result of immune mediation or non-immune mediation.

Immune-Mediated

Immune- or antibody-mediated TRALI is a result of cellular activation and neutrophil-mediated damage to the pulmonary vasculature basement membranes, resulting in leaky vessels and ultimately the characteristic protein-rich, exudative noncardiogenic pulmonary

edema.^{2,40} This neutrophil activation and secondary damage is due to infusion of antibodies against their corresponding antigens on the neutrophil surface. The targeted antigens include human leukocyte antigen (HLA) class I and II and/or human neutrophil antigens (HNAs) with specificities toward HNA-1a, HNA-2 (CD117), and HNA-3.⁴¹ These donor antibodies present in the infused blood product have been shown to form in the donor following prior antigen exposure through pregnancy, previous blood product transfusion, or transplantation.

The prevailing theory to explain TRALI is the “two-hit” hypothesis. This “two-hit” or “double-hit” mechanism refers to the stepwise process of priming neutrophils followed by neutrophil activation, a hypothesis that has been repeatedly replicated in animal models.⁴² The first “hit” involves the development of a systemic proinflammatory condition such as sepsis, surgery, or massive blood product transfusion, which is thought to essentially prime the patient for TRALI before transfusion. Studies of murine and human models have demonstrated this initial priming event through pretreatment with neutrophil priming and activating agents, such as lipopolysaccharide.⁴³⁻⁴⁵ These inciting inflammatory events lead to elevations in inflammatory cytokines (IL-6, IL-8, CRP), followed by enhanced

Table 3
Comparison of TRALI Case Definitions, Past and Present^{10,16,37,38}

2004 Canadian Consensus Conference	2019 Consensus Redefinition	2018 NHSN (CDC) TRALI Definition
TRALI	TRALI type I	TRALI definitive
I.	No risk factors for ARDS	I. No evidence of ALI before transfusion
i. Acute onset	I.	II. ALI onset during or within 6 hours of cessation of transfusion
ii. Hypoxemia (P/F less than or equal to 300 mm Hg or SpO ₂ less than 90% on room air or other clinical evidence of hypoxemia)	i. Acute onset	III. Hypoxemia defined by any of:
iii. Bilateral infiltrates on chest radiograph	ii. Hypoxemia (P/F less than or equal to 300 mm Hg or SpO ₂ less than 90% on room air)	i. P/F less than or equal to 300 mm Hg
iv. No evidence of LAH and/or CVP less than 18 mm Hg	iii. Clear evidence of bilateral pulmonary edema on imaging (ie, chest radiograph, chest CT, or ultrasound)	ii. SaO ₂ less than 90% on room air
II. No existing ALI before transfusion	iv. No evidence of LAH or if LAH is present, it is judged to not be the main contributor to the hypoxemia	iii. Other clinical evidence
III. During or within 6 hours of transfusion	II. Onset during or within 6 hours of transfusion	IV. Radiographic evidence of bilateral infiltrates
IV. No temporal relationship to an alternative risk factor for ALI	III. No temporal relationship to an alternative risk factor for ARDS	V. No evidence of LAH (ie, circulatory overload)
Possible TRALI	TRALI type II	Definition requires I, II, III (one of), IV, and V
I. Same criteria mentioned above	Has risk factors for ARDS (but no diagnosis of ARDS) or have mild ARDS but with respiratory deterioration as a result of transfusion	Probable: NA
II. In the presence of an alternative risk factor for ALI	I. Findings as described above in I and II	Possible: NA
	II. Stable respiratory status in the 12 hours before transfusion	

ALI, acute lung injury; ARDS, acute respiratory disease syndrome; CDC, Centers for Disease Control and Prevention; CT, computed tomography; CVP, central venous pressure; NA, not applicable; P/F, PPaO₂/FiO₂ ratio; SaO₂, oxygen saturation of arterial blood; SpO₂, oxygen saturation by pulse oximeter; TRALI, transfusion-related acute lung injury.

expression of cell adhesion molecules.⁴⁶ These stimuli ultimately cause the neutrophils, usually malleable under physiologic conditions, to become stiffened and sequester in the pulmonary vasculature.^{2,44,47} Following neutrophil priming and the activation of pulmonary vascular endothelial cells, the “second-hit” event encompasses the passive transfer of antineutrophil or anti-HLA antibodies from the donor into the primed environment.⁴⁸ The antibodies target the primed neutrophils and trigger activation. Neutrophil activation leads to a release of reactive oxygen species, which injure the pulmonary vasculature. Damaged pulmonary capillaries become leaky and allow for the extravasation of exudative fluid into the pulmonary spaces, therefore giving rise to noncardiogenic pulmonary edema.⁴⁹

Non-Immune-Mediated

Non-immune-mediated TRALI comprises about 10% to 20% of TRALI cases.^{46,48} In the absence of antibodies, confirmed with sensitive antibody detection assays, TRALI has been observed to occur as a result of biologically active lipids (BALs) within the donor plasma. Specifically, nonimmune TRALI has been most associated with stored platelet and erythrocyte concentrates.⁴¹ Similar to the immune-mediated counterpart, BALs are able to trigger ALI in a previously primed patient, therefore following the same two-hit hypothesis. The predisposing proinflammatory medical condition with pulmonary endothelial cell activation then prefaces the second step of transfusing BALs within a plasma-containing product.^{37,38} These BALs, particularly lysophosphatidylcholines, are breakdown products of cell membranes that accumulate in older cellular blood components.⁴⁸ The transfusion of BALs into a primed individual ultimately results in pulmonary microvascular endothelial damage, leaky capillaries, and noncardiogenic pulmonary edema. In general, compared with immune causes, nonimmune TRALI tends to follow a much more benign clinical course and can often be treated solely with oxygen support.⁴¹

Incidence

Like TACO, the incidence of TRALI depends on the passive reporting of adverse outcomes by clinical teams. Reporting to hemovigilance systems is based on initial symptom and risk factor recognition by clinicians and transfusing personnel. While TRALI is discussed extensively in the transfusion medicine literature, it receives little attention among clinical literature.⁵ Kopko et al⁵ referenced a case report of a TRALI fatality that initiated a look-back investigation. The look-back not only

discovered 13 prior cases of TRALI following fresh-frozen plasma transfusion from the same donor but also revealed that all went unrecognized and unreported. The case is immensely instructive regarding the importance of appropriate recognition and reporting, which can lead to immediate treatment and prevention. Despite improvements in surveillance, the current estimated incidence of TRALI continues to range from 1:1,200 to 1:190,000, but data from the National Blood Collection and Utilization Surveys have narrowed TRALI reaction rates to 1 in every 57,000 to 64,000 transfusions.^{2,28}

Mitigation Strategies

With our improved understanding of TRALI, many mitigation efforts have been made to prevent these adverse reactions. Antibodies responsible for the development of immune TRALI (anti-HNA and anti-HLA antibodies) are commonly present in the plasma of multiparous female plasma donors following exposure to paternal HNA or HLA antigens during pregnancy. Therefore, with each subsequent pregnancy, the risk of developing antibodies increases, thus leaving plasma from multiparous female donors posing the greatest risk.⁴¹ With this understanding, steps have been taken to shift toward nearly male-only plasma donations, with the exception of nulliparous female donors and prescreened anti-HLA-negative female donors.⁵⁰ International hemovigilance data have shown a reduction in TRALI cases and TRALI-associated mortality following the implementation of this strategy.^{51,52} In 2016, the same screening restrictions were extended to apheresis-donated platelets following AABB requirements.⁵⁰

Another mitigation strategy has been the use of pooled solvent detergent (S/D)-treated plasma. S/D-treated plasma is a technique traditionally used in pathogen reduction. In preparing products for pathogen reduction, plasma units from up to 2,500 donors are pooled together before treatment.⁴⁶ This pooling inadvertently results in dilution of any anti-HLA/HNA antibodies present. Studies from Norway and the United Kingdom have demonstrated further reductions in TRALI following this technique.^{50,53,54}

As antibodies are present in the plasma of cellular products, removing any undesired plasma would therefore diminish the risk of developing TRALI in nonplasma products. This has been hypothesized in platelets with the use of platelet additive solution (PAS). Along with its intended use of extending platelet storage times and minimization of platelet lesions encountered with pathogen inactivation, PAS has also demonstrated additional advantages of reducing allergic transfusion reactions and potential TRALI mitigation (with the associated plasma removal), but the latter is not used in practice.^{50,55}

Finally, in the prevention of nonimmune causes of TRALI, suggestions have been made to use washed or

fresh blood components for patients potentially at risk (ie, primed).^{41,56} Utilization of fresh products would reduce the time available for cell membrane breakdown and secondary accumulation of BALs, while washing would potentially remove already formed BALs in older units.

Conclusion

TRALI and TACO are serious, potentially fatal pulmonary manifestations of adverse transfusion events. According to the report provided by the FDA on transfusion-associated reactions, in FYs 2012 to 2016, TRALI resulted in the highest number of fatalities, followed by TACO. In FY 2016, TACO surpassed TRALI as the leading cause of reported transfusion-associated deaths.⁹ Despite the severe morbidity and mortality associated with these conditions, they go unrecognized and underreported to blood banks and hemovigilance systems. Lack of recognition or distinction can lead to inappropriate or delays in treatment and lack of prevention measures.

Improvements and modifications of defining criteria have undergone many revisions in attempts to standardize a definition to assist clinicians and transfusion medicine physicians in distinguishing TACO and TRALI from each other and other acute respiratory conditions. In 2018, experts of the ISBT, in collaboration with the IHN and AABB, collaborated to revise the existing definition of TACO. This revision expanded the time frame in which cases may present, allowed for reporting of TACO with or without imaging, and removed the restrictions of cardiovascular changes beyond just tachycardia and increased blood pressure (Table 2). In the case of TRALI, the decision to revise was in response to the 2012 revision of the ARDS definition, in the hope of incorporating new information to harmonize the two definitions. From the 2004 CCC definition, the terminology of “possible TRALI” was dropped and the subclasses TRALI type I and TRALI type II were introduced. In these definitions, the term ALI was redefined to ARDS to encompass the Berlin definition. The identification of pulmonary edema was expanded from just the use of chest radiograph to CT and/or ultrasound. The definition also acknowledges that although many cases of TRALI have no LAH, some cases do, and therefore the definition emphasizes the importance of determining that it is not the main cause of the hypoxemia. Type II requires meeting the criteria of type I along with the presence of ARDS risk factors and inclusion of a new criterion: stable respiratory status in the 12 hours before transfusion. It is of the utmost importance for clinicians and treating medical professionals to be knowledgeable and aware of TACO

risk factors, potential TRALI primed conditions, and ARDS risk factors. With the heightened awareness that TACO or TRALI is more likely to occur in certain settings, prompt recognition and reporting can follow if it does. Moving forward, it is hoped that these new definitions will provide information to treating clinicians and other medical professionals with the knowledge to readily identify transfusion reactions and distinguish reaction type with ease, with a higher percentage of recognition and ultimately more reporting.

At this time, there remain no readily specific measurable biomarkers for the identification of TACO or TRALI. In the search to identify more specific diagnostic tests, studies have looked at bronchoalveolar lavage fluid (BALF) from intubated patients to assess pulmonary vascular barrier function. One study found that a BALF-to-serum protein ratio of less than 0.65 was suggestive of an intact vascular barrier.⁵⁷ Confirmation of an intact barrier could potentially rule out TRALI, immune and nonimmune causes, as both are a result of vascular endothelium damage. The use of BALF does have drawbacks, however. BALF is limited to intubated patients, and as reabsorption of the pulmonary edema can occur, results have the potential to be skewed.⁵⁷ In addition, as previously mentioned, the use of BNP in patients with circulatory overload has been a suggested biomarker in both the 2011 and 2018 TACO defining criteria. Currently, the AABB recommends a level greater than 1.5 times the pretransfusion value to diagnose TACO.¹² BNP, like other clinical tests, has its limitations and discrepancies and can be elevated in critically ill patients without circulatory overload.⁵⁸ Despite scientific efforts, a single diagnostic test remains to be identified.

Continued advancements in the understanding of pathogenesis, risk factors, clinical presentation, and distinguishing features are required to contribute to management improvements and prevention of these potentially serious transfusion reactions.

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