



Advancing Transfusion and
Cellular Therapies Worldwide

ASSOCIATION BULLETIN #05-09

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To: AABB Members
From: Paul D. Mintz, MD – President
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Re: Transfusion-Related Acute Lung Injury

Summary

This bulletin is intended to provide background information and guidance to members regarding transfusion-related acute lung injury (TRALI). The bulletin, which supplements Association Bulletin #05-06, includes background regarding recently proposed definitions for TRALI. AABB recommends that research into TRALI be conducted to understand better the incidence of and mechanisms behind this condition. In addition, this bulletin provides members with guidance regarding possible means of complying with revised Standard 5.4.2.1.

Background

At present, TRALI is the most commonly reported cause of transfusion-related death in the United States, surpassing deaths caused by ABO incompatibility and bacterial contamination.¹ Although the actual incidence of TRALI remains unknown in the United States, with improved recognition, the number of TRALI cases reported in the literature has increased significantly since 1985. Additionally, much about this clinical syndrome that may complicate blood transfusions remains poorly understood.

To address the issues surrounding TRALI, a Consensus Conference was convened in Toronto, Canada, in April 2004, titled “Towards an Understanding of TRALI.” Canadian Blood Services and Héma-Québec sponsored the conference, with support from the International Society of Blood Transfusion’s Biomedical Excellence for Safer Transfusion (BEST) subcommittee. Numerous experts presented data to approximately 240 international attendees, including a Consensus Panel of 11 members representing a wide range of medical and other disciplines including specialists in transfusion medicine, epidemiology, immunology, anesthesiology, critical care medicine, and ethics, as well as a regular blood donor and a chronic transfusion recipient. The full conference proceedings have been published, as have the recommendations of the Consensus Panel.^{2, 3}

Definition of TRALI

Two definitions of TRALI were published recently: one by the Canadian Consensus Conference Panel on TRALI³ and one by a National Heart, Lung, and Blood Institute (NHLBI) Working Group on TRALI.⁴ These definitions are virtually identical in patients without other risk factors for acute lung injury (ALI). In these cases, TRALI is defined as new acute lung injury (ALI) within six hours of a completed transfusion. Table 1 lists ALI criteria.

Table 1 Criteria for ALI	
Consensus Panel³	NHLBI Working Group⁴
1. Acute onset	1. Acute onset
2. Hypoxemia Research setting: PaO ₂ /FiO ₂ ≤ 300 mm Hg, or SpO ₂ < 90% on room air Nonresearch setting: PaO ₂ /FiO ₂ ≤ 300 mm Hg, or SpO ₂ < 90% on room air, or other clinical evidence of hypoxemia	2. Hypoxemia PaO ₂ /FiO ₂ ≤ 300 mm Hg regardless of positive end- expiratory pressure level, or oxygen saturation of ≤ 90% on room air
3. Bilateral infiltrates on frontal chest radiograph	3. Bilateral infiltrates on frontal chest radiograph
4. No evidence of left atrial hypertension (i.e., circulatory overload)	4. Pulmonary artery occlusion pressure: ≤ 18 mm Hg when measured, or lack of clinical evidence of left atrial hypertension

Applying this definition, TRALI is a clinical syndrome, rather than a disease with a single etiology. The diagnosis is a clinical and radiographic diagnosis. It must be emphasized that the diagnosis of TRALI is NOT made on the basis of reference laboratory test results, including those for white cell (HLA, neutrophil) antigen and/or antibody testing.

Because the diagnosis of ALI can be difficult, it is important for the hospital blood bank or transfusion service medical director to communicate with the clinician to determine whether a particular case has a high probability of increased left atrial pressure. If so, the pulmonary edema is then more likely hydrostatic pulmonary edema, rather than ALI, although obviously the two conditions can coexist.

It is important to note that the NHLBI Working Group recommended that a critical care expert make the assessment of whether a case of ALI in a patient with another recognized ALI risk factor (other than massive transfusion) is actually TRALI. The Working Group recognized that these cases would be difficult to classify as TRALI and that sometimes such cases would be designated as “indeterminate.” The Consensus Panel would

designate these “indeterminate” cases as “possible TRALI,” a category used by the Consensus Panel for cases in which ALI is temporally related to a transfusion but at least one other risk factor for ALI is also temporally related (see Table 2).

Table 2	
Risk Factors for ALI*	
<u>Direct lung injury</u> Aspiration Pneumonia Toxic inhalation Lung contusion Near drowning	<u>Indirect lung injury</u> Severe sepsis Shock Multiple trauma Burn injury Acute pancreatitis Cardiopulmonary bypass Drug overdose

* The incidence of ALI varies considerably among these conditions and may be over 40 percent for cases of septic shock or as low as 2 percent for cases of cardiopulmonary bypass and drug overdose related to treatment in an intensive care unit.^{3,4} Massive transfusion is also a recognized risk factor for ALI but has been excluded from this list by both the NHLBI Working Group and the Consensus Panel. Both groups stated that ALI in the presence of massive transfusion (in the absence of other ALI risk factors noted above) should be considered to be TRALI.

Emerging data and research regarding TRALI should be carefully monitored to determine if refinements to these definitions are necessary over time.

Incidence of TRALI

The incidence of TRALI has not been well established. Rates reported in the literature and in presentations made at the Consensus Conference vary widely from 1 in 432⁵ to 1 in 88,000⁶ per platelet transfusion, and 1 in 4,000⁵ to 1 in 557,000⁶ per unit of Red Blood Cells. AABB believes that additional research is needed to better determine the actual incidence of TRALI and continues to urge the NHLBI to invest in this research.

Mechanisms Leading to TRALI

There are two proposed pathophysiologic mechanisms for TRALI: the antibody hypothesis and the neutrophil priming hypothesis. Clinical and experimental observations support each of these mechanisms. Both proposed mechanisms lead to a final common pathway of increased pulmonary capillary permeability, resulting in pulmonary edema.

In the antibody mechanism, an antigen-antibody reaction triggers a series of events leading to TRALI. Most often, the causative blood component contains antibodies against recipient white blood cell (WBC) antigens. In far fewer instances, the antibody is present in the recipient and reacts with antigens on transfused donor WBCs. Antibodies may be directed against HLA Class I or II antigens or human neutrophil antigens (HNAs). It is possible that transfused HLA antibodies may directly activate or injure pulmonary endothelial cells.

The neutrophil priming or “two-event” hypothesis for TRALI states that TRALI is the result of two independent events. The first event causes neutrophils to be primed, but not activated (first hit), and the second event causes activation of primed neutrophils (second hit). The first event may be caused by the patient’s underlying clinical condition (e.g., infection, surgery, inflammation), whereas the second event is a consequence of transfusion. Specifically, neutrophil activation may occur with the infusion of substances in the plasma of the transfused product; these may be antibodies (via antigen-antibody reactions) or other biologically active substances (e.g., biologically active lipids) that accumulate in the blood product.

Again, AABB believes that additional research is needed to understand fully the mechanisms that cause TRALI. The association continues to recommend that NHLBI establish a multi-center study to lead to a better understanding of these mechanisms.

AABB Interim Standard

As noted in Association Bulletin #05-06, AABB recently issued a TRALI-related interim standard that is intended to supplement *Standards for Blood Banks and Transfusion Services* (23rd edition). Standard 5.4.2.1 states:

5.4.2.1 Donors implicated in TRALI or associated with multiple events of TRALI shall be evaluated regarding their continued eligibility to donate.

For purposes of this standard, “associated” and “implicated” donors are defined as follows:

- A donor is *associated* with a TRALI reaction if one of his or her blood components was transfused during the six hours preceding the first clinical manifestation of TRALI.
- An associated donor is *implicated* in TRALI only if found to have antibodies to an HLA Class I or II antigen or HNA and either 1) that antibody has specificity for an antigen present on the recipient’s WBCs or 2) there is a positive reaction demonstrated between donor serum and recipient WBCs (i.e., a positive crossmatch).

The intent of this requirement is to ensure that there is a process to evaluate donors and their continued eligibility to donate should they be implicated in TRALI or associated with multiple TRALI events. This standard is not intended to aid in the diagnosis of TRALI, which is a clinical determination. Once a diagnosis has been made, donor management should be undertaken according to the standard. This standard does not apply to cases where the diagnosis of TRALI is not clear cut; in such cases, each institution may choose to conduct donor assessments.

Donor Management and Laboratory Case Investigation

In possible cases of TRALI and when TRALI has been diagnosed, management of the donors involved is extremely complex. Each facility must decide on the extent of the

workup including laboratory testing, use of existing components from the donor, limitations on the use of future donations, and, ultimately, deferral of the donor.

In evaluating donors implicated in TRALI or associated with multiple events of TRALI facilitates may want to consider options that include, but are not necessarily limited to, the following:

- Defer donor from donation
- Divert plasma for fractionation or discard plasma from future whole blood donations from donor
- Manufacture no platelet or plasma components from donor
- Wash (or freeze and deglycerolize) RBCs from donor
- Permanently defer donor from future plasmapheresis donation
- Permanently defer donor from future plateletpheresis donation
- Evaluate previous donations from donor
- Avoid giving the same recipient future transfusions from the same donor implicated in TRALI

Individual facilities should determine the status of the evaluated donor(s) and the need for any special processing of components from the donor. There are no specific requirements as to how the donor evaluation should take place; the methods may differ among individual investigations. The intent of the standard is to ensure that there is a process to evaluate a donor who is implicated in TRALI, or associated with multiple TRALI events. The outcome of the evaluation is not addressed by this standard.

In order to determine if a donor is implicated, a workup will require the determination of the HLA type and/or the neutrophil type of the recipient, or a crossmatch between donor serum and patient cells. Blood centers and hospitals should have a system in place to coordinate how and by whom the workup will be conducted. For example, blood centers may communicate with the transfusing facility the need to obtain, as soon as possible, a recipient specimen containing adequate cells for crossmatching and/or for HLA and/or HNA typing. As soon as TRALI is diagnosed, transfusing facilities would collect and provide these samples to blood centers.

Several scenarios exist for describing donors whose blood components may be involved in TRALI or possible TRALI cases.

1. The diagnosis of TRALI is not clear cut.
2. The donor is associated with a single event of TRALI.
3. The donor is associated with multiple events of TRALI.
4. The donor is associated with TRALI but is antibody negative.
5. The donor is associated with TRALI and is antibody positive but specificity is not directed against a recipient antigen evidenced by antigen typing or crossmatching.
6. The donor is associated with TRALI and is positive for an antibody directed against a recipient antigen and/or the crossmatch is positive (i.e. the donor is implicated).

Depending on the facts surrounding each investigation, facilities may consider taking the following steps.

Situations in which the laboratory workup has not been performed.

1. The diagnosis of TRALI is not clear cut.

The AABB standard does not apply to cases where the diagnosis of TRALI is not clear cut. In such cases, each institution may choose whether to conduct donor assessments. Institutions adopting the “possible TRALI” definition endorsed by the Consensus Panel should consider how such cases will be treated. Facilities may opt to handle laboratory case investigation and donor management in the same way or differently for possible TRALI cases. The Consensus Panel noted that, from a research perspective, it is important to perform such investigations.

2. The donor is associated with a single event of TRALI.

The AABB standard applies to cases where the diagnosis of TRALI has been established on the basis of clinical and radiographic findings. Each blood component associated with a TRALI event must be identified and traced to the individual who donated the component. If an individual’s donated component is associated with a TRALI event, co-components from the current donation and components from previous donations can be evaluated for recipient complications, the donor’s medical history can be evaluated for events that may have resulted in antibody development (pregnancy, transfusion, etc.), and the medical director can evaluate the circumstances of the TRALI event to determine the donor’s eligibility for continued donation or special processing of future donations.

3. The donor is associated with multiple events of TRALI.

The AABB standard applies to cases where the diagnosis of TRALI has been established on the basis of clinical and radiographic findings. Each blood component associated with a TRALI event must be identified and traced to the individual who donated the component. If more than one of an individual’s donated components (either from the same or separate donations) are associated with TRALI events, co-components from the current donation and components from previous donations can be evaluated for recipient complications, the donor’s medical history can be evaluated for events that may have resulted in antibody development (pregnancy, transfusion, etc.), and the medical director can evaluate the circumstances of the TRALI event to determine the donor’s eligibility for continued donation or special processing of future donations.

Situations in which a laboratory workup is performed.

A donor can be *implicated* in TRALI only if laboratory testing is performed and determined to be positive. The following scenarios occur only if the laboratory workup has been performed.

4. The donor is associated with TRALI but is antibody negative.

Donors determined to be negative upon further laboratory testing may continue to donate.

5. The donor is associated with TRALI and is antibody positive but specificity is not directed against a recipient antigen evidenced by antigen typing or crossmatching. During the laboratory workup, a donor with antibodies not specific to the recipient experiencing TRALI may be identified. Donor management in these cases is not clear cut. Because the donor was not *implicated*, some facilities may allow the donor to continue to donate or to donate with restrictions (e.g. limited to washed RBCs). Others may decide to defer the donor owing to the potential of TRALI in future recipients. The most appropriate course of action has not been defined in this circumstance because many multiparous donors can be shown to have HLA antibodies without having been associated with TRALI cases.

6. The donor is associated with TRALI and is positive for an antibody directed against a recipient antigen and/or the crossmatch is positive.

This situation is one where the donor is determined to be *implicated* in TRALI. Donors who have been identified as *implicated* in TRALI by HLA Class I, HLA Class II, or HNA antibodies with specificity directed against an antigen of the recipient or by a positive crossmatch should be deferred from whole blood and platelet and plasma apheresis donation or restricted to donating specific components (e.g. washed RBCs or frozen deglycerolized RBCs) with very limited residual plasma.

In all cases, the goal should be to prevent TRALI in future recipients while avoiding unnecessary donor deferrals.

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