TRALI: An Update

Introduction. Transfusion Related Acute Lung Injury (TRALI), first described as a distinct clinical entity in 1985, is characterized by acute non-cardiogenic pulmonary edema with hypoxia occurring immediately or within a few hours of receiving a blood product. Its precise incidence is unknown. In the last decade, as other adverse consequences of transfusion have decreased due to improved donor screening and manufacture of blood products, TRALI has emerged as a leading cause of transfusion mortality in the US.[1,2]

Clinical Features and Diagnosis of TRALI. A recent Canadian Consensus Panel recommends that TRALI be defined as a new episode of acute lung injury (ALI) occurring during or within 6 hours of a transfusion, which is not temporally related to another risk factor for acute lung injury (Table 1).[3] ALI implies acute hypoxemia demonstrated by a $PaO_2/FiO_2 \leq 300$, SpO_2 <90% on room air or other clinical evidence of hypoxemia; bilateral infiltrates on frontal chest radiograph; and no evidence of left atrial hypertension. If other possible causes of ALI exist and the ALI was still temporally related to a transfusion, then "possible TRALI" may be present.

Frequent presenting signs and symptoms of TRALI include: dyspnea, hypoxemia, bilateral pulmonary edema, and fever (1-2ºC rise). Other reported findings have been hypotension not responsive to fluid administration and tachycardia. Characteristic chest X-rays show pulmonary infiltrates, usually bilateral with alveolar and/or interstitial patterns without evidence of cardiac enlargement or other evidence of fluid overload.

Differential Diagnosis. TRALI should be suspected in all cases of dyspnea and hypoxia temporally related to blood transfusion. Dyspnea due to bronchspasm associated with allergic/anaphylactic reactions can be readily identified based on the accompanying urticarial rash.   Dyspnea associated with pulmonary edema after transfusion may result from TRALI or from transfusion–associated circulatory overload (TACO). Differentiation between TACO and TRALI is important from patient treatment and blood donor management perspectives. Laboratory and diagnostic procedures that may aid in the diagnosis are listed in Table 2.   Recently, an algorithm was developed to help clinicians and researchers in managing patients with respiratory symptoms associated with blood transfusion.[4,5] Hydrostatic (TACO) and permeability (TRALI) pulmonary edema may coexist. Hence, evaluation by critical care specialist may be necessary.

Pathogenesis. The final common pathway in all of the proposed pathophysiologic mechanisms of TRALI involves increased pulmonary capillary permeability. The resultant movement of plasma into the alveolar space causes pulmonary edema. Two leading proposed mechanisms for TRALI are the antibody hypothesis and the "2-Event" hypothesis.[1, 3, 6-7]

Table 1. Risk Factors for Acute Lung Injury	
Direct lung injury	**Indirect lung injury**
Aspiration	Severe sepsis
Pneumonia	Shock
Toxic inhalation	Multiple trauma
Lung contusion	Burn injury
Near drowning	Acute pancreatitis
	Drug overdose
	Cardiopulmonary bypass

The antibody hypothesis holds that transfused donor antibodies bind and stimulate circulating white blood cells (WBCs), particularly neutrophils, via complement activation. Few cases due to recipient antibodies reacting with donor WBC exist. Through either cellular adhesive mechanisms or physical trapping, these activated leukocytes become lodged in pulmonary capillaries. Subsequently, vasoactive substances are released and cause pulmonary endothelial damage resulting in pulmonary edema. HLA antibodies (class I and class II) and neutrophil-specific antibodies have been implicated in TRALI reactions. Lookback studies suggest that TRALI is a rare event even in the setting of donor antibody and cognate recipient antigen.[3]

The "2-event" or neutrophil priming hypothesis states that TRALI is the result of two independent events. The first may relate to an underlying condition of the patient that causes neutrophils to be primed and sequestered in pulmonary vessels. The second event causes activation of the primed neutrophils with release of toxic substances resulting in damage to the pulmonary endothelial cells. Either of these two events may be provided by transfusion of biologic response modifiers such as "bio-active lipids" or cytokines in stored blood products. Some recent preliminary data support the possibility that the two main proposed mechanisms for TRALI might be merged since antibodies can be demonstrated to take the role of one of the events in the "2 event" model.[8, 9]

Clinical Management and Prognosis of TRALI. The management of a patient with suspected TRALI is supportive: O_2 and ventilation support appropriate for the degree of hypoxia present and fluid administration for hypotension. Diuretics are not indicated, and may worsen the patient's condition by causing hypovolemia. Most cases begin to show clinical improvement within the first few hours of onset and symptoms generally resolve completely within 24-96 hours. Infiltrates on the chest x-ray resolve within 96 hours in about 80% of affected patients but may persist for 7 days or more. Mortality has been reported to be 6-23%, highlighting the importance of early recognition.

Table 2. Laboratory and Diagnostic Procedures to Distinguish TACO from TRALI

- White blood cell count
- Plasma brain natriuretic peptide (BNP)
- Plasma troponin
- Pulmonary edema fluid/plasma protein ratio
- Chest x-ray
- Electrocardiogram
- Echocardiogram
- Central venous pressure
- Pulmonary artery wedge pressure
- Test for leukocyte antigen and antibody
- Tests for neutrophil priming activity

Investigation of a TRALI reaction. Recent AABB guidelines recommend that transfusion services and blood providers establish policies for evaluating donors involved in TRALI reactions in order to minimize reoccurrence.[10] Recognizing the uncertainty around TRALI pathogenesis and the lack of standardized testing procedures, a reasonable approach to investigating a report of TRALI might entail:

- Acquiring a complete description of the reaction from the reporting hospital, *e.g.* does the event meet the definition for TRALI or possible TRALI outlined above?
- Securing patient samples for HLA typing and antibody screening when necessary (if antibodies are identified in a donor);
- Ascertaining which donors contributed to transfusions given during 6 hours prior to the event (TRALI-associated donors);
- Determining which of the TRALI-associated donors are at risk of having anti-leukocyte antibodies (those with histories of past pregnancies or transfusions);
- Securing samples from at risk TRALI-associated donors and testing for anti-HLA (class I and class II) and for anti-neutrophil-specific antibodies; and
- Considering those donors found to be positive for either HLA and/or neutrophil-specific antibodies TRALI-implicated, if testing on the patient demonstrates a cognate antigen, *e.g.* either an HLA or neutrophil-specific antigen matching the specificity of a donor antibody. Alternatively, a positive crossmatch between recipient leukocytes and donor serum may be demonstrated.

Prevention of TRALI. Results of a TRALI event investigation will provide guidance for the management of the TRALI associated donors. As a first step, after a TRALI event is reported to the blood provider, all plasma-containing components from TRALI associated donors should be recalled and quarantined pending completion of the investigation. Plasma-containing blood products from TRALI implicated donor(s) should not be transfused in the future. In addition, if a clear-cut neutrophil-specific antibody is detected in testing of a TRALI associated donor, such donors should also be deferred even if typing of the patient has either not been performed or fails to demonstrate the cognate antigen.

In practice, laboratory evaluations of TRALI events may lead to incomplete answers, *e.g.* 1) anti-leukocyte antibodies are detected in TRALI associated donors but the specificities are not present in the recipient or 2) antibodies are detected in the donor but the recipient is not available for testing or 3) donor samples are not available for testing. Currently there are no agreed upon standards for how future donations from such donors should be managed.[3]

While the above policy is aimed at preventing subsequent TRALI reactions from already implicated donors, other proposals seek more global prevention by restricting donations from certain groups of donors who are known to have higher rates of anti-leukocyte antibodies, either because of gender and parity or through detection of anti-leukocyte antibodies by laboratory screening.[1] Policies that aim to prevent TRALI by exclusion of donors with increased risk of having anti-leukocyte antibodies, while likely to prevent some future TRALI reactions, are unlikely to prevent all and would unnecessarily exclude many safe blood donors. The "2-event" hypothesis of TRALI suggests that TRALI is caused by biological response modifiers that accumulate in stored blood, predicting that these reactions will occur irrespective of the presence or absence of antibodies in donor plasma. To date, there are no proposed comprehensive strategies to prevent TRALI due to this mechanism. Moreover, since many current blood donors have anti-leukocyte, in particular anti-HLA antibodies (estimated 10-20% of female donors) and have not been implicated in TRALI reactions, the wholesale exclusion of such donors would have a negative impact of the blood supply and exclude many safe donors.

Ongoing studies should provide better understanding of the pathogenesis of TRALI and the identification of donor and recipient risk factors – leading to the implementation of effective measures to prevent this rare, but extremely serious complication of transfusion.

References
1. Goldman M. et al. Proceedings of a consensus conference: towards an understanding of TRALI. Trans Med Rev 2005;19: 2-31.
2. Holness L et al. Fatalities caused by TRALI. Transfusion Medicine Reviews 2004;18:184-8.
3. Kleinman S. et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004;44: 1774-89.
4. Gajic O. et al. Pulmonary edema after transfusion: how to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury. Crit Care Med 2006; 34 (5 Suppl.):S109-13.
5. Finlay HE et al. Designing and testing a computer-based screening system for transfusion-related acute lung injury. Am J Clin Pathol 2005;124:601-9
6. .Silliman CC et al. Transfusion-related acute lung injury. Blood 2005;105:2266-73.
7. Bux J. Transfusion-related acute lung injury (TRALI): a serious adverse event of blood transfusion. Vox Sang 2005;89:1-10.
8. Kopko P et al. Merging the pathogenesis of transfusion related acute lung injury: the priming activity of the 5b (HNA-3a) antibody. Transfusion 2004; 44(Suppl.):22A.
9. Curtis BR et al. The two-event model of transfusion-related acute lung injury: antibodies to HNA-3a cause PMN cytotoxicity. Blood 2004; 104(Suppl.):237a.)
10. AABB. Transfusion-Related Acute Lung Injury. Association Bulletin #05-09, August 11, 2005