Promoting Recognition and Prevention of Transfusion-Related Acute Lung Injury

Steven Kleinman, MD, Ognjen Gajic, MD, and Eduardo Nunes on behalf of the American Association of Blood Banks Transfusion-Related Acute Lung Injury Task Force

Transfusion-related acute lung injury (TRALI) is one of several non-infectious hazards of transfusion that are receiving greater attention as a result of the blood banking community’s success in reducing many of the infectious risks of transfusion. Although some non-infectious risks, such as mistransfusion of an incompatible blood component, have always represented a clear and discernible risk to patients, the threat of TRALI has been less well appreciated because of challenges in diagnosis. TRALI is thought to be underrecognized and underreported, particularly in critically ill patients who have multiple additional risk factors for acute lung injury (ALI).

Currently, TRALI is the most commonly reported cause of transfusion-related death in the United States, surpassing deaths caused by ABO incompatibility and bacterial contamination. The actual incidence of TRALI remains unknown in the United States; however, with improved recognition, the number of cases of TRALI reported in the literature has increased significantly since the initial case series was reported in 1985. Nevertheless, much about this clinical syndrome that may complicate blood transfusions remains poorly understood, and TRALI remains an important topic of research in transfusion medicine.

In 2006, the AABB (formerly the American Association of Blood Banks) assembled a TRALI task force to develop recommendations for the prevention of TRALI. This article is a summary of AABB actions on TRALI and includes a summary of the recommendations made by the AABB task force.

Definition of TRALI

In order to address the issues associated with TRALI, a consensus conference, Towards an Understanding of TRALI, was convened in Toronto, Canada, in April 2004. 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. Possibly the most important of these recommendations is the clinical definition of TRALI, which is detailed here. A nearly identical definition has been endorsed by the National Heart, Lung, and Blood Institute’s working group on TRALI. Both groups adopted the American-European Consensus Conference definition of new ALI (Table 1) and defined TRALI as occurrence of ALI within 6 hours of a completed transfusion. The Canadian consensus panel further distinguished patients with TRALI (in whom transfusion is thought to be the only risk factor for ALI) from “possible TRALI” (ALI occurring in the presence of additional nontransfusion risk factors for ALI such as sepsis or aspiration).

According to this definition, TRALI is a clinical syndrome, rather than a disease with a single cause. The diagnosis is made on the basis of clinical and radiographic findings. It must be emphasized that the diagnosis of TRALI is not made on the basis of laboratory test results.

The National Heart, Lung, and Blood Institute’s working group recommended that a critical care expert assess whether a case of pulmonary edema after transfusion is likely to represent TRALI, circulatory overload (ie, hydrostatic pulmonary edema, transfusion-associated circulatory overload), or ALI due to risk factors other than transfusion (Table 2). Because distinguishing pulmonary edema due to acute lung injury from pulmonary edema due to circulatory overload can be difficult, good communication between the bedside care provider reporting the case and the transfusion service’s medical director is vital in order to determine whether a particular case has a high probability of being TRALI.

Incidence of TRALI

In order to understand TRALI, it is important to understand the burden of this syndrome. TRALI was the most frequent cause of transfusion-related death reported to the Food and Drug Administration (FDA) from October 2003 through September 2005. An average of 24 such deaths were reported annually from 2003 to 2005 (personal communication, Leslie Holness, MD, of the FDA). If we assume that 5.3 million persons receive transfusions per year and that all transfusion-related fatalities are reported to the FDA, it can be estimated that TRALI contributes to mortality in at least 1 in 220000 transfusion recipients. If we assume underreporting to the FDA and use published estimates (a TRALI incidence of 1 in 5000 transfused components, a fatality rate of 5%, and the annual transfusion of 22 million components), TRALI may be a contributing factor in approximately 220 deaths each year.

TRALI may be more frequent in the intensive care setting, where susceptible patients have many transfusions of blood products. Recent data from 2 studies conducted in specific patient settings (1 in multiple intensive care units and 1 throughout a tertiary care hospital) suggest that the incidence of fatal and nonfatal TRALI is between 1 in 1300 and 1 in 2400 components transfused once cases with other ALI risk factors are excluded and between 1 in 370 and 1 in 1000 components transfused if such cases are included.

Causes of TRALI

Substantial circumstantial evidence exists that many cases of

Table 1 Definition of transfusion-related acute lung injury

1. Acute onset (within 6 hours of transfusion)
2. Hypoxemia
   \[ \text{PaO}_2/\text{FIO}_2 \leq 300 \text{ mm Hg, or } \text{SpO}_2 < 90\% \text{ on room air} \]
3. New bilateral infiltrates apparent on frontal chest radiograph consistent with edema
4. Absence of clinical evidence of left atrial hypertension (ie, circulatory overload) as a principal explanation for pulmonary edema

Table 2 Risk factors for acute lung injury

<table>
<thead>
<tr>
<th>Direct lung injury</th>
<th>Indirect lung injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration</td>
<td>Severe sepsis</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Shock</td>
</tr>
<tr>
<td>Inhalation of toxin</td>
<td>Multiple trauma</td>
</tr>
<tr>
<td>Lung contusion</td>
<td>Burn injury</td>
</tr>
<tr>
<td>Near drowning</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td></td>
<td>Drug overdose</td>
</tr>
</tbody>
</table>

* The incidence of acute lung injury varies considerably among these conditions and may be greater than 40% for cases of septic shock or as low as 2% for cases of cardiopulmonary bypass and drug overdose related to treatment in an intensive care unit. Massive transfusion is also a recognized risk factor for acute lung injury but has been excluded from this list by both the National Heart Lung Blood Institute Working Group and the Consensus Panel. Both groups stated that acute lung injury in the presence of massive transfusion (in the absence of other risk factors for acute lung injury noted in the table) should be considered to be transfusion-related acute lung injury.
TRALI are caused by transfusion of components containing antibodies to leukocytes. Studies in animal and ex vivo models of TRALI support this cause, and in the clinical setting, many recipients in whom TRALI develops have received a donor unit with antibodies directed against an antigen present on the recipient’s leukocytes. Such antibodies may be directed against HLA class I or class II antigens or against non-HLA neutrophil antigens (HNA). Donors with antibodies to HLA and/or HNA may also have other types of antibodies that have not been identified, and these antibodies could be the cause of TRALI in some cases.

Data from a small number of look-back studies performed on previous recipients of components from donors implicated in TRALI cases indicate that pulmonary signs and symptoms develop more frequently in recipients given transfusions with components containing specific antibodies to HNA than in recipients who receive transfusions with antibodies to HLA from similarly implicated donors. Evidence also suggests that recipient antibodies to donor leukocytes might be implicated in some TRALI cases, but this association has been reported less frequently. In some TRALI cases, no antibody is detected in either the donor or the recipient. Evidence indicates that some of these cases are caused by nonantibody substances accumulated in stored blood (ie, biological response modifiers such as lipids that activate neutrophils). Although the relative incidence of TRALI caused by antibodies versus biological response modifiers is unknown, a review of the largest series of cases caused by biological response modifiers indicates that this mechanism is associated with less severe complications (less frequent need for ventilator support and lower mortality rate) than cases attributed to the antibody mechanism.

The highest frequency of antibodies to leukocytes occurs in female donors of blood and blood products who have previously been pregnant. The prevalence of antibody increases with the number of pregnancies, from a small percentage in women who report no pregnancy history to approximately 25% after 3 or more pregnancies. Overall, about 15% to 20% of female donors have antibodies to HLA compared with an estimate of less than 1% of male donors (who presumably acquired their antibodies from alloimmunization to leukocyte antigens after previous transfusions). The frequency of antibodies to HNA in donors has not been well studied, but limited data indicate that this frequency is very low, even in previously pregnant women.

Several years ago, investigators from the United Kingdom Serious Hazards of Transfusion system determined that the rate of TRALI occurrence was 5-fold to 7-fold greater for blood components that contained high volumes of plasma (eg, fresh-frozen plasma [FFP] and buffy coat–derived platelets) than for lower plasma-volume components (eg, additive solution red blood cells and cryoprecipitated antihemophilic factor). These data also showed that the majority of TRALI cases due to transfusion of these 2 types of components involved a female donor with antibodies to leukocytes. On the basis of the United Kingdom Serious Hazards of Transfusion analysis, the United Kingdom adopted a policy to minimize the transfusion of FFP and buffy coat–derived platelets from female donors. Since the implementation of this policy in October 2003, the number of reported cases of TRALI arising from these components has decreased substantially.

Recently, the American Red Cross (Red Cross) has accumulated data leading to the same conclusion. From 2003 to 2005, a total of 550 reports of suspected TRALI (including 72 fatalities) were reported to the Red Cross. All fatalities were reviewed and classified by 3 physicians as either “probable TRALI” or of “unrelated etiology,” with independent review of the associated serological investigation. Retrospective review of the 72 fatalities revealed 38 cases of probable TRALI, the majority of which (24 of 38) occurred after plasma transfusion. A female donor with antibodies to leukocytes was involved in 75% of cases (18 of 24) involving plasma transfusion and in 60% of cases (3 of 5) involving apheresis platelets. Female donors with antibodies to leukocytes were more likely to be associated with probable TRALI than with cases of unrelated origin (P < .001; odds ratio 9.5; 95% confidence interval [CI] 2.9-31.1). The rate of probable TRALI among recipient fatalities was higher for plasma components (1 per 202673; odds ratio 12.5; 95% CI 5.4-28.9) and apheresis platelets (1 per 320572; odds ratio 7.9; 95% CI 2.5-24.8) than for red blood cells (1 per 2527437). Plasma was concluded to be responsible for most probable TRALI fatalities in the Red Cross system, and as many as 6 fatalities per year (or 47% of all TRALI
fatalities) were linked to plasma from female donors with antibodies to leukocytes.

On the basis of the available data, it is not possible today to select a single intervention to prevent all cases of TRALI. However, current data about the incidence and severity of antibody-mediated TRALI in the United States have prompted the AABB Task Force to recommend a number of precautionary risk-reduction strategies that should be implemented at this time.

**AABB Recommendations to Reduce Risk of TRALI**

In an AABB bulletin published on November 3, 2006, a series of recommendations to prevent TRALI were announced. These recommendations were developed by a task force that is continuing to work on developing educational material on TRALI diagnosis, the management of TRALI patients, and procedures for laboratory investigations of donors and patients.

The recommendations published in November 2006 are directed toward an audience of blood collectors and transfusion services and include the following actions:

- Blood collecting facilities should implement interventions to minimize the preparation of high–plasma-volume components from donors known to be leukocyte-alloimmunized or at increased risk for leukocyte alloimmunization.
- Blood transfusion facilities should work toward implementing appropriate evidence-based hemotherapy practices to minimize unnecessary transfusion.
- Blood collection and transfusion facilities should monitor the incidence of reported TRALI and TRALI-related mortality.
- Blood transfusion facilities should work with clinicians to educate bedside providers (including nurses and physicians) about the risks of TRALI and about the need to work toward implementing evidence-based hemotherapy practices for all blood components, with special emphasis on high–plasma-volume components.

Recent randomized clinical trials in critically ill patients provide evidence for a causal relationship between the number of units of red blood cells transfused and the development of ALI and also suggest that restrictive transfusion practice may be an effective way to reduce the incidence of TRALI. Other studies have clearly shown that red blood cells, platelets, and FFP are still used excessively in clinical settings such as the intensive care unit, that active interventions are required to decrease inappropriate use, and that decreasing inappropriate use will decrease the number of adverse transfusion reactions.

Transfusion services and bedside providers should participate in the interdisciplinary effort required to confirm a TRALI diagnosis. Because TRALI can coexist with other transfusion reactions and with pulmonary complications unrelated to transfusion, the correct diagnosis of TRALI is difficult, but it is an essential first step in monitoring the effectiveness of TRALI risk-reduction strategies. Equally important is the rigorous reporting of suspected TRALI cases to the transfusion service. Cases diagnosed as TRALI should then be reported by the transfusion service to the blood supplier so that a donor investigation can be conducted and so that high-quality surveillance data can be obtained.
Where Can I Go to Learn More?
AABB offers a course on TRALI case studies with the assistance of the Commission on Office Laboratory Accreditation. For more information, please visit the commission’s Web site: http://www.cola.org/category.html?CategoryID=40.

Acknowledgments
Members of the TRALI Task Force include Richard Benjamin, MScB, Brian Curtis, MS, MT(ASCP)SH, Ronald Gilcher, MD, Bruce Kloster, MD, Daniel Ambruso, MD, Leslie Holness, MD, Mark Popovsky, MD, Paul Mintz, MD, and Peter Tomasalo, MD, FACP.

Financial Disclosures
None reported.

References
Promoting Recognition and Prevention of Transfusion-Related Acute Lung Injury
Steven Kleinman, Ognjen Gajic and Eduardo Nunes

Crit Care Nurse 2007;27 49-53
Copyright © 2007 by the American Association of Critical-Care Nurses
Published online http://ccn.aacnjournals.org/

Personal use only. For copyright permission information:
http://ccn.aacnjournals.org/cgi/external_ref?link_type=PERMISSIONDIRECT

Subscription Information
http://ccn.aacnjournals.org/subscriptions/

Information for authors
http://ccn.aacnjournals.org/misc/ifora.xhtml

Submit a manuscript
http://www.editorialmanager.com/ccn

Email alerts
http://ccn.aacnjournals.org/subscriptions/etoc.xhtml