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TRALI - Definition, mechanisms, incidence and clinical relevance

Pearl Toy, MD[Professor of Laboratory Medicine] and
University of California San Francisco, San Francisco, CA 94143-0100,
pearl.toy@clinlab.ucsfmedctr.org, Phone: 415-353-1671, FAX: 415-476-9815

Clifford Lowell, MD, PhD[Chairman][Professor of Laboratory Medicine]
University of California San Francisco, San Francisco, CA 94143-0134, clifford.lowell@ucsf.edu,
Phone: 415-476-2540, FAX: 415-502-6497

Abstract

Transfusion-related acute lung injury (TRALI) is defined as new acute lung injury (ALI) that occurs during or within six hours of transfusion, not explained by another ALI risk factor. Transfusion of part of one unit of any blood product can cause TRALI. The mechanism may include factors in unit(s) of blood, such as antibody and biologic response modifiers. In addition, yet to be described factors in a patient's illness may predispose to the condition. The current incidence is estimated to be 1 in 5,000 units. Patients present with acute dyspnea, or froth in the endotracheal tube in intubated patients. Hypertension, hypotension, acute leukopenia have been described. Management is similar to that for ALI and is predominantly supportive. When TRALI is suspected, Blood banks should be notified to quarantine other components from the same donation. No special blood product is required for subsequent transfusion of a patient who has developed TRALI.

Keywords

Blood transfusion/ adverse effects; Pulmonary edema; Acute lung injury

Transfusion-related acute lung injury (TRALI) is a syndrome of acute lung injury (ALI) associated with transfusion. The term TRALI was coined by Drs. Popovsky and Moore when they reported a case series at the Mayo Clinic in 1985 (1). In this case series, the typical clinical presentation included acute respiratory distress characterized by hypoxemia and fulminant pulmonary edema. The onset was usually within 4 hours of transfusion and was often accompanied by fever, tachycardia, hypotension or hypertension. In most patients (81%), recovery was rapid and complete. The incidence was 1:5,000 units transfused and the TRALI patients were comprised of mainly surgical patients. There is still no consensus on the incidence, pathogenesis or laboratory diagnosis of the syndrome. However, reports of TRALI are increasing due to increasing awareness of the syndrome, although underreporting is still strongly suspected. An analysis of the United States Food and Drug Administration fatality reports for the last three fiscal years showed bacterial contamination, TRALI, and ABO hemolytic reactions to be the leading causes of deaths from transfusion. TRALI became the leading cause of fatalities reported to the FDA in fiscal 2003. Fatalities were associated with fresh frozen plasma (FFP), red blood cells (RBCs) or platelets (2). Based on

these data, it is clear that TRALI is one of the most significant complications of modern blood transfusion. This paper reviews what is known and unknown regarding the definition, mechanisms, incidence and clinical relevance of the syndrome.

A. Definition

Practice Points:

- TRALI is a clinical diagnosis
- Suspect TRALI when new ALI develops during or within six hours of transfusion
- Rule out other ALI risk factors such as sepsis and aspiration
- TRALI has been associated with all blood components that contain plasma
- Transfusion of even part of one unit has been associated with TRALI

1. Definition of ALI

According to the American-European Consensus Conference of acute respiratory distress syndrome (3), the criteria for acute lung injury (ALI) are:

a. Timing: Acute onset

b. Pulmonary artery wedge pressure: ≤ 18 mm Hg when measured, or a lack of clinical evidence of left atrial hypertension

c. Chest radiograph: Bilateral infiltrates seen on frontal chest radiograph

d. Hypoxemia: Ratio of $PaO_2/FIO_2 \leq 300$ mm Hg regardless of PEEP level (Note: In patients in whom an arterial blood gas is not available, an oxygen saturation of <90% when the patient is breathing room air meets the criterion for hypoxemia)

2. Definition of clinical TRALI

The National Heart Lung and Blood Institute (NHLBI) Working Group on TRALI developed a definition (4). In patients with no ALI immediately before transfusion, and no other ALI risk factor (Table 1) is present, a diagnosis of TRALI is made if there is:

a. New ALI after transfusion, and

b. The onset of symptoms or signs is during or within 6 hours after transfusion

The definition includes patients who are massively transfused who develop new ALI, and such patients may be at greater risk for TRALI as they receive multiple units. The definition excludes patients with ALI before transfusion; even though worsening of existing ALI after transfusion could be due to TRALI, defining this form of TRALI is problematic.

In patients who have other ALI risk factors can also develop TRALI, and thus TRALI should not be excluded from consideration in these patients. The incidence of ALI in prospective studies of patient groups with ALI risk factors is less than 50% (see Table 1). Thus, the presence of an ALI risk factor does not mean the patient will definitely develop ALI. New ALI in a transfused patient with an ALI risk factor could be mechanistically due to the transfusion and/or the risk factor, i.e. TRALI and/or ALI due to the risk factor. In such patients who have another ALI risk factor, the diagnosis of TRALI can be difficult. The NHLBI working group recommended that critical care experts judge whether the new ALI is temporally associated with the transfusion, or whether the new ALI is temporally associated

with worsening of the other ALI risk factor. The Canadian Consensus Conference proposed no such judgment evaluation and proposed the term “possible TRALI” for new ALI in a transfused patient who also has another ALI risk factor (5).

Currently there is no definitive laboratory test for the diagnosis of TRALI. Leucopenia or neutropenia has been observed in case reports (6-12) but has not been studied in small case series (1,13). Leukocyte antigen-antibody match between donor and recipient (HLA class I or II, granulocytes or monocytes), and neutrophil priming activity in donor blood have been reported but are not diagnostic (14)

Research Agenda:

- In patients with other ALI risk factors, research is warranted to determine whether transfusion contributes to new ALI, and whether ALI risk factors predispose patients to TRALI
- Research is warranted to determine whether the mechanism of ALI after multiple transfusions is the same as the mechanism for TRALI after a single unit transfusion.
- Diagnostic laboratory tests for TRALI need to be evaluated in prospective studies

B. Mechanisms

Although the association of transfusion with lung injury has been observed for almost 30 years, the mechanisms are still unclear. In massive transfusion, the mechanism of lung injury was initially thought to be microaggregates in stored blood causing micro-pulmonary emboli and lung damage, but this theory has been discredited, since transfusion of stored blood through microaggregate filters has not prevented lung injury in animals (15) nor in humans (16,17). Pathologically, the disease involves sequestration of activated neutrophils within the pulmonary capillaries, leading to acute lung injury (18). The contribution of neutrophils to multiple types of acute lung injury is well understood and has been validated in several animal models (19). The major pathophysiologic question in TRALI then becomes how the transfusion is associated with or leads to wide spread neutrophil activation in these patients.

In the past two decades, two hypotheses that lead to neutrophil activation in TRALI have been proposed: antigen-antibody hypothesis versus the two-event hypothesis. Recipient factors that may be involved in the pathogenesis include the recipient’s underlying condition and genetic predisposition. Donor unit factors that may be involved in the pathogenesis include leukocyte antibody, cytokines, lipids and factor(s) that increase pulmonary endothelial cell permeability. These hypotheses and factors are discussed below.

1. The antigen-antibody hypothesis

The first evidence supporting this came from observation that classic findings of TRALI (including leukopenia) developed in a healthy volunteer injected with 50 ml of blood from a patient with a strong leukoagglutinin (6). This healthy volunteer was not ill and his neutrophils should not have been primed. In this case, leukocyte antibody alone seemed to cause TRALI. The evidence supporting immunologic activation of neutrophils by antibody revolves around the association of this disease with the presence of anti-HLA class I and II and anti-neutrophil antibodies in the donor units implicated in TRALI. The primary hypothesis is that the alloantibodies in the donor blood product directly activate either the patient neutrophils, monocytes or tissue macrophages, leading to initiation of the

inflammatory cascade (20,21). Antibodies recognizing neutrophil HNA-2a (CD177) or HNA-3 antigens have been implicated in cellular injury in both *ex vivo* perfused rat lung models and in cell culture models (22,23). In both cases, the evidence suggests direct binding of the antibodies to the neutrophils results in cellular activation leading to degranulation and respiratory burst responses, which in turn damage pulmonary endothelium. Donor alloantibodies may also attach directly to vascular endothelial cells, and thus form the equivalent of immune complexes, which in turn recruit circulating neutrophils and lead to sequestration/activation of these cells. This latter hypothesis is supported by the observation of a TRALI reaction occurring in only one lung following lung transplantation (suggesting that the alloantibodies recognized only new donor lung endothelium) (24). This mechanism of alloantibody mediated TRALI has also been modeled in mice, where is was demonstrated that recognition of endothelial bound anti-MHC-1 mAb (the murine equivalent of anti-HLA Abs) by neutrophil Fc receptors caused neutrophil activation (degranulation/respiratory burst) and subsequent pulmonary damage (25). Interestingly, it has been observed that the presence of leukocyte antibodies in donors is common, while the occurrence of TRALI is uncommon, and thus antibody alone can not be the sole explanation for TRALI. The incidence of neutrophil antibody of 7.7% in blood donors and components was reported in an abstract (26). The incidence of HLA antibodies has been studied in female donors (not male) and the incidence is dependent on the technique used and donor parity. Using the less sensitive cytotoxity technique, Rodey found an incidence of 18.7% among donors with a history of four or more pregnancies (27). Densmore found HLA antibodies in 8% of female plateletpheresis donors, with frequencies of 7.9% to 26.3% among those with parity between 0 and ≥3 pregnancies (28). Insunza found an incidence of 18.1% in female plateletpheresis donors who have had one or more pregnancies (29). Recently, using the sensitive Luminex flow method, investigators at Emory University found HLA antibodies in 22.5% of segments of randomly selected blood components (30), but the specificities of these antibodies were not defined.

2. The two-event hypothesis hypothesis

Silliman et al noted an association of TRALI cases with use of aged blood products (31). They propose that the first event is the patient's condition (surgery, inflammation) that enhances the risk of TRALI. The second event is transfusion of mediators, such as lipids and cytokines from stored blood products, which can prime or directly activate neutrophils, leading to pulmonary damage. These lipids include lysophosphatidylcholines, which are released from apoptotic white blood cells and platelets and have the capacity to enhance neutrophil function (32).

3. Patient underlying condition

In both hypotheses (either direct antibody mediated activation or the two-event mechanism), it is quite likely that underlying risk factors in patients, including surgery or inflammation, enhance the risk of TRALI reactions. Inflammation has been associated with upregulation of HLA and neutrophil antigens, thus increasing the number of targets for transfused antibody and potentially increasing the probability that transfused antibodies can directly activate neutrophil function(33,34). In addition, inflammation may upregulate vascular adhesion molecules such as P, E-selectin and ICAM-1, which in turn will facilitate accumulation of neutrophils in tissues. TRALI may occur if a second hit (ie transfusion of a lipid mediator or cytokine) enhances or directly activates neutrophil function - rapid injury of tissues, such as pulmonary parenchyma, containing the accumulated neutrophils would ensue.

4. Cytokines

Elevation of cytokines in the plasma of ALI patients, probably as a result of lung injury, has been long observed, and some cytokines are prognostic markers for patient outcome.

However, it is also likely that cytokines present in donor blood products can be directly causative of ALI. Cytokines in the plasma of stored blood products are derived from two sources: leukocytes and platelets, or possibly, from a donor who was incubating an inflammatory but subclinical illness at the time of donation. Proinflammatory cytokines that accumulate with stored red cell blood products are removed by prestorage leukoreduction, while those that are released by platelet activation may not be removed by leukoreduction. TRALI decreased, but did not disappear, with the implementation of universal leukodepletion in Canada (35). Two reasons account for the decrease in TRALI with leukoreduction: First, the 10% of TRALI cases due to patient antibody against donor leukocytes in the unit of blood would not occur. Second, leukoreduction reduces accumulation proinflammatory cytokines in stored blood products During storage of red cells or platelet units that are not leukoreduced, proinflammatory cytokines such as IL-1β, IL-6, IL-8 and TNFα accumulate in the supernatant plasma, and are virtually eliminated by prestorage leukoreduction (36-39). IL-8 has neutrophil priming activity that could be important in causing TRALI (14). Other cytokines are not reduced by leukoreduction, e.g. RANTES and TGF-β1 accumulate in platelet components during storage (39). RANTES (Regulated upon activation, normal T-cell expressed and presumably secreted) evokes the release of histamine from basophils, may be related to allergic reactions. There are conflicting data regarding the role of RANTES in animal models of lung injury (40,41). TGF-β1 is mostly bound in an inactive form to extracellular components, but there is evidence of a link to ALI (42). PAI-1 is also released by platelets, and but its levels in leukoreduced platelet products is unknown. More recently, direct priming/activation of neutrophils has been demonstrated to occur through the surface molecule CD40, which is recognized by the molecule sCD40L, a major product of platelets and found in high levels in platelet concentrates (43).

5. Genetic predisposition

There is new evidence that there may be genetic predispositions to the development of clinical acute lung injury. For example, polymorphisms in the *SP-B* gene have been associated with the development of ALI (44-47). Homozygosity for the deletion polymorphism in the angiotensin converting enzyme (*ACE*) gene which is associated with higher ACE levels and activity was found in an increased frequency among patients with ALI (47). Also, there has been some work that associated polymorphisms in the *IL-6* and *TNF-α* genes with susceptibility to sepsis and acute lung injury. Moreover, there has been a growing interest in examining whether common polymorphisms of genes that encode mediators of inflammation, innate immunity, as well as coagulation may allow for host phenotypic differences in the susceptibility to ALI, thus accounting for some of the individual susceptibility to ALI (48). Genetic predispositions to TRALI are thus possible but have not yet been defined.

6. Endothelial cell injury

Another contributor to TRALI reactions is the potential that transfusion products may directly injure vascular endothelial cells in the lung. Recently, Rao et al (49) have found that supernatants from stored red blood cell units can contain a soluble, transferable factor that directly increases vascular permeability in cultured microvascular endothelial cells. The nature of such an agent, which resulted in partial endothelial cell retraction and development of increased intercellular space, remains unclear. However, the component appears to have a molecular weight greater than 100kD, ruling out common cytokines. Further investigation of the potential that stored blood products may alter vascular endothelial cell integrity is clearly warranted.

Research agenda:

- Research is needed to identify donor or donor unit factors that cause TRALI.
- Research is needed to identify recipient factors that predispose to TRALI

C. Incidence

The actual incidence of TRALI is unknown because of lack of large, current prospective studies that use a standard definition for the syndrome. The lack of such studies account for the wide range in the reported incidence of TRALI, from approximately 1 in 500 to 1 in 100,000, as reviewed at the consensus conference in Toronto in 2004, including series from University of Denver, University of Alberta, Mayo Clinic, UK, and Canada (50). TRALI has been reported following transfusion of all plasma-containing blood components. Estimates of the incidence of TRALI have been 1 in 5,000 components, mostly in whole blood (1), 1 in 7,900 units of fresh frozen plasma (51), and 1 in 432 units of whole blood-derived platelet concentrates (13). Critically ill patients may be at greater risk for TRALI because of underlying severe illness, and a retrospective study estimated the risk of TRALI and possible TRALI to be 1 in 1271 units transfused to patients in intensive care units (52).

Evidence for underreporting was found in a study of recipients of previous donations of donor with neutrophil 5b antibody. Some patients developed signs and symptoms of TRALI, but these cases had not been reported to the Blood Bank (53). Underreporting is due to several reasons. First, TRALI is acute lung injury (ALI), and there is yet no uniformly agreed upon criteria that distinguish TRALI from ALI (34) due to other causes. Second, some clinicians attribute ALI to massive transfusion (44,54,55), rather than to TRALI from a single unit of blood. Third, the treatment of TRALI is currently the same as for other forms of ALI, primarily supportive with a lung protective ventilatory strategy, so clinicians who recognize the syndrome may see no reason for reporting the case to the Blood Bank. Fourth, distinguishing between intravascular fluid overload vs. TRALI is difficult. Finally, making a diagnosis of TRALI is costly to Blood Banks. The cost of a complete antibody investigation is several thousand dollars, and in addition, implicated donors may be prohibited from further donations, even if they have donated before without reported adverse reactions in recipients. The cost of investigation and loss of blood donors may understandably bias Blood Bank personnel to attribute pulmonary edema after transfusion to fluid overload rather than TRALI.

These barriers to determination of the actual incidence of TRALI can be overcome. Recognizing the need for a common definition, the NHLBI Working Group on TRALI determined criteria for clinical TRALI (4). The common definition described earlier in this paper provides a foundation for studies of incidence. To study true incidence, large prospective studies are needed using a standard protocol. In such studies, a surveillance system is needed that does not depend on clinician reports and will capture all cases of TRALI (56). Also, in such studies, experts are needed to assess fluid overload vs. ALI vs. TRALI and the experts should be blinded to donor unit attributes and donor test results.

Research Agenda:

- Prospective studies are needed to determine the incidence of TRALI
- Surveillance methods that capture all cases of TRALI are needed

D. Clinical Relevance

Practice points:

- Stop the transfusion immediately if TRALI is suspected.
- Obtain a white blood cell count and chest radiograph.
- Request Blood Bank to quarantine other units from the same donation(s).
- Request other units for transfusion if indicated (no special requirements).
- Follow institutional polices for a transfusion reaction workup.
- Return bags of units of blood transfused in the last 6 hours, indicating the last unit transfused prior to onset of signs or symptoms

Patients with TRALI present with acute dyspnea during or within hours of transfusion. Intubated patients develop oxygen desaturation and froth may be observed in the endotracheal tube if the patient is supine. For acute management, any transfusion should be stopped immediately and supportive care provided to the patient. A white blood cell count should be obtained soon, as acute leucopenia may develop immediately after transfusion of an implicated unit (12). The leucopenia may be easily missed later, because the white blood cell count returns to normal within hours, when the marginating pool of neutrophils move into the circulation. The Blood Bank should be notified to quarantine other units from the same donation(s). If the patient requires further transfusions, no special blood products are required. The institutional policies for a transfusion reaction workup should be followed. If available, bags of units of blood transfused in the six hours before onset of signs and symptoms should be returned to the Blood Bank. To facilitate workup, it is helpful to indicate the order the units of blood were transfused, and which unit was transfused during or just prior to onset of signs and symptoms. To determine whether leukocyte antibody was transfused to recipient cognate antigens, blood banks may test for leukocyte antigens in the recipient and leukocyte antibodies in implicated donors units. With supportive therapy, most patients recover without permanent pulmonary disease.

The best strategy to prevent TRALI is unknown because the etiology and pathogenesis of the condition is unclear. However, plasma is currently being diverted from FFP manufacture in UK when the donor is female, on the hypothesis that females are more likely to contain alloreactive antibodies that may induce TRALI in recipient patients. In contrast, the United States has not defined any strategy to prevent or reduce TRALI. In April of 2004, a consensus conference on TRALI was held in Toronto, and an expert panel did not find an adequate scientific basis for new regulations to prevent TRALI. Aside from diversion of all female plasma, other possible strategies include:

- Preventative HLA and granulocyte antibody testing, and /or questioning of female donors on parity, followed by plasma product diversion and washing of red blood cells from donors at increased risk.
- Plasma product diversion of donors involved in a case of TRALI

Research agenda:

- Modeling the impact of donor deferral or screening interventions, and
- Research into etiology, diagnostic testing, epidemiology, treatment, and prevention.

E. Summary

TRALI is clinically defined as new ALI that develops during or within hours of transfusion of any blood product. In the absence of another ALI risk factor such as sepsis, pneumonia or aspiration, and when onset clearly develops after the transfusion, the diagnosis is clear. However in the presence of another ALI risk factor, the new ALI may be caused by the transfusion and/or the ALI risk factor. The mechanism of TRALI is unclear and may be multifactorial, including donor and recipient factors. The incidence was 1:5,000 units transfused in older studies, and new studies need to be performed to determine current incidence among transfusion recipients, especially those in intensive care units. The condition is under diagnosed and anesthesiologists should be aware of the possibility in their patients who develop new ALI after transfusion. Treatment is supportive. Research is much needed to elucidate the mechanisms and to institute effective methods to prevent the disease.

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Table 1
Risk factors for ALI in prospective studies (44,54,55,57)

RISK FACTOR	INCIDENCE OF ALI
Septic shock	47%
Pneumonia source	35%
Extrapulmonary source	13%
Sepsis syndrome without hypotension	29 %
Pneumonia source	24%
Extrapulmonary source	6%
Aspiration of gastric contents	15%, 22%, 30%, 36%
Multiple transfusions	36%, 36%, 24%
Near drowning	33%
Disseminated intravascular coagulation	22%
Pulmonary contusion	17%, 22 %
Pneumonia requiring ICU care	12%
Drug overdose requiring ICU care	9%
Fracture of long bones or pelvis	5%, 8%, 11%
Burn, any percent of body surface	2%
Cardiopulmonary bypass	2%