

## Transfusion-related acute lung injury: Definition and review

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### LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Define transfusion-related acute lung injury (TRALI).
2. Explain the mechanisms of TRALI.
3. Demonstrate this knowledge in the clinical setting.

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**Background:** Transfusion-related acute lung injury (TRALI) is now the leading cause of transfusion-associated mortality, even though it is probably still underdiagnosed and underreported.

**National Heart, Lung, and Blood Institute Action:** The National Heart, Lung, and Blood Institute convened a working group to identify areas of research needed in TRALI. The working group identified the immediate need for a common definition and thus developed the clinical definition in this report.

**Major Concepts in the Definition:** The major concept is that TRALI is defined as new acute lung injury occurring during or within 6 hrs after a transfusion, with a clear temporal relationship to the transfusion. Also, another important concept is that acute lung injury

temporally associated with multiple transfusions can be TRALI, because each unit of blood or blood component can carry one or more of the possible causative agents: antileukocyte antibody, biologically active substances, and other yet unidentified agents.

**Recommendation:** Using the definition in this report, clinicians can diagnose and report TRALI cases to the blood bank; importantly, researchers can use this definition to determine incidence, pathophysiology, and strategies to prevent this leading cause of transfusion-associated mortality. (*Crit Care Med* 2005; 33:721–726)

**KEY WORDS:** blood transfusion; red blood cell transfusion; platelet transfusion; acute lung injury; acute respiratory distress syndrome; shock lung; critical care

**T**ransfusion-related acute lung injury (TRALI) is a clinical syndrome that presents as acute hypoxemia and noncardiogenic pulmonary edema during or after blood transfusion (1). TRALI was the

leading cause of transfusion-related mortality in 2003, according to Food and Drug Administration (FDA) data presented at the TRALI conference on April 1, 2004, in Toronto. Still, underdiagnosis and underreporting are likely. This work-

ing group, convened by the National Heart, Lung, and Blood Institute to identify areas of research for TRALI, quickly identified the need to first establish a common definition. Authors of two recent reviews on TRALI also identified the

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need for a definition as a priority (2, 3). Lack of a common definition hampers research and prevents informative comparison of TRALI reports between centers. Current underdiagnosis is due, in part, to excluding patients with other risk factors for acute lung injury (ALI), for example, patients who receive multiple transfusions. The goal of this article is to review knowledge regarding transfusion and ALI and to provide a definition of TRALI that can be used for patient care, epidemiology, and future research.

## Clinical Manifestations

One of the first cases reported in the 1950s was a normal subject who, as an experimental subject, was transfused with 50 mL of whole blood from a patient whose blood contained strong leukoagglutinins, antibodies that agglutinate leukocytes *in vitro* (4). The subject developed fever, hypotension, respiratory distress, bilateral pulmonary infiltrates on chest radiograph, and transient leukopenia. The subject recovered completely in 3 days. Other early reports of patients with what now would be called TRALI were described in a variety of terms: pulmonary hypersensitivity reaction to transfusion (5), pulmonary infiltrates associated with leukoagglutinin in transfusion reactions (6), pulmonary "hypersensitivity" reactions induced by transfusion of non-human leukocyte antigen (HLA) leukoagglutinins (7), pulmonary edema in the course of a blood transfusion without overloading the circulation (8), transfusion reactions with pulmonary infiltration associated with HLA-specific leukocyte antibodies (9), and fulminating noncardiogenic pulmonary edema—a newly recognized hazard during cardiac operations (10).

In 1985, authors of a case series from the Mayo Clinic originated the term "transfusion-related acute lung injury," or TRALI (11). Between 1982 and 1984, they observed 36 cases, mostly surgical (31 cases) and some medical (five cases). TRALI was described as respiratory distress, hypoxemia, and hypotension in the absence of circulatory overload, occurring within 1–6 hrs, and usually within 1–2 hrs, after transfusion of plasma-containing blood components. Mechanical ventilation was required in 72% of cases. Rapid resolution within 96 hrs was observed in 81% of cases, and the mortality rate was 6%. Since the term TRALI was established, many publications of

case reports followed, but the reports did not use a common definition.

In the largest report of 90 cases at the University of Alberta, Canada, between 1991 and 1995 (12), investigators defined TRALI by four criteria: a) respiratory insufficiency (tachypnea, shortness of breath, increased work of breathing, and cyanosis) was accompanied by significant oxygen desaturation, quantified by pulse oximetry or arterial blood gas measurement; b) the degree of respiratory compromise required immediate medical intervention; c) onset of symptoms was temporally related to transfusion (within 4 hrs, most occurred within 10–30 mins); and d) no other clinical cause (ABO incompatibility, volume overload, allergic manifestation, or sepsis) was evident for the pulmonary compromise.

It is possible that TRALI may have been the unrecognized cause of lung injury in some transfused patients. Some cases of ALI attributed to massive transfusion or other ALI risk factors may have been TRALI. In addition, some cases of acute chest syndrome in sickle cell disease may be TRALI (13). Some cases of lung injury associated with granulocyte transfusions may have been TRALI (14). Furthermore, TRALI in thrombocytopenic stem cell transplant patients with recovering neutrophils may be diagnosed as diffuse alveolar hemorrhage (15, 16).

Acute management of TRALI is supportive and similar to management of other forms of ALI (17). Immediate notification of the blood bank is important to quarantine other units from the same donor, to investigate the transfusion reaction, to defer an implicated donor, and to report TRALI cases to the FDA. Units from other donors can be transfused to the patient with TRALI, without special requirements.

## Incidence

All plasma-containing blood and blood components have been implicated (whole blood, packed cells, fresh frozen plasma, platelet concentrates produced from whole blood donation or collected by apheresis, granulocytes, and, rarely, intravenous immunoglobulin and cryoprecipitate). The incidence of TRALI reported varies and includes an estimate of 1 in 5,000 blood and blood components (11), 1 in 2,000 plasma-containing components (18), 1 in 7,900 units of fresh frozen plasma (19), and 1 in 432 units of whole blood derived platelets (12).

According to the report of the FDA at the Toronto conference in 2004, TRALI has now become the leading cause of transfusion-related death in the United States. Cases include patients of both genders and of all ages, although there are no published reports in newborns. The recent increase in reporting to the FDA may have occurred with increased awareness of TRALI. Nevertheless, TRALI is probably still underrecognized and underreported to the local blood bank and to the FDA (20–22). Using the lower estimate of 1 in 5,000 units, 5,000 TRALI cases would be expected to occur every year in the United States, as an estimated 25 million units are transfused annually. If the mortality rate were 6% (11), 300 deaths attributable to TRALI would occur annually. The FDA requires the reporting of all fatal cases attributable to transfusion and received reports of only eight to 21 fatal TRALI cases annually between 1998 and 2003. Reasons for underreporting may include underrecognition and an overly restrictive definition. A definition should not exclude patients who are massively transfused and patients who have other ALI risk factors. The current incidence of TRALI is unclear, and a clinical definition is needed to conduct the research to answer this question.

## Pathophysiology

Increased pulmonary microvascular permeability with increased protein in the edema fluid is the hallmark of ALI regardless of cause (23). In TRALI, two causes of the increased pulmonary microvascular permeability have been proposed: leukocyte antibodies (11) and biologically active substances such as lipids and cytokines that have neutrophil priming activity (12, 18, 24, 25). These two mechanisms may not be mutually exclusive, and a patient may have TRALI due to one or both mechanisms.

According to the first hypothesis, leukocyte antibody in donors, often multiparous women, activates recipient neutrophils in pulmonary capillaries and causes pulmonary damage and capillary leak. Supporting this hypothesis is the first experimental case, in which transfusion of blood from a donor with leukocyte agglutinins caused TRALI in a normal recipient (4). In addition, among the donors tested in the Mayo Clinic series of TRALI cases, 89% had antibodies to granulocytes and 72% had antibodies to lymphocytes (11). Although most antibodies

found in TRALI cases were in the donor plasma, in a minority of cases, antibodies against donor leukocytes were found in patient plasma. Leukoreduction of blood products has been temporally associated with a decrease in TRALI (26). Furthermore, patient granulocyte agglutinins caused abnormal pulmonary sequestration of injected normal 111-indium-labeled granulocytes in three patients (27). In an *ex vivo* rabbit lung model, granulocyte antibody caused acute pulmonary edema in the presence of a complement source (28). Antibodies to HLA class I and II, granulocytes, monocytes, and immunoglobulin A have been found in other cases of TRALI (2). Importantly, transfusion of HLA antibodies to recipients with matching antigens does not always cause TRALI (16) for reasons that are unclear. Transient leukopenia has been observed in leukocyte antibody-mediated TRALI (29).

In the other hypothesis, TRALI is caused by two events (30). The first event is linked to the patient's condition at the time of the transfusion (e.g., sepsis, surgery) that primes and sequesters neutrophils in the lungs. The second event is the transfusion of biologically active substances, for example, lipids or cytokines, that prime and activate neutrophils, leading to lung damage and capillary leak. Supporting this hypothesis is the finding that noxious factors in stored blood plasma (not microaggregates) caused lung injury in a canine model (31). In humans, leukocyte antibodies were detected in only 3.6% of TRALI reactions in the University of Alberta study, and neutrophil priming activity was greater in implicated units than in control units (12). Lipids accumulated during storage are present in cellular blood components, and these lipids have neutrophil priming activity (32, 33). Such priming activity was found in neutral lipids and lysophosphatidylcholines in the plasma of stored red cells (34) and platelets (24). Priming activity and lipids were increased in samples taken from patients at the time of the TRALI reaction (12, 18). Furthermore, lipids detected in the plasma of stored red cells (35) and platelets (25) caused ALI in an *ex vivo* rat primed lung model. Of note is that the two-event model is also pertinent for the antibody-mediated TRALI; antibody can be the second event in a primed patient, and thus the two models are not mutually exclusive.

## Definition of Acute Lung Injury

The North American-European Consensus Conference defined ALI in 1994 (36), and the common definition paved the way for a decade of investigation in acute lung injury. As summarized in Table 1, ALI is defined as acute hypoxemia with  $\text{PaO}_2/\text{FiO}_2$  ratio of  $\leq 300$  mm Hg, found together with the appearance of bilateral infiltrates in the absence of left atrial hypertension (i.e., circulatory overload). Because ALI/acute respiratory distress syndrome is permeability pulmonary edema, the edema fluid to plasma protein ratio is  $\geq 0.6$  (37). If undiluted edema fluid is obtained in intubated patients within 15 mins of onset, this edema fluid to plasma protein ratio can be determined (38).

## Risk Factors for Acute Lung Injury

The risk factors for ALI are well known to critical care specialists. To summarize the incidence of ALI associated with risk factors, we extracted data from the four prospective studies that investigated the incidence of ALI in patients with risk factors (Table 2) (39–42). It is important to note from Table 2 that  $<50\%$  of patients with risk factors develop ALI. The

risk factors associated with the highest ALI risk are sepsis, aspiration of gastric contents, and multiple transfusion. Table 2 is not meant to include all ALI risk factors and lists only major risk factors for which the incidence of ALI has been studied prospectively. Other risk factors where the incidence of ALI is less clear include cirrhosis, toxic inhalation, pneumonia, neurogenic pulmonary edema, pancreatitis, prolonged hypotension, trauma, and lung resection. In addition, there may be yet other unidentified ALI risk factors. Comorbid factors that increase the risk of ALI include older age, chronic alcoholism, tobacco abuse, absence of diabetes, greater severity of illness, and variant surfactant B gene in women (42). Although multiple unit transfusion has been identified as a risk for ALI, transfusion of a small number of units was not studied as a risk factor for ALI in these prospective studies.

## Transfusion as a Risk Factor for Acute Lung Injury

Transfusion of multiple units has long been considered a risk factor for ALI (39, 41, 42). Multiple transfusions have been defined as transfusion of  $>10$  units of red cells or whole blood within a 12-hr period

Table 1. Criteria for acute lung injury (Ref. 36)

1. Timing: Acute onset
2. a) Pulmonary artery occlusion pressure:  $\leq 18$  mm Hg when measured, or  
b) A lack of clinical evidence of left atrial hypertension
3. Chest radiograph: Bilateral infiltrates seen on frontal chest radiograph
4. Hypoxemia: Ratio of  $\text{PaO}_2/\text{FiO}_2 \leq 300$  mm Hg regardless of positive end-expiratory pressure level, or Oxygen saturation of  $\leq 90\%$  on room air (added by working group)

Table 2. Risk factors for acute lung injury (ALI) in prospective studies (Refs. 36, 39, 41–42)

Risk Factor	Incidence of ALI, % (No.)
Septic shock	47 (42)
Pneumonia source	35
Extrapulmonary source	13
Sepsis syndrome without hypotension	29 (42)
Pneumonia source	24
Extrapulmonary source	6
Aspiration of gastric contents	15% (42), 22 (41), 30 (39), 36% (40)
Multiple transfusions	36 (42), 36 (41), 24 (39)
Near drowning	33 (41)
Disseminated intravascular coagulation	22 (40)
Pulmonary contusion	17 (39), 22 (41)
Pneumonia requiring ICU care	12 (40)
Drug overdose requiring ICU care	9 (41)
Fracture of long bones or pelvis	5 (40), 8 (39), 11 (41)
Burn, any percent of body surface	2 (40)
Cardiopulmonary bypass	2 (40)

ICU, intensive care unit.



(39),  $\geq 15$  units of blood within 24 hrs (41), or  $\geq 8$  units of red cells within 24 hrs (42). All these criteria meet or closely meet the common definition of massive transfusion in the blood bank literature: transfusion of one or more blood volumes within 24 hrs (e.g., transfusion of  $\geq 10$  units of red cells or whole blood to a 70-kg adult within 24 hrs). The prospective studies found that when multiple transfusion was the sole risk factor, 24–36% of patients developed ALI (39, 41, 42). Some of these ALI cases associated with massive transfusion could have been TRALI (43).

Transfusion was an independent risk factor for development of ALI in medical intensive care patients who were ventilated (44). Transfusions may cause lung injury in patients without other ALI risk factors; that is, blood products may incite acute lung injury. In addition, it is possible that transfusion may have a facilitating or permissive role in the development of lung injury in patients who have other risk factors for ALI. It is interesting to note that in the Transfusion Requirements in Critical Care trial, patients who were randomized to the liberal transfusion strategy had a greater, albeit non-statistically significant, risk of developing ALI (11.4% vs. 7.7%,  $p = .06$ ) and a greater mortality rate (23.3% vs. 18.7%,  $p = .11$ ) than the patients in the restrictive transfusion group (45).

In terms of mechanism, leukocyte antibody and/or biologically active substances in blood products may incite or exacerbate lung injury during massive or nonmassive transfusion, as described in the pathophysiology section. In theory, allogeneic blood transfusion may indirectly cause ALI through immunosuppression (46, 47) and thus predispose to sepsis, the leading risk factor for ALI. However, this is unlikely to occur within hours after transfusion. Finally, the old theory that ALI associated with massive transfusion is due to microaggregates in transfused blood is no longer accepted (31), and microaggregate filters do not prevent ALI (48, 49).

### Working Group Definition of TRALI

The Working Group decided to include the following principles in creating a new definition of TRALI: a) Instead of reinventing a new definition of acute lung injury, the successful and now universal 1994 North American-European

Consensus Conference definition of ALI (23) should be adapted; b) there should be no preexisting ALI before transfusion; c) the traditional temporal relationship of onset of symptoms or signs during or within 6 hrs of transfusion should be used; d) in patients with an alternative ALI risk factor, TRALI is still possible; e) massive transfusion should not exclude the possibility of TRALI. Validation and improvement of these principles will be based on data from future large prospective studies.

The criteria for ALI summarized in Table 1 use the North American-European Consensus Conference definition of ALI (23). In addition, the working group considered patients in whom an arterial blood gas is not available. If the oxygen saturation is  $\leq 90\%$  when a patient is breathing room air, the  $\text{PaO}_2$  is usually  $\leq 60$  mm Hg. These patients have a  $\text{PaO}_2/\text{FiO}_2$  ratio of  $\leq 60$  mm Hg/0.21 or  $\leq 300$  mm Hg and therefore meet the standard  $\text{PaO}_2/\text{FiO}_2$  ratio criteria for ALI. To include some less severe cases, we did not set a requirement for respiratory failure or mechanical ventilation. Because transfused patients are often elderly and often receive other resuscitative fluids, establishing a lack of clinical evidence of left atrial hypertension (circulatory overload) is an important diagnostic challenge for critical care experts.

Table 3 outlines the working group's definition of TRALI as new ALI that develops with a clear temporal relationship to transfusion, in patients without or with alternative risk factor(s) for ALI. First, in patients without alternative risk factor(s) for ALI, the diagnosis of TRALI is made if there is new ALI (Table 1) during or within 6 hrs after a completed infusion of one or more plasma-containing or plasma-derived blood products. The definition excludes patients with preexistent ALI, because defining criteria for worsening ALI is difficult. However, the definition does not exclude patients with preexisting lung disease before transfusion. The same mechanisms that produce TRALI in normal lungs would also produce TRALI in lungs with preexistent lung disease. The definition states a 6-hr limit for onset of symptoms or signs during or after transfusion. Although most reported cases of TRALI occur within 1 or 2 hrs of transfusion, traditionally a limit of 6 hrs has been used. We set a time limit of 6 hrs after the end of transfusion but emphasize that this is in keeping with tradition but may change based on data

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from future larger prospective studies. Note also that the definition states that TRALI can occur with transfusion of only one unit. Thus, ALI after multiple-unit transfusion may merely represent a greater risk of infusion of a unit containing antileukocyte antibodies, biologically active substances, or both (43). The definition also includes the fact that TRALI has been associated with all plasma-containing blood products but not with washed red cells.

Second, in patients with ALI risk factors other than transfusion, the new ALI may be either TRALI or not TRALI (Table 3, sections 2.a and 2.b). Risk factors are described in the previous section, "Risk Factors for Acute Lung Injury." In such patients, the new ALI may be TRALI (Table 3, section 2.a) due to the transfusion alone, or the two-event model suggests that the new ALI is mechanistically linked to the transfusion as the second event. Alternatively, the new ALI is not TRALI (Table 3, section 2.b) and is related to the other risk factor alone, and transfusion is coincidental. Assessment of the patient's clinical course is needed to determine whether the new ALI is TRALI. In such cases, critical care specialists can assess the likelihood of TRALI by determining the following: a) whether other TRALI-associated findings are present (Table 4); b) whether the patient was stable before transfusion; c) whether the new ALI clearly developed with the trans-

Table 3. Clinical definition of transfusion-related acute lung injury (TRALI)

1. Patients without ALI risk factor(s) other than transfusion  
In patients with no ALI immediately before transfusion, a temporal association of transfusion and ALI is made if there is:
  - New ALI (defined in Table 1), and
  - The onset of symptoms or signs is during or within 6 hrs after the end of transfusion of one or more plasma-containing blood products.
 As there is no other ALI risk factor, the new ALI is inferred to be mechanistically related to transfusion, i.e., TRALI.
2. Patients with ALI risk factor(s) other than transfusion  
In patients with no ALI immediately before transfusion, a temporal association of transfusion and ALI is made if there is:
  - New ALI (defined in Table 1), and
  - The onset of symptoms or signs is during or within 6 hrs after the end of transfusion of one or more plasma-containing blood products.
 By assessing the patient's clinical course (see text), the new ALI is either:
  - a. TRALI, and the new ALI is inferred to be mechanistically related to the transfusion, or both the transfusion and the alternative risk factor, or
  - b. Not TRALI, and the new ALI is mechanistically related to the alternative ALI risk factor alone, while the transfusion is coincidental.

Table 4. Other findings associated with transfusion-related acute lung injury (TRALI)

- Other findings that have been associated with TRALI but are not required for the clinical diagnosis include these:
1. Symptoms: dyspnea
  2. Physical findings: tachypnea, cyanosis, fever, tachycardia, hypotension or hypertension, froth in endotracheal tube
  3. Laboratory findings:
    - a. Transient acute leukopenia
    - b. Leukocyte antigen-antibody match between donor and recipient (HLA class I or II, granulocytes or monocytes)
    - c. Increased neutrophil priming activity in the plasma of blood products

HLA, human leukocyte antigen.

fusion; and d) the incidence of ALI with the risk factor (Table 2). No doubt, even experts will consider some cases indeterminate.

Table 4 describes additional findings associated with TRALI, but not essential to the clinical diagnosis. The laboratory findings in TRALI cases have not been consistent and may reflect more than one etiology. A laboratory workup of a case of TRALI depends on the tests available to an institution and can be discussed with the institution's blood bank. A white blood cell count is inexpensive and always available but must be obtained immediately on recognition of the signs and symptoms, because the leukopenia is transient. Tests for leukocyte antigen and antibody are expensive and vary in availability, and tests for neutrophil priming activity are performed primarily in the research laboratory. The role of the natriuretic peptides in distinguishing TRALI from circulatory overload remains to be defined. Definitive laboratory tests for TRALI are clearly needed.

## Limitations and Ramifications

With our present understanding, this definition provides a start in the definition of TRALI, and further research will allow refinement of this definition. This definition has limitations. First, the definition only identifies new, severe cases of hypoxemia. Cases of TRALI in patients who already have ALI would not be included, nor will milder forms of TRALI that may be associated with  $\text{PaO}_2/\text{FiO}_2 > 300$  mm Hg or oxygen saturation  $> 90\%$  on room air. Further work is needed to set criteria for worsening ALI and mild TRALI. Second, the diagnosis of TRALI in a patient with an alternative ALI risk factor requires critical care expert assessment of the clinical course, and even experts will consider some cases indeterminate. Third, there may be other clinical risk factors such as major surgery that predispose to TRALI but are not on the list of identified ALI risk factors. Fourth, the definition does not include definitive laboratory tests. When etiolo-

gies are better understood, a more precise definition can be made by testing the causes in patients and/or blood units associated with cases suggestive of TRALI. Finally, the traditional 6-hr limit may not capture cases that develop later.

The inclusion of patients who have ALI after massive transfusion as possible cases of TRALI raises the practical question whether the multiple donor units transfused within 24 hrs should be tested for leukocyte antibody. Because these tests are expensive, it is reasonable to limit testing to the units transfused within 6 hrs of development of TRALI.

## SUMMARY

TRALI is a syndrome that may span a spectrum from mild to fatal acute lung injury associated with transfusion of blood and blood components. There are likely at least two distinguishable causes: leukocyte antibodies and neutrophil priming agents. As greater understanding is gained into the epidemiology and mechanisms, the definition will change as well. We encourage nurses and others who administer transfusions to be aware of the signs and symptoms of TRALI in all patients, both inpatients and outpatients. When possible, pulse oximetry in addition to the usual vital signs monitoring of all transfused patients may be reasonable. We encourage physicians to use the criteria proposed here to diagnose and report cases of TRALI to the local blood bank. The blood bank will quarantine other units from a suspect donor, investigate implicated donors per local policy, report fatal cases to the FDA, and report nonfatal cases to MedWatch.

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