Guidelines
For the
Management
of Transfusion-
Related Acute
Lung Injury

American Association of Blood Banks
Guidelines for the Management of Transfusion-Related Acute Lung Injury

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Continuous improvement in the practice of all aspects of medicine is the goal of every health-care provider. In transfusion medicine, those charged with oversight and improvement of practices are faced with difficult challenges. This Guideline is intended to facilitate this improvement process.

Transfusion-related acute lung injury (TRALI) is a life-threatening complication of transfusion. In fact, it is the second or third most common cause of transfusion-associated death in developed countries. The diagnosis of TRALI is problematic. First, there are no risk factors that distinguish patients at risk. Second, all plasma-containing blood components (including Red Blood Cells preserved in additive solutions, platelet concentrates, and Cryoprecipitated AHF) have been implicated. Third, TRALI is clinically indistinguishable from adult respiratory distress syndrome (ARDS). Thus, there is no sign, symptom, or laboratory finding that clearly identifies TRALI. The diagnosis depends on a clinician’s ability to sort through various clinical and laboratory findings.

As with other Guidelines in this series, the recommendations included in this document do not represent the sole approach to the diagnosis and management of TRALI. Indeed, there remain many unresolved questions about this important cause of morbidity and mortality in transfusion recipients.

The Scientific Section Coordinating Committee (SSCC) oversaw the development of this Guideline. The SSCC appreciates the diligent efforts of the author in compiling and interpreting the information presented. Thoughtful input from the numerous reviewers is also gratefully acknowledged. With careful consideration of the concepts detailed herein, it is hoped that this Guideline will serve to advance patient safety.

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INTRODUCTION

Transfusion-related acute lung injury (TRALI) is characterized by acute respiratory distress, bilateral pulmonary edema, and hypoxemia in the setting of transfusion of plasma-containing blood components. Hypotension (unresponsive to fluid administration) and fever (1-2°C rise) are frequent manifestations. The hypoxemia and pulmonary edema are frequently severe. The onset of symptoms is typically 1 to 2 hours following the beginning of transfusion; however, cases commencing up to 6 hours after transfusion are found in the literature. All plasma-containing blood components, including platelet concentrates, cryoprecipitate, and additive-preserved Red Blood Cells (RBCs) have been implicated. Rare cases involving plasma derivatives, namely intravenous immune globulin, have been reported. More than 400 cases of TRALI have been described in the literature.

Although TRALI was first described in 1982, this syndrome was previously referred to as pulmonary hypersensitivity reaction, allergic pulmonary edema, noncardiogenic pulmonary edema, and pulmonary leukoagglutinin syndrome. There is little doubt that these are synonyms for the same clinical entity.

There are no risk factors that distinguish patients at risk for TRALI. Both sexes are equally involved and all age groups have been affected. TRALI is clinically indistinguishable from acute respiratory distress syndrome (ARDS), but has a milder prognosis. Still, 5% to 10% of patients with TRALI die. In surviving patients, the pulmonary infiltrates typically clear (or are resolving) within 96 hours in 80% of cases, with commensurate physiologic improvement. In the remaining 20% of surviving patients, the pulmonary infiltrates may persist, but usually clear without residual pulmonary sequela.

PATHOGENESIS OF TRALI

The pathogenesis of TRALI is thought by most investigators to be antibody-mediated. In 80% of cases, HLA Class I or II antibodies and/or granulocyte-specific antibodies can be found in at least one plasma-containing blood component transfused to the patient in the preceding 2 hours. In 5% of patients, these antibodies may be found in the patient’s serum prior to transfusion. In about 50% of cases, the anti-
bodies in the blood component have specificity for at least one epitope on the patient's cells.

Current evidence suggests that the pathogenesis of TRALI depends on the activation of complement or other biologic modifiers (e.g., tumor necrosis factor-α) by antibodies in blood components. An experimental model of TRALI as well as that of ARDS indicates that the presence of antibody, antigen, and complement result in lung injury and pulmonary edema. Studies of ARDS demonstrate that complement activation leads to granulocyte aggregation in the pulmonary microvasculature, which results in endothelial damage, presumably from superoxide and other metabolite release from the activated granulocytes. One group of investigators demonstrated that receipt of plasma from multiparous donors results in significant alteration of the PaO₂/FiO₂ ratio. Several investigators have shown that many cases of TRALI are associated with the blood products made from multiparous donors. The relationship between parity and the development of HLA antibodies is well established.

However, approximately 10% of cases may be related to “antibody-negative” units. At least one group of investigators believes that other factors, such as lipids found in stored blood components, may play a role in the lung injury seen in these patients. In this model, underlying hypoxemia or some other insult predisposes the patient for TRALI. This “two-event” model presupposes that the patient's neutrophils must first be primed by conditions such as sepsis or trauma for them to respond to transfusion (the second event). Lipid mediators in donor plasma have been shown to activate neutrophils, leading to respiratory burst and release of proteases.

DIAGNOSIS OF TRALI

As there is no pathognomonic sign, symptom, or laboratory finding, the diagnosis rests on a combination of clinical and laboratory findings. Other causes of pulmonary injury (e.g., circulatory overload, acute left ventricular dysfunction secondary to cardiac ischemia) should be ruled out. In the setting of transfusion (absent the signs of the aforementioned), the presence of hypoxemia, pulmonary edema, and hypotension coupled with one or all of the following laboratory findings establish a high probability for the diagnosis: 1) HLA Class I or II antibodies and/or granulocyte antibodies in a blood component that has been transfused within 2 hours of symptoms; 2) HLA Class I or II antibodies or granulocyte antibodies in the pretransfusion serum of
the patient; 3) positive lymphocyte crossmatch between the serum of 
the implicated blood component (or the donor) and the patient's lym-
phocytes; 4) correspondence of donor antibody with HLA or granulo-
cyte epitope in the recipient.

Many aspects of TRALI remain uncertain. The key unresolved 
questions are:
1. Are patients who have had TRALI at increased risk for recurrence?
2. What types of patients are at increased risk?
3. Are there milder forms of TRALI?
4. Is there a mechanism of injury that does not involve passive trans-
fer of donor antibodies?
5. Should the blood components collected from donors who have 
had multiple pregnancies or have been transfused be handled dif-
ferently?
6. What is the most cost-effective work-up for patients suspected of 
TRALI?

MANAGEMENT OF TRALI

Management of Suspected Cases

Laboratory investigation of suspected TRALI patients may be very ex-
pensive; however, confirmatory testing is not necessary for treatment. 
Once the diagnosis is entertained, the transfusion must be stopped 
immediately and pulmonary intervention initiated. Supplemental ox-
ygen and mechanical ventilation, as well as pressor agents (in cases of 
hypotension), may be indicated.

The laboratory work-up should begin with testing the plasma-con-
taining blood components that were given 1 to 2 hours prior to the on-
sset of symptoms. A plasma (or serum) sample from the component or 
from the donor, and a pretransfusion sample from the patient should 
be obtained.

The following findings are supportive of the diagnosis:
• Positive lymphocyte crossmatch between donor serum and recipi-
ent lymphocytes.
• HLA Class I or II antibodies or granulocyte-specific antibodies in a 
transfused blood component or in the pretransfusion serum of the 
patient.
• Correspondence of antibody in the blood component (or donor) and an epitope on the recipient’s cells.
While many laboratories can perform these tests, additional tests such as one to identify granulocyte antibodies may need to be performed by specialized laboratories. Most blood center reference laboratories can direct specimens to an appropriate facility.

Management of Future Transfusions in the Patients Diagnosed with TRALI

There are only a few reports of repeat episodes of TRALI in a single patient due to the (unusual) reverse situation of TRALI being attributable to leukocyte alloantibodies in the recipient. As a rule, special precautions are not necessary for subsequent transfusions to a patient who has experienced TRALI. Leukocyte reduction of cellular blood components will, at best, prevent the 5% to 10% of cases caused by antibodies in the recipient.

Management of the Implicated Blood Components and Donor

Once a donor has been implicated, all other untransfused blood components made from that donation should be quarantined and destroyed. Future donations must be handled to eliminate the chance of plasma being transfused.

RECOMMENDATIONS

Despite the difficulties in diagnosing TRALI, management of this serious transfusion complication is better defined.

1. Early recognition or suspicion of TRALI is warranted. Stop the transfusion as soon as the diagnosis is suspected.
2. Once TRALI is considered a diagnostic possibility, pulmonary support should begin promptly. The degree of intervention is dictated by the severity of pulmonary distress and/or hypotension.
3. The laboratory work-up can be handled in a step-wise fashion. In cases with a high index of suspicion, once a recommended test is found to be positive, the work-up can be terminated. However, truncating the protocol may risk missing a truly implicated unit if another antibody-positive donor is coincidentally associated with the case.
4. Plasma-containing blood components, including Red Blood Cells (RBCs), from implicated donors should be quarantined and destroyed. Because all plasma-containing blood components have been implicated, including RBCs prepared in additive solutions,
the safest route to follow is one in which all components made from a "suspect" donor are removed from the general inventory.
5. The handling of a donor who has been implicated remains controversial. Collection agencies must reevaluate the eligibility of implicated donors. Once a donor has been implicated, at the very least, future blood donations should be managed to prevent the release of any plasma-containing components for transfusion. Options include: 1) permanent deferral of the donor, and 2) restricting the use of the donor's components to washed or frozen RBCs.

REFERENCES