

Transfusion-Related Acute Lung Injury

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SUMMARY

Transfusion-related acute lung injury (TRALI) is the adult respiratory distress syndrome arising from transfusion of a plasma-containing blood product. It occurs within 1-6 hours of transfusion and is the third leading cause of transfusion-related mortality in developed countries. TRALI patients present with dyspnea, hypotension, fever, and bilateral noncardiogenic pulmonary edema. Effective treatment includes stopping the transfusion and providing supportive care, whose intensity will depend on the clinical picture. Approximately 80% of TRALI patients recover within 96 hours. TRALI may result from multiple mechanisms. In most cases, pathogenesis appears to reflect the presence of granulocyte or HLA antibodies in donor blood. These react with and fix complement to antigens in the recipient, which leads to granulocyte aggregation, activation, and severe capillary leakage. Preventive measures should focus on limiting exposure to donors most likely to precipitate TRALI. Implicated donors are multiparous females and donors with previous multiple exposure to allogeneic transfusions. Clear recommendations and guidelines for preventing TRALI are needed.

Transfusion-related acute lung injury (TRALI) is a form of noncardiogenic pulmonary edema following the transfusion of plasma-containing blood components. This complication of transfusion is being observed with increasing frequency. Over the last few years, TRALI has been implicated in 10.5-14% of annually reported posttransfusion fatalities (FDA reports). Its estimated frequency is about 0.02% per transfused plasma-containing unit.¹ However, the incidence of TRALI may be much higher than reported.

At times, TRALI is not recognized, mainly in patients presenting with mild initial symptoms, or it is misdiagnosed as circulatory overload. This review summarizes most of the work concerning this life-threatening syndrome and is intended to contribute to the awareness of TRALI through broad physicians education.

Incidence

Although the actual incidence of TRALI is not clearly known, its estimated frequency ranges from 0.014% to 0.02% per plasma-containing transfusion^{1,2} and 0.04% to 0.16% per transfused patient.^{1,2,3}

Of particular concern is that TRALI has been reported as the third leading cause of transfusion-related death, after ABO incompatibility and bacterial contamination.⁴ This complication of transfusion may evade clinical recognition. The absence of prospective studies and the range of severity of symptoms—from mild to life-threatening—may be contributing to misdiagnosis and perhaps to the underreporting of TRALI.

In previous studies, the risk of death ranged from 5 to 8%^{1,5} while in a recent study 13% of 46 cases were fatal.⁶

There is no age or sex prevalence. The male-to-female ratio is 1:1. TRALI has been described in transfusion recipients from the age of 1 month to 87 years.¹ Most patients have no prior history of transfusion reactions.

Pathophysiology

TRALI may result from multiple mechanisms. Numerous reports have documented the presence of antibodies to HLA or to granulocyte antigens in the plasma of the donors of implicated blood components. In a series of 36 cases of TRALI, granulocyte antibodies, in the serum of at least one donor, were identified in 89% and lymphocyte antibodies, in at least one donor, in 72% of the cases.¹ In another, larger and more recent study, granulocyte antibodies were also identified more frequently (41%) than HLA antibodies (28%).⁶

HLA antibodies have frequently been found in multiparous women donors. A recent study of plateletpheresis donors found HLA antibodies in 26% of the women with three or more previous pregnancies.⁷ In a randomized controlled trial, the transfusion of plasma from multiparous donors to patients in an intensive care unit was associated with significantly lower oxygen saturation and higher tumor necrosis factor (TNF) concentrations than the transfusion of control plasma.^{8,9} In addition, several cases of TRALI resulting from mother-to-child directed donations have been reported.^{10,11}

In 5-11% of TRALI cases, causative antibodies have been found in the recipients' plasma but not in the donors' plasma.^{1,2} In 5-15% of cases, no antibody has been identified in either the patient or donor. In approximately 50% of cases, the implicated donor antibodies are directed against HLA-A or HLA-B epitopes in the recipient.¹² Recently, HLA class II rather than class I antibodies have been described in the serum of implicated donors.^{12,13}

The exact specificity of the granulocyte antibodies involved has been identified in only a few cases. These include anti-NA2,¹⁴ anti-NB1,¹⁵ anti-NB2,¹⁶ and anti-5b.¹⁷

It appears that TRALI begins with the passive transfer of antibodies from the donor's plasma to the recipient, which causes a sequence of events. These antibodies fix complement. When complement is activated, C5a promotes neutrophil aggregation, margination and sequestration in the pulmonary microvasculature. Complement-activated neutrophils

release proteases and oxygen radicals. The underlying pulmonary vascular endothelium is damaged, with subsequent extravasation of proteins and fluids from the vascular space into adjacent interstitium and alveoli.¹⁸

This mechanism does not explain the fact that although 1-2% of blood donors have HLA antibodies, TRALI occurs much less frequently than expected. Nor does it explain why TRALI occurs in the absence of antibodies in either the patient or the donor. Some cases of TRALI appear to result from other mechanisms. Alternative mechanisms may include the following:

- Direct adhesion between pulmonary endothelium and neutrophils may also contribute to TRALI.^{9,19}
- Another mechanism in the pathogenesis of TRALI involves cytokines.⁹ Several reports implicate cytokines, including tumor necrosis factor (TNF- α), Il-1, Il-6 and Il-8. The neutrophil β 2 integrins CD11/CD18 and endothelial ICAM-1 primarily mediate these adhesive interactions.
 - TNF- α and Il-1 increase endothelial cell ICAM-1 expression.
 - Recent reports have postulated another possible etiology for TRALI.^{20,21,22} The theory suggests that two events must coincide for TRALI to occur: (1) a predisposing condition that releases cytokines or other factors that prime neutrophils, causing adherence to endothelium; and (2) reactive lipid products from donor blood cell membranes that accumulate during blood bank storage and that are capable of recipient neutrophil priming, with subsequent damage of pulmonary capillary endothelium.

Implicated Blood Components

All blood components containing plasma have been implicated in the induction of TRALI. These components include whole blood, packed red cells, fresh frozen plasma, apheresis platelets or granulocytes, and cryoprecipitate.¹⁸

Recently, intravenous immunoglobulin infusion was associated with at least one documented case of TRALI.²³

In most instances, the implicated component contains more than 60 mL of plasma, but even smaller amounts of plasma (10-15 mL) may induce TRALI.¹⁸

The majority of deaths have been associated with transfusions of fresh frozen plasma (FDA report, Oct. 2001).

Clinical Presentation

Symptoms and signs include dyspnea, mild to moderate hypotension, tachycardia, cyanosis, fever (38-39°C), cough, the production of fluid from the endotracheal tube in intubated patients, and severe hypoxemia (pO₂ as low as 30-50 torr). Symptoms typically begin 1 to 2 hours after transfusion and are fully manifest within 1 to 6 hours.¹

In the largest series reported to date, which consisted of 46 cases, the most common predominant symptoms were respiratory distress and hypotension.⁶

In patients under general anesthesia who present with TRALI, the main finding is a decrease in the hemoglobin oxygen saturation.

On clinical examination, patients will have bilateral pulmonary edema and no signs of cardiac decompensation.

Typically, a chest x-ray will show bilateral interstitial and alveolar infiltrates consistent with pulmonary edema, a normal cardiac silhouette, and the absence of pulmonary vascular congestion. The radiographic findings tend to be more remarkable than the physical findings.¹

There is a growing appreciation of less common forms of TRALI with mild or no initial symptoms and the development of a full-blown syndrome as late as two days following transfusion.^{6,24,25}

In its classic and fulminant presentation, TRALI is indistinguishable from adult respiratory distress syndrome (ARDS) secondary to other causes (e.g., sepsis, toxic inhalation, drugs, trauma, or aspiration). TRALI differs from ARDS in as follows:^{1,6}

1. The death rate is 40-50% in ARDS, while in TRALI it is 5-13%.
2. In many ARDS patients, the lung injury is irreversible, while in TRALI pulmonary lesions are typically transient.

Approximately 80% of TRALI-affected patients improve clinically and physiologically within 96 hours. Arterial blood gas values return to baseline and pulmonary infiltrates resolve within this time frame. However, in the remaining 20% of patients, infiltrates persist for at least 7 days.¹

Diagnosis^{18,25}

The diagnosis of TRALI is based primarily on clinical signs and symptoms. There is no diagnostic test or pathognomonic sign. Other causes of respiratory distress and pulmonary edema in the transfusion setting, such as circulatory overload, bacterial infection, or acute anaphylactic reaction, should be ruled out.

Clinically, TRALI is distinguished from circulatory overload by patients having normal or low pulmonary capillary wedge pressure, normal pulmonary artery pressure, and normal central venous pressure.

The presence of HLA or granulocyte antibodies in donor or recipient serum strongly suggests a diagnosis of TRALI. When antibodies are found, a lymphocytotoxicity crossmatch between donor serum and recipient WBC is performed. If the crossmatch is positive, the diagnosis of TRALI is confirmed. If the crossmatch is negative, a diagnosis of TRALI is still presumed.

Treatment^{18,25}

If symptoms develop during the infusion of a blood product, the transfusion should be terminated. Clinical management focuses on maintaining hemodynamic status and reversing progressive hypoxemia with oxygen supplementation and ventilatory assistance, if necessary. Vasopressors may be necessary for prolonged hypotension. Corticosteroids are felt to have little benefit.

Diuretics play no role in TRALI treatment, as the underlying pathology involves microvascular injury rather than fluid overload.

Additional blood component therapy should not be withheld if a clear indication for transfusion exists.

Prevention

Measures should focus on limiting exposure to donors most likely to precipitate TRALI. Although there are no clear recommendations or guidelines from authoritative organizations, some investigators^{9,18,25} have made recommendations that include the following:

- Donors who have been shown to be implicated in TRALI should be deferred, or blood from these donors should not be used for plasma-containing products. Subsequent donation should be limited to the production of frozen deglycerolized or washed red blood cells only.
 - No special precautions are needed for the recipient if the problem was donor-specific and components from other donors are available.
 - If an antibody has been identified in the recipient, it is recommended that the transfusion of cellular components be leukocyte-depleted, using filters that significantly reduce the number of leukocytes.
 - Multiparous donors (three or more pregnancies) and donors with previous allogeneic transfusions (two or more donor exposures) should be prospectively identified and their blood either screened for HLA and granulocyte antibodies or diverted for uses other than plasma-containing products.
 - Multiparous or previously transfused donors identified to be positive for anti-HLA or antigranulocyte antibodies should be permanently deferred, or donation should be limited to the production of frozen deglycerolized and washed red blood cells only, or their plasma collections should be diverted to the manufacture of noninjectable products.
 - Multiparous or previously transfused donors negative for anti-HLA or antigranulocyte antibodies are permitted to continue donating on a routine basis.
 - Special precautions may need to be taken in cases of directed maternal-blood donation. Patients and families should be informed that TRALI could result from mother-to-child transfusion.^{9,25}
 - Theoretically, directed donation of blood from a woman to her children's father could also result in a TRALI reaction, if the donor developed antibodies to the paternal WBC antigens during pregnancy.²⁵
 - Prestorage leukoreduction may play a role in limiting the incidence of TRALI for the following reasons: (a) prestorage leukoreduction may reduce the accumulation of lipid mediators during storage;^{20,21,22} and (b) leukoreduction filtration will remove significant numbers of neutrophils. These have a theoretical impact on the less common reaction due to anti-neutrophil antibodies in the recipient.

CONCLUSION

TRALI is a life-threatening complication of blood component transfusion therapy. It is characterized by a clinical constellation of symptoms and signs, including dyspnea, hypotension, fever, and bilateral noncardiogenic pulmonary edema. Its estimated frequency is about 0.02% per plasma-containing transfusion and 0.16% per transfused patient¹ but may be much higher than reported. Recognition of this serious syndrome and immediate treatment are imperative. Reporting fatal and nonfatal TRALI events through Med Watch to authoritative national organizations or committees could contribute to a better understanding of the incidence and causes of this syndrome. Increased awareness of TRALI through broad health professional education could improve prompt and appropriate treatment of this complication of transfusion. Recommendations and guidelines regarding the prevention of TRALI from authoritative organizations or committees or blood transfusion societies are needed.

Key Points

1. TRALI has been reported as the third leading cause of transfusion-related death.
2. The actual incidence of TRALI is not clearly known. Its estimated frequency is about 0.02% per plasma-containing transfusion but may be higher than reported.
3. TRALI may result from multiple mechanisms. Many reports have documented the presence of antibodies to HLA or to granulocyte antigens in the plasma of implicated blood components. One or both of these antibody types have been found in 89% of TRALI cases.
4. All plasma-containing blood components have been implicated in the induction of TRALI. The majority of deaths have been associated with the transfusion of fresh frozen plasma. As well, intravenous IgG infusion was recently implicated in at least one documented case.
5. Effective treatment includes stopping the transfusion and providing supportive care.
6. Measures for prevention should focus on limiting exposure to donors most likely to precipitate TRALI. Implicated donors are multiparous females and donors with previous multiple exposure to allogeneic transfusions.
7. Clear recommendations and guidelines regarding the prevention of TRALI are needed.

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