

# Review Article

## Transfusion-related acute lung injury\*

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### Abstract

Transfusion-related acute lung injury (TRALI) is a serious clinical syndrome associated with the transfusion of plasma-containing blood components. Recently, TRALI has come to be recognized as the leading cause of transfusion-related death in the United States and United Kingdom. This complication typically presents as shortness of breath, hypoxemia, hypotension, fever and noncardiogenic pulmonary edema, all occurring during or within 6 h after transfusion. Although the mechanism of TRALI has not been fully elucidated, it has been associated with human leukocyte antigen antibodies (class I, class II or neutrophil alloantigens) and with biologically active mediators in stored cellular blood components. Most of the donors implicated in cases of TRALI are multiparous women. Rarely diagnosed, TRALI can be confused with other causes of acute respiratory failure. Greater knowledge regarding TRALI on the part of clinicians could be crucial in preventing and treating this severe complication of blood transfusion.

**Keywords:** Blood transfusion; Respiratory insufficiency; HLA antigens.

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## Introduction

Transfusion-related acute lung injury (TRALI) was recognized as a clinical entity in 1985.<sup>(1)</sup> Although there is no definitive consensus, TRALI is considered a serious complication related to the transfusion of plasma-containing blood components. It is characterized by acute respiratory failure, bilateral pulmonary edema and severe hypoxemia without cardiac involvement, all occurring during or at  $\leq 6$  h after transfusion.<sup>(2,3)</sup>

In the United States and United Kingdom, TRALI is among the most common causes of transfusion reactions, being considered the leading cause of transfusion-related morbidity and mortality in recent years.<sup>(2-4)</sup>

In fact, TRALI is a clinical syndrome. Although much has been learned about this syndrome, its pathogenesis, treatment and prevention remain little understood.

## Epidemiology

The exact incidence of TRALI is unknown, and it is probably underdiagnosed. It is estimated to occur in 0.014–0.08% of all units of transfused allogeneic blood components or in 0.04–0.16% of all transfused patients.<sup>(3,5)</sup> A relatively rare complication, TRALI occurs at a ratio of 1 in 5000 transfused units and of 1 in 625 transfused patients. However, TRALI is considered the leading cause of transfusion-related morbidity and mortality (Table 1).<sup>(2)</sup>

Since many clinicians, as well as some hematologists working in blood banks, are not familiar with the syndrome, TRALI might be underdiagnosed. It can even be confused with other situations involving acute respiratory failure, such as acute respiratory distress syndrome (ARDS) and transfusion-related circulatory overload. Therefore, the prevalence of TRALI could be higher than that estimated above.<sup>(2,5,6)</sup>

Although the risk factors that contribute to the triggering of TRALI are unknown, certain serious clinical conditions at the moment of transfusion can trigger this syndrome. Notable among the principal factors are malignant hematologic diseases and heart surgery.<sup>(5)</sup> The syndrome can occur in all age groups and is distributed uniformly between males and females.

All plasma-containing blood components can cause TRALI. The majority of the cases involve the use of whole blood, fresh frozen plasma, packed red blood cells, packed platelets and granulocytes collected through apheresis. Fresh frozen plasma is the blood product most frequently implicated. The clinical severity of TRALI does not appear to be related to the volume or type of blood component transfused. Stored blood components are also implicated in the increased occurrence of TRALI.<sup>(7)</sup>

## Pathophysiology

Although the exact pathological mechanism of TRALI is not known, and despite the fact that there is no consensus as to its pathogenesis, there is increasing evidence that this reaction can be triggered by two distinct mechanisms. The traditional theory proposes an immunologically mediated reaction through the binding of donor antibodies against recipient leukocyte antigens. An alternate mechanism has been suggested, in which inflammatory molecules, predominantly lipid products originating from the cell degradation accumulated during the storage of blood cell products, are implicated in the triggering of TRALI through a non-immunological reaction.<sup>(8)</sup>

In the immunologically-mediated form of TRALI (immune TRALI), the antibodies of the donor are passively infused during the transfusion of the blood components.<sup>(9)</sup> These antibodies are directed against specific human neutrophil antigens (HNAs) or human leukocyte antigens (HLAs)<sup>(2)</sup> and are present,

**Table 1 – Transfusion-related acute lung injury in epidemiological reports.**<sup>(2)</sup>

	United Kingdom	Germany	Denmark	France	Canada (Québec)
Study period	1996–2003	1995–2002	1999–2002	1994–1998	2000–2003
TRALI cases	139	101	6	34	21
Adverse effects (%)	7	3	7	0.15	0.5
Mortality (%)	9 (24)*	NR	NR	20	9.5

\*Including possible deaths attributed to TRALI; e NR: not reported; TRALI: transfusion-related acute lung injury.

for the most part, in plasma-rich components, principally those originating from multiparous donors (3 or more gestations), who are frequently immunized against leukocyte antigens during pregnancy.<sup>(3)</sup> In approximately 6% of all cases of immune TRALI, the antibodies originate from the recipient.<sup>(2)</sup>

Once present in the recipient of the blood components, the alloantibodies (anti-HLA or anti-HNA) activate the complement pathways, which results in the activation and sequestration of polymorphonuclear cells for pulmonary microcirculation.<sup>(5,9,10)</sup> The anti-leukocyte antibodies can also induce a direct response from the neutrophils, which shows that the activation of the complement system is not a prerequisite for the inducement of TRALI.<sup>(4)</sup>

The activated neutrophils present in the pulmonary microcirculation generate an oxidative and cytotoxic response through the release of oxygen-reactive substances and cytokines that cause endothelial cell damage and increased vascular permeability. Therefore, there is profound capillary leakage of fluids within the alveoli, which results in edema and respiratory failure.<sup>(4-6,9,10)</sup>

Most clinicians believe that TRALI is triggered by an immunological mechanism. However, in 11–39% of TRALI cases, no antibody against leukocyte antigens is present either in the donor or in the recipient, which suggests that a non-immunological mechanism can trigger the reaction. In this mechanism, the reaction might be triggered by the infusion of biologically active lipids during the transfusion of stored blood products, generally in patients with clinical complications such as malignant blood diseases or heart diseases.<sup>(2)</sup> Those lipids are capable of activating granulocytes, thereby triggering an oxidative process and tissue injury which together result in edema and respiratory failure.<sup>(6)</sup>

More recently, it has been suggested that TRALI is caused by two independent events. The first of these might be related to predisposing clinical factors, such as surgery, trauma and severe infection, the last leading to the production of inflammatory mediators, thereby activating the pulmonary endothelium and resulting in neutrophil sequestration in the lung. The second event might involve the infusion of antibodies specific for neutrophils adhered to the lung or the infusion of biological response modifiers, including lipid compounds also capable of activating the same neutrophils.<sup>(9)</sup> Once activated, the neutrophils release oxygen-derived

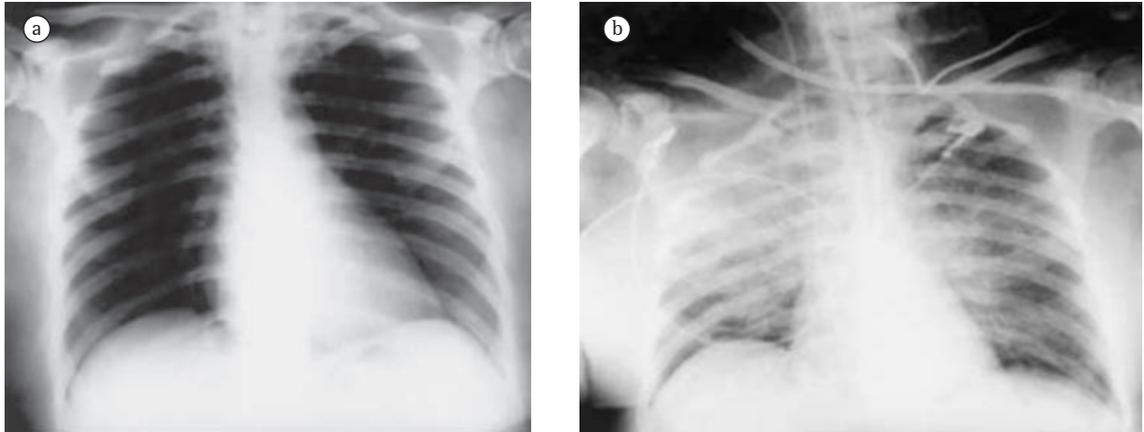
free radicals and toxic enzymes that injure the endothelial cells of the pulmonary capillaries. That is followed by capillary rupture, together with the exudation of fluids and proteins within the alveoli, which results in pulmonary edema.<sup>(2)</sup>

Using an experimental (ex vivo) model involving rat lungs, some authors<sup>(4)</sup> demonstrated that TRALI induced by anti-leukocyte antibodies is dependent on the density of specific antigens and does not necessarily require either the leuko-agglutinating properties of the antibodies or the presence of proteins of the complement system. Therefore, the antibody-mediated direct cell response contributes to the pathogenesis of immune TRALI. Similarly, the application of lipopolysaccharides and plasma or stored blood lipids in a rat model induces non-immune TRALI. Neutrophil activation therefore leads to the production of oxygen-reactive species. This appears to be an important pathological mechanism of TRALI and a central process in endothelial damage and capillary rupture.<sup>(4)</sup>

## Clinical presentation

The TRALI syndrome is represented by a group of clinical symptoms that generally develop during or within 6 h after transfusion, with the manifestation of fever (increase of  $> 1$  °C in temperature), tachypnea, cyanosis, dyspnea, acute hypoxemia with arterial oxygen tension/fraction of inspired oxygen  $< 300$  mmHg and oxygen desaturation.<sup>(2,6,9,11)</sup> In the first hours, bilateral pulmonary edema, together with the progression of alveolar and interstitial infiltrate without cardiogenic involvement, can be monitored in the first hours using radiological exams (Figure 1).<sup>(2,12)</sup> In most patients, TRALI resolves within 48 h, and such patients present normal radiological exams within 4 days. However, hypoxemia and pulmonary infiltrates can persist for up to 7 days in some patients.<sup>(2,6)</sup> The frequency of those, as well as of other signs and symptoms observed in TRALI, are shown in Table 2.<sup>(13)</sup>

A diagnosis of TRALI is not always easily made, since the clinical signs of TRALI can be confused with those of ARDS, which is induced by factors other than transfusion.<sup>(2)</sup> Pulmonary autopsy of ARDS patients has shown extensive leukocyte infiltration with interalveolar and interstitial pulmonary edema. In addition, epidemiological studies of ARDS have shown that transfusion is the most common



**Figure 1** – Pre- and post-transfusion X-rays of a patient with TRALI. Bilateral lung infiltrate with pulmonary edema is an essential criterion for the clinical diagnosis of TRALI. Radiographic discrepancies can be seen in the first hours after transfusion, with progression of the alveolar and interstitial infiltrate throughout the lung. Radiographic findings tend to be more specific than the results of physical examinations. TRALI: transfusion-related acute lung injury.

cause of its genesis, which makes it possible that a significant number of those were severe cases of TRALI.<sup>(9)</sup>

According to the most recent Consensus Conference on TRALI, the diagnosis of that reaction is made in patients with the occurrence of acute respiratory distress during or within 6 h after transfusion without any sign of circulatory overload, evidence of bilateral pulmonary edema and the absence of additional risk factors for acute respiratory failure. The criterion for the clinical diagnosis of TRALI is summarized in Chart 1. The differential diagnosis of patients with acute respiratory failure unrelated to TRALI includes transfusion-related circulatory overload, cardiogenic edema, allergic and anaphylactic transfusion reactions as well as the transfusion of bacteria-contaminated blood components.<sup>(2)</sup>

**Table 2** – Symptoms associated with transfusion-related acute lung injury.<sup>(13)</sup>

Signs and Symptoms	Frequency
Dyspnea	Quite common
Hypoxemia	Quite common
Bilateral pulmonary edema	Quite common
Fever (increase of 1–2 °C)	Quite common
Tachycardia	Common
Hypotension	Common
Cyanosis	Common
Hypertension	Rare

TRALI: transfusion-related acute lung injury.

Although hypotension has been reported in many patients in clinical studies of TRALI, it is not a consistent finding and is generally unresponsive to the infusion of endovenous fluids. Although the majority of TRALI cases reported in the literature are referred to in the classic way and are considered severe, TRALI represents a variation in clinical severity, and milder cases have been reported,<sup>(12)</sup> as have atypical forms of TRALI with late onset of symptoms (48 h after transfusion).<sup>(2)</sup>

### Laboratory testing

There is no rapid or conclusive laboratory test for the diagnosis of TRALI.<sup>(5)</sup> What exists, in reality, is merely a clinical diagnosis that is supported by laboratory test-based evidence.<sup>(10)</sup> Laboratory tests used to diagnose TRALI should be carried out whenever there is clinical evidence of TRALI in a recipient of blood components. Information concerning the donor can be important for the identification of potential donors implicated in the reaction, since multiparous donors and recipients of prior transfusions are at high risk for the development of antibodies against granulocyte and lymphocyte antigens.<sup>(10)</sup>

In a recent study, we used immunoenzymatic assays to analyze the plasma of donors from the Blood Center of the Federal University of São Paulo.<sup>(15)</sup> We observed that 28 (24%) of the 118 donors evaluated presented anti-HLA antibodies.<sup>(15)</sup>

**Chart 1** – Criteria for the clinical diagnosis of transfusion-related acute lung injury.<sup>(2)</sup>

<p>Definition of TRALI according to the European Haemovigilance Network</p> <ul style="list-style-type: none"> <li>Acute respiratory failure</li> <li>Bilateral pulmonary infiltrate on X-rays</li> <li>Occurrence during or within 6 h after transfusion</li> <li>No evidence of transfusion-related circulatory overload</li> </ul> <p>Criteria for the diagnosis of TRALI according to the Consensus Conference Committee in Toronto, 2004</p> <ul style="list-style-type: none"> <li>Hypoxemia (<math>\text{PaO}_2/\text{FiO}_2 &lt; 300</math>, oxygen saturation <math>&lt; 90\%</math> or other clinical evidence)</li> <li>New ARF and no other risk factor for ARF present, including aspiration, multiple trauma, pneumonia, cardiopulmonary bypass, burns, toxin inhalation, pulmonary contusion, acute pancreatitis, drug overdose, drowning, shock and sepsis</li> <li>If one or more risk factors for ARF are present, possible TRALI could be diagnosed</li> </ul>
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TRALI: transfusion-related acute lung injury;  $\text{PaO}_2/\text{FiO}_2$ : arterial oxygen tension/fraction of inspired oxygen; ARF: acute respiratory failure.

Samples from all the donors implicated in a TRALI case should be tested for the presence of alloantibodies,<sup>(10)</sup> generally beginning with the most recently transfused products. The current method of identifying alloantibodies is using fresh serum or plasma samples to carry out immunoenzymatic assays involving flow cytometry or immunofluorescence of lymphocytes.<sup>(2)</sup>

The detection of one or more alloantibodies in donor samples of blood components for a patient implicated in a TRALI case suggests that the reaction was mediated immunologically. However, it is possible that not all of the anti-HLA antibodies or specific neutrophils implicated in clinically diagnosed TRALI cases will be identified.<sup>(5)</sup>

The gold standard for a laboratory test-based diagnosis of immune TRALI is concordance between the antibodies detected in the donor and the lymphocyte/granulocyte antigens of the recipient (positive crossmatch). However, when there is no such concordance (negative crossmatch), the presence of alloantibodies in the serum of the donor is considered strong evidence of having triggered TRALI. In addition, non-concordance does not exclude a diagnosis of TRALI, since some are cases of non-immune TRALI.<sup>(2)</sup>

The aforementioned diagnostic methods are incapable of identifying non-immune TRALI.<sup>(10)</sup>

## Treatment and evolution

There is no specific treatment for TRALI. According to the consensus discussed at the International Forum,<sup>(16)</sup> the treatment of TRALI is based on the maintenance of the hemodynamic balance of the

patient and on the necessity for the earliest possible application of ventilatory support.<sup>(5,16)</sup> In mild TRALI cases clinical improvement is generally achieved only with nasal oxygen administration. However, 70% of the patients presenting the most severe form require orotracheal intubation and mechanical ventilation. The use of vasopressor agents can be indicated for the treatment of hypotension. The use of diuretics remains controversial and, since some patients benefit from the administration of fluids, these medications should not be used.<sup>(2,5)</sup> As in patients with acute respiratory failure or ARDS, corticosteroids, non-steroidal anti-inflammatory drugs and surfactant protein, as well as other therapeutic agents, do not provide any benefits for patients with TRALI.<sup>(5,9)</sup> Unlike ARDS, TRALI generally has a good prognosis. Many patients present clinical improvement by 48 to 96 h after the onset of the reaction.<sup>(5,10)</sup> In 80% of all TRALI patients, there is resolution of the pulmonary infiltration within the first 4 days.<sup>(5)</sup> However, in a minority of patients, hypoxemia and pulmonary infiltrate can persist for more than 7 days.<sup>(6)</sup> The resolution of TRALI frequently occurs rapidly and does not have any long-term sequelae.<sup>(5,6)</sup> In spite of having a favorable prognosis, TRALI mortality is estimated at 5 to 10% of the cases, which is still considered low when compared with ARDS, which has a mortality rate of approximately 40 to 50%.<sup>(5,6,10)</sup>

## Preventive measures

Since the pathophysiology and etiology of TRALI have yet to be fully elucidated, and because there is no rapid diagnostic test, there are no clear recom-

recommendations for the prevention of new TRALI cases.<sup>(2)</sup> However, the American Blood Bank Association recommends the temporary disqualification of donors implicated in TRALI cases until tests for the detection of antibodies against highly common antigens are carried out. Since the donors of blood components implicated in TRALI are generally multiparous women, the exclusion of these donors and using their plasma only for fractionation has been suggested. However, that would be an unreasonable measure, principally because it would provoke a substantial decrease in the number of donors at some blood banks.<sup>(2,3,5,9,17)</sup>

As a means of preventing new TRALI cases, the following additional measures have recently been suggested: i) leukoreduction of blood components prior to their storage; ii) filtration of blood components with the objective of removing antibodies, lipids and other biological response modifiers of the plasma fraction; and iii) storing products for shorter periods (using packed red blood cells within 14 days and packed platelets within 2 days) in order to avoid the effect of substances that accumulate during storage and that could induce TRALI.<sup>(9,14)</sup>

## Conclusions

Since TRALI is a complex clinical syndrome, it probably does not represent a simple pathogenic entity. The exact definition and diagnosis of TRALI has been impossible due to the limited understanding of the pathophysiological mechanisms involved in this reaction.<sup>(5)</sup>

Due to the relatively high rates of morbidity and mortality, TRALI has become one of the most serious transfusion-related complications today. Although knowledge of the clinical and pathophysiological presentation of TRALI has improved significantly, many questions remain unanswered.<sup>(2)</sup>

The potential causes of TRALI include the passive infusion of anti-HLA antibodies into the recipient and biological response modifiers in susceptible individuals. This event in the pathophysiology of immune TRALI seems plausible but does not explain why TRALI can occur without the infusion of specific antibodies directly targeting recipient leukocytes or why this reaction does not occur even when there is an infused antibody in a patient who carries a specific antigen. Therefore, TRALI might be

a multifunctional syndrome caused by at least two distinct clinical events.

Support therapy is the treatment recommended for most TRALI patients. Mechanical ventilation is often required, and most cases present a favorable evolution without any sequelae.

A better understanding of the epidemiology and pathophysiology of TRALI, which could be achieved by collecting more data and conducting more systematic research, could be useful for the implementation of new strategies aimed at lowering the risk for developing this potentially fatal complication among transfusion patients. In addition, without a clear understanding of the etiology of TRALI, preventive measures involving restrictions on donors or donated blood components might be inappropriate.

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