

REVIEW

The pathogenesis of transfusion-related acute lung injury in critically ill patients

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Abstract. Transfusion-related acute lung injury (TRALI) is probably under-reported, particularly in the critically ill. The pathogenesis of TRALI is thought to be a “two hit”-entity. The first hit is a pro-inflammatory response of any origin, resulting in activation of endothelium and priming of sequestered neutrophils, thereby resembling acute lung injury. The second hit is provided by mediators in a transfused blood product. The critically ill are often exposed to clinical conditions which cause priming of pulmonary neutrophils such as pneumonia, aspiration and mechanical ventilation, and may therefore be at risk of developing a TRALI reaction. The aetiology and the course of TRALI may differ in the critically ill when compared with the general hospital population. The threshold model holds that patients with a pro-inflammatory response, in which pulmonary neutrophils are primed, require only a weak mediator in the transfused blood product to induce a TRALI reaction, whereas patients without acute lung injury need a strong mediator to overcome the threshold. However, as specific disease markers are lacking, distinguishing TRALI from pulmonary dysfunction of other origin remains a challenge. Whether specific clinical conditions causing acute lung injury also predispose to TRALI remains to be established. Prospective studies are needed to fully assess attributable risk related to transfusion.

Introduction

Transfusion-related acute lung injury (TRALI) is a subcategory of acute lung injury/acute respiratory distress syndrome (ALI/ARDS). By definition, the occurrence of ALI within 6 hours of transfusion of a blood product should be considered as TRALI (Table) [1-3]. Possible TRALI is defined when other risk factors for ALI are present.

Although TRALI is assumed to be rare, it is probably under-reported [4;5]. Lack of specific disease markers hampers the diagnosis of TRALI, which may contribute to its under-recognition. Several recent studies have reported an increase in the incidence of TRALI, in particular in patients on Intensive Care Units (ICU) [6-8]. At the same time, however, fewer blood transfusions are being given to critically ill patients [9].

The concomitant increase in the incidence of TRALI and the decrease in blood transfusions in ICU patients requires an explanation. Either increased awareness has led to an increase in reported TRALI cases, or other disease entities causing hypoxia in the critically ill are being mistaken for TRALI. It has been suggested that TRALI pathogenesis may differ in critically ill patients on comparison with the general hospital population [10;11]. In this article TRALI pathogenesis will be discussed, focusing on the possible susceptibility of the critically ill to the development of a TRALI reaction, with the use of a threshold model.

TRALI incidence

TRALI incidence in the general hospital population.

The absence of specific disease markers and diagnostic tests, as well as the lack of a clear definition have resulted in a large variation in estimations of the incidence of TRALI. In general hospital populations, the initial reported incidence ranged from 1 in 2000 to 5000 transfusions of cellular components [12;13]. A more recent study

reported an incidence of 1 in 1120 transfused blood products in the United States [14]. Compared to previous figures this is a 4-fold increase. The national haemovigilance office of the Netherlands (TRIP, *Transfusie Reacties In Patiënten*) registers all reported TRALI cases. Since the start of registration, an increase has been observed in the number of reported TRALI cases. A rise from eight cases in 2002 to 18 cases in 2005 suggests that TRALI is under-reported in the Netherlands (<http://www.tripnet.nl/pages/nl/publicaties.php>).

TRALI incidence on the ICU.

The above-mentioned incidence may not apply to the critically ill. These patients are highly exposed to the risks of transfusion, as up to 50-85% of them receive a blood product during their stay on the ICU [15;16]. In a randomized clinical trial on the transfusion threshold in critically ill patients a restrictive transfusion policy on red blood cells was associated with a decrease in the incidence of ALI (7.7% vs. 11.4%) [17]. This suggests that some of these patients may have had TRALI. Retrospective studies suggest that ALI develops more often in critically ill transfused patients than in those who have not received transfusion [6;18]. In a cohort of mechanically ventilated patients, transfusion of blood products is related to the occurrence of ALI in up to 33% of cases [7]. A recent prospective study confirms a higher incidence in critically ill patients [8]. In this study, patients consecutively transfused in an ICU were observed for the development of ALI within 6 hours after transfusion. Of 904 transfused patients, 74 developed ALI (8%), which is 50-100 fold higher than in the general hospital population.

TRALI pathogenesis

TRALI is mediated by the interaction of neutrophils with pulmonary endothelial cells. Presently, there are two hypotheses on the pathogenesis of TRALI. The first hypothesis suggests that TRALI is caused by donor antibodies against human neutrophil antigens (HNA) or human leukocyte antigens (HLA). This antibody-mediated reaction can not explain all TRALI cases however. Many TRALI cases are re-

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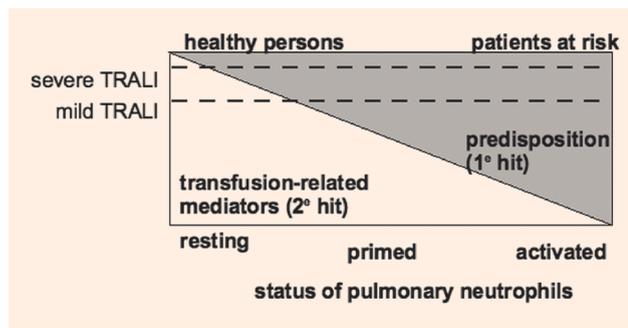


Figure 1. Edited from Bux et al (ref. 10, reprinted with permission). Threshold model of TRALI. A certain threshold must be overcome to induce a TRALI reaction. To overcome a threshold, several factors act together: the activation status of the pulmonary neutrophils at the time of transfusion, the strength of the neutrophil-priming activity of transfused mediators (light box) and the clinical status of the patient (grey box).

ported in which no specific anti-neutrophil antibodies are detected [5;19;20]. Also, the majority of recipients do not develop TRALI even when their neutrophils express the cognate antigen which the transfused antibody recognizes [21-23]. The second hypothesis implicates two independent “hits”. The first hit is the clinical condition of the patient at the time of the transfusion. An inflammatory reaction due to any cause attracts neutrophils to the pulmonary compartment. Primed neutrophils, trapped in the microvasculature of the lungs, are functionally hyperactive. The second hit is the transfusion. Either anti-neutrophil antibodies or bioactive lipids (lysophosphatidylcholines, lysoPCs) or cytokines that have accumulated during blood storage, further activate the primed neutrophils in the lung vasculature of the recipient. The result is endothelial damage, capillary leak and extravasation of neutrophils [10;11]. Accordingly, lysoPCs as well as out-of-date blood products were used to cause TRALI in experimental models [13;24;25]. Also, observational studies have reported associations between prolonged storage of blood products and ARDS in the critically ill [14;26;27].

In conclusion, both leucocyte antibodies and neutrophil priming agents released in stored cellular blood products are considered as causative in TRALI. A priming condition may be required for a TRALI reaction to develop.

Diagnosis of TRALI

There are no specific tests to diagnose TRALI. Anti-leucocyte (HLA) antibodies class I and II and anti-neutrophil (HNA) antibodies have been implicated in TRALI. Serological workup consists of testing blood from the recipient and the implicated donors for the presence of HLA- and HNA-antibodies. Incompatibility is tested by cross-matching donor plasma against the recipient’s leucocytes. Alternatively, incompatibility can be studied by typing the recipient’s leucocytes for expression of the cognate HLA or HNA antigen. A donor with leucocyte-reactive antibodies which are incompatible with the patient, is excluded from further donation of blood for transfusion products. Testing for bioactive lipids such as lysoPCs is more difficult. No quantitative tests yet exist. Also, the implicated blood product often is not available [11].

As pointed out above, aetiology and laboratory diagnosis are controversial. Serological tests for TRALI have yet to be validated against an accepted gold standard and serve only to support the clinical diagnosis of TRALI. Also, the serological workup for TRALI takes a few months, rendering this kind of diagnostic procedure unfit for clinical

guidance. Therefore, TRALI remains a clinical diagnosis. Serological testing should be regarded as a preventive measure.

TRALI in the critically ill

Pathogenesis

The higher incidence of TRALI in patients on the ICU suggests that the aetiology may differ in the critically ill when compared with a general hospital population. The clinical status of a patient plays a significant role in the development of TRALI. At the time of transfusion, considerable neutrophil priming activity can be shown in TRALI patients [14], which could conceivably be caused by a predisposing clinical condition. When compared with patients who did not develop TRALI after transfusion, TRALI patients had more often had a first event, i.e. “hit” before the transfusion [13]. Implicated events include recent surgery, active infection and massive transfusion [11;13;28;29].

Risk factors for the development of TRALI have been identified by a prospective study and epidemiological data from haemovigilance systems. Risk factors include surgery, in particular coronary bypass surgery, and haematological malignancies [14;30]. Indeed, an inflammatory reaction causing ALI is a common finding after cardiothoracic surgery and is associated with the number of transfusion products [31-33]. Transfusion after cardiothoracic surgery is related to increased morbidity, the mechanism of which may well be TRALI [34;35]. Other clinical entities that predispose the lungs to TRALI have not yet been identified.

Possible risk factors for TRALI

As the two hit model of TRALI holds that priming of lung neutrophils at the time of transfusion can occur by a pro-inflammatory response of any origin [10], it is conceivable that clinical conditions causing ALI may also predispose to TRALI. In the critically ill, ALI is a common complication which can result from numerous conditions, ranging from direct pulmonary insults, such as pneumonia and aspiration, to indirect pulmonary insults, such as sepsis. Indeed, in the only prospective study on TRALI in the critically ill, patients developing ALI after transfusion were more likely to have sepsis than were controls [8]. Also mechanical ventilation may induce or worsen ALI (ventilator-associated lung injury). Of note, one-third of ventilated patients develop ALI after transfusion of a blood product [7]. This number exceeds that in non-ventilated patients [6]. The risk of acquiring ALI tended to be associated with high tidal volumes, which may suggest that mechanical ventilation is a risk factor for TRALI [7].

Regardless of aetiology, the definition of TRALI requiring the absence of other risk factors for ALI poses a problem in the severely ill population. The Canadian Blood Services and the National Heart, Lung and Blood Institute have modified the AECC definition which allows the presence of other ALI risk factors [3;36]. If indeed ALI of any origin predisposes to TRALI, the multiple possible first hits may explain the increased incidence of TRALI in the critically ill, when compared with the general hospital population.

Threshold model of TRALI.

The concept that ICU patients are susceptible to a TRALI reaction due to an inflammatory response resulting in priming of pulmonary neutrophils, has recently been underlined by the proposal of a threshold model of TRALI [10]. In this model, a threshold must be overcome to induce a TRALI reaction (Figure). The factors that determine this threshold are the predisposition of the patient that determines prim-

ing of the lung neutrophils and the ability of the mediators in the transfusion to cause activation of primed neutrophils. In this model, one side of the spectrum is a strong antibody-mediated response which can cause overwhelming TRALI in an otherwise “healthy” recipient. Conversely, it is possible that priming factors in the transfusion are not strong enough to overcome the threshold when activation status is too low. This would explain why TRALI does not develop in transfused patient even when an antibody-antigen match is present. At the other side of the spectrum is a patient with predisposing factors, i.e. a critically ill patient with ALI due to another cause. Transfusion of mediators with low neutrophil-priming activity is sufficient to overcome the threshold to induce a TRALI reaction.

Differentiation of TRALI from pulmonary dysfunction of other origin in the ICU.

Clinical diagnosis of TRALI in the critically ill is difficult, as multiple conditions can cause pulmonary abnormalities and hypoxia. The absence of specific disease markers for TRALI hampers the distinction between other entities causing bilateral pulmonary abnormalities and hypoxia. This issue is important, not only from the perspective of treatment but also in determining when to start complex and expensive TRALI workup and donor exclusion.

In TRALI, the inflammatory response typically results in increased vascular permeability. In critically ill patients with multiple comorbidity and risk factors for ALI, clinical distinction between hydrostatic and permeability pulmonary oedema is a challenge. Specific diagnostic tools such as echocardiography, B-type natriuretic peptide, or the more invasive techniques such as measurement of pulmonary leakage index may help in the differentiation, but no single test can establish a diagnosis by itself [37]. A considerable number of patients with clinical criteria for ALI are misclassified when compared to lung pathology findings [38] or after measurement of the pulmonary artery occlusion pressure, irrespective of pre-existing cardiac function [39;40]. Also, permeability oedema and hydrostatic oedema are not mutually exclusive and may occur simultaneously. Severity of ALI/ARDS is related to altered left and right ventricular performance [41]. Therefore, cardiac dysfunction in the course of ALI may contribute to pulmonary dysfunction and mortality. In ALI patients, a restrictive fluid balance reduces the number of ventilation days, suggesting that hydrostatic oedema contributes to pulmonary injury [42].

In cardiothoracic surgery, which has been identified as a TRALI risk factor, postoperative pulmonary dysfunction is often present, the cause of which is not clear. Postoperative mild pulmonary oedema has been attributed to increased pulmonary permeability [32], but also to a low colloid osmotic pressure, even in the absence of heart failure [43]. Moreover, how the presence of non-hydrostatic or hydrostatic oedema relates to radiographic and ventilatory criteria for TRALI is unclear. Other factors such as atelectasis have been found to contribute to postoperative pulmonary abnormalities [32].

In summary, distinction between TRALI and other conditions that cause hypoxia is difficult. Elaborate algorithms have been put forward to guide clinicians and researchers dealing with patients with pulmonary dysfunction after a blood transfusion [37]. Attempts to distinguish between hydrostatic and permeability mechanisms of oedema formation assume that these mechanisms do not co-exist. This assumption may not be true. The critically ill patient rarely suffers from a single disease or single organ failure. Typically, ICU patients experience multiple hits, ranging from infection, shock,

Table. Definition Acute Lung Injury (ALI) and Transfusion Related Acute Lung Injury (TRALI, reference 1-3)

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| Definition ALI |
| - Acute onset of hypoxia: PaO ₂ /FiO ₂ <300mm Hg or SpO ₂ <90% on room air |
| - Bilateral pulmonary infiltrates |
| - Pulmonary artery wedge pressure ≤ 18 mm Hg or the absence of left ventricular overload |
| Definition TRALI |
| - No ALI before transfusion |
| - ALI during or < 6 hours after transfusion |
| - No other risk factors for ALI |
| Definition ‘possible’ TRALI |
| - No ALI before transfusion |
| - ALI during transfusion or < 6 hours after transfusion |
| - One or more risk factors for ALI present |

trauma and surgery to mechanical ventilation, all of which have been shown to contribute to lung injury.

Outcome of TRALI in the critically ill

TRALI is generally considered to have a good outcome. However, mortality rates of 45% from TRALI in the critically ill have been reported [44;45], as compared to the 5-15% reported mortality in other settings [46]. Transfusion adversely affects clinical outcome in the critically ill. Length of ICU and hospital stay are increased, and a relationship between mortality and transfusion is reported [16;47].

It should be stressed that no reports have distinguished to what extent transfusion or other ALI risk factors have contributed to mortality. This issue warrants further investigation.

Prevention of TRALI

Specific treatment for TRALI does not exist. Prevention of TRALI seems the best approach to reducing the incidence.

Transfusion guidelines

Fewer transfusions will lead to fewer cases of TRALI. Restrictions in transfusion of erythrocytes are well tolerated in ICU patients. However, guidelines for erythrocyte transfusions are not always followed [47]. Also, fresh frozen plasma and platelets are the blood products most often implicated in TRALI reactions [8;18;44;47]. Guidelines on transfusion of plasma and platelets in the critically ill are less clear than guidelines on transfusion of red cells. Whether a restrictive transfusion policy in patients with a coagulopathy outweighs the risk of bleeding remains to be determined.

Exclusion of women and persons who have previously received a blood transfusion from donorship

After a pregnancy or after a transfusion, leucocyte antibodies are more often present. In the United Kingdom, women and transfused males have been excluded from donation since 2004. So far, no TRALI cases have been reported by British blood banks (<http://www.shotuk.org/SHOT%20report%202005.pdf>).

Based on these results, Sanquin decided to adopt this preventive measure in the Netherlands. Since October 2006, only plasma from non-transfused males is used for preparation of fresh frozen plasma.

Conclusion

TRALI is difficult to diagnose, especially in the critically ill. Considering TRALI pathogenesis, critically ill patients may be at

risk for a TRALI reaction, as these patients are exposed to multiple hits resulting in the priming of pulmonary neutrophils. However, whether specific clinical conditions that cause ALI also predispose to TRALI remains to be established. Because critically ill patients have

additional predisposing factors for acute lung injury, carefully designed prospective studies are needed to fully assess attributable risk related to transfusion.

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