Transfusion-related acute lung injury: a clinical review

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Three decades ago, transfusion-related acute lung injury (TRALI) was considered a rare complication of transfusion medicine. Nowadays, the US Food and Drug Administration acknowledge the syndrome as the leading cause of transfusion-related mortality. Understanding of the pathogenesis of TRALI has resulted in the design of preventive strategies from a blood-bank perspective. A major breakthrough in efforts to reduce the incidence of TRALI has been to exclude female donors of products with high plasma volume, resulting in a decrease of roughly two-thirds in incidence. However, this strategy has not completely eradicated the complication. In the past few years, research has identified patient-related risk factors for the onset of TRALI, which have empowered physicians to take an individualised approach to patients who need transfusion.

Introduction

Transfusion-related acute lung injury (TRALI), defined as the onset of respiratory distress after blood transfusion, has long been regarded as a rare complication of transfusion medicine.[1] However, in the past decade, perspective has changed. Development of an international consensus definition has aided TRALI research, yielding a higher incidence in specific patient populations than previously acknowledged.[2,3] Patients suffering from a clinical disorder such as sepsis are increasingly recognised as being at risk for development of TRALI.[4] Thereby, from a diagnosis by exclusion, TRALI has become the leading cause of transfusion-related mortality.[2,3,5,6] However, the syndrome is still underdiagnosed and under-reported in some countries.[7–9]

Although blood transfusion can be life saving, it can also be a life-threatening intervention. Physicians use blood transfusion on a daily basis. Increased awareness of the risks of this procedure is needed, because management of patient-tailored transfusion could reduce the risk of TRALI. Such an individualised approach is now possible as insight into TRALI risk factors evolves. Furthermore, proper reporting of TRALI could prevent recurrence. In this Review, we discuss the pathogenesis, incidence, risk factors, and clinical picture of TRALI. We also outline existing strategies to mitigate the syndrome, and the remaining clinical challenges ahead.

Definition and diagnosis

Possible TRALI and delayed TRALI

TRALI is a clinical diagnosis for which no diagnostic tests are available. The syndrome was initially regarded as the onset of respiratory distress due to antibody-induced non-cardiogenic lung oedema. Absence of an international definition for TRALI previously contributed to underdiagnosis. As such, a consensus panel, and the US National Heart, Lung and Blood Institute Working Group in 2004, formulated a case definition of TRALI based on clinical and radiological parameters.[2,10,11] The definition is derived from the widely used definition of acute lung injury (panel 1).[12] Suspected TRALI is defined as fulfilment of the definition of acute lung injury within 6 h of transfusion in the absence of another risk factor (panel 1).[2,10,11]

Although this definition seems to be straightforward, the characteristics of TRALI are indistinguishable from acute lung injury due to other causes, such as sepsis or lung contusion. Therefore, this definition would rule out the possibility of diagnosing TRALI in a patient with an underlying risk factor for acute lung injury who has also received a transfusion. To identify such cases, the term possible TRALI was developed (panel 1),[2] which allows for the presence of another risk factor for acute lung injury.

Although the TRALI definition is an international consensus definition, surveillance systems in some countries, including the USA, France and the Netherlands, use an alternative in which imputability is scored.[13,14] Imputability aims to identify the likelihood that transfusion is the causal factor. Imputability scores mostly imply that other causes of acute lung injury can be ruled out, so that diagnosis of TRALI is by exclusion. However, observational and animal studies[8,9,15–18] suggest that risk factors for TRALI include other disorders, such as sepsis. Therefore, an imputability definition would result in underdiagnosis of TRALI. The consensus definition accommodates the uncertainty of the association of acute lung injury to the transfusion in possible TRALI. The conventional definition of TRALI uses a timeframe of 6 h in which acute lung injury needs to develop after a blood transfusion. In critically ill patients, transfusion increases the risk (odds ratio 2·13, 95% CI 1·75–2·52) for development of acute lung injury 6–72 h after transfusion.[19] However, whether the pathogenesis of delayed TRALI is similar to that of TRALI is unclear. In this Review, we focus on TRALI developing within 6 h of transfusion.

Search strategy and selection criteria

We searched PubMed from 1980 to 2012, with the terms "transfusion related acute lung injury", "TRALI", "plasma", "storage", "therapy" and "prevention", and selected citations on the basis of their specific applicability to specialties pertinent to clinical aspects of TRALI. We largely focused on recent publications and those that have provided pivotal insights into TRALI.

Pathogenesis

The two-hit model

A two-hit hypothesis has been proposed for TRALI.[20] The first hit is underlying patient factors, resulting in adherence of primed neutrophils to the pulmonary endothelium. The second hit is caused by mediators in the blood transfusion that activate the endothelial cells and pulmonary neutrophils, resulting in capillary leakage and subsequent pulmonary oedema. The second hit can be antibody-mediated or non-antibody-mediated.

Chain of events

Independent of the transfusion factor, activation of pulmonary neutrophils is an important part of TRALI.[8,21,22] TRALI is preceded by increased concentrations of interleukin-8, interleukin-6, and the elastase-α1-antitrypsin (EA) complex (figure 1). Although the exact mechanism is not known, investigators have postulated that endothelial cells produce interleukin-8 in response to a so-called first hit, which contributes to attraction of neutrophils to the pulmonary compartment[23] by increasing the surface expression of cellular adhesion molecules.[24] These conformational changes in β2 integrins allow for close contact of the primed neutrophils with endothelial cells,[25] followed by adherence of neutrophils in the small-diameter capillaries of the lung. This adherence of neutrophils to pulmonary endothelial cells is the first hit in TRALI pathogenesis.

The second hit is the blood transfusion. Findings from animal studies suggest that interaction of platelets with neutrophils is important (figure 1) because both platelet depletion and pretreatment with aspirin prevents TRALI.[26] Platelet activation also contributes to formation of neutrophil extracellular traps.[27,28] Although protective against infection, these traps are harmful to tissue and have been identified in the blood and lungs of patients with TRALI. Animal experiments showed that treatment with DNase reduced the formation of neutrophil extracellular traps and the severity of TRALI.[27,28] Apart from clinical observations of a transient thrombocytopenia in TRALI,[29,30] suggesting that platelets might migrate to the lungs, clinical studies of the involvement of platelets are largely absent. Furthermore, increases have been noted in pulmonary levels of interleukin-8, -6, and -1B, and elastase-α1-antitrypsin complexes; the latter of which indicates activation of pulmonary neutrophils.[9,31] The first hit primes the NADPH oxidase of the neutrophils, but the second hit is what activates the NADPH oxidase and leads to release of elastase. Furthermore, an influx of neutrophils often takes place in the alveolar space. In patients who have cardiac surgery, TRALI is also characterised by activation of coagulation, shown by an increase in thrombin-antithrombin complexes and plasminogen activator inhibitor, and by decreased fibrinolysis, shown by a decrease in concentrations of plasminogen activator activity.[9] Although the pulmonary compartment is the most obviously injured organ in the onset of TRALI,

***Panel 1:* Definition of transfusion-related acute lung injury (TRALI)**

Suspected TRALI

- Acute onset within 6 h of blood transfusion
- PaO_2/F_IO_2<300 mm Hg, or worsening of P to F ratio
- Bilateral infiltrative changes on chest radiograph
- No sign of hydrostatic pulmonary oedema (pulmonary arterial occlusion pressure ≤18 mm Hg or central venous pressure ≤15 mm Hg)
- No other risk factor for acute lung injury

Possible TRALI

Same as for suspected TRALI, but another risk factor present for acute lung injury

Delayed TRALI

Same as for (possible) TRALI and onset within 6–72 h of blood transfusion

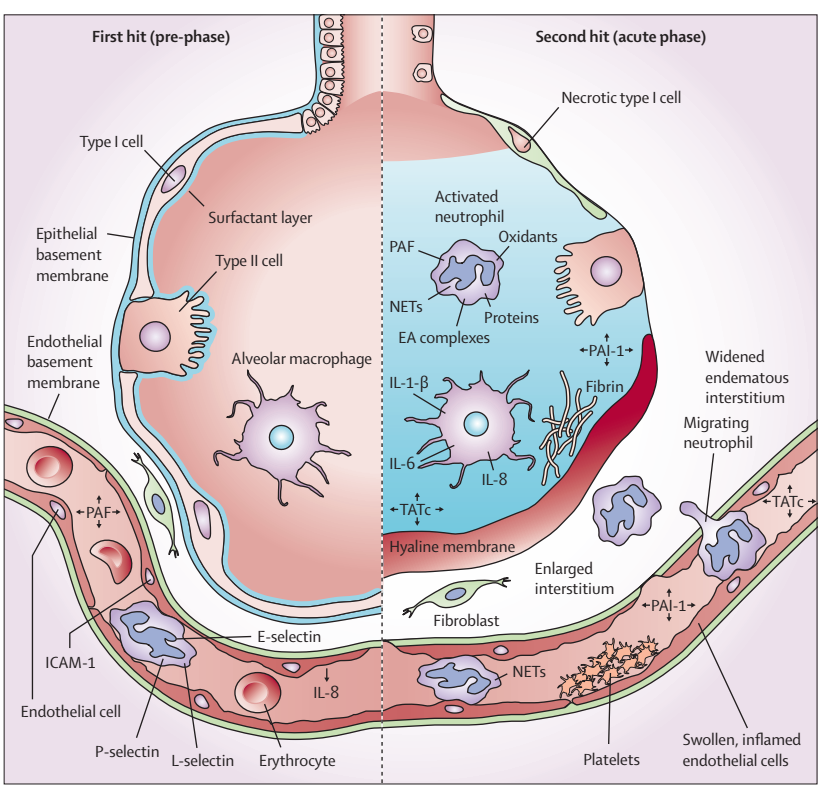

***Figure 1:* Pathophysiology of two-hit mediated transfusion-related acute lung injury (TRALI)**

The pre-phase of the syndrome consists of a first hit, which is mainly systemic. This first hit is the underlying disorder of the patient (eg, sepsis or pneumonia) causing neutrophil attraction to the capillary of the lung. Neutrophils are attracted to the lung by release of cytokines and chemokines from upregulated lung endothelium. Loose binding by L-selectin takes place. Firm adhesion is mediated by E-selectin and platelet-derived P-selectin and intracellular adhesion molecules (ICAM-1). In the acute phase of the syndrome, a second hit caused by mediators in the blood transfusion takes place. This hit results in activation of inflammation and coagulation in the pulmonary compartment. Neutrophils adhere to the injured capillary endothelium and marginate through the interstitium into the air space, which is filled with protein-rich oedema fluid. In the air space, cytokines interleukin-1, -6, and -8, (IL-1, IL-6, and IL-8, respectively) are secreted, which act locally to stimulate chemotaxis and activate neutrophils resulting in formation of the elastase-α1-antitrypsin (EA) complex. Neutrophils can release oxidants, proteases, and other proinflammatory molecules, such as platelet-activating factor (PAF), and form neutrophil extracellular traps (NETs). Furthermore, activation of the coagulation system happens, shown by an increase in thrombin-antithrombin complexes (TATc), as does a decrease in activity of the fibrinolysis system, shown by a reduction in plasminogen activator activity. The influx of protein-rich oedema fluid into the alveolus leads to the inactivation of surfactant, which contributes to the clinical picture of acute respiratory distress in the onset of TRALI. PAI-1=plasminogen activator inhibitor-1.

animal studies show that onset of antibody-mediated TRALI also results in kidney and liver injury by local antibody reaction.[32]

Antibody-mediated TRALI

Antibody-mediated TRALI is caused by passive transfusion of HLA or human neutrophil antigen (HNA) and corresponding antibodies from the donor directed against antigens of the recipient.[33,34] Neutrophil activation occurs directly by binding of the antibody to the neutrophil surface (HNA antibodies) or indirectly, mainly by binding to the endothelial cells with activation of the neutrophil (HLA class I antibodies) or to monocytes with subsequent activation of the neutrophil (HLA class II antibodies).[33,35] The antibody titre and the volume of antibody containing plasma both increase the risk for onset of TRALI.[8,36] Although the role of donor HLA and HNA antibodies from transfused blood is widely accepted,[33] not all TRALI cases are antibody mediated. In many patients, antibodies cannot be detected.[7,37] Furthermore, many blood products containing antibodies do not lead to TRALI.[38–40] This finding has led to development of an alternative hypothesis for the onset of TRALI, termed non-antibody-mediated TRALI.

Non-antibody-mediated TRALI

Non-antibody-mediated TRALI is caused by accumulation of proinflammatory mediators during storage of blood products, and possibly by ageing of the erythrocytes and platelets themselves.[16,41,42] Although most preclinical studies have noted a positive correlation between storage time of cell-containing blood products and TRALI, the mechanism is controversial. Two mechanisms have been suggested, including either plasma or the aged cells. In a small-case study and animal experiments, accumulation of bioactive lipids and soluble CD40 ligand (sCD40L) in the plasma layer of cell-containing blood products has been associated with TRALI.[16,17,43,44] Bioactive lipids are thought to cause neutrophil activation through the G-protein coupled receptor on the neutrophil.[45] Transfusion of sCD40L activates the CD40 receptor on the neutrophils and endothelium resulting in release of proinflammatory cytokines. However, involvement of these mediators in TRALI has not been confirmed in other studies.[8,46,47]

Other than plasma, the aged cells might have a role. During storage, erythrocytes undergo morphological changes. The loss of Duffy antigen expression on the aged erythrocyte reduces erythrocyte chemokine scavenging and contributes to TRALI in an experimental setting.[41] Additionally, loss of the ability to release adenosine-5′-triphosphate takes place during storage,[42] which increases adhesion of the erythrocyte to the endothelial cells and resulted in hypoxia and extravasation of the erythrocytes in the alveolar space in an animal model.[42] Clinical data show conflicting results for the role of aged blood in TRALI.[8,15,18] Preclinical studies showed that washing of stored red blood cells and platelets before transfusion prevented onset of TRALI in a two-hit animal model.[48,49] Few data are available to support this policy in clinical practice.

Threshold model

The two-hit model suggests that patients in a poor clinical state are at risk for development of TRALI. However, cases have been described of antibody-mediated TRALI developing in fairly healthy recipients.[11,50] To explain this discrepancy, a threshold model has been suggested[51] in which a threshold must be overcome to induce a TRALI reaction (figure 2). The threshold is dependent both on the predisposition of the patient (first hit) and the quantity of antibodies in the transfusion (second hit). A large quantity of antibody that matches the recipient's antigen can cause severe TRALI in a recipient with no predisposition. In a fairly healthy patient in whom no priming of neutrophils takes place, antibodies might not be strong enough or large enough in quantity to overcome the threshold. This model emphasises the concept that specific patient populations are susceptible to a TRALI reaction due to the presence of an inflammatory response, resulting in priming of pulmonary neutrophils.[2,11]

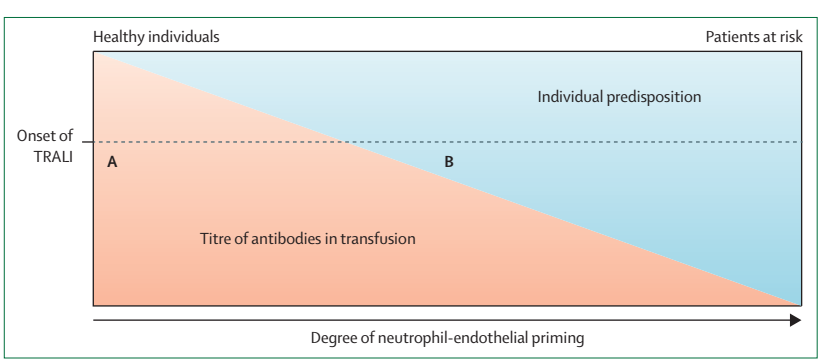

Figure 2: **Threshold model of antibody-mediated transfusion-related acute lung injury (TRALI)**
A specific threshold must be overcome to induce a TRALI reaction. To overcome a threshold, several factors act together: the activation status of the pulmonary neutrophils at the time of transfusion, the strength of the neutrophil-priming activity of transfused mediators (A), and the clinical status of the patient (B). The figure is a modified version of Bux and colleagues' threshold model, reproduced by permission of the publisher and the author.[51]

Incidence

TRALI incidence is estimated to be between 0·08% and 15% of patients receiving a blood transfusion (table 1). Diversity in clinical symptoms, absence of specific disease markers and diagnostic tests, and the absence of a clear definition could all have contributed to a large variation in estimations of the incidence of TRALI. Differences in study design should likewise be noted. Passive reporting typically yields lower incidences than active surveillance (table 1). The consensus definition in 2004 allowed for estimates of TRALI and possible TRALI for populations in whom other risk factors for acute lung injury are often present, mostly critically ill patients. Of note, the incidence of TRALI is 50–100 times higher in the critically ill than the general hospital population (table 1).

	Study type and inclusion	Population	Country	Study year	Incidence of TRALI	
					Per patient transfused	Per product transfused
Popovsky et al[34]	Retrospective, active	Hospital	USA	1983	..	0·02%*
Henderson et al[52]	Retrospective, passive	Regional	Australia	1981–89	..	0·001%
Clarke[53]	Retrospective, passive	Hospital	USA	1994	..	0·33%†
Silliman et al[22]	Retrospective, active	Hospital	Canada	1991–95	0·08%	0·22%†
Wallis et al[54]	Retrospective, passive	Hospital	UK	1991–2003	..	0·01%*
Wiersum-Osselton et al[14]	Retrospective, passive	National	The Netherlands	2002–05	..	0·002%
Rana et al[55]	Retrospective, active	ICU	USA	2003	1·8%	0·26%
Vlaar et al[18]	Retrospective, active	ICU	The Netherlands	2004–07	5·1%	0·9%
Gajic et al[19]	Prospective, active	ICU	USA	2005–07	8·0%	1·12%
Benson et al[56]	Retrospective, active	ICU	USA	2002–08	15·0%	..
Vlaar et al[15]	Prospective, active	ICU	The Netherlands	2006–09	3·3%	0·61%
Toy et al[8]	Prospective, active	Regional	USA	2006–09	..	0·02%

TRALI=transfusion-related acute lung injury. ICU=intensive-care unit. *Incidence identified only in plasma products transfused. †Incidence identified only in products of platelet concentrates transfused.

Table 1: **Incidence of TRALI**

Several reasons could explain the high incidence in some patient populations. Critically ill patients are greatly exposed to the risks of transfusion, because up to 50–70% receive a blood product during their stay in the intensive-care unit.[57,58] Furthermore, there are differences regarding the first hit. Critically ill patients often have a clinical disorder, which can induce neutrophil priming activity rendering them susceptible to mediators in the blood product and the subsequent development of TRALI. In line with this factor, critically ill patients with TRALI often had a first hit before the transfusion unlike patients who do not develop the complication after transfusion,[18] which might explain the increased TRALI incidence in the critically ill population.

Clinical presentation

Respiratory disorders, including dyspnoea, tachypnoea and hypoxaemia, are the central clinical symptoms in TRALI. Such problems are a result of increased pulmonary vascular permeability and ensuing lung oedema. However, a wide range of other reactions can take place because of antibody infusion, including rigors, tachycardia, and fever, and hypothermia and hypotension, and rarely hypertension.[59,60] Bilateral interstitial abnormalities should be present on chest radiograph for the definition of TRALI. The original case description of TRALI depicted development of acute respiratory failure in patients 1 hour after a transfusion of a high-volume plasma product, with lungs having a white-out appearance on the radiograph. However, white-out lungs are not always present; radiological abnormalities might be much less prominent (figure 3).[60]

Laboratory testing in TRALI is not specific. The most prevalent symptom is a transient leukopenia, which arises in 5–35% of patients after transfusion with an antibody-containing blood product, and is thought to be due to neutrophil-specific antibodies.[59] Thrombopenia might also be present.[29,30] An intriguing question remains as to why symptoms of this transfusion reaction are so prominent in the pulmonary compartment. Although TRALI can result in organ dysfunction other than acute lung injury,[32] most reactions present as single organ failure. The lungs function as primary defence mechanisms because

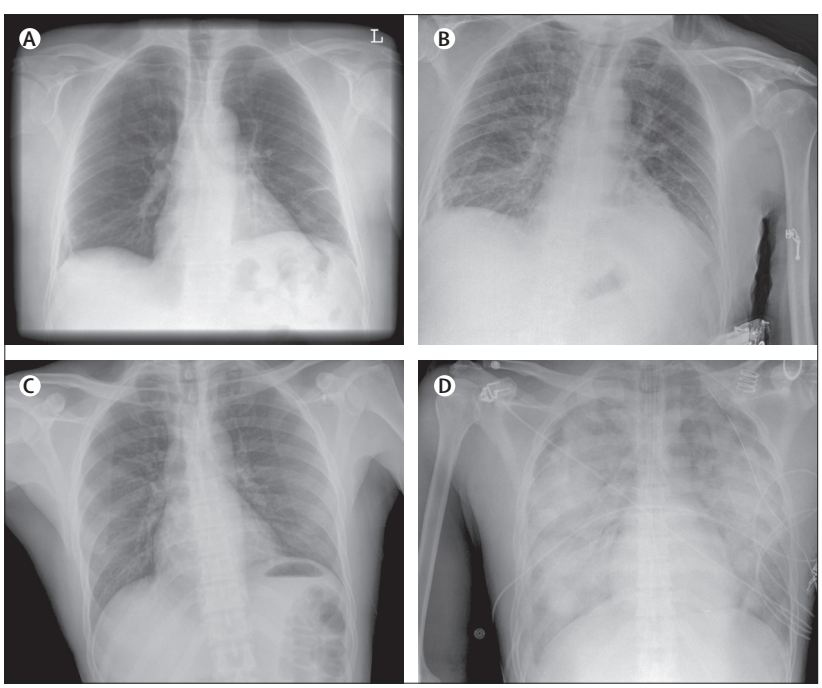

Figure 3: **Chest radiographs of patients presenting with transfusion-related acute lung injury (TRALI)**
Chest radiographs of two patients before (A, C) and after (B, D) onset of TRALI. Radiographs A and C show normal pulmonary vasculature with no signs of pulmonary oedema; B and D show infiltrative changes suggestive of pulmonary oedema. D shows the classic severe bilateral infiltrative changes that present with TRALI; however, frequently such changes are less apparent with chest x-rays, as shown in B.

***Panel 2*: Clinical characteristics of transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO)**

TRALI

- Dyspnoea
- Fever
- Usually hypotension
- Hypoxia
- Leukopenia
- Thrombopenia
- Pulmonary oedema on chest x-ray
- Normal left ventricular function*
- Normal pulmonary artery occlusion pressure

TACO

- Dyspnoea
- Usually hypertension
- Hypoxia
- Pulmonary oedema on chest radiographs
- Normal or decreased left ventricular function
- Increased pulmonary artery occlusion pressure
- Raised brain natriuretic peptide

*A decreased left ventricular function does not exclude TRALI.

infectious microorganisms can be readily inhaled. Additionally, primed neutrophils undergo elongation and lose their deformability. Passage of these neutrophils through the narrow pulmonary capillaries allows for close contact and interaction with endothelial cells, which can result in neutrophil activation.[51] Anatomically the lungs are the first immune-rich organ through which the blood transfusion passes; as such, mediators involved in the onset of TRALI might not reach the other organs.

Differentiation of TRALI from pulmonary oedema of other origin

A septic transfusion reaction can present as TRALI.[61] If signs of sepsis are present, sepsis treatment should be started promptly while Gram stain and culture of the blood bag and blood cultures of the patient are pending. Anaphylactic transfusion reactions, including tachypnoea and wheezing, also present with respiratory distress. Because symptoms are a result of laryngeal and bronchial oedema and not of pulmonary oedema, a chest radiograph can aid diagnosis. Other signs that suggest allergic reaction are urticaria and erythema of the face and trunk.

The clinical distinction between hydrostatic oedema resulting from cardiac decompensation due to volume overload (transfusion-associated circulatory overload) and permeability pulmonary oedema in TRALI is a challenge. Chest radiography is not helpful in distinguishing these disorders (panel 2). Specific diagnostic techniques—eg, echocardiography or brain natriuretic peptide—have been used in algorithms that might guide clinicians,[62] but no test can establish a diagnosis by itself.[63] Pulmonary artery occlusion pressure has been added to the TRALI definition to exclude patients with volume overload. However, permeability oedema and hydrostatic oedema are not mutually exclusive and can occur simultaneously. Acute lung injury can lead to worsening of left-ventricular and right-ventricular performance.[64] Conversely, a restrictive fluid balance reduces the number of ventilation days of patients with acute lung injury, suggesting that hydrostatic oedema contributes to the pulmonary injury.[65] Recognition of the TRALI syndrome is a challenge. As a consequence, many cases go unreported, as proven by look-back studies.[7] Therefore, the true incidence of TRALI is probably higher then perceived in clinical practice.

Diversity in disease severity

From case series, the severity of TRALI symptoms differs. Cases range from need for supplemental oxygen to mechanical ventilation, and even fatal reactions occur.[54] Whether antibody-mediated and non-antibody-mediated TRALI differ in symptom severity is unknown. Reports[33] suggest that antibodies to HNA are more often associated with fatal TRALI reactions than are other antibodies, but this association is not yet confirmed. Of note, many episodes of TRALI can go undetected. The consensus guideline excludes mild forms of the syndrome. This exclusion was justified because inclusion of mild cases was thought to complicate tracking and comparison of cases in and between surveillance systems.[3] From case reports, TRALI could induce mild reactions, some of which do not meet criteria of the consensus definition.[66]

Timecourse of symptoms

Generally, there is agreement that respiratory distress should occur within the first few hours after transfusion; however, this assumption is largely based on personal experience.[67] The time window of 6 h was chosen on the basis of a description of the first case series from 1985,[34] and is based on the opinion of an expert panel.

Treatment

No treatment exists for this life-threatening syndrome. Management of TRALI is supportive. Patients need additional oxygen, and mechanical ventilation is unavoidable in 70–90% of cases.[34,54] TRALI is regarded as part of acute lung injury or acute respiratory distress syndrome; therefore, application of restrictive tidal volume ventilation is logical, because this method is beneficial in patients with these disorders.[68] Although some case reports describe use of corticosteroids in patients with TRALI, no evidence exists to show that these drugs should be applied. Diuretics might have a place in the treatment of TRALI, because a positive fluid balance is a risk factor for TRALI and a restrictive fluid strategy is beneficial in ALI/acute respiratory

distress syndrome (ARDS) due to other causes. Animal experiments show promising results for aspirin.[26] Of note, the use of platelet aggregation inhibitors was associated with reduced lung injury in patients with ARDS, but the effectiveness of these interventions has not been tested in patients.

Prognosis

TRALI generally has a good prognosis. Mortality is considered to be low at roughly 5–10%.[54,67,69] However, data for outcome are sparse, and mostly based on small case series. In observational studies, TRALI mortality was higher in critically ill and surgical patients than in transfused controls.[9,18,19,56] An association has also been reported between transfusion of red blood cells, plasma, and platelets, and acute lung injury in several other observational studies.[70,71] However, findings from these observational studies do not clarify to what extent the transfusion or other risk factors for acute lung injury contribute to mortality.

Patient risk factors for onset of TRALI

In the past 5 years, investigators have identified specific risk factors for TRALI in recipients of blood transfusion. 33% of patients on mechanical ventilation developed acute lung injury within 48 h of transfusion in an observational study.[55] A retrospective study confirmed that the presence of mechanical ventilation predisposes to development of TRALI (table 2 and figure 4). Because the application of high peak airway pressures increases the risk for TRALI in patients and in experimental settings,[36,72] we assume that mechanical stretch of the lungs due to positive pressure ventilation results in priming of pulmonary neutrophils or endothelium.

Extrapulmonary hits also predispose to TRALI. Specific surgical procedures are a particular risk factor (table 2). The increased risk with some procedures might be because of a systemic inflammatory response syndrome, as suggested by endotoxaemia models[26,43] and which was noted in cardiac surgery patients who were prospectively followed up for the occurrence of TRALI.[9] In agreement with this finding, sepsis has been identified as a risk factor for TRALI in several studies of patients in intensive care (table 2). In cardiac surgery, the time on cardiopulmonary bypass was associated with TRALI,[15] suggesting that this device might contribute to neutrophil priming, as shown in previous studies.[73] Conditions in which patients typically receive several transfusions, including haematological malignancy, bleeding with liver failure, and massive transfusion, seem to be clear risk factors for TRALI. Whether the risk is mainly determined by the underlying condition or the many transfusions remains to be identified. A positive fluid balance is associated with development of TRALI, suggesting that fluid overload might have a role in TRALI pathogenesis.[8,55] Identification of specific host-related risk factors enables physicians to take an active approach to patients in need of transfusion.

What can the attending physician do?

Restrictive transfusion policy

The most effective prevention is a restrictive transfusion strategy. In a randomised clinical trial in critically ill patients, a restrictive transfusion policy for red blood cells was associated with a decrease in incidence of acute lung injury compared with a liberal strategy (7·7% *vs* 11·4%),[74] suggesting that some of these patients might have had TRALI. The restrictive threshold was well tolerated and has greatly helped in guidance of red blood cell transfusion in the intensive-care unit.[74] However, results of this landmark trial have been only partly implemented in intensive-care units since then,[58,75] and a large variance in transfusion practice remains.[76] For fresh frozen plasma, audits consistently report a high use of plasma with no clear clinical indication.[77–80] Use of electronic decision support has successfully reduced inappropriate transfusions, which has in turn been associated with a decrease in lung injury.[81] For non-emergency transfusions, delaying of the transfusion has been suggested until the acute inflammation has subsided.

Patient-tailored transfusion policy

Transfusion cannot be avoided altogether. A multivariate analysis in patients in intensive care showed that patient-related risk factors contributed more to the onset of TRALI than did transfusion-related risk factors, suggesting that development of a TRALI reaction is dependent more on host factors then on factors in the blood product.[18] Therefore, a patient-tailored approach aimed at reducing TRALI risk factors could be effective to alleviate the risk of TRALI.

Identification of specific risk factors empowers physicians to manage their patient in need of a transfusion. Fluid balance should be monitored. Shock before transfusion should be avoided, as should prior fluid overload. For patients on mechanical ventilation, airway pressures should be restricted before transfusion. Because ventilation with low tidal volumes decreases mortality in patients with acute lung injury,[68] application of such ventilation in patients in need of a transfusion seems appropriate.

Ordering of specific transfusion products for at-risk patients

Transfusion risk factors for the onset of non-antibody-mediated TRALI seem to be storage related; therefore, patients at risk for TRALI might benefit from fresh blood products. Whereas storage time seems to play a part in the onset of TRALI in most experimental models,[16,17,41,43,48,49] clinical studies show conflicting results (table 3). A randomised trial of premature infants did not show a difference on outcome between fresh and stored red blood cells.[83] A trial in adult patients in intensive care is ongoing.[84] However, these studies do not directly investigate

	Type of study and inclusion	Population	Country	Study year	Risk factors	Odds ratio (95% CI)
Silliman et al[22]	Retrospective, active	Hospital	Canada	1991–95	Haematological malignancy Cardiovascular disease	.. ..
Rana et al[55]	Retrospective, active	ICU	USA	2003	Sepsis Fluid balance	24·1 (1·1–530)* 1·3 (0·9–1·9)*
Vlaar et al[18]	Retrospective, active	ICU	Netherlands	2004–07	Emergency cardiac surgery Haematological malignancy Massive transfusion Mechanical ventilation Sepsis APACHE-II score	17·6 (1·8–168·5) 13·1 (2·7–63·8) 4·5 (2·1–9·8) 3·0 (1·3–7·1) 2·5 (1·2–5·2) 1·1 (1·0–1·1)
Gajic et al[19]	Prospective, active	ICU	USA	2005–07	Sepsis Chronic alcohol abuse APACHE-III score	2·1 (1·0–4·3) 2·7 (1·3–5·8) ..
Vlaar et al[15]	Prospective, active	ICU	Netherlands	2006–09	Age Heart-lung machine	1·1 (1·02–1·28) 1·0 (1·00–1·03)
Toy et al[8]	Prospective, active	Regional	USA	2006–09	Massive transfusion Shock Positive fluid balance Peak airway pressure >30 cm H_2O† Chronic alcohol abuse Severe liver disease Inflammation (increased concentration of interleukin-8 before transfusion)	1·2 (1·1–1·3) 4·3 (2·2–8·4) 1·2 (1·1–1·3) 5·6 (2·1–14·9) 3·0 (1·1–8·7) 2·9 (1·3–6·2) ..
Benson et al[56]	Retrospective, active	ICU	USA	2002–08	End-stage liver disease	..

ICU=intensive-care unit. APACHE=Acute Physiology and Chronic Health Evaluation II score. *Adjusted for total plasma transfused. †If mechanically ventilated.

Table 2: **Patient risk factors for onset of transfusion-related acute lung injury**

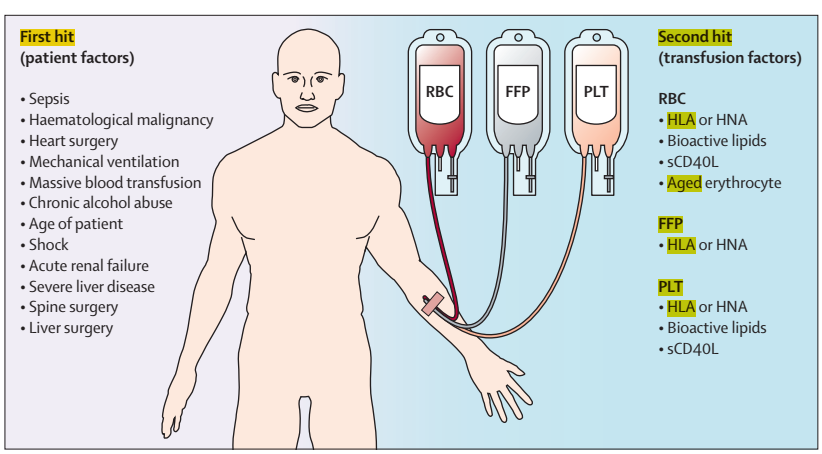

Figure 4: **The two-hit model of TRALI**

The first hit consists of patient factors resulting in priming of the pulmonary neutrophils. Risk factors have been suggested that might function as a first hit. The second hit is the blood transfusion resulting in activation of the endothelial cells, and the primed pulmonary neutrophils resulting in capillary leakage, culminating in pulmonary oedema. Some transfusion factors are independent of the type of blood product, whereas others are specific for a type of product. RBC=red blood cells. HLA=human leucocyte antibodies. HNA=human neutrophil antibodies. sCD40L=soluble CD40 ligand. FFP=fresh frozen plasma. PLT=platelet concentrate.

TRALI, so no recommendation can yet be given. Instead of providing fresh red blood cells, preclinical findings showed that washing of stored cell-containing blood products prevents onset of TRALI.[48,49] Clinical studies show that washing of such products at the bedside is safe and feasible. Whether washed cell-containing blood products prevent onset of TRALI in the clinical setting remains to be determined.

Reporting of TRALI

Suspected TRALI reactions should be reported to the blood bank for identification and exclusion of involved donors with antibodies to prevent future reactions. Many disciplines are implicated in the care of suspected cases, including haemovigilance workers, haematologists, transfusion medicine physicians, and critical-care physicians. Because TRALI is a clinical diagnosis, the practice of reporting can differ; indeed, an audit among these disciplines showed that substantial differences exist.[85] Moreover, the practice of reporting is not in keeping with the two-hit theory, because sepsis before transfusion is considered an important reason to withhold from reporting a suspected case.

What can the blood service do?

All blood products can induce antibody-mediated TRALI if the antibody is strong enough and the patient has susceptible risk factors, even red blood cells containing 10–20 mL of plasma (figure 4).[86] Instead of focusing on the type of blood product, information about which donors have a high incidence of HLA or HNA antibodies is more important. Two groups of high-risk donors could be identified: multiparous donors and donors exposed to blood transfusion. The likelihood of HLA alloimmunisation in donors increases with the number of pregnancies.[87–89] The clinical significance of the sex of the donor was shown in two studies of critically ill patients reporting worsened oxygenation after transfusion of frozen fresh

	Type of study and inclusion	Population	Country	Study year	Relation between storage time and onset TRALI?		Role for bioactive lipids?*
					Red blood cells	Platelets	
Silliman et al[17]	Prospective, active	Hospital	USA	1991–95	No	Yes	Yes
Vlaar et al[18]	Retrospective, active	ICU	The Netherlands	2004–07	No	No	..
Gajic et al[19]	Prospective, active	ICU	USA	2005–07	No	No	Yes
Vlaar et al[15]	Prospective, active	Surgery	The Netherlands	2006–09	Yes	No	No
Middelburg et al[82]	Retrospective, passive	National	The Netherlands	2005–07	No	Yes	..
Toy et al[8]	Prospective, active	Hospital	USA	2006–09	No	No	No

ICU=intensive-care unit. *Lysophosphatidylcholines.

Table 3: **Results of clinical studies of aged blood products and onset of transfusion-related acute lung injury**

	Type of study and inclusion	Population	Country	Study year	Endpoint	Effect size	Effective?
Palfi et al[90]	RCT, active	ICU	Sweden	1995–97	PaO_2 to F_iO_2 ratio	..	Yes
Wright et al[91]	Retrospective, active	Surgery	UK	1998–2006	TRALI onset	OR 0·39 (0·16–0·90)	Yes
SHOT[92]	Retrospective, passive	National	UK	2002–05	TRALI onset	..	Yes
Vlaar et al[18]	Retrospective, active	ICU	The Netherlands	2004–07	TRALI onset	RR 0·35 (0·14–0·88)	Yes
Eder et al[93]	Retrospective, passive	National	US	2006–08	TRALI onset	OR 0·21 (0·08–0·45)	Yes
Wiersum-Osselton et al[94]	Retrospective, passive	National	The Netherlands	2002–09	TRALI onset	PAR 0·33 (0·09–0·51)	Yes
Vlaar et al[15]	Prospective, active	Surgery	The Netherlands	2006–09	TRALI onset	..	No
Nakazawa et al[95]	Prospective, active	Surgery	Japan	2008–08	PaO_2 to F_iO_2 <300	..	Yes
Toy et al[8]	Prospective, active	Hospital	USA	2006–09	TRALI onset	Incidence: before 2·57% (1·72–3·86), after 0·81% (0·44–1·49)*	Yes

Data in parentheses are 95% CI. RCT=randomised controlled trial. ICU=intensive-care unit. TRALI=transfusion-related acute lung injury. OR=odds ratio. RR=relative risk. PAR=population attributable risk. *Incidence per 10 000 units transfused before (2006) and after (2009) introduction of a male-only donor strategy.

Table 4: **Results of male-only and mostly male donor strategies**

plasma from female donors and multiparous female donors.[54,90] A study showed an association between transfusion and the presence of leucocyte antibodies in 3% of previously transfused donors, rendering these donors high risk.[88]

Exclusion of donors

To reduce risk of TRALI, the US Food and Drug Administration encourages blood banks to adopt a mainly male donor strategy. A reactive exclusion policy is exclusion of donors in a TRALI case with proven HLA or HNA antibodies that match with the recipient antigen. In the Netherlands, donors implicated twice in a TRALI reaction are excluded from future donation, even in the absence of HLA or HNA antibodies. This approach relies on proper reporting of suspected TRALI cases; however, it can result in an unnecessary loss of donors.

An alternative approach is a proactive exclusion policy with exclusion of donors at risk for HLA or HNA antibodies. As mentioned above, blood products derived from multiparous donors are associated with onset of TRALI. Since 2003, the policy to use plasma only from male donors for the production of high plasma-volume blood components has been implemented. This policy resulted in up to a two-third reduction in TRALI cases (table 4).[13,91,94,96,97] Whether a male-only donor policy prevents TRALI associated with low plasma volume products, such as red blood cells, needs to be determined.

A less rigorous policy is testing of all donors or at-risk donors for HLA or HNA antibodies. Besides the high labour and costs involved, possibilities for large-scale HLA and HNA antibody screening were not readily available in 2003. Some of these difficulties have been overcome with introduction of beads-based flow cytometry techniques for HLA antibody screening. However, what cutoff titre should be applied is unclear. In a critically ill patient, even a low antibody titre or volume can be sufficient to introduce TRALI.

Pooling of plasma

Another solution to reduce exposure of the recipient to antibodies present in plasma is pooling of up to 300 units, which dilutes any leucocyte antibodies present. Neither HNA nor HLA antibodies are detectable in solvent-detergent plasma.[98] Countries using solvent-detergent plasma have not reported any TRALI case originating from transfusion of these plasma products.[99] Concerns of pooling are exposure to many donors and transmission of viruses and prion diseases. A prion filter has now been introduced to prevent transmission of Creutzfeldt-Jacob disease;[100] however, exposure of a patient to hundreds of donors might still be undesirable.

Another uncertainty is the effectiveness of solvent-detergent plasma in prevention of TRALI in critically ill patients, because those patients might still develop TRALI after dilution of the antibodies.

Conclusion

Despite limitations of diagnostic tests, TRALI incidence seems to be high in at-risk patient populations. Therefore, TRALI is an underestimated health-care problem. Preventive measures, such as mainly male donor strategies, have been successful in reducing risk of TRALI. Identification of risk factors further improves the risk–benefit assessment of a blood transfusion. Efforts to further decrease the risk of TRALI needs increased awareness of this syndrome among physicians.

Contributors

APVJ designed the study and the tables. APVJ and NPJ reviewed the scientific literature, designed the figures, and wrote the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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