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REVIEW

Transfusion-related acute lung injury: a change of perspective

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Abstract: Two decades ago, transfusion-related acute lung injury (TRALI) was considered a rare complication of transfusion medicine. Nowadays, TRALI has emerged as the leading cause of transfusion-related mortality, presumably as a consequence of reaching international agreement on defining TRALI with subsequent increased recognition and reporting of TRALI cases. Specific patient populations such as critically ill patients have an increased risk of developing TRALI, which may be explained by the two-event hypothesis. The first event is the underlying condition of the patient resulting in priming of neutrophils. The second event is the transfusion of a blood product, after which either antibodies or bioactive lipids activate the primed neutrophils, resulting in pulmonary oedema. As opposed to the traditional view that TRALI has a good prognosis, TRALI may have a significant impact on morbidity and outcome, at least in specific patient groups. The association of transfusion with adverse outcome calls for blood product and donor management strategies aimed at decreasing the risk of acquiring TRALI. Excluding female donors from plasma donation seems to have reduced, but not prevented the occurrence of TRALI. Additional research is needed to determine whether the use of fresh blood products may be an additional measure to reduce TRALI. Studies are also needed to identify at-risk patients. In these studies, we advocate the use of the consensus definition to improve comparability of risk factors and outcome of TRALI across patient populations.

KEYWORDS

Blood donor, critically ill, incidence, prevention, TRALI

INTRODUCTION

Acute respiratory distress after transfusion of a plasma-rich blood product is known as transfusion-related (TR) acute lung injury (ALI). Of all adverse reactions associated with transfusion, TRALI is the most common and the most serious complication. According to the Food and Drug Administration and to several surveillance systems, TRALI has become the leading cause of transfusion-related death.[1-4] Originally, TRALI was thought to be an antibody-mediated reaction, in which antibodies in the blood product react with a matching antigen in the recipient, leading to pulmonary neutrophil activation and increased pulmonary capillary permeability and subsequent pulmonary oedema.[5] Although the exact incidence of TRALI is unknown, TRALI is considered to be a rare event. With supportive therapy, TRALI is generally reported to have a good prognosis.[6]

The above-described traditional outlook on TRALI has changed in recent years. The development of a case definition has greatly facilitated research and estimates of incidence of TRALI. Studies using this definition showed that TRALI occurs more frequently then previously reported, in particular in the critically ill and injured patient population.[7,8] Also, insight into TRALI pathogenesis has evolved. In addition to the original antibody hypothesis, a two-event hypothesis of TRALI has been postulated.[9,10] The first event is the patient's underlying clinical condition, including infection, surgery, or trauma, causing inflammation with priming of the pulmonary neutrophils. The second event is caused by the blood product. Either bioactive molecules which have accumulated during storage of cell-containing blood products or antibodies activate the primed neutrophils, resulting in permeability oedema. Previously regarded as a relatively self-limiting disease,[1,5,6,11] some observations suggest that TRALI may significantly contribute to morbidity and mortality in certain patient groups.[7]

In this manuscript, we describe the change in perspective on incidence, pathogenesis and outcome of TRALI. The impact of these changes on current and possibly implicated future management of TRALI is discussed.

METHODS – SYSTEMATIC SEARCH OF THE LITERATURE

The Medline database was used to identify medical subject's headings (MeSH) to select search terms. In addition to MeSH terms, we also used free-text words. Search terms referred to aspects of the condition ("TRALI", "blood transfusion/adverse effects") as well as related topics ("storage", "human leukocyte antibodies", "red blood cells", "fresh frozen plasma" and "platelet transfusion"). All papers back to 1985 were assessed on relevance using the online abstracts. In addition, the reference lists of retrieved papers were screened for potentially important papers.

TRALI DEFINITION

As distinguishing biomarkers are absent, TRALI is a clinical diagnosis. The lack of a consensus definition of TRALI has contributed to under-diagnosing of this syndrome. In recognition of this problem, a case definition of TRALI based on clinical and radiological parameters was formulated during a consensus conference and by the US National Heart, Lung and Blood Institute in 2004.[1,11,12] The definition is derived from the widely used definition of ALI and its more severe form acute respiratory distress syndrome (ARDS), as proposed by the North American-European Consensus Conference (NAECC) consensus.[13] These criteria include the acute onset of hypoxia with bilateral pulmonary infiltrates, no evidence of left ventricular overload and the presence of a risk factor for ALI/ARDS (*table 1*). TRALI is defined as the fulfilment of the definition of ALI within six hours after transfusion in the absence of another risk factor for ALI (*table 1*).[1,11,12]

Although this definition appears straightforward, a complicating factor is that the characteristics of TRALI are indistinguishable from ALI due to other aetiologies, such as pneumonia, sepsis or lung contusion. Using this definition would rule out the possibility of diagnosing TRALI in a patient with an underlying ALI risk factor who has also received a transfusion. To identify such cases, the term 'possible TRALI' was developed (*table 1*), which allows for the presence of another risk factor for ALI. Given the uncertainty of the relationship of ALI to the transfusion in possible TRALI, this term facilitates separate categorisation in surveillance systems to permit comparisons across systems.

Table 1. *Definition of transfusion-related acute lung injury (TRALI)*

TRALI

- Acute onset within 6 hours after a blood transfusion
- PaO_2/FiO_2 <300 mmHg
- Bilateral infiltrative changes on the chest X-ray
- No sign of hydrostatic pulmonary oedema (pulmonary arterial occlusion pressure <18 mmHg or central venous pressure <15 mmHg)
- No other risk factor for ALI present

Possible TRALI

All of the above but another risk factor for ALI present

TRALI INCIDENCE

The incidence of TRALI has not been well established. Estimated incidence rates vary widely, ranging from 0.002% to 1.12% per product transfused and from 0.08 to 8% per patient transfused,[5,7,8,14-19] (*table 2*). The rates presented should be regarded with caution for several reasons. First, the definition used for TRALI differed between studies. Some required the presence of antibodies against human neutrophil antigen (anti-HNA) or against human leukocyte antigen (anti-HLA),[4,5] whereas others used only clinical criteria.[7,17,18] In addition, surveillance systems in some countries, including the United States and the Netherlands, use an alternative definition to the consensus definition, in which imputability is scored.[19,20] A case definition which rules out the possibility of TRALI when another ALI risk factor is present will lead to lower incidence rates compared with studies that have allowed for an alternative risk, i.e. possible TRALI. In critically ill patients, alternative ALI risk factors are often present. A prospective study in this patient group reported a high incidence of suspected and possible TRALI cases taken together.[7] However, the high incidence is probably not merely a consequence of applying a broader definition. In addition to fulfilling the clinical diagnosis, immunological workup of these cases showed the presence of HLA/HNA antibodies in the plasma of associated donors, contributing to the suspicion that most of these were indeed TRALI cases. Second, the method of surveillance differs between studies. Obviously, studies with an active case investigational approach yield higher incidence rates than outcomes of passive surveillance systems. Third, the population under investigation differs between studies, which may hamper comparability of the available incidence data. Finally, in the absence of a biomarker, TRALI is diagnosed using clinical and radiological parameters. Subjective interpretation of clinical findings may contribute to differences in estimates of incidence.

Studies that have applied the consensus definition formulated in 2004 report higher TRALI rates then before, in particular in critically ill patients.[7,8] These findings support the general notion that TRALI is

Table 2. *Overview of incidence reports of TRALI*

Reference	Type of study and inclusion	Population	Country	Study year	Incidence of TRALI	
					Per patient transfused	Per product transfused
Popovsky[5]	Retrospective Active	Hospital	United States	1983	N/A	0.02%*
Henderson[15]	Retrospective Passive	Regional	Australia	1981-89	N/A	0.001%
Clarke[14]	Retrospective Passive	Hospital	United States	1994	N/A	0.33%**
Silliman[16]	Retrospective Active	Hospital	Canada	1991-95	0.08%	0.22%**
Wallis[18]	Retrospective Passive	Hospital	United Kingdom	1991-2003	N/A	0.01%*
Wiersum[19]	Retrospective Passive	National	The Netherlands	2002-05	N/A	0.002%
Rana[8]	Retrospective Active	ICU	United States	2003	1.8%	0.26%
Vlaar[55]	Retrospective Active	ICU	The Netherlands	2004-07	5.1%	0.9%
Gajic[7]	Prospective Acive	ICU	United States	2005-07	8%	1.12%

***Incidence determined only in plasma products transfused; **incidence determined only in platelets concentrate products transfused.**

under-diagnosed and under-reported.[3,11] An increase in reporting may have occurred with increased awareness of TRALI. Nevertheless, a look-back study, in which recipients of blood products from a donor linked to a TRALI fatality were analysed for symptoms of TRALI, showed that TRALI was frequently not recognised.[21] Therefore, under-diagnosing is not merely a consequence of awareness, but also of a failure to recognise the syndrome.

A rise in incidence has also been reported by national surveillance systems,[1,2,19,20] suggesting that the rise in incidence is not limited to the critically ill patient population. Rather, before the consensus definition, the presence of other risk factors for ALI excluded critically ill or injured patients from a diagnosis of TRALI and consequently, from estimates of the incidence of TRALI in this patient population. The consensus definition has made estimates of incidence in this patient group possible. Overall, the consensus definition may also have facilitated clinical recognition of TRALI cases.

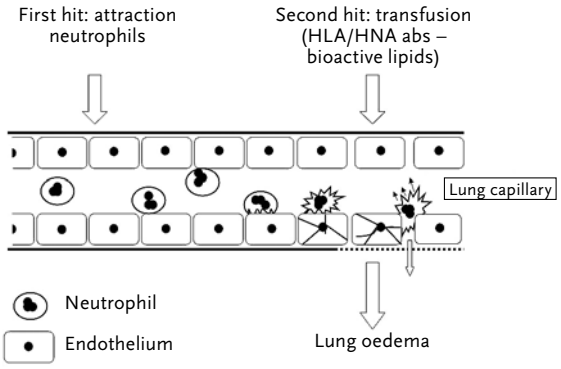
The more recent figures suggest that TRALI may be a significant health problem. Several other observations support this notion. Transfusion of blood products is associated with development of respiratory complications in ICU patients, including ALI.[22-24] Also, a liberal transfusion strategy was associated with an increased risk of ALI when compared with a restrictive policy.[25] Although the temporal relation in most of these studies was not defined, it is likely that a significant number of these patients may have had TRALI. Therefore, the traditionally held view that TRALI is a rare event may not hold true, at least not in the intensive care unit.

The observations that blood transfusion is associated with respiratory complications are in keeping with the two-event hypothesis of TRALI, discussed below, in which transfusion worsens microvascular injury characteristic of ALI.

TRALI PATHOGENESIS

Any cell-containing blood product or plasma-rich blood product can cause TRALI. The pathogenesis has not been fully elucidated. Two hypotheses have been formulated. The first hypothesis suggests that TRALI is caused by donor antibodies against human neutrophil antigens (HNA) or human leukocyte antigens (HLA) in the lungs of the recipient.[5,26] However, the association between HLA antibodies in donor plasma and TRALI is not very strong. A significant fraction of TRALI cases have no detectable antibodies.[21,27,28] Also, many antibody-containing blood products fail to produce TRALI.[29-31] An alternative hypothesis implicates a two-event model.[9,32,33] The first event is an inflammatory condition of the patient (e.g. sepsis, recent surgery) causing sequestration and priming of neutrophils in the pulmonary compartment (*figure 1*). The second event is the transfusion, containing either antibodies or bioactive lipids that have accumulated during blood storage, stimulating the primed neutrophils to release proteases. The result in both hypotheses is endothelial damage, capillary leak and extravasation of neutrophils.[33-35] The two-event model is supported by experimental studies, in which bioactive lipids as well as outdated blood products

Figure 1. *Pathophysiology of transfusion-related acute lung injury (TRALI)*



Neutrophils are attracted to the lung by release of cytokines and chemokines. Firm adhesion to the endothelium of the lung capillaries is realised. Neutrophils are then activated by the 'second hit' of bioactive lipids or HLA/HNA antibodies. This results in alveolar capillary damage and leakage of fluid into the alveolar space, resulting in the clinical picture of TRALI.

have been used to cause TRALI after a priming hit.[32,33,36] Also, observational studies report associations between prolonged storage of blood products and ARDS in the critically ill.

However, the premise that only patients in a poor clinical condition develop TRALI does not hold true in some case reports, in which a relatively active patient and a healthy research volunteer developed TRALI.[11,37] A threshold model has been suggested,[9] in which a threshold must be overcome to induce a TRALI reaction. Factors that determine the threshold are the predisposition of the patient that determines priming of the lung neutrophils and the ability of the mediators in the transfusion to cause activation of primed neutrophils. A strong antibody-mediated response can cause severe TRALI in an otherwise 'healthy' recipient. When activation status is too low, it is possible that priming factors in the transfusion are not strong enough to overcome the threshold. This would explain why TRALI does not develop in a transfused patient even when an antibody-antigen match is present. In a critically ill patient with predisposing factors for ALI, such as pneumonia, sepsis or trauma, transfusion of mediators with low neutrophil-priming activity may be sufficient to overcome the threshold to induce a TRALI reaction.

The above-mentioned model underlines the concept that critically ill patients are susceptible to a TRALI reaction due to an inflammatory response, resulting in priming of pulmonary neutrophils.[1,11] If indeed risk factors for ALI of any origin predispose to TRALI, the multiple possible 'first events' may explain the increased incidence of TRALI in the critically ill, when compared with the general hospital population.

TRALI SYMPTOMS

In its fulminant presentation, TRALI is indistinguishable from ALI secondary to other causes. Symptoms include rapid onset of respiratory distress due to severe bilateral pulmonary oedema. Chest radiographs classically demonstrate bilateral 'white out' lungs, indistinguishable from hydrostatic pulmonary oedema,[38] but in the first few hours, a patchy pattern may be observed.[5] Typically, patients develop the symptoms of TRALI within one to two hours after transfusion, but an onset of six hours has also been accepted. Some case reports indicate an incubation period of up to 48 hours.[39,40] Hypotension is not a consistent finding. Transient neutropenia has been described.[41]

Most clinical cases described in the medical literature refer to the above-mentioned severe presentation.[42-45] However, there is growing appreciation that milder forms of respiratory distress may still represent the syndrome. A spectrum of severity is noted in TRALI cases, ranging from transient dyspnoea to fulminant ALI/ARDS.[1,6] Reports from a donor with neutrophil antibodies involved in multiple transfusion reactions showed a wide variety of transfusion reactions, including mild symptoms that do not meet the definition of TRALI.[46]

A particular challenge is the distinction between TRALI and transfusion-associated circulatory overload (TACO), as clinical and radiological features are similar.[47] The TRALI definition holds that the pulmonary artery occlusion pressure should not exceed 18 mmHg (*table 1*), whereas in TACO, elevated wedge pressure is a common finding. However, the scenario that TRALI and TACO are mutually exclusive is probably not true. Indeed, a considerable number of patients with clinical criteria for ALI are misclassified after measurement of the pulmonary artery occlusion pressure.[48] Vice versa, pulmonary oedema due to capillary leak, as found in TRALI, may also increase pulmonary arterial pressure, thereby no longer satisfying the TRALI consensus definition. Other markers, such as brain natriuretic peptide and N-terminal pro-brain natriuretic peptide, were not helpful in discriminating between TACO (or cardiogenic pulmonary oedema) and TRALI,[49] rendering distinction between TRALI and TACO a continuing challenge.

Considering the spectrum of disease severity, including a mild presentation, as well as the difficulty in distinguishing TRALI from circulatory overload, TRALI may often be overlooked. Failure to recognise TRALI clinically may contribute to low incidence rates which may represent only a small part of lung injury inflicted by transfusion. Efforts to increase recognition of the TRALI syndrome are important to determine when to start complex and expensive immunological workup of involved donors in a suspected TRALI case and subsequent donor exclusion to prevent future TRALI reactions.

TRALI OUTCOME

It is often stated that TRALI differs from ALI due to other causes in terms of outcome. Whereas mortality of ALI is 40 to 60%,[50] the majority of TRALI patients improve within 48 to 96 hours after the insult, when appropriate respiratory support is supplied. The mortality rate of TRALI is considered to be low, around 5 to 10%.[5,6,11,16] Also, in contrast to many ALI patients who develop irreversible lung injury, it is stated that pulmonary function of TRALI patients usually recovers, without apparent structural damage such as the occurrence of fibrosis.[6] However, data on outcome of TRALI are sparse, mostly based on case series.

In contrast with the above, studies in critically ill or injured patients report that blood transfusion is associated with considerable morbidity and mortality. Transfusion of blood is an independent risk factor for developing ALI in trauma patients and in ICU patients,[22-24,51] thereby increasing length of ICU and hospital stay. Adverse outcome appears to be associated with the number of units transfused and with transfusion of fresh frozen plasma or platelets.[24,52] An association of transfusion with mortality was found in established ALI patients,[23] and in patients after cardiothoracic surgery.[53] The impact of red blood cell transfusion on outcome was reviewed recently, showing that red blood cell transfusion increased the risk of developing ALI and contributed to mortality in ICU, trauma and surgical patients.[54]

Of note, these studies show an association between transfusion and adverse outcome, not between TRALI and outcome. The association between TRALI and outcome has still not firmly been established. However, although the time frame was generally not determined in these studies, it is likely that some of these patients complied with the TRALI definition. Indeed, mortality of TRALI was found to be higher compared with transfused controls in a critically ill patient population.[7] In addition, we have recently performed a retrospective study of TRALI in a large cohort of over 5000 critically ill patients admitted to our ICU, using the consensus definition. We found that patients developing TRALI had a prolonged ICU stay and were mechanically ventilated for longer compared with transfused controls.[55] Mortality was higher in the TRALI group compared with the transfused controls (24 *vs* 13%, p=0.04).

Importantly, from these reports on the association between transfusion and adverse outcome, it is not clear to what extent the transfusion or other ALI risk factors contributed to mortality. These observations have the potential limitation that blood is more frequently administered to sick patients and sick patients more frequently develop complications and die. Therefore, whether transfusion is a marker or a mediator of disease is an important question that remains to be answered.

TRALI MANAGEMENT

Management of TRALI is supportive, as is the management of any patient with permeability oedema. All patients require additional oxygen and mechanical ventilation is unavoidable in 70 to 90%.[5,18] In line with treatment of ALI patients, it could be speculated that a restrictive tidal volume ventilation should be applied to avoid worsening of lung injury.[56] Specific treatment strategies for TRALI, however, do not exist.

TRALI management consists mainly of preventing future adverse reactions. A patient in whom TRALI is suspected should be reported to the National Blood Bank for a serological workup of the recipient and the implicated donors on the presence of HLA and HNA antibodies. Incompatibility is tested by cross-matching donor plasma against recipient's leucocytes. A donor with antibodies which are incompatible with the patient is excluded from further donation of blood for transfusion products. As stated before, the two-event hypothesis does not exclude the role of antibodies in the occurrence of TRALI. Therefore, we would like to underscore that 'possible TRALI', i.e. a TRALI reaction in a patient with an additional TRALI risk factor, should be reported to the National Blood Bank, to allow for reliable incidence estimates in this patient group and to determine whether serological workup should be initiated to identify an implicated donor.

The two TRALI theories yield different approaches to further preventive strategies. In the antibody-based theory, blood products with the highest antibody content (fresh frozen plasma and platelet concentrates) would be more likely to cause TRALI. Most donors associated with cases of TRALI are multiparous women. The likelihood of HLA allo-immunisation increases with the number of pregnancies, from 8% in the absence of previous pregnancies up to 26% of multiparous women harbouring HLA antibodies.[57] The clinical significance of donor gender was demonstrated in two studies in critically ill patients reporting worsened oxygenation after fresh frozen plasma (FFP) transfusion from (multiparous) female donors.[8,58] Given the association of female donors with TRALI, the UK National Blood Service has deferred women from plasma donation since 2003. Since then, reports of TRALI cases have diminished. It should be noted, however, that the UK haemovigilance system only reports a TRALI case in the presence of antibodies. Two clinical studies have appeared, showing that excluding female donor plasma may prove effective. In the UK, the onset of ALI in patients receiving multiple transfusions while undergoing repair of a ruptured abdominal aortic aneurysm was reduced from 36 to 21%.[59] Excluding all females from plasma donation was copied by the Dutch National Blood Service in 2006. We showed that this policy also reduced, but did not prevent, the occurrence of

ALI in a mixed medical-surgical population of critically ill patients.[17]

Regardless of which theory one accepts, the deferral of women from plasma donation will not prevent all cases of TRALI. Measures aimed at preventing two-event TRALI include an alternative approach. Obviously, less transfusion results in less TRALI. In the critically ill, a restrictive transfusion trigger is well tolerated and associated with improved outcome in selected patient groups.[25] However, restrictive guidelines for erythrocyte transfusions are not always followed.[60] Also, blood transfusions are not avoidable. An alternative approach which is increasingly receiving attention is the transfusion of fresh red blood cells. Stored red blood cells undergo functional and morphological changes over time, referred to as storage lesions. Studies on the impact of aged blood on respiratory complications have yielded conflicting results. In cardiothoracic surgery patients, respiratory insufficiency and mortality was lower in patients who had received blood stored for less then 14 days compared with patients that had received blood stored for more then 14 days (7.4 *vs* 11.0%, p<0.001).[61] However, similar studies did not confirm these findings.[62,63] The age of platelets has also been associated with ALI in a clinical observational study.[16] Well-designed prospective studies are needed to determine whether patients 'at risk' for TRALI (i.e. critically ill or injured patients) would benefit from a differential transfusion policy using fresh products only.

Without doubt, both the deferral of female donors and the use of fresh blood only, has serious consequences on blood availability. For the sake of the patient, product management strategies as well as donor-exclusion policies should be aimed at decreasing the risk of acquiring TRALI without impeding a continuous reliable blood supply.

CONCLUSION

The perspective on TRALI has changed in the past years. TRALI is an under-estimated health problem, with a significant impact on outcome in specific patient groups. Recognition of the association of transfusion with pulmonary injury is important, in terms of adherence to restrictive transfusion policies, but also in terms of reporting suspected TRALI cases for immunological workup to prevent future reactions. We propose to use the consensus definition rather then national protocols to identify TRALI cases to improve comparability of incidence rates, course of disease and outcome in different patient populations. Excluding females from plasma donation has reduced, but not prevented TRALI. Future research is needed to determine whether transfusion of fresh blood will only reduce the risk of a TRALI reaction in at risk patients.

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