Title

Transfusion Reactions Newer Concepts on the Pathophysiology, Incidence, Treatment, and Prevention of Transfusion-Related Acute Lung Injury

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Transfusion Reactions: Newer Concepts on the Pathophysiology, Incidence, Treatment and Prevention of Transfusion Related Acute Lung Injury (TRALI)

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SYNOPSIS

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related mortality. Clinically, TRALI presents as acute lung injury (ALI) (characterized by dyspnea and hypoxemia, with bilateral pulmonary infiltrates) within 6 hours after transfusion of one or more blood products. The pathophysiology of TRALI is incompletely understood, but in part is due to transfusion of certain anti-leukocyte antibodies, or possibly other bioactive substances, into susceptible recipients. Transfusion recipient risk factors are higher interleukin-8 levels, liver surgery, chronic alcohol abuse, shock, higher peak airway pressure while being mechanically ventilated, current smoking and higher positive fluid balance. Transfusion risk factors are female plasma, quantity of strong antibody that matches recipient class II human leukocyte antigens, and volume of plasma containing antibody to human neutrophil antigens. Diagnosing TRALI requires a high index of suspicion, and the exclusion of circulatory overload, heart failure or other major ALI risk factors as the cause of pulmonary edema. Treatment should include cessation of the offending transfusion, but is otherwise supportive. Reduced transfusion of female plasma has been associated with a lower TRALI incidence. Further prevention strategies may include reduced transfusion of platelets that contain leukocyte antibodies, and reduction of recipient susceptibility by improving treatment of shock and limiting peak airway pressure while being mechanically ventilated.

Keywords

Introduction

Since 2003, the leading cause of transfusion-related fatality has been transfusion-related acute lung injury (TRALI),[1] defined as acute lung injury (ALI)[2] that develops during or within six hours after transfusion of one or more units of blood or blood components.[3,4] Included in this definition are cases of ALI after multiple transfusions, a well-known ALI risk factor.[6] The condition has been underreported since the first description by Popovsky

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and Moore.[5] In the United States, the incidence of TRALI before 2007 is estimated at 1:4000 to 1:5000 units transfused,[7,8] though preventative measures (described below) may have reduced this incidence to 1:12,000 by 2009.[8] TRALI mortality has been estimated at ~6%,[7] considerably lower than the estimated mortality of other forms of ALI/ARDS.[9]

Definition of TRALI

TRALI is defined as new ALI that develops during or within 6 hours of transfusion of one or more units, not attributable to another ALI risk factor (Table 1).[4] To diagnose patients with the highest likelihood of TRALI, patients who concurrently have another major ALI risk factor (pneumonia, sepsis, aspiration, multiple fractures, and pancreatitis) are usually excluded. Such patients are labeled "possible TRALI" [3] or "transfused ALI".[8]

Pathophysiology

The pathogenesis of TRALI has usually been explained by the transfusion of a blood product that contains anti-human leukocyte antigen (anti-HLA) or anti-human neutrophil antigen (anti-HNA) antibodies that recognize cognate antigen in the transfusion recipient. Case series have documented the presence of such antibodies and their cognate antigens in TRALI patients,[7] and animal models of TRALI have been developed that employ anti-MHC I or anti-HNA antibodies to promote TRALI.[10,11] In these experimental models of TRALI, allo-recognition by such antibodies leads to neutrophil-dependent ALI, characterized by robust neutrophilic inflammation of the lung and disruption of the lung alveolar-capillary permeability barrier, similar to what is seen in other forms of ALI/ARDS.[10,11] A role for monocytes has also been implicated.[12,13] Furthermore, activated platelets have also been shown to play a pathogenic role in experimental models of TRALI, likely via interactions with neutrophils.[14,15]

Despite the substantial evidence implicating transfused antibodies in the pathogenesis of TRALI, uncertainty remains. One important observation is that cognate antibodies are not detected in all clinically diagnosed cases of TRALI.[7,8] Experimental models have implicated biologically active lipids in the pathogenesis of TRALI that develops in the absence of anti-leukocyte antibodies.[16,17] Such lipids have been shown to be breakdown products of cell membrane phospholipids that form during prolonged storage of cellular blood components.[18] In particular, Lysophosphatidylcholine (LysoPC), has been identified as a component of such blood products that can prime neutrophils. However, a case-control study in cardiac surgery patients[19], and a recent large case-control study in general transfused patients failed to demonstrate an association between such biologically active lipids (as well as other bioreactive substances including soluble CD40 ligand), and an increased risk of TRALI.[8] In addition, non-polar lipids in the plasma of stored leukoreduced red blood cells also prime neutrophils *in vitro*, but the clinical relevance of this observation remains to be determined.[20]

A second important observation is that not all recipients transfused with a blood product containing a matched anti-HLA or anti-HNA antibody develop evidence of TRALI. Thus, it is likely that factors other than transfusion of any of these antibodies are capable of initiating TRALI, and that co-factors, related either to the transfused product or to the recipient, are important in the pathogenesis of antibody-mediated TRALI. These observations have led to a multiple event hypothesis of TRALI pathogenesis, which states that a transfusion recipient must have an underlying medical condition(s) that, likely via immune priming, leads to a susceptibility to TRALI that is then triggered by the transfusion of alloantibody or other bioreactive substances.[21] This multi-event hypothesis is supported by animal models in which antibody-induced TRALI develops only when there is a pre-existing inflammatory stimulus, and by case-control human studies of TRALI risk factors (described below).[8,14]

TRALI Risk Factors

Risk of greater number of transfusions

TRALI has long been known to be associated with multiple transfusions.[6] In a case-control study, increased number of transfusions was associated with increased risk, which was partially explained by transfusion and patient risk factors identified by multivariate analysis.[8]

Transfusion risk factors

Although all blood components have been implicated in TRALI, three strong predictors of TRALI risk by multivariate analysis are receipt of female plasma or whole blood, larger quantity of strong cognate anti-HLA-Class II (cognate is defined as antibody specificity that matches recipient antigen), and larger volume of anti-HNA.[8] Multiparous females can be allo-immunized and produce anti-leukocyte antibodies,[22] explaining the higher risk of TRALI associated with blood products from female donors.

Regarding the relative importance of Class I vs Class II HLA antibody, Class II is more important.[8] The association of HLA Class II antibodies with TRALI was first reported by Kopko et al.[23] Case series have reported cognate anti-HLA-Class II was the most frequent antibody implicated in TRALI.[24,25] This predominance occurs despite the fact that frequencies of Class I (10 %) and Class II (12 %) antibodies are comparable in female donors.[26]

Regarding class I HLA antibody, there is evidence against anti-HLA-Class I being an important risk, even for strong cognate antibody with MFI > 2500.[8] Others have reported similar results [27] and similar conclusions.[28] There are reports that cognate anti-HLA-Class I can be associated with TRALI.[24,25,29] However, studies of previous recipients of blood from donors implicated in TRALI have found that this is rare.[30,31]

Often in previous studies and current practice, the finding of any cognate HLA antibody or HNA antibody in any transfused unit has been considered presumptive evidence of TRALI, regardless of antibody strength or volume. A case-control study suggests however, that with a multivariate analysis of risk factors, cognate anti-HLA-Class I and weak cognate anti-HLA-Class II have little or no impact on TRALI risk.[8]

Bioreactive substances in blood units did not appear to be associated with substantial risk in two clinical studies.[8,19] This result was surprising, given many basic studies that indicate bioreactive substances are important in the development of TRALI. [17,32,33]

Why do some patients develop TRALI and others who receive blood from the same donor do not? Cognate antibody matters,[8] and patients who developed TRALI may have received cognate antibody and others did not. However, cognate vs. non-cognate antibody is not the only reason, as several studies of previous recipients of blood from implicated donors have found patients who received cognate antibody but did not develop TRALI.[30,31,34] Three additional factors influence why some patients develop TRALI and others do not: first, the quantity of cognate antibody transfused (antibody strength times volume of plasma containing the antibody), second, the class of the HLA antibody, and third, the presence or absence of patient factors that increase the risk for TRALI.[8]

Patient risk factors

By multivariate analysis in a case-control study, patient risk factors are:[8]

- higher IL-8 level

- shock

- liver surgery (mainly transplantation)

- chronic alcohol abuse

- positive fluid balance

- peak airway pressure greater than 30 cm H_2O if mechanically ventilated before transfusion

- current smoking

The diverse patient-associated risk factors are consistent with the known underlying co-morbidities that predispose and lower the threshold for ALI, thus supporting the validity of these results. Shock results in tissue injury,[35] perhaps predisposing to TRALI through priming of the recipient's endothelium and immune cells. Chronic alcohol abuse increases risk, likely due to reduced levels of the antioxidant glutathione in the lung,[36] reduced phagocytosis of apoptotic cells, and the resulting enhanced pulmonary inflammatory response.[37] Patients with intravascular volume overload are more likely to manifest clinical pulmonary edema when there is ALI.[38] Previous studies have documented the risk for developing ALI with peak airway pressure greater than 30 cm H_2O[39] and current smoking.[40,41]

Higher levels of IL-8, a marker of inflammation and increased mortality risk,[42] may prime neutrophils and the lung endothelium. Acute contemporaneous events that increase inflammation and tissue injury could be "first hits" as first suggested by Silliman.[17] Experimental models of TRALI have shown that host inflammation may be necessary to produce ALI before challenge with cognate antibody.[14,32] Inflammation (first hit) may upregulate expression of HLA Class II antigens on classic antigen presenting cells (macrophages, dendritic cells), activated neutrophils,[43] and activated lung endothelial cells,[44] and exposure to large quantities of strong HLA Class II cognate antibody may then lead to ALI (second hit). [45] While "first hit" traditionally refers to neutrophil priming usually associated with inflammation in the recipient,[17] it is now known that additional recipient conditions predispose patients to TRALI.[8] These are general factors that predispose a patient to any form of ALI. Thus, it is reasonable to revise and broaden the concept of "first hit" in the multiple event model of TRALI to include not only conditions that result in neutrophil priming, but also patient conditions that predispose to and reduce the threshold for ALI.

Clinical Manifestations and Diagnosis

TRALI is under-recognized, and making the diagnosis requires a high index of suspicion. The diagnosis of TRALI is based on clinical findings of ALI manifested within 6 hours of receiving a blood product transfusion, in the absence of another risk factor for the development of lung injury (Tables 1 and 2). TRALI commonly develops well prior to the 6-hour timepoint, often during the first hour of a transfusion. Clinical hallmarks of TRALI include:

- dyspnea

- tachypnea

- hypoxemia

- bilateral pulmonary opacities on chest radiograph

- edema fluid in the endotracheal tube of intubated patients (severe TRALI)

- absence of evidence of volume overload or cardiac dysfunction as the principal cause of pulmonary edema

Febrile reactions as well as hypothermia have been reported in patients with TRALI, as have both hypotension and hypertension.

In mechanically ventilated patients, the diagnosis should be considered whenever there is an acute, unexplained worsening in respiratory status that is temporally associated with a transfusion. In such patients, copious frothy pink edema fluid is often recovered from the endotracheal tube. The differential diagnosis includes cardiogenic pulmonary edema, including transfusion-associated circulatory overload (TACO), and other causes of ALI/ARDS. In the context of a recent transfusion and the absence of other apparent risk factors for ALI/ARDS, the exclusion of cardiogenic pulmonary edema strongly supports the diagnosis of TRALI.

While there are no specific diagnostic tests for TRALI, several common clinical tests can be employed to support the diagnosis:

- echocardiogram

- brain natriuretic peptide (BNP)

- pulmonary edema fluid protein analysis

- white blood cell count (WBC)

Echocardiography, measurement of the BNP level, and analysis of pulmonary edema fluid are useful and complementary tests in helping to exclude cardiac dysfunction and volume overload. Echocardiography can be particularly helpful by providing insight into both cardiac function and volume status. BNP can similarly be used to help exclude volume overload. If undiluted pulmonary edema fluid is collected along with a matched plasma sample, the presence of a permeability pulmonary edema can be established which generally excludes cardiogenic edema.[46] While pulmonary artery catheterization and determination of pulmonary artery occlusion pressure provides additional information regarding volume status, routine use of this invasive procedure is not warranted. Transient leukopenia has been temporally associated with the onset of TRALI, and serial measurements of WBC may reveal this finding.[47] While none of these adjunctive tests is specific for TRALI, in the right clinical context they can build a clinical case for the diagnosis.

In addition to the supportive clinical diagnostic tests above, confirmatory laboratory testing can provide definitive evidence for the diagnosis of TRALI by investigating for the presence of transfused cognate antibodies. The blood bank should be notified of all cases of suspected TRALI, so that other components from the same involved donation can be quarantined. Donor retention specimens in the blood bank or donor recall samples should be used for antibody testing. A patient blood sample should be saved for HLA antigen testing, should strong HLA Class II antibody be found in an involved donor. However, as discussed above, it is important to note that cognate anti-leukocyte antibodies are not found in all cases of TRALI, and that the diagnosis of TRALI is ultimately based upon the clinical scenario and the exclusion of other diagnoses.

In a TRALI patient with fever and hypotension, it is important to rapidly exclude the possibility of ALI associated with sepsis due to the transfusion of bacteria contaminated platelets. The diagnosis is made by a positive gram stain of the residual contents of the transfused platelet unit, and by identification of the same organism in blood cultures of the patient and culture of the involved platelet unit.

Treatment

As with other forms of ALI/ARDS, there is no specific treatment for TRALI. In most cases, TRALI is self-limited and carries a better prognosis than other causes of ALI/ARDS. However, prompt diagnosis allows for the implementation of proper supportive care, which is generally the same as for any patient with ALI/ARDS. In addition, potentially harmful interventions, such as the administration of diuretics, should be avoided. In fact, patients with TRALI who are hypotensive may require intravenous fluids to maintain an adequate blood pressure.

If the patient is still being transfused when the diagnosis is first suspected, the transfusion should be stopped immediately. For mild cases, supplemental oxygen and routine supportive care may be sufficient. For severe cases, mechanical ventilation, intravenous fluids, invasive hemodynamic monitoring and vasopressors may be required. In rare cases, the hypoxemia resulting from TRALI can be so severe that extracorporeal oxygenation may be required as a temporizing measure while the lungs heal.[48,49] In patients who require mechanical ventilation, a low tidal volume strategy, as would be used in other cases of ALI/ARDS, should be employed.[39] While several case reports describe the treatment of TRALI with glucocorticoids, no randomized, controlled trials have studied this therapy in TRALI. Given the potential complications associated with glucocorticoids, and the typically self-limited course of TRALI, there is no clear role for glucocorticoids in the treatment of TRALI.

Prevention

Receipt of female plasma (including whole blood) is a strong risk factor and reduction of this risk factor in 2007–8 was concurrent with a decrease in TRALI incidence determined by active surveillance at two academic medical centers from year 2006 to 2009 from ~ 1:4,000 units to ~ 1:12,000 units.[8] The pre-mitigation incidence of ~1:4,000 units found in 2006 was close to the ~1:5,000 units found by a careful study at the Mayo Clinic where a transfusion team performed and monitored transfusions,[7] but ten-fold higher than the 2005 pre-mitigation incidence of ~1:40,000 units distributed found by passive surveillance (26.3 cases in 10^6 units).[50] Decreases in TRALI after conversion to male predominant plasma have been reported by passive surveillance studies from the UK,[51] the FDA,[1] and the American Red Cross.[52] Patient factors likely contributed to the decrease in incidence, e.g. institutional improvements in critical care delivery that reduce patient risk factors that appear to render patients susceptible to TRALI,[19] such as improving treatment of septic shock and decreasing high peak airway pressure >30 cm H_2O while being mechanically ventilated.

The American Association of Blood Banks recommended the reduction of the transfusion of plasma and platelets from probable high-risk donors.[53,54] The decrease in TRALI observed after implementation of such programs support the effectiveness of this approach. To further reduce TRALI risk in female plasma-rich components, clinical evidence support the suggested screening for strong anti-HLA-Class II in platelet donors [55] and the development of high-throughput GIFT methods to screen for known and unknown human neutrophil antigens.[8] In addition, reduction of modifiable patient risk factors should also reduce the risk for developing TRALI.

Acknowledgments

Abbreviations

anti-HLA-Class I	HLA class I antibody
anti-HLA-Class II	HLA class II antibody
anti-HNA	antibody to human neutrophil antigen
GIFT	granulocyte immunofluoresence test by flow cytometry for antibody to HNA
HNA	human neutrophil antigens
LysoPC	lysophosphatidylcholine
MFI	mean fluorescent intensity for specific HLA antibody determined by single antigen bead assay for anti-HLA antibody specificity
SAB	single antigen bead assay for HLA antibody specificity

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KEY POINTS

- Transfusion-related acute lung injury (TRALI), a form of acute lung injury (ALI) that develops shortly after blood product transfusion, is the leading cause of transfusion-related mortality.

- The development of TRALI is influenced by both transfusion-related and patient-related risk factors, which have now been identified.

- Diagnosis of TRALI requires a high index of suspicion, and is based upon the exclusion of cardiogenic pulmonary edema, sepsis from a bacteria-contaminated blood product, and other causes of acute lung injury.

- Treatment of TRALI is largely supportive and is similar to that of other forms of ALI.

- TRALI incidence can be reduced by reducing the transfusion of plasma from previously pregnant donors.

Table 1

Summary of NHLBI consensus working group definition of TRALI[4]

Development of ALI, defined as:[2]

- Acute onset

- Hypoxemia (PaO$_2$/FIO$_2$ Ratio   300 mm Hg)

- Bilateral pulmonary opacities on frontal chest radiograph

- Absence of left atrial hypertension (pulmonary artery occlusion pressure   18 mm Hg if measured).

In patients <u>without</u> other ALI risk factors:

- New onset of ALI during or within 6 hours after the end of transfusion of a plasma-containing blood product

In patients <u>with</u> other ALI risk factors:

- New onset of ALI during or within 6 hours after the end of transfusion of a plasma-containing blood product

- Clinical course suggestive of TRALI – the ALI is not attributable to the ALI risk factor, and the patient was clinically stable before transfusion

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Table 2

ALI Risk Factors (adapted from Toy et al, 2005[4])

- Septic shock
- Sepsis syndrome without hypotension
- Aspiration of gastric contents
- Near-drowning
- Disseminated intravascular coagulation
- Pulmonary contusion
- Pneumonia requiring ICU care
- Drug overdose requiring ICU care
- Fracture of long bones or pelvis
- Burn, any percent of body surface
- Cardiopulmonary bypass