Transfusion-related acute lung injury (TRALI): a clinical review with emphasis on the critically ill

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Summary

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related morbidity and mortality worldwide. Although first described in 1983, it took two decades to develop consensus definitions, which remain controversial. The pathogenesis of TRALI is related to the infusion of donor antibodies that recognize leucocyte antigens in the transfused host or the infusion of lipids and other biological response modifiers that accumulate during the storage or processing of blood components. TRALI appears to be the result of at least two sequential events and treatment is supportive. This review demonstrates that critically ill patients are more susceptible to TRALI and require special attention by critical care specialists, haematologists and transfusion medicine experts. Further research is required into TRALI and its pathogenesis so that transfusions are safer and administered appropriately. Avoidance including male-only transfusion practises, the use of leucoreduced components, fresher blood/blood components and solvent detergent plasma are also discussed.

Keywords: neutrophils, vascular endothelium, antibodies, lipid mediators, critically ill.

With the decrease of infectious transmission and bacterial contamination of transfused blood products, transfusion-related acute lung injury (TRALI) has become the leading cause of transfusion-related mortality reported by both the British Serious Hazards of Transfusion (SHOT) initiative and the US Food and Drug Administration (FDA 2009) which has garnered the attention of the transfusion medicine community. Simultaneously, the critical care and trauma communities have published multiple articles showing an independent, dose-dependent relationship between transfusion and the subsequent development of acute lung injury (ALI). Merging this literature, refining definitions and working together to educate clinicians and perform prospective trials in the area of TRALI is vital for future prevention. This review will synthesize these two bodies of literature and summarize the history, epidemiology, and pathogenesis of TRALI in the critically ill patient.

History

Non-cardiogenic pulmonary oedema shortly following transfusion was first described in the 1950’s (Barnard, 1951; Brittingham, 1957). In 1966 the first case series of TRALI described three patients who developed ALI during transfusion of whole blood (Philipps & Fleischner, 1966). This clinical syndrome was given many different names including hypersensitivity pulmonary oedema, allergic pulmonary oedema, incompatibility of undetermined nature and an anaphylactoid reaction (Philipps & Fleischner, 1966; Kernoff et al, 1972; Wolf & Canale, 1976).

Popovsky et al (1983) described five cases of non-cardiogenic pulmonary oedema after transfusion of packed red blood cells (PRBCs) or whole blood and gave the syndrome its current name, transfusion-related acute lung injury (TRALI). All five donors had leucoagglutinating and lymphocytotoxic antibodies in the serum and three of five recipients expressed the cognate antigens (Popovsky et al, 1983). This case series substantiated that a leucoagglutinating antibody may be aetiological in TRALI. This series also produced the first measure of TRALI incidence. These findings were confirmed in a series of 36 TRALI cases that included detailed clinical presentation data, prognosis, and incidence (Popovsky & Moore, 1985). Donor antibodies were present in the majority of cases, which led to a number of mechanistic studies that confirmed that antibodies could elicit TRALI (Popovsky & Moore, 1985). Though coined in 1983, the consensus definitions of TRALI were published two decades later and remain controversial.

Definitions

In 2004, the National Heart, Lung, and Blood Institute convened a working group to identify a common clinical definition to promote research in TRALI. The diagnosis must satisfy the criteria for ALI as summarized in Table I (Bernard et al, 1994). If an arterial blood gas measurement is not available, the diagnosis may be made if the criteria for ALI are met and there is a clinical syndrome consistent with acute lung injury (ALI). The diagnosis of TRALI should be considered if the donor is female, the recipient is male, and the transfusion is not the trigger for the ALI or if the recipient has a blood type that is not compatible with the donor. The diagnosis of TRALI should also be considered if the donor has been transfused within the past 60 days and the recipient has received a blood product that was compatible with the donor.

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available, oxygen saturations (SPO\textsubscript{2} ≤ 90\%) are considered to meet the acute hypoxaemia criterion when a patient is breathing room air at sea level. The use of oxygen saturation in the definition of TRALI is justified because an SPO\textsubscript{2} ≤ 90\% usually correlates with an arterial partial pressure of oxygen (PaO\textsubscript{2}) ≤ 60 mm Hg and therefore the PaO\textsubscript{2}/fraction of inspired oxygen (FiO\textsubscript{2}) ratio would be <300 mm Hg (60/0.21 = 286) (Toy et al., 2005).

In addition to meeting the standard criteria for ALI, TRALI requires additional criteria (Table II). A patient must (a) develop ALI during or within 6 h of transfusion and (b) no ALI may be present before transfusion. (c) If alternative ALI risk factors exist (Table III), TRALI can still be diagnosed if the clinical course of the patient suggests that ALI resulted mechanistically from the transfusion alone or a synergistic relationship between the transfusion and the underlying risk factor. If the temporal relationship between the transfusion and ALI (within 6 h) is considered coincidental to the factor. If the temporal relationship between the transfusion and the underlying risk factors exist (Table III), TRALI can still be diagnosed if the clinical course of the patient suggests that ALI resulted mechanistically from the transfusion alone or a synergistic relationship between the transfusion and the underlying risk factor.

<table>
<thead>
<tr>
<th>Table I. American-European Consensus definition of ALI (Bernard et al., 1994).</th>
<th>Timing</th>
<th>Acute onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxaemia</td>
<td>PaO\textsubscript{2}/FiO\textsubscript{2} ≤ 300 mm Hg regardless of PEEP</td>
<td>or</td>
</tr>
<tr>
<td>If arterial blood gas unavailable SPO\textsubscript{2} &lt; 90%</td>
<td>at sea level on room air</td>
<td></td>
</tr>
<tr>
<td>Chest Radiograph</td>
<td>Bilateral infiltrates on frontal chest radiograph</td>
<td></td>
</tr>
<tr>
<td>Permeability/Oedema</td>
<td>Pulmonary artery occlusion pressure ≤ 18 mm Hg</td>
<td>or</td>
</tr>
<tr>
<td>No clinical evidence of left atrial hypertension</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALI, acute lung injury; PEEP, positive end-expiratory pressure.

<table>
<thead>
<tr>
<th>Table II. National Heart Lung and Blood Institute (NHLBI) Consensus Conference Definition of TRALI (Toy et al., 2005).</th>
<th>a) Onset of signs or symptoms ≤ 6 h after transfusion</th>
<th>b) No ALI may be present prior to transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>c) Alternative ALI risk factors may be present, but the patients’ clinical course should determine whether the ALI is mechanistically related to the transfusion*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Helpful determinants (not required for diagnosis) for TRALI in patients with ALI include: transient leucopenia and antigen-antibody cross match between the donor and the recipient. (TR)ALI, (transfusion-related) acute lung injury.

<table>
<thead>
<tr>
<th>Table III. Risk factors for ALI in prospective studies (Fowler et al., 1983; Gong et al., 2005; Hudson et al., 1995; Pepe et al., 1982).</th>
<th>ALI Risk Factor</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary sepsis</td>
<td>Shock-35%, non-Shock-24%</td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td>15–36%</td>
<td></td>
</tr>
<tr>
<td>Multiple Transfusions</td>
<td>21–45%</td>
<td></td>
</tr>
<tr>
<td>Drug overdose in ICU</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Long Bone Fracture</td>
<td>5–11%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Contusion</td>
<td>17–22%</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary Bypass</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Burn</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

ALI, acute lung injury; ICU, intensive care unit.

In the intensive care unit (ICU), 37–44\% of patients receive blood products with the incidence rising to 85\% in patients remaining in the ICU ≥ 7 d (Vincent et al., 2002; Corwin et al., 2004). The incidence of TRALI in critically ill patients is estimated to be 8\%, the transfusion incidence approaches 40\%, and thus approximately 3\% of all ICU admissions will develop TRALI, indicating that critically ill patients are the most vulnerable patient population (Gajic et al., 2007a). Because ALI is so common in ICUs it is rarely recognized as TRALI despite multiple studies showing an independent, dose-dependent increase in ALI with transfused blood products when controlling for severity of illness and other known ALI risk factors (Gajic et al., 2004; Croce et al., 2005; Gong et al., 2005; Silverboard et al., 2005; Khan et al., 2007; Zilberberg et al., 2007; Chaiwat et al., 2009). In light of these studies and in response to the limitations of the consensus conference definition regarding timing of ALI in our critically ill patients, a 2008 review suggested expanding the definition of TRALI (Marik & Corwin, 2008). The term delayed TRALI syndrome describes ALI that develops 6–72 h after transfusion regardless of the presence or absence of pre-existing ALI risk factors. Unlike the consensus definition, delayed TRALI syndrome occurs in up to 25\% of critically ill patients receiving a blood transfusion, and is associated with a mortality approaching 40\% (Marik & Corwin, 2008). In addition, the risk of delayed TRALI syndrome rises with increasing numbers of transfused blood products (Marik & Corwin, 2008). It is unclear whether similar pathophysiological mechanisms apply, but an expanded clinical definition lays the groundwork for further clinical and mechanistic research in critically ill patients.

**Differential diagnosis**

The differential diagnosis for patients who develop respiratory distress during or after transfusion include: TRALI,
transfusion-associated circulatory overload (TACO), an anaphylactic transfusion reaction, and transfusion of contaminated (bacteria) blood products. Differentiating these four syndromes is often difficult due to similarities in their clinical presentation (Table IV).

TRALI is the acute onset of severe dyspnea, tachypnea, worsening or new hypoxaemia, fever, occasional hypotension and cyanosis that is temporally related to receiving transfused blood products (Popovsky & Moore, 1985). This clinical presentation is clearly recognizable in non-critically ill patients, with 72% eventually requiring mechanical ventilation. In contrast, in critically ill patients with other ALI risk factors such a presentation is common and therefore is rarely attributed to transfusion even when a clear temporal relationship exists. Differentiating TRALI (characterized by permeability oedema) from TACO (characterized by hydrostatic oedema) is difficult in critically ill patients, especially in the setting of massive transfusion and resuscitation. In the ICU, TACO has been reported to be three times more common than TRALI (Rana et al., 2006). Because pulmonary artery catheters lack clinical efficacy and are seldom used, hydrostatic oedema must be ruled out on clinical grounds. Potential laboratory tests differentiating TACO from TRALI include: (i) Undiluted oedema fluid obtained within 15 min of endotracheal intubation exhibiting an oedema fluid to plasma protein ratio of ≥0.6 suggests permeability oedema rather than hydrostatic pulmonary oedema (Ware & Matthay, 2005); (ii) The utility of the levels of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP) in differentiating TACO from TRALI is questionable though values at either extreme may aid in differentiating between these syndromes (Tobian et al., 2008; Li et al., 2009); (iii) Transient neutropenia may support the diagnosis of TRALI due to neutrophil sequestration in the lung, but it is not universal (Nakagawa & Toy, 2004).

Clinical factors differentiating TACO from TRALI include distended neck veins, S3 on cardiac examination and peripheral oedema consistent with volume overload. Acute onset hypertension suggests TACO while fever suggests TRALI (Skeate & Eastlund, 2007). A chest radiograph with septal lines, cephalealization and an enlarged vascular pedicle (>65 mm) are more consistent with TACO. Rapid resolution of pulmonary oedema with the institution of diuretics also strongly suggests TACO while a leucocyte antibody-antigen cross-match supports TRALI. Simple donor leucocyte antibody testing alone is unlikely to be clinically useful as 7–25% of donors are positive for leucocyte antibodies (Curtis & McFarland, 2006).

Anaphylactic transfusion reactions usually present with bronchospasm, resulting in tachypnea, wheezing, cyanosis, and severe hypotension. Facial and truncal erythema and oedema are also common, with urticaria over the head, neck, and trunk (Silliman & McLaughlin, 2006). The respiratory distress from anaphylactic transfusion reactions is related to laryngeal and bronchial oedema rather than pulmonary oedema so a chest radiograph will generally be clear. The transfusion of contaminated PRBCs or platelet concentrates may result in transfusion-related bacterial sepsis that manifests as fever, hypotension, and vascular collapse, and these patients may also experience ALI. Transfusion-related bacterial sepsis must be considered in transfused patients with pulmonary insufficiency and culturing the component bags is essential for diagnosis (Silliman & McLaughlin, 2006).

### Epidemiology

TRALI has been described with the infusion of most blood products including PRBCs (leucodepleted and non leucodepleted), fresh frozen plasma (multiparous and male donors), platelets (apheresed or random donor, whole blood-derived), and a few case reports of intravenous immunoglobulin (IVIG), cryoprecipitate, allogeneic bone marrow stem cells and transfused granulocytes (Reese et al., 1975; Rizk et al., 2001; Sachs & Bux, 2003; Urahama et al., 2003).

#### The incidence of TRALI is variable and underreported

The reported incidence of TRALI is extremely variable. In addition, the incidence of TRALI for different blood products is dependent on the inflammatory state and characteristics of the patient population studied. The majority of incidence studies predate the acceptance of consensus definitions and therefore used a variety of diagnostic criteria to define TRALI. In addition, these studies utilized different methods of surveillance (passive surveillance versus active case investigation versus prospective data collection) that may impact the accuracy of the data due to reporting bias. Geographic regions

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Table IV. The Clinical and Laboratory Findings Associated with TRALI.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>WBC</th>
<th>BP</th>
<th>Fever</th>
<th>Volume overload</th>
<th>Crackles on lung examination</th>
<th>Wheezing on lung examination</th>
<th>Pulmonary oedema on CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRALI</td>
<td>↓</td>
<td>↓</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>TACO</td>
<td>↔</td>
<td>↑</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>↓ or ↑</td>
<td>↓</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sepsis</td>
<td>↓ or ↑</td>
<td>↓</td>
<td>Yes</td>
<td>No</td>
<td>Possible</td>
<td>No</td>
<td>Possible</td>
</tr>
</tbody>
</table>

↑: increased, ↓: decreased, ↔: not affected.

TRALI, transfusion-related acute lung injury; TACO, transfusion associated circulatory overload; WBC, white blood cell count; BP, blood pressure; CXR, chest radiograph.
have different blood banking practises which may also influence the incidence of TRALI. Retrospective ‘look-back’ studies suggest that TRALI is grossly under-reported so the incidence reported in passive surveillance reports probably underestimates the true incidence, especially in the critically ill (Kopko et al., 2002; Kleinman et al., 2004).

**TRALI is common in critically ill patients**

The presence of multiple at-risk diagnoses, such as aspiration in conjunction with sepsis, is associated with an increased susceptibility to develop ALI (Table III) (Pepe et al., 1982; Fowler et al., 1983; Hudson et al., 1995). Similarly, transfusion is an independent risk factor for the subsequent development of ALI in patients with pre-existing non-transfusion related ALI risk factors (Hudson et al., 1995; Gajic et al., 2004; Croce et al., 2005; Gong et al., 2005; Silverboard et al., 2005; Chaiwat et al., 2009). Incidence comparisons in these patient populations suggest that transfusion acts synergistically with other diagnoses that predispose patients to ALI. Furthermore, patients with established ALI have a dose-dependent increase in mortality with each subsequent unit of transfused blood product (Gong et al., 2005). These observations were substantiated by a 2-year prospective study of consecutively transfused critically ill medical ICU patients that reported an overall TRALI incidence of 8%. The subgroup of patients with pre-existing ALI risk factors had the greatest risk of TRALI; moreover, an additional 11.6% of patients had worsening of their existing ALI after transfused blood products (Gajic et al., 2007a).

Critically ill patients have the highest incidence of TRALI, suggesting that patient-specific risk factors are very important in the pathogenesis. Because of under reporting, prospective observational studies that follow transfused patients for the subsequent development of TRALI are the best study design to determine the incidence. Unfortunately, prospective studies are lacking in most patient populations. The largest prospective trial to date enrolled 901 consecutively transfused medical ICU patients over a 2-year period (Gajic et al., 2007a). 8% (74/901) of these patients developed TRALI, resulting in an incidence of 1 in 12 patients as compared to the 1 in 317 units, respectively. In this same study the incidence of TRALI from FFP was 1/19 411 units, but has been reported at 1/7900 units in a single centre in the United Kingdom (Wallis et al., 2003). In contrast to the Canadian single centre study (Silliman et al., 2003a), where TRALI from FFP was less common than from red blood cells, in the UK study (Wallis et al., 2003), 10/11 cases of TRALI seen over a 12-year period were temporally and mechanistically attributed to FFP. A report from the Red Cross TRALI surveillance system implicates FFP as the aetiopathological agent in 75% of cases and 63% of deaths from TRALI (Eder et al., 2007). An examination of reported TRALI fatalities to the United States FDA between 1997–2002 implicated FFP in 50% of the 58 deaths reported (Holness et al., 2004).

In critically ill patients, epidemiological studies reporting an association between massive transfusion and the development of ARDS failed to control for FFP, which is universally administered as part of a massive transfusion protocol (Pepe et al., 1982; Fowler et al., 1983; Hudson et al., 1995). More recently, FFP administration has emerged as an independent risk factor for TRALI in both trauma, medical and surgical ICU populations (Gajic et al., 2004, 2007a,b; Khan et al., 2007; Sadis et al., 2007; Chaiwat et al., 2009). In most of these studies, plasma containing blood products (FFP), not PRBCs, were associated with TRALI (Gajic et al., 2004, 2007a; Rana et al., 2006; Khan et al., 2007; Sadis et al., 2007). Only recently have studies begun to sort out the risk of ALI and TRALI (ALI within 6 h) with the transfusion of plasma-containing blood products as opposed to red blood cells in critically ill patients.

**Transfusion increases mortality in patients with existing ALI**

Mortality rates vary based on the patient population studied. In single centre studies TRALI-associated mortality was 6–13% (Popovsky & Moore, 1985; Popovsky & Haley, 2000). National reporting systems probably over-estimate the mortality rate in the general population due to reporting bias for cases resulting in death. Haemovigilance data from Great Britain (SHOT), Quebec, and France reported a TRALI mortality rate of 9%;
Pathophysiology

We refer the reader to two excellent reviews for details regarding TRALI pathogenesis. One was recently published in this journal (Bux & Sachs, 2007) and the other was written by one of the authors of this review (Silliman & McLaughlin, 2006) (Fig 1). In this review, we will give a brief overview of the current pathophysiological understanding of TRALI and speculate on how epidemiological observations in TRALI and transfusion-associated ALI in critically ill patients may be described by our current mechanistic understanding.

The two-event model

Multiple animal studies and histological data from humans with TRALI support the following chain of events. First, the pulmonary vascular endothelium is activated (pro-inflammatory) resulting in priming (adherence) of neutrophils by one or more endogenous stimuli (i.e. sepsis, surgery), which are considered the ‘first event’. These primed, sequestered neutrophils are hyper-reactive in that agents that do not normally activate polymorphonuclear leukocytes (PMNs) cause release of the microbicidal arsenal (Silliman & McLaughlin, 2006). A second event, the transfusion of antibodies to leucocyte antigens or the infusion of bioactive lipids, soluble CD40 ligand (sCD40L), etc., results in activation and neutrophil-mediated cytotoxicity of the vascular endothelium resulting in capillary leak and ALI (Silliman & McLaughlin, 2006; Sachs, 2007). However, in rare situations, a ‘first event’ is not required because certain antibody-antigen interactions from blood products alone appear to induce neutrophilic lung injury. In the more common scenario, neutrophils are repeatedly primed so that they eventually reach a threshold where a second hit (transfusion) results in neutrophil activation and the destruction of the vascular endothelium leading to capillary leak (Silliman, 2006; Bux & Sachs, 2007). Neutrophilic lung injury can also occur independent of neutrophil priming when endogenous stimuli activate the pulmonary vascular endothelium, which leads to neutrophil trapping and subsequent activation (Silliman, 2006; Bux & Sachs, 2007). The interplay between neutrophil priming, trapping and activation with endothelial cell activation is probably dependent on the particular mechanism involved (antibody-antigen complex versus bioactive lipid activation versus sepsis versus other) but all pathways result in the same downstream event, neutrophilic lung injury (Silliman, 2006; Bux & Sachs, 2007). In the ‘two-event model’ of TRALI the first hit probably represents a threshold effect whereby more stimulus through similar or different mechanisms work through an additive or synergistic mechanism to bring neutrophils closer to subsequent activation and resulting lung injury (Silliman, 2006; Bux & Sachs, 2007). This is supported by the clinical observations that patients with different first hit ALI risk factors have very different risks of developing TRALI (Popovsky & Moore, 1985; Gajic et al, 2007a). It is also likely that continued stimulus in the face of existing lung injury potentiates neutrophilic sequestration, invasion, and resulting pulmonary tissue damage leading to worse outcomes. Multiple animal studies show that when lipopolysaccharide (LPS) or tumour necrosis factor-α (TNFα) are used to activate the pulmonary endothelium eliciting priming and sequestration of neutrophils, subsequent transfusion of biological mediators in blood products activate neutrophils and lead to the development of TRALI (Silliman et al, 1998, 2003b). All mediators implicated...
in TRALI, including lipids, other biological response modifiers, and antibodies, can be explained by the two-event mechanism (Silliman & McLaughlin, 2006; Bux & Sachs, 2007).

**Epidemiological support for a two-event mechanism in ALI and TRALI**

Multiple disease processes causing systemic inflammation are capable of activating the vascular endothelium and inducing adherence of PMNs with subsequent neutrophil activation and ALI. A broad range of substances exist in blood products that are capable of priming or activating primed neutrophils directly. Priming substances found in blood products include antibodies to human neutrophil antigens, HLA type I and HLA type II antigens, bioactive lipids, and sCD40L. Some antibody-antigen interactions can prime and activate neutrophils de novo through a variety of potential mechanisms, but more commonly a patient requires pre-primed neutrophils or activated endothelial cells that are subsequently activated by one or more of the above substances. The higher incidence of TRALI in ICU patients 8% vs. 0.16% in a mixed population of hospitalized patients may be related to the observation that the neutrophils in these patients have a greater degree of priming and are closer to the threshold of activation as compared to other patient populations (Popovsky & Moore, 1985; Gajic et al., 2007a). Alternatively these patients could have activated endothelium for similar reasons. Though antibodies are present in the majority of TRALI cases, they are also present in 17% of randomly selected donors (Middelburg et al., 2008). Probability calculations suggest and look back studies confirm that antibody-antigen interactions occur commonly in transfused patients who never develop TRALI, supporting that a first hit from inflammatory stimuli makes the antibody-antigen interaction more likely to result in neutrophil activation and resulting lung injury. Look-back studies have shown that the majority of patients transfused with blood products that contain antibodies do not develop TRALI even if their leucocytes contain the cognate antigen (Van Buren et al., 1990; Kopko et al., 2002; Nicolle et al., 2004; Toy et al., 2004). In the original series of 36 patients, 89% had donor antibodies implicated, but 86% (31/36) of the cohort had an operation within 48 h, a known neutrophil priming stimulus (Popovsky & Moore, 1985; Silliman, 2006). Of the 195 TRALI cases reported between 1996 and 2006 to the British SHOT haemovigilance scheme, 40.5% of these patients had surgery or sepsis as reported reasons for transfusion (Chapman et al., 2009). In a case comparison of 10 TRALI patients to 10 patients with urticarial or febrile transfusion reactions, neutrophil priming was found to be significantly greater in the pre-transfusion sera in TRALI patients. All of the TRALI patients had an antecedent first insult (sepsis, surgery, massive transfusion, cytokine administration) compared with only 2/10 in the non-TRALI transfusion reaction group (Silliman et al., 1997).

**Leucoreduction and TRALI risk**

Residual leucocytes contaminating stored PRBCs can theoretically potentiate TRALI by increasing the amount of lipids and inflammatory cytokines (interleukin [IL]-6, IL-8, TNF-α) that accumulate during storage (Kristiansson et al., 1996; Silliman et al., 1997). These substances may act as a second hit when transfused into a patient with endothelial activation and/or primed neutrophils resulting in TRALI (Silliman et al., 1997, 1998; Luk et al., 2003). Unfortunately, in vitro and in vivo data do not support a decrease neutrophil priming activity or TRALI risk with leucoreduction (Biffil et al., 2001; Silliman et al., 2003b). One retrospective study showed a significant difference in TRALI reports before and after leucoreduction (Yazer et al., 2004). Unfortunately, no benefit was shown in a large (n = 14 786) Canadian pre-leucoreduction versus post-leucoreduction retrospective cohort study in the need for mechanical ventilation (10.1% vs. 9.6%, adjusted odds ratio 0.97, P = 0.63) (Hebert et al., 2003). Because 72% of patients with TRALI require mechanical ventilation it is reasonable to conclude that the TRALI incidence was unchanged by leucoreduction in this study. Similarly, there was no decrease in the development of ALI with leucoreduction in a double blind randomized controlled trial performed in 268 injured patients requiring blood transfusion within 24 h of injury (Watkins et al., 2008). Another randomized controlled trial of 2780 patients revealed no benefit to leucoreduction with respect to hospital mortality, length of stay or any other secondary end point. However, the development of TRALI was not specifically reported in this study (Dzik et al., 2002). In summary, pre-storage leucoreduction may reduce the accumulation of some of the biologically active components associated with storage, but does not seem to significantly alter TRALI risk.

**Age of blood and TRALI risk**

Storage of RBCs results in a number of morphological and biochemical alterations known as the RBC storage lesion. During routine storage of cellular components, a mixture of neutrophil priming substances, such as lysophosphatidylcholines, accumulate. These substances can prime and activate neutrophils, cause endothelial cell activation and alter permeability in the alveolar capillary membrane (Silliman et al., 1994, 1996, 1997, 2003b). The use of fresher blood products has been postulated to decrease the deleterious effects from prolonged storage in high risk patients. For example, the use of PRBCs <14 d old and platelet concentrates <2 d old may prevent the development of neutrophil priming activity in blood (Silliman et al., 1994, 1996). Multiple epidemiological studies have shown an association between increasing age of red blood cells and increased mortality in trauma, medical, and surgical ICU patients (Purdy et al., 1997; Zallen et al., 1999; Basran et al., 2006; Koch et al., 2008). Age of blood was shown to be an independent
risk factor for mortality in trauma after the institution of leucoreduction (Weinberg et al, 2008a,b). In critically ill and post-surgical patients, storage duration has also been associated with increased nosocomial infection risk (Vamvakas & Carven, 1999; Leal-Noval et al, 2003; Koch et al, 2008). However, until the data from prospective clinical trials are available the effect of storage duration on TRALI risk and outcome is undefined.

Multiparity and TRALI risk

The majority of severe TRALI cases are associated with alloantibodies to leucocytes (Popovsky & Moore, 1985; Popovsky & Haley, 2000; Kopko et al, 2001; Lydaki et al, 2005; Eder et al, 2007; Win et al, 2007). Due to the increased incidence of antibodies in female donor plasma and the specificities of these common antibodies, it is feasible that as many as 1 in 25 units from female donors could cause an antibody-antigen reaction in a random recipient. The probability would obviously change depending on the parity of the donor. The frequency of antibodies in plasma-containing blood products increases in multiparous donors as a result of multiple exposures to paternal antigens from the fetus during pregnancy. A large prospective study of 8171 volunteer blood donors in the United States revealed a 17.3% prevalence of HLA antibody presence in female donors. The prevalence increased with number of pregnancies: 1.7% (zero), 11.2% (one), 22.5% (two), 27.5% (three) and 32.2% (four or more) (Triulzi et al, 2009). These values are strikingly similar to prospective data collected in 332 platelet pheresis donors a decade ago (Densmore et al, 1999). In a separate study, 39.7% of females reporting three or more pregnancies had antibodies to either HLA class I, HLA class II or granulocytes (Sachs et al, 2008). Therefore, multiparity is associated with an increase in antibodies in donated blood products.

Several studies have examined the clinical significance of multiparity on the risk of developing TRALI. The British SHOT initiative reported that from 1999–2005, there were 49 cases in which FFP or platelets from female donors were implicated in TRALI and the implementation of male-only, a surrogate for antibody negative, plasma transfusion strategies have decreased fatal TRALI although these antibody-mediated TRALI reactions were in the critically ill (Chapman et al, 2009). In a review of reported TRALI fatalities to the American Red Cross, female donors with leucocyte antibodies were identified in 75% of fatal TRALI cases involving FFP administration (Eder et al, 2007). The Dutch reported a significant decrease in TRALI a year after male-only plasma administration (Vlaar et al, 2008). Lastly, TRALI incidence decreased from 36% to 21% [CI 0.16–0.90], P = 0.04) at a single centre in patients undergoing repair of a ruptured abdominal aeurysm after removal of females from the donor pool (Wright et al, 2008).

The clinical effects of multiparous plasma in critically ill patients was also studied in a prospective, randomized, crossover trial (Palfi et al, 2001). Critically ill patients (n = 105) judged to require at least 2 units of plasma, received a unit of plasma from a multiparous woman (≥3 live births) and, 4 h later, a unit of control plasma, or vice versa. Transfusion of plasma from multiparous women was associated with significantly lower post transfusion oxygen saturation and higher TNF-α concentrations. Another retrospective case-control study of 3567 critically ill patients compared oxygenation (PaO2/FiO2 ratio) change after receipt of male versus female donor high volume plasma containing blood products. Groups were well matched for baseline characteristics and presence of other ALI risk factors. For patients receiving female plasma there was a significant drop in PaO2/FiO2 ratio (−52 mm Hg) but, similar to the previous study, there was no increase in the development of TRALI (Palfi et al, 2001; Gajic et al, 2007b).

The United Kingdom started antibody-negative (male-only) plasma transfusion protocols in July, 2003, the Dutch in October, 2006, and many blood banks in the United States followed suit (Chapman et al, 2009), Eder et al, 2007; Vlaar et al, 2008). Though there is mechanistic plausibility and epidemiological support to remove multiparous females from the donor pool for the creation of plasma containing blood products, there has not been a randomized controlled trial with appropriate outcome variables (TRALI, mortality) to support this practise. Leucoreduction offers similar mechanistic and epidemiological rationale, but did not reduce TRALI incidence in prospective trials. In addition, eliminating multiparous female donors from the donor pool for plasma containing blood products (FFP and platelets) would result in the loss of approximately 30% of donors with a larger loss of platelet donors (Densmore et al, 1999; Webert & Blajchman, 2003; Eder et al, 2007). It is unclear how to balance the current data implicating multiparous donors in TRALI with the potential shortages in plasma containing blood products created by eliminating multiparous females or all females from the donor pool. Though many countries and blood banks have eliminated females from the plasma donor pool and shown differences in before and after TRALI incidence reports, a least one prospective randomized controlled trial is needed to justify this action before it becomes universal.

Management

Figure 2 shows an algorithm for diagnosis and management of TRALI. When TRALI is diagnosed the management is similar to the management of ALI from other causes. This includes supportive care including optimization of mechanical ventilator parameters to avoid further injuring the lung while making sure the patient does not become intravascularly fluid overloaded (Wheeler & Bernard, 2007). Daily awakenings from sedation timed with a breathing trial to assess for extubation decreases time on mechanical ventilation and improves outcomes (Girard et al, 2008). A restrictive transfusion strategy should be employed as transfusions in patients with existing ALI worsen outcome (Gong et al, 2005). In patients with unresolved TRALI
or with other ALI risk factors (i.e. ongoing sepsis) consideration should be given to using washed PRBCs and male only plasma-containing blood products for future transfusions with the rationale that removing all potential biological mediators and antibodies may prevent further worsening of lung injury in these vulnerable hosts. It should be noted that this recommendation is not evidence based, but instead is based on good pathophysiological rationale.

**Prevention and future directions**

When a patient is diagnosed with TRALI, the donor and recipient’s blood serum should be analysed for a leucocyte antigen-antibody match. The recommendations from the 2008 International Society of Blood Transfusion meeting stress that HLA class I, HLA class II and human neutrophil antibody testing be done with established validated techniques (Bierling et al, 2009). In addition, HLA class I antibody detection should be restricted to antibodies clinically relevant for TRALI. When multiple blood products are implicated, this process can be time intensive and expensive. If a donor or donors are found to have leucocyte antibodies matching the recipient’s antigens, most blood banks recall and discard current plasma containing blood products from the implicated donor and exclude future donation. Look-back studies of recipients of an implicated donor’s blood product with known antibodies have revealed conflicting results, questioning whether donor elimination is warranted. In one study, 103 patients receiving plasma-rich blood product from a donor with multiple common HLA antibodies were analysed for TRALI (Toy et al, 2004). None of the patients developed TRALI even though 98% of the patients with known HLA types (54/55) had 1–5 corresponding HLA antigens. Other look-back studies have shown TRALI risk to be higher in patients receiving plasma products from a donor with implicated antibodies, although a majority of the patients transfused did not develop TRALI (Kopko et al, 2002). Because 17% of randomly selected donors contain leucocyte antibodies, vigilant reporting or donor exclusion based on antibody testing may significantly decrease the plasma donor pool with unclear benefit (Bray et al, 2004; Middelburg et al, 2008). Considering the high incidence of TRALI in critically ill patients a vigilant reporting strategy would require a significant amount of resource utilization to test all implicated blood products and perform the necessary donor follow-up when an antibody-antigen cross match is confirmed (Kopko et al, 2002; Wallis, 2003; Kram & Loer, 2005).

The first step in preventing TRALI and other transfusion-related complications is education and enforcement of the appropriate use of blood products. In the critically ill, two randomized controlled trials have reported a decrease in the development of ALI by decreasing red blood cell transfusions. Furthermore, a prospective randomized controlled trial in non bleeding critically ill patients compared a restrictive transfusion strategy with target haemoglobin 70–90 g/l to a more liberal transfusion strategy targeting haemoglobin of 100–120 g/l. Patients in the restrictive group received less red blood cells.

Fig 2. The Diagnosis and Management of transfusion-related acute lung injury (TRALI). In a patient who developed acute lung injury (ALI) within 6 h of transfusion other aetiologies of pulmonary oedema must be ruled out, especially volume overload (transfusion-associated circulatory overload, TACO). If there are other risk factors for ALI present then a clinical determination of the role of the transfusion must be determined and if transfusion is thought to be aetiological then the observed ALI is TRALI. Antigen-antibody testing is completed to aid in confirmation and if positive, then the donor is excluded from future plasma donations. If negative, the observed TRALI is probably due to other agents including lipids or sCD40L and testing for these agents may currently be done in Denver or Brisbane. Management of TRALI involves supportive care and ventilation with low tidal volumes (Vt). Further transfusions should be minimized, a restrictive transfusion policy, and washing of cellular blood products to remove antibodies and other biological response modifiers should be considered. BNP, B-type natriuretic peptide; CXR, chest X-ray; PRBCs, packed red blood cells.
and showed a decrease in red cell transfusions and a concomitant decrease in ALI (16% vs. 4%, P = 0.03) in the FVIIa group (Boffard et al, 2005). In critically ill patients, transfusion of red blood cells rarely improves oxygen utilization, plasma is often used outside of guideline recommendations, restrictive transfusion strategies improve outcomes, and these patients are at risk to develop TRALI. Physician education is required to adopt a restrictive transfusion policy in these patients.

Restricting FFP administration may have a potential larger benefit because FFP is used inappropriately in 45% of hospitalized patients and 47-6% of critically ill patients (Luk et al, 2002; Lauzier et al, 2007). Even guideline-induced use lacks level I evidence in many instances as there is evidence to suggest that FFP administration in bleeding patients with liver disease or before minor procedures to correct the International Normalized Ratio (INR) is not beneficial (Wallis & Dzik, 2004; Dara et al, 2005; Holland & Sarode, 2006; Lauzier et al, 2007; Verghese, 2008; Tripodi, 2009). Prospective examination of FFP correction of mild coagulation abnormalities demonstrated that the INR normalized in only 0.8% of the patients and decreased by at least 50% in only 15% of patients (Abdel-Wahab et al, 2006). FFP and other high plasma-containing blood products (platelets) contain more antibodies than red cell products and are more commonly implicated in severe TRALI cases. Therefore, prospective randomized controlled trials are needed to examine different FFP transfusion strategies in critically ill patients.

Alternative strategies to reduce TRALI include washing cellular components to remove the biologically active mediators, including antibodies, associated with TRALI (Silliman & McLaughlin, 2006). This strategy could be deployed for patients prior to major surgical procedures and those with a predicted need for ongoing blood transfusion (i.e. gastrointestinal bleeding, thermal injuries and septic shock). Unfortunately, washing cells a priori for use in emergent situations may reduce the product quality and shelf life of the blood product (Mair et al, 2006). Another alternative is solvent-detergent (S/D) treated plasma (Octaplas®) which dilutes or eliminates anti-lycocyte antibodies during the manufacturing process and, to date, neither antibodies to granulocyte-specific antigens nor to HLA class I and class II antigens have been identified (Sinnott et al, 2004; Sachs et al, 2005). More than 13 million units of S/D FFP have been used and no cases of TRALI have been reported (Flesland, 2007; Sachs, 2007). Concern remains about the theoretic risk of infectious complications because solvent/detergent-treated plasma (SDP) is made from the pooled plasma from thousands of donors and its efficacy compared to FFP has not been studied in a large, prospective clinical trial to substantiate its efficacy.

Conclusions

In summary, TRALI is a potentially fatal complication of blood transfusion. The mechanism is usually multifactorial due to both transfusion- and patient-specific risk factors. Epidemiological evidence suggests that TRALI is very common (8%) in the ICU because critically ill patients are more frequently transfused and often have activated endothelium and primed neutrophils (Gajic et al, 2007a). The critically ill are less frequently included in the TRALI literature because these patients often have other disease processes that can cause ALI in absence of transfusion. Due to a higher incidence of TRALI in critically ill patients, prospective randomized controlled trials in this patient population are feasible and can effectively evaluate current and novel transfusion strategies aimed at decreasing TRALI incidence. Because critically ill patients seem to have both an early and delayed TRALI syndrome, the transfusion and critical care communities should consider expanded definitions for critically ill patients (Marik & Corwin, 2008). These different stages of TRALI could be validated with mechanistic studies that reveal different pathophysiological factors. Lastly, we need to increase awareness of the deleterious effects of TRALI throughout the critical care community. Currently, a restricted red blood cell transfusion approach is recommended in the ICU, but more dangerous plasma-containing blood products, such as FFP, are often used inappropriately (Lauzier et al, 2007). Philosophically, we should treat blood products like pharmaceuticals with continued refinement of the product in response to common and deadly side effects and perform large multicentre trials to show efficacy.

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