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ORIGINAL PAPER

Transfusion-Related Acute Lung Injury (TRALI): Current Clinical and Pathophysiologic Considerations

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Abstract Transfusion-related acute lung injury (TRALI) is a rare transfusion reaction presenting as respiratory distress during or after transfusion of blood products. TRALI varies in severity, and mortality is not uncommon. TRALI reactions have equal gender distributions and can occur in all age groups. All blood products, except albumin, have been implicated in TRALI reactions. TRALI presents as acute respiratory compromise occurring in temporal proximity to a transfusion of a blood product. Other causes of acute lung injury should be excluded in order to definitively diagnose TRALI. Clinically and pathologically, TRALI mimics acute respiratory distress syndrome (ARDS), with neutrophil-derived inflammatory chemokines and cytokines believed to be involved in the pathogenesis of both entities. Anti-HLA and anti-neutrophil antibodies have been implicated in some cases of TRALI. Treatment for TRALI is supportive; prevention is important. It is suspected that TRALI is both underdiagnosed and underreported. One of the difficulties in the evaluation of potential TRALI reactions is, until recently, the lack of diagnostic criteria. A group of transfusion medicine experts, the American–European Consensus Conference (AECC), recently met and developed diagnostic criteria of TRALI, as well as recommendations for management of donors to prevent future TRALI reactions. In light of the AECC consensus recommendations, we report an incident of TRALI in an oncology patient as an example of the potential severity of the lung disease and the clinical and laboratory evaluation of the patient. We also review the literature on this important complication of blood transfusion that internists may encounter.

Keywords TRALI · Transfusion reaction · Leukocyte · Pulmonary injury

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Background

Since the first human-to-human blood transfusion in 1818, complications related to blood transfusion have been recognized as a cause of significant morbidity and mortality for some patients [11]. Transfusion-related acute lung injury (TRALI) is one potentially serious complication.

The first report of what was later recognized as TRALI was published in 1951. Barnard [2] reported a case of a transfusion reaction associated with the development of pulmonary edema leading to respiratory failure and death. In 1968, Ward et al. [65] described a pulmonary-hypersensitivity transfusion reaction and made the first association of this process with high titers of anti-leukocyte antibody. In 1983, Popovsky et al. [40] reported five cases of similar episodes of acute lung injury occurring after transfusions and popularized the term TRALI. Although awareness of TRALI has increased, the pathogenic mechanism in some patients is still poorly understood, and its occurrence is likely underreported [20]. We report an incident of TRALI as an example of this potentially serious transfusion reaction, with the intent of increasing the awareness and understanding of TRALI.

Case Report

A 44-year-old female with melanoma and pulmonary metastases underwent two cycles of biochemotherapy with cisplatin, dacarbazine, vinblastine, interleukin-2, and interferon-α. On admission for a third cycle of therapy, her hemoglobin was 7.4 g/dl. Chemotherapeutic agents were administered per protocol and the interleukin-2 was withheld. Infusion of chemotherapy was followed by transfusion of two units of leukoreduced packed red blood cells (RBCs). The patient tolerated the first unit well. The second unit was transfused immediately following the first. She developed shortness of breath at the end of the second unit. Vital signs at the time of the reaction included a temperature of 101.3°F, a pulse of 140 beats per minute, blood pressure of 190/120 mm Hg, and an oxygen saturation of 76% (as measured by pulse oximetry). Auscultation revealed crackles in the lower two-thirds of both lung fields. The patient was placed on 60%–80% O_2, which increased her oxygen saturation to 80%–90%. She was given furosemide and diphenhydramine without improvement in pulmonary function. An arterial blood gas obtained at this time showed pH 7.34, pCO_2 29 mmHg, pO_2 58 mmHg, $CO_2$16 mmol/L, and an O_2 saturation of 88%.

The patient was emergently intubated. Subsequent blood gas obtained on an FiO_2 of 100% was pH 7.17, pCO_2 43 mmHg, pO_2 76 mmHg, CO_2 16 mmol/L, and O_2 saturation 90%. Pressors were also required to maintain the patient's blood pressure. A chest radiograph revealed diffuse pulmonary infiltrates without cardiomegaly. A pulmonary artery catheter showed a pulmonary artery pressure of 34/15 mmHg (normal range = 15–30/4–12 mmHg), pulmonary capillary wedge pressure of 14 mmHg (normal range = 2–10 mmHg), central venous pressure of 16 mmHg (normal range = 8–12 mmHg), cardiac index of 4.31 L/min/m^2 (normal range = 2.6–4.2 L/min/m^2), and a systemic vascular resistance of 444 dyn/s/cm (normal range = 700–1600 dyn/s/cm). These values suggested possible mild fluid overload without evidence of shock; a transfusion reaction could not be ruled out. The patient received empiric vancomycin and cefepime. Acidosis and hypotension worsened and, despite aggressive treatment, the patient expired 24 hours after infusion of the second unit of RBCs.

A transfusion reaction workup revealed no evidence of serologic incompatibility by clerical reevaluation. There was no evidence of intravascular hemolysis as demonstrated by visual evaluation of the plasma. Post-transfusion, the hemoglobin was 10.4 g/dl, the total serum bilirubin was 0.2 mg/dl, and the urinalysis demonstrated clear urine without bilirubin and 7 RBC/high power field. The pre- and post direct antiglobulin tests were both negative for the presence of antibody on the patient's RBCs. Culture of the blood product and the patient's blood did not grow bacteria.

Serologic workup of the donors of the RBCs was performed to evaluate a presumptive diagnosis of TRALI. Testing for anti-HLA or anti-neutrophil antibodies in the donors of the RBC units showed a positive HLA antibody screen using an ELISA method in a sample from the second donor. Confirmatory testing, using a monoclonal antibody immobilization of granulocyte antigens (MAIGA) assay, demonstrated anti-HLA-A2 antibody specificity. No anti-neutrophil antibodies were identified in the second donor. The donor of the first unit and the recipient subsequently tested negative for anti-neutrophil and anti-HLA antibodies using neutrophil agglutination and HLA antibody ELISA screening tests. Antigen testing on the deceased transfusion recipient was not performed.

Epidemiology

The diagnosis of TRALI is clinical, frequently unsuspected, and therefore often missed. The underrecognition of TRALI was demonstrated by Kopko et al. [21] who retrospectively identified 11 patients with symptoms of TRALI that occurred after receiving transfusions from one donor implicated in a fatal case involving an anti-neutrophil antibody. Only two of the 11 other identified ''look-back'' cases with reactions had been reported and were attributed to a blood transfusion [21]. Two other look-back studies, however, failed to identify additional cases of TRALI involving a previously implicated donor [59, 68]. The recent study by Toy et al. [59] did not identify additional TRALI cases in a look-back of 103 patients when multiple anti-HLA class I and II antibodies where present in the donor.

The risk of developing TRALI is estimated at 0.02% per unit of blood product transfused, or 0.16% per transfused patient [40]. Implicated blood components include RBCs [28, 40], whole blood [40], fresh frozen plasma [29], cryoprecipitate [44], platelets [43], granulocytes [58], immune globulin [5, 45], and stem cells [61]. Albumin has not been associated with TRALI [37].

TRALI accounts for 8% of all adverse transfusion reactions [66] and 13% of all transfusion-related fatalities. It is at least the third most common cause of transfusion-related death [70], and the most common cause of transfusion-related death in some single-institution studies [64]. Overall mortality is 5%–10%. Recurrent TRALI appears to be rare [12, 57, 67], although we have recently observed a case of recurrent TRALI at our institution. TRALI has an equal male-to-female distribution and predominantly oc-

Table 1 Criteria for the diagnosis of TRALI: AECC recommendations [19]

TRALI	Possible TRALI
1. Acute lung injury as evidenced by: A. Acute onset of signs/symptoms. B. Hypoxemia: $PaO_2/FiO_2 < 300$ or $SpO_2 < 90\%$ on room air OR other clinical evidence of hypoxemia. C. Bilateral infiltrates on chest radiography without cardiomegaly D. No clinical evidence of left atrial hypertension.	1. Acute lung injury. A. Acute onset of signs/symptoms. B. Hypoxemia: $PaO_2/FiO_2 < 300$ or $SpO_2 < 90\%$ on room air OR other clinical evidence of hypoxemia. C. Bilateral infiltrates on chest radiography.
2. No preexisting acute lung injury before transfusion.	2. No preexisting acute lung injury before transfusion.
3. Evidence of lung function compromise during or within 6 h of transfusion.	3. Evidence of lung function compromise during or within 6 h of transfusion.
4. No temporal relationship to an alternative risk factor for acute lung injury (circulatory fluid overload, atrial fibrillation, etc.)	4. Other etiology for lung injury possible based upon temporal association.

curs in adults. It is rarely reported in infants and children [10, 23]. The mean age at diagnosis is 54 years, and the mean age for fatal cases of TRALI is 58 years [38].

Clinical Manifestations

TRALI is characterized by sudden onset of respiratory distress in patients receiving a transfusion of blood products. Symptoms typically develop within 1–6 hours after initiation of the transfusion and may include sudden onset of dyspnea and tachypnea. These symptoms are associated with findings of hypoxemia with arterial oxygen tensions typically in the range of 30–50 torr [28]. In most studies, 100% of patients required oxygen support with up to 72% requiring mechanical ventilation [39]. TRALI may also be associated with fever and either hypotension or hypertension. TRALI typically resolves within 48–96 hours of onset, with 17% of patients demonstrating pulmonary infiltrates persisting more than seven days [39]. In nonfatal cases there is little evidence of chronic lung disease or other long-term sequelae resulting from TRALI.

Because acute respiratory distress is a nonspecific finding, TRALI is a diagnosis of exclusion. Other processes, such as anaphylactic reaction, cardiogenic pulmonary edema, acute respiratory distress syndrome (ARDS), and bacterial contamination, must be excluded. Chest radiography in TRALI usually demonstrates bilateral pulmonary edema without cardiomegaly. Infiltrates may initially appear only in the lower lung fields, but over several hours can involve the entire lung [38]. Hemodynamic monitoring differentiates TRALI from cardiogenic pulmonary edema. Normal to low pulmonary wedge pressure with normal central venous pressure is characteristic in TRALI. Other findings may include a significant decrease in albumin, transient leukopenia [25], leukocytosis [64], neutropenia [32], or significant monocytopenia [8].

In 2004 an American–European Consensus Conference (AECC) was held to discuss and standardize the diagnosis of TRALI. The published conference proceedings included recommended clinical criteria for diagnosis of TRALI [19] (Table 1).

Histopathology

Histologic changes in the lung in TRALI are characterized by diffuse alveolar damage. Diffuse alveolar damage is a nonspecific finding that occurs in numerous disease processes including infection, drug-related lung injury, collagen vascular disease, vasculitis, inhalant injury, shock, sepsis, and radiation injury. Early findings include capillary congestion with endothelial cell swelling and minimal eosinophilic alveolar fluid. When a homogeneous ground glass appearance is noted on chest radiograph, corresponding histopathologic findings include sloughing of epithelial lining of the alveoli and flooding of airspaces with eosinophilic proteinaceous fluid. When the chest radiograph demonstrates further consolidation in dependent areas, histopathologic findings include alveolar atelectasis with hyaline membrane formation. As the disease progresses, there is hyaline membrane formation and proliferation of fibroblasts and type II pneumocytes[27].

Serologic Diagnosis

Serology demonstrating anti-HLA or anti-neutrophil-specific antibodies in donor blood is considered supporting evidence for the diagnosis of TRALI. Detection of a leukocyte antigen phenotype in the patient that matches the specificity of antibodies in implicated donor blood further supports a diagnosis of TRALI. Performance of serologic testing can be a challenge because the diagnosis of TRALI often is not made in time to obtain appropriate samples. The recipient may be deceased, and the donors may no longer be available for further testing. Furthermore, methods for serologic testing vary widely. For complete

serologic investigations, the plasma of implicated donors should be tested for the presence of anti-HLA class I, anti-HLA class II, and anti-human neutrophil antibodies. Concurrently, TRALI patients should be typed for HLA class I and II antigens, and neutrophil antigens. If multiple donors are implicated, a pragmatic, stepwise approach is used to focus testing on the most high-risk donors, such as multiparous donors [41]. In addition to identifying matching leukocyte antibodies and antigens in blood donors and TRALI patients, methods such as flow cytometry detection of donor antibody binding to TRALI patient leukocytes may play a role in the diagnosis of TRALI in the future [42]. The AECC summarized recommendations for the serologic diagnosis of TRALI, and a more detailed consensus approach is expected from the group in the near future [19].

Pathophysiology

The neutrophil is believed to be key in the mechanism of lung damage in TRALI. Because of the high level of interaction between leukocytes and pulmonary capillary endothelium, the lung is a vulnerable target for neutrophil-mediated injury. An average of 72 L of blood flows through the pulmonary vascular bed every 24 h. The transit time for leukocytes is slower than that for erythrocytes and there is an increased leukocyte:erythrocyte ratio in the pulmonary circulation, resulting in greater duration of exposure of the lung to leukocytes [16].

Although the pathophysiology of TRALI is not well understood, there are close similarities with ARDS, most notably the pathogenic role of neutrophils. Therefore, a review of mechanisms leading to the development of ARDS is useful in understanding TRALI. Since the first description of ARDS in 1967 [1], neutrophils have played a central role in pathogenic models. Normal neutrophil function involves recruitment to sites of infection, activation of vascular endothelial cells, release of chemoattractants, adherence of neutrophils to endothelial cells, diapedesis through endothelial cells to sites of infection, phagocytosis of bacteria, and release of oxygen metabolites [51]. When this process is disrupted, as occurs with ARDS, neutrophil sequestration may occur. Sequestered neutrophils release toxic oxygen metabolites that damage endothelial tissue, increase tissue permeability, and cause fluid accumulation in extravascular spaces such as pulmonary alveoli.

Activation of neutrophils stimulates activity of the NADPH:O_2 oxidoreductase enzyme, which generates oxygen free radicals. The oxidative reaction is capable of releasing toxic oxygen metabolites, arachidonate metabolites, platelet activating factor (PAF), and various proteases [3]. Agents known to prime this reaction include PAF [63], IL-1, tumor necrosis factor, granulocyte-colony stimulating factor (G-CSF), granulocyte/macrophage-colony stimulating factor (GM-CSF), and bacterial lipopolysaccharide (LPS). In turn, activated neutrophils also stimulate production of biologically active mediators, such as thromboxane A2 and endothelin-1. In *ex vivo* animal models, stimulation of neutrophils and release of these mediators increases pulmonary artery pressure and lung edema [48]. Some mediators, such as LPS, have been used in laboratory models of both ARDS and TRALI.

Neutrophil apoptosis may promote resolution of the acute inflammatory response in ARDS [47]. Inhibitors of neutrophil apoptosis, such as G-CSF and GM-CSF, are found to be elevated in early ARDS, with higher concentrations of GM-CSF found in patients who survive ARDS [31]. Bronchoalveolar lavage (BAL) fluid from ARDS patients contains significantly higher percentages of neutrophils compared with that from healthy controls and a lower percentage of neutrophils in the BAL is associated with better survival [46]. These findings demonstrate the importance of neutrophils in the pathogenesis of ARDS and the association of increased neutrophil activation with poor outcomes in ARDS patients. It can be postulated that because of the presence of neutrophils, inflammation, and edema, the pathophysiology of TRALI may involve some of the same effects of neutrophil toxicity as ARDS.

Popovsky's Immune-Mediated Model

Popovsky et al. [40] first popularized the immune-mediated model of TRALI in 1983. According to this model, donor antibodies, and less frequently recipient antibodies, cause an immune reaction targeting leukocyte antigens. Soluble circulating antibody–antigen complexes activate complement in lung, promoting neutrophil influx. Accumulation of neutrophils leads to microvascular damage and extravasation of proteinaceous fluid into the alveoli and interstitium, similar to pathogenic models of ARDS. This sequence of events produces the clinical signs and symptoms of TRALI (Fig. 1). The observation that recipient antibodies are found in association with TRALI far less often than donor antibodies is consistent with a dose-dependent effect of leukocytes, reflecting a far larger leukocyte pool in the recipient compared with the leukocyte dose in transfused blood.

Lung injury mimicking TRALI has been reproduced in animal models. Seeger et al. [49] used an *ex vivo* rabbit lung model in which rabbit lungs were perfused with plasma containing antibody against the 5b neutrophil antigen and neutrophils expressing the 5b antigen. Fol-

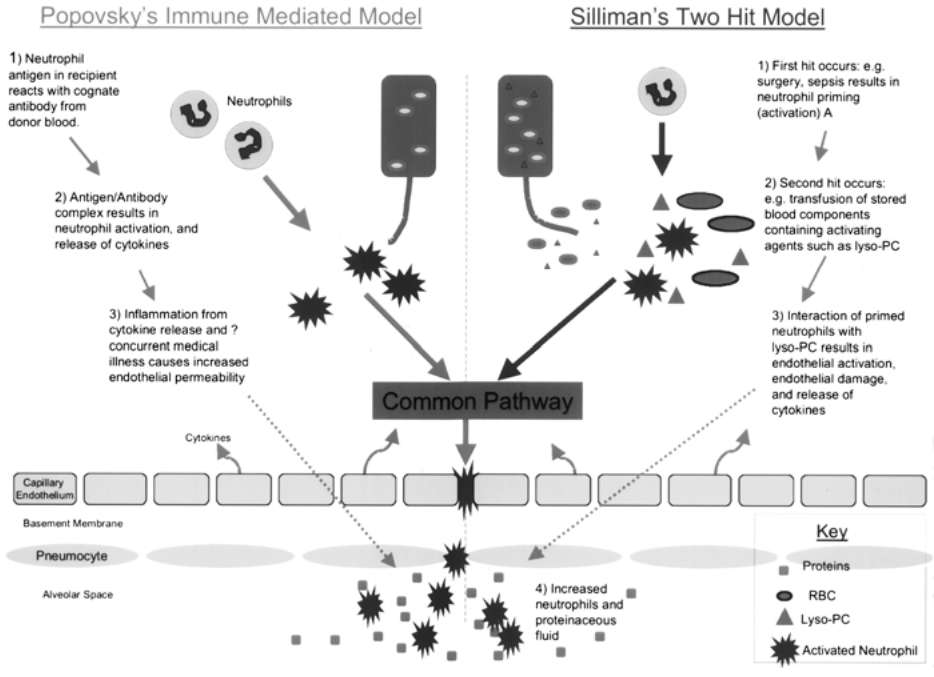

Fig. 1 A schematic illustration of Popovsky's immune mediated model and Silliman's two-hit model of TRALI pathogenesis. In both models transfused blood products introduce factors that activate neutrophils. Interaction of activated neutrophils with pulmonary endothelium and inflammatory cytokine release from neutrophils and pulmonary endothelium result in capillary leakage and pulmonary edema.

lowing infusion, significant increases in vascular permeability and pulmonary artery pressure occurred in the experimental lungs. In addition, neutrophils from the experimental group demonstrated higher levels of arachidonic acid and lipoxygenase product release. In a similar experiment, Hicks et al. [15] injected mice expressing the major histocompatibility complex class H-2^d with anti-$H2^d$ monoclonal antibodies. The mice developed hypothermia, pulmonary edema, alveolar protein leak, and lung mononuclear infiltrates. These experiments established proof-of-principle that leukocyte–antibody interactions can produce physiologic responses consistent with TRALI.

In human studies, Popovsky and Moore demonstrated in 1985 [39] a relationship between the presence of antibody in transfused blood and the development of TRALI symptoms in transfusion recipients. They investigated 22,292 transfused patients and identified 36 cases of TRALI. Pre-transfusion patient sera and donor sera were tested for neutrophil antibodies, lymphocytotoxic antibodies, and HLA specificity. Donor neutrophil antibodies were identified in 89% of cases, lymphocytotoxic antibodies in 72% of cases, and HLA-specific antibodies in 65% of suspected TRALI cases [39].

Since the Popovsky study, other reports have identified specific anti-HLA class I and anti-neutrophil antibodies in TRALI, including anti-HLA-A2 [4], anti-NB1 [4, 25], anti-5b [71] anti-HNA 1a [30], and anti-monocyte antibodies [22]. Anti-HLA class II antibodies have also been implicated [8, 18, 33, 42]. One interesting case report described TRALI developing in only the transplanted lung of a patient who had received a single lung transplant [6]. The patient's allograft lung had HLA B44 antigen and the blood donor had anti-HLA B44 antibody. Presumably, few leukocytes remained from the lung donor, suggesting that the other HLA antigen-containing tissues, such as pulmonary endothelium, could be involved in the pathogenesis of TRALI.

Another human study by Palfi et al. [35] implicated antibodies from multiparous female blood donors. In a randomized, double-blind, crossover study, 100 patients requiring transfusion were randomly assigned to receive two units of FFP, with only one of the two units donated from a multiparous donor. A significant decrease in the PaO_2:FiO_2 ratio was noted after the transfusion from the multiparous donor unit but not after the nonparous donor unit [35]. Since multiparity is associated with an increased frequency of antibodies [36], a possible explanation for the difference is the presence of antibodies in multiparous donor blood.

The main criticism of Popovsky's model of TRALI is that not all cases of TRALI are associated with a detectable antibody, and only a small fraction of antibody-containing blood products are associated with TRALI [17]. These observations suggest that the conditions required for TRALI are more complex and stringent than simply the presence of anti-leukocyte antibodies in transfused blood. An alternative model of the pathogenesis of TRALI involves several concurrent factors.

Silliman's Two-Hit Model

In 1992, Silliman et al. [52] proposed the ''two-hit'' model of TRALI. In this model, the first hit is a physiologic insult

that activates pulmonary endothelium and promotes priming and adhesion of neutrophils. The second hit is an event that activates neutrophils, causing release of cytotoxic factors and endothelial damage with capillary leakage (Fig. 1). It has been hypothesized [57] that the first hit may include a number of comorbid conditions such as sepsis, cardiac disease, trauma, or hematologic malignancy. The second hit involves exposure to biologically active agents from transfused blood. The concept of the second hit being from blood products derives from the observations that the age of stored blood correlates positively with likelihood of transfusion reactions [14], and that potentially responsible biologically active agents in blood products increase in concentration with time of storage [55, 57].

Silliman et al. [55, 56] tested the two-hit hypothesis using animal models. In a perfused rat lung model, neutrophils in the pulmonary circulation were activated by LPS. Subsequent exposure to blood products transfused on the day of outdate produced significant increases in pulmonary artery pressure and pulmonary edema compared with exposure to fresh blood or fresh frozen plasma. Both hits (LPS and aged blood products) were necessary to produce the physiologic effects [55].

In addition, Silliman et al. [52] demonstrated that stored blood components, but not fresh blood, were capable of priming neutrophil NADPH oxidase *in vitro*. Plasma at the day of outdate or fresh plasma was added to primed neutrophils and respiratory burst was measured. Only day-of-outdate plasma primed NADPH oxidase [52], suggesting that substances present only in aging stored blood can activate neutrophils. Silliman et al. [53] subsequently identified a possible priming agent as lysophosphatidylcholine (Lyso-PC).

In clinical studies correlating these results, TRALI patients' post-transfusion serum was found to have a 2.1-fold increase in neutrophil priming activity compared with pretransfusion serum or control plasma [54]. The lack of priming activity in the pretransfusion serum of TRALI patients implied that transfusion was required to initiate neutrophil priming. Other studies have also demonstrated increased NADPH oxidase activity in the serum of TRALI patients [26].

The two-hit model of TRALI proposed by Silliman is appealing in that it requires the convergence of two specific sets of conditions, the relatively low probability of which might account for the relative rarity of TRALI. However, neither the precise nature of the physiologic conditions required for the first hit nor the exact nature of the factors in blood constituting the second hit, be they lysoPC, antibodies, or other factors, are as yet well understood. As such, the ability to predict TRALI or prevent its occurrence in individual patients remains a goal for further research.

Recently, Kopko et al. [22] in an attempt to explain cases of TRALI not attributable to known antibodies, theorized that monocyte activation, with resultant cytokine production, occurs in TRALI [49]. Although not proven, the ultimate culprit may be monocytes, and not solely neutrophils. It has yet to be resolved whether a unifying theory, such as this one, can resolve the mechanism of TRALI. Alternatively, TRALI may be a mix of diseases with one commonality, i.e., lung damage.

Treatment

Treatment of TRALI is supportive. Supplemental oxygen is the first line of therapy. Mechanical ventilation is required for refractory hypoxemia or respiratory failure. Intravenous fluids are used to treat hypotension, and pressor support may be necessary for refractory hypotension and shock. Glucocorticoids are often administered empirically, although there is little evidence to support their use. Diuretics may worsen outcome secondary to intravascular volume depletion [28]. One case report suggests that the use of synthetic surfactant may be of benefit. In that report, however, the patient recovered rapidly, and the benefit of surfactant is uncertain [69]. Case reports have suggested that cardiopulmonary bypass or extracorporeal cardiopulmonary support may be useful in surgical patients who develop TRALI during or immediately after surgery [24, 34]. However, no randomized studies of TRALI and cardiopulmonary bypass have been performed to date.

Prevention

Since treatment of TRALI is currently limited to supportive care, prevention is a primary goal. Identifying the blood products at highest risk for causing a TRALI reaction is a key strategy. Prevention of TRALI is a challenging task, however, because the nature of the factors involved in TRALI remain poorly defined. Moreover, the disorder is rare, and the potential cost of screening and disposal of possible TRALI-inducing blood products may be high [7].

If Popovsky's pathogenic model is assumed to be accurate, eliminating multiparous donors from the blood donation pool should reduce the incidence of TRALI. However, this tactic may be impractical because it eliminates a large percentage of potential donors. If Silliman's model is valid, prestorage leukocyte filtration and avoidance of the use of older blood products in at-risk patients should reduce the incidence of TRALI. However, while some biologically active mediators can be reduced by prestorage white blood cell reduction [50], this approach

does not appear to reduce overall transfusion reactions compared with bedside filtration [60]. Moreover, there are no clear criteria for identifying at-risk patients or the appropriate age for blood products. A combined approach of eliminating the use of both multiparous donor blood and older blood products in identified at-risk patients would impose an onerous burden on transfusion services.

Compromise measures are presently recommended to reduce the incidence of TRALI. The most common practice is the deferral of blood donors who have been implicated in a TRALI reaction. This practical measure, along with a high clinical suspicion for TRALI and early intervention, is the best means to reduce morbidity and mortality. In the future, when TRALI is better understood, more specific prevention techniques may be developed.

As is the case with any unpredictable adverse effect of medical treatment, a simple measure for reducing the risk of TRALI is to limit blood exposure by the adoption of conservative transfusion practices. Three recent large studies provided evidence for equal or reduced morbidity and mortality from using conservative transfusion practices in critical care patients [13], postcoronary bypass [62], and surgical patients [9]. These studies illustrate the principle that conservative blood use is compatible with favorable outcomes; because TRALI is a rare event, however, there are no data showing that the incidence of TRALI is affected by conservative blood usage.

Future Research

Although TRALI is rare, the consequences can be devastating, as demonstrated in our case of report. While existing pathogenic models of TRALI have support in both animal and human studies, no single model explains all cases. The incidence of TRALI is far less expected relative to the prevalence of implicated pathogenic factors in patients or blood products. The two-hit model may help explain the lower-than-predicted incidence of TRALI, whether the inciting factors in blood are antibodies or other biologically active factors. However, a refined model of the syndrome remains to be established.

Historically, the diagnosis has been based solely on clinical impression. The lack of diagnostic criteria, variable presentation, and rarity of TRALI have hampered systematic studies. It is possible that there is a spectrum of disease for which the diagnosis of TRALI is appropriate. The lack of a uniform definition has limited understanding of the disease and the development of appropriate prevention and treatment strategies. The AECC consensus TRALI diagnosis guidelines may now provide the opportunity to conduct investigational and interventional studies that had not previously been feasible. We therefore advocate adoption of the guidelines and anticipate new progress emerging from more uniform and interpretable data.

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