

## critical care review

# Transfusion-Related Acute Lung Injury\*

## A Review

Mark R. Looney, MD; Michael A. Gropper, MD, PhD, FCCP; and  
Michael A. Matthay, MD, FCCP

Transfusion-related acute lung injury (TRALI) is an underreported complication of transfusion therapy, and it is the third most common cause of transfusion-associated death. TRALI is defined as noncardiogenic pulmonary edema temporally related to transfusion therapy. The diagnosis of TRALI relies on excluding other diagnoses such as sepsis, volume overload, and cardiogenic pulmonary edema. Supportive diagnostic evidence includes identifying neutrophil or human leukocyte antigen (HLA) antibodies in the donor or recipient plasma. All plasma-containing blood products have been implicated in TRALI, with the majority of cases linked to whole blood, packed RBCs, platelets, and fresh-frozen plasma. The pathogenesis of TRALI may be explained by a “two-hit” hypothesis, with the first “hit” being a predisposing inflammatory condition commonly present in the operating room or ICU. The second hit may involve the passive transfer of neutrophil or HLA antibodies from the donor or the transfusion of biologically active lipids from older, cellular blood products. Treatment is supportive, with a prognosis substantially better than most causes of clinical acute lung injury. (CHEST 2004; 126:249–258)

**Key words:** ARDS; lung injury; pulmonary edema; transfusion; transfusion-related acute lung injury

**Abbreviations:** ALI = acute lung injury; FDA = Food and Drug Administration; FIO<sub>2</sub> = fraction of inspired oxygen; HLA = human leukocyte antigen; PRBC = packed RBC; TRALI = transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) was first coined by Popovsky et al<sup>1</sup> in 1983 to refer to noncardiogenic pulmonary edema complicating transfusion therapy. The syndrome had previously been referred to as *pulmonary hypersensitivity reaction*,<sup>2,3</sup> *allergic pulmonary edema*,<sup>4</sup> *noncardiogenic pulmonary edema*,<sup>5–7</sup> and *pulmonary leukoagglutinin reaction*.<sup>8</sup> Barnard<sup>9</sup> in 1951 described the first case of fatal pulmonary edema accompanying transfusion therapy. Brittingham<sup>10</sup> in 1957 was the

first to initially shed light on the pathogenesis of TRALI. He transfused a strong leukoagglutinin to a volunteer who developed bilateral pulmonary infiltrates. This review will summarize the clinical features of TRALI and highlight potential mechanisms that may precipitate acute lung injury (ALI) and the ARDS.

### DEFINITION AND CLINICAL PRESENTATION

TRALI is defined as noncardiogenic pulmonary edema temporally related to the transfusion of blood products. The development of TRALI has been associated with all plasma-containing blood products, but most commonly involves whole blood, packed RBCs (PRBCs), fresh-frozen plasma, and platelets. TRALI has also occurred after the transfusion of cryoprecipitate and IV Ig.<sup>11,12</sup> The most common symptoms associated with TRALI are dyspnea, cough, and fever.<sup>13,14</sup> Fever was a nearly constant finding in one series.<sup>15</sup> Both systemic hypertension and hypotension have been commonly

\*From the Division of Pulmonary and Critical Care Medicine (Drs. Looney and Matthay), Department of Medicine, Cardiovascular Research Institute; and the Department of Anesthesia and Perioperative Care (Dr. Gropper), University of California, San Francisco, CA.

Manuscript received August 25, 2003; revision accepted January 14, 2004.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

Correspondence to: Mark R. Looney, MD, Cardiovascular Research Institute, University of California, San Francisco, 505 Parnassus Ave, HSW-825, San Francisco, CA 94143-0130; e-mail: mlooney@itsa.ucsf.edu

reported, with the incidence of each possibly related to the severity of the reaction.<sup>1,16</sup> In patients receiving mechanical ventilation who acquire TRALI, copious quantities of pulmonary edema fluid can be collected from the endotracheal tube. Symptoms associated with TRALI can be sudden and fulminant, and most commonly occur between 1 h and 2 h after the onset of transfusion, but may develop within 30 min of transfusion. Almost all reactions occur within 6 h from the start of a transfusion.<sup>1,14,15</sup> The first and still one of the largest series of TRALI cases was published by Popovsky and Moore<sup>13</sup> in 1985. These investigators published 36 cases of TRALI from the Mayo Clinic occurring over a 2-year period. All patients in that study required oxygen supplementation, and 72% required mechanical ventilation. Bilateral pulmonary infiltrates were present in all patients (Fig 1, *top*), and were rapidly resolved (< 96 h) in 81% of the patients (Fig 1, *bottom*). For the remaining patients, the pulmonary infiltrates resolved more slowly ( $\geq 7$  days). Mortality was only 6%, with no survivors having long-term sequelae. The 5 to 8% mortality rate in TRALI cases distinguishes it from ALI/ARDS, which has a mortality rate of 30 to 50%.<sup>17</sup>

#### INCIDENCE

The true incidence of TRALI is not known because there is significant underreporting of cases.<sup>18</sup> Too often, hypoxia that develops after transfusion therapy is ascribed to volume overload, and diuretics are empirically administered. Mild-to-moderate cases of TRALI may be misdiagnosed as volume overload, and the chance to make a diagnosis of TRALI, and possibly prevent future cases, is lost. Popovsky et al<sup>1</sup> reported five cases of TRALI that occurred in a total of 3,130 patients transfused with 21,000 blood products. This yielded an incidence of 0.02% per unit transfused and 0.16% per patient transfused. Others have found lower estimates at 0.014% per unit and 0.08% per patient transfused.<sup>19</sup> Silliman et al<sup>15</sup> reported a slightly higher incidence of TRALI at 0.09% for all cellular components transfused, and 0.08% for all components transfused. TRALI is the third most common cause of fatal transfusion reactions next to ABO blood type incompatibility and hepatitis.<sup>20,21</sup> As of 2001, the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research had received 45 fatality reports of TRALI since the first report in 1992.<sup>22</sup>

#### PATHOGENESIS

Empiric observations have indicated that most TRALI cases occur in the operating room and the

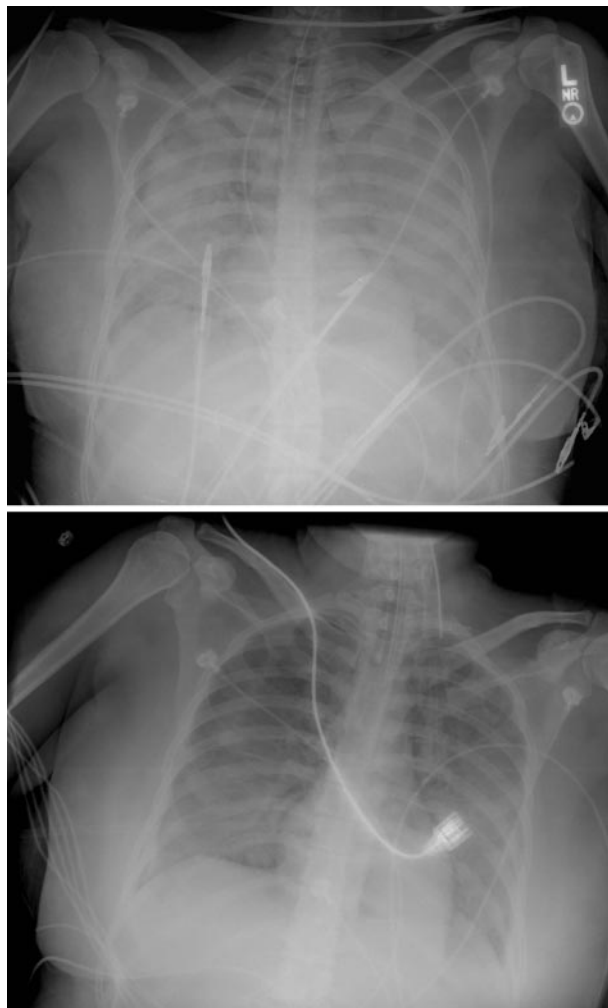


FIGURE 1. *Top*: Anteroposterior chest radiograph from a 37-year-old woman with cholangitis who received 2 U of fresh-frozen plasma and acquired TRALI. The patient has an endotracheal tube in place and has diffuse bilateral alveolar infiltrates and a normal cardiac silhouette. This is a characteristic radiograph appearance for severe ALI in TRALI. *Bottom*: Anteroposterior chest radiograph from the same patient 24 h later showing significant resolution of the alveolar infiltrates, as seems to occur in 80% of patients with TRALI.

ICUs.<sup>13,23</sup> What is it that predisposes patients in these settings to TRALI? It has been proposed that patients in these settings have the first “hit” in a generally accepted “two-hit” hypothesis for the pathogenesis of TRALI. The first hit is thought to be the underlying condition of the patient, with the second hit being the transfusion of injurious blood products.<sup>24</sup> This two-event hypothesis has been used in animal models of ALI/ARDS.<sup>25,26</sup> These same animal models have shown that ALI/ARDS is usually a neutrophil-dependent process. The first insult in ALI/ARDS is the priming and adherence of neutrophils to the pulmonary endothelium. The second insult activates these primed neutrophils, resulting in

the release of reactive oxygen species that cause capillary leak and pulmonary edema.<sup>27</sup> Candidate conditions for producing the first insult in TRALI include surgery, sepsis, trauma, and massive transfusions themselves. Silliman et al,<sup>15</sup> in a retrospective case control analysis of etiologic factors in TRALI, identified hematologic malignancies and cardiac disease as significant risk factors. Patients receiving induction chemotherapy or undergoing cardiopulmonary bypass appeared to be particularly at risk. Massive transfusions can produce a systemic inflammatory response syndrome-like condition that can progress to multiorgan failure if the appropriate second insult is present.<sup>28,29</sup>

### *Antibody-Mediated Lung Injury*

There is controversy as to what constitutes the second insult in TRALI. Two main pathogenetic explanations exist and are both backed by solid evidence from both animal and human studies. The two mechanisms are passively transfused antibodies and biologically active lipids. As discussed previously, the first reports of lung injury complicating transfusion therapy (1950s) implicated a passively transfused leucoagglutinin.<sup>10</sup> The antibody theory remains the most inclusive and published etiology of TRALI. The medical literature is replete with reports of the identification of passively transfused antibodies producing TRALI.<sup>1-3,10,13,14,19,30-37</sup> The classic scenario is that donor antibodies are transfused with the plasma-containing blood product. These antibodies attach to specific antigens on primed neutrophils leading to the release of oxidative and nonoxidative products that damages the pulmonary endothelium and leads to an increased permeability pulmonary edema. These antibodies may also attach to the pulmonary endothelium and monocytes and directly activate these cells.<sup>34,36</sup> Rare reports<sup>34,38</sup> exist of recipient antibodies attacking donor WBCs and producing TRALI. Much more frequently, this scenario produces a febrile transfusion reaction without lung injury. Reports even exist of interdonor TRALI, in which antibodies of one donor attack the WBCs of another donor within the recipient's bloodstream.<sup>39-41</sup> These latter two explanations for TRALI are less likely to occur compared to the classic donor antibody/recipient WBC scenario, which involves the entire circulating pool of WBCs and not a small number of transfused leukocytes. In addition, stored granulocytes undergo rapid senescence and defunctionalization, which limits their role in antibody-mediated lung injury. Large quantities of plasma are not necessary to produce TRALI since there are reports of TRALI occurring with the transfusion of only 10 to 15 mL of plasma.<sup>11</sup>

The targets of the passively transfused antibodies are neutrophil specific and human leukocyte antigen (HLA) class I and II antigens. The neutrophil-specific epitopes (*eg*, 5b, NA2, NB1, NB2) are poorly characterized cell surface antigens. In the case series of Popovsky and Moore<sup>13</sup> of TRALI in 36 patients, granulocyte antibodies were identified in the serum of at least one donor in 89% of the cases. Lymphocytotoxic antibodies were identified in 72% of the cases, and in 59% of the cases these antibodies corresponded to a specific patient HLA antigen on crossmatching. What is not known is the number of non-TRALI patients who received blood products from donors with granulocyte or lymphocytotoxic antibodies. Other studies have shed light on this issue. In a study<sup>42</sup> of female plateletpheresis donors, 17% of the donors had detectable HLA antibodies; however, in > 9,000 donations, no cases of TRALI were reported. In an investigation by Kopko et al,<sup>14</sup> a multiparous donor with granulocyte 5b antibodies was implicated in a fatal case of TRALI. During a look-back investigation over 2 years, 36% of this patient's donations (which were available for review) were associated with clinical cases of TRALI. However, the prevalence of the granulocyte 5b antigen is approximately 90% in the general population. Therefore, many more cases of TRALI would have been expected if antibody-antigen factors were solely responsible for TRALI. These data suggest that other factors are involved in producing TRALI, such as factors inherent in the first hit of the two-hit hypothesis. However, more studies are needed.

Modeling TRALI experimentally, Seeger et al<sup>43</sup> used an *ex vivo* rabbit lung model and a human anti-5b antibody isolated from a multiparous donor implicated in a TRALI case. Lung weight (pulmonary edema) and the capillary filtration coefficient were calculated using the isolated, perfused rabbit lungs. When 5b-positive granulocytes, plasma containing anti-5b antibody, and rabbit plasma as a complement source were perfused, increased lung vascular permeability and pulmonary edema occurred after a latent period of 3 to 6 h. This reaction was dependent on all three of the transfused constituents. For instance, when 5b-negative granulocytes were transfused with the anti-5b plasma and rabbit complement, no reaction occurred. Thus, this experiment provided confirmation of the proposed constituents and time course of the antibody theory of TRALI.

There are limitations to the application of an *ex vivo* lung model to *in vivo* human disease. Is there any *in vivo* evidence for the localization of these activated leukocytes to the pulmonary circulation? McCullough and colleagues,<sup>44</sup> while studying the recovery, survival, and tissue localization of <sup>111</sup>In

granulocytes in humans, made an interesting observation. When patients with granulocyte antibodies were perfused with  $^{111}\text{In}$  granulocytes, the indium-labeled granulocytes were sequestered in the pulmonary circulation as assessed by a total-body indium scan. None of the patients experienced any pulmonary symptoms, presumably because this scenario is the reverse of the usual cause of TRALI, when donor antibody reacts with recipient granulocytes. Nevertheless, the indium study provides circumstantial evidence to the antibody theory of TRALI.

### *Role of Biologically Active Lipids*

In some cases of TRALI (approximately 10%), no leukocyte antibody can be found in either the donor or recipient.<sup>13</sup> How can these cases be adequately explained using the antibody theory? It has recently been learned that HLA class II antibodies can be found in donors implicated in TRALI.<sup>31</sup> Previous studies<sup>1,13</sup> examining the presence of donor antibodies often examined only granulocyte and HLA class I antibodies and possibly missed the presence of HLA class II antibodies. However, a recent study<sup>15</sup> of TRALI from the transfusion of primarily whole-blood platelets included testing for granulocyte and HLA class I and II antibodies; this study found a much lower prevalence of leukocyte antibodies (< 25%). The incomplete presence of leukocyte antibodies in TRALI has focused attention on an alternative explanation. Biologically active lipids are breakdown products of cell membranes that normally accumulate in older, cellular blood components. Lysophosphatidylcholines have been identified as a component of these lipids and have been shown to prime neutrophils. Lysophosphatidylcholines probably act through the platelet activating factor receptor, as their priming actions can be blocked by a specific inhibitor of that receptor.<sup>45,46</sup> Platelet activating factor has been implicated as a potential mediator in sepsis and ALI/ARDS, and clinical studies<sup>47,48</sup> have been carried out to block its actions. Silliman et al<sup>24</sup> were the first to show that biologically active lipids present in posttransfusion sera of TRALI patients primed neutrophils to a greater degree than posttransfusion sera from control subjects (febrile or urticarial reactions). In a larger, prospective study of TRALI patients, Silliman et al<sup>15</sup> found that implicated blood components had greater neutrophil priming activity compared to control subjects. In addition, the posttransfusion plasma of the patients with TRALI had increased lipid priming activity compared to before transfusion.

Just as an animal model of the antibody theory of TRALI has strengthened its potential role, so has an animal model supported the biologically active lipid

theory. Silliman et al<sup>49</sup> pretreated rats with intraperitoneal endotoxin (priming) or saline solution. After a 2-h incubation period, the rat lungs were isolated and perfused. Next, fresh human plasma, plasma from stored PRBCs on the first day of isolation (day 0), or plasma from the day of outdate (day 42) was perfused. Only the plasma from the day 42 PRBCs produced lung injury as assessed by an increase in lung weight and light microscopic evidence of pulmonary edema and hyaline membranes. In addition, pretreatment with endotoxin was required for this injury, thus replicating the two-hit theory of TRALI. To prove that it was the biologically active lipids in the day 42 plasma that was causing the lung injury, lipid extracts from day 42 plasma were perfused. This resulted in lung injury similar to the day 42 plasma. A similar animal model with similar results has been published using platelets instead of PRBCs.<sup>50</sup>

There are strengths and weaknesses to both the antibody and biologically active lipid theories of TRALI. The main strength of the antibody theory is the preponderance of studies detailing the presence of these antibodies in many documented TRALI cases. The main weakness of the lipid theory is that it requires cellular blood products. Fresh-frozen plasma, a blood product often implicated in TRALI, does not possess these biologically active lipids. These two explanations for TRALI are not necessarily mutually exclusive and may even be complementary. Threshold effects may be present that could potentially allow both mechanisms to participate in injury.

### PATHOLOGY AND EDEMA FLUID ANALYSIS

As summarized in one article,<sup>51</sup> autopsy studies of patients dying of TRALI have shown massive pulmonary edema with granulocyte aggregation within the pulmonary microvasculature and extravasation into alveoli (Fig 2). In one autopsy report,<sup>51</sup> the granulocyte/RBC ratio approached 1:1 in the pulmonary capillaries. Electron microscopy revealed activated granulocytes in contact with the alveolar basement membrane (Fig 3).

Several investigators<sup>6,7</sup> have established that TRALI is a high-permeability pulmonary edema. Yost et al<sup>52</sup> published a case series of orthotopic liver transplant patients who acquired intraoperative pulmonary edema. The patients received a mean of 20 U of fresh-frozen plasma, 7 U of PRBCs, and 1.5 U of platelets. Cardiogenic pulmonary edema and volume overload were ruled out by central venous and/or pulmonary artery pressure monitoring or by transthoracic echocardiography. Edema fluid was

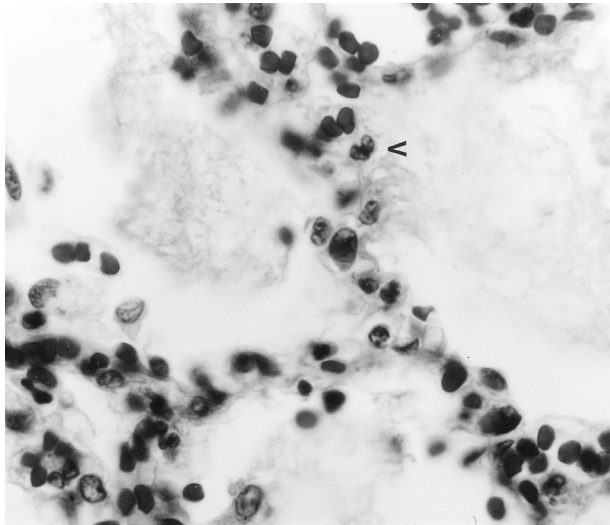


FIGURE 2. Lung pathology from a patient who died from TRALI: alveolar proteinaceous material and alveolar capillaries congested with granulocytes (arrow) and RBCs (hematoxylin-eosin, original  $\times 1,000$ ). Reprinted with permission from the American Society of Clinical Pathologists.<sup>51</sup>

collected in all of the patients within 15 min of first appearance and was analyzed for protein content. Six of the seven patients had edema fluid/plasma protein ratios  $\geq 0.75$ , which is characteristic of increased permeability pulmonary edema (one patient had a ratio of 0.73).<sup>53,54</sup> Although none of the patients had TRALI confirmed with antibody testing, the authors



FIGURE 3. Electron micrograph from the same patient in Figure 2 showing alveolar basement membrane (BM) with an intravascular, adherent granulocyte (G), desquamated alveolar epithelium, and amorphous proteinaceous alveolar material (A) [original  $\times 10,000$ ]. Reprinted with permission from the American Society of Clinical Pathologists.<sup>51</sup>

concluded that given the large amounts of transfused blood products and the exclusion of other diagnoses, TRALI was the most likely diagnosis.

#### CLINICAL RISK FACTORS

As mentioned earlier when discussing the first hit of the two-hit hypothesis, conditions such as recent surgery, sepsis, trauma, massive transfusions, hematologic malignancies, and cardiac disease can all predispose a patient to TRALI. For the second hit, parity of the blood donor, relationship to the blood donor, and the age of the blood products can all be potential risk factors for the development of TRALI.

Multiparity is a risk factor for TRALI due to the high prevalence of HLA sensitization in these donors.<sup>55</sup> A mother is exposed to the paternal HLA antigens of the *in utero* fetus, and antibodies can develop to these antigens. With increasing parity, the percentage of women with HLA antibodies increases. This relationship was detailed well in a study that investigated the rate of HLA sensitization in female apheresis donors: Densmore et al<sup>42</sup> showed that the HLA sensitization of women reporting one to two pregnancies was 15%. For women with three or more pregnancies, the sensitization rate was 26%. Expressed a different way, antibody-negative donors reported an average of 1.8 pregnancies and antibody-positive donors reported an average of 2.9 pregnancies. As discussed earlier, even if an antibody is transfused to a recipient with the corresponding antigen, TRALI does not necessarily develop. However, case reports and case series abound detailing the multiparity of donors implicated in cases of TRALI.

In the only prospective, randomized trial in the TRALI literature, intensive care patients were transfused with plasma from a multiparous donor or a control donor (presumably male or nulliparous female donors, though not explicitly stated) in a double-blind, crossover fashion.<sup>56</sup> These intensive care patients were determined *a priori* to need at least 2 U of frozen plasma. The interval between transfusion of the two randomized units of plasma was at least 4 h. Hemodynamics,  $\text{PaO}_2/\text{fraction of inspired oxygen (FIO}_2\text{)}$  ratio, and cytokine levels were measured. Only one case of TRALI occurred after the transfusion of 200 U of plasma to 100 patients. The donor in this case was multiparous and possessed a granulocyte antibody. A small but statistically significant decrease in the  $\text{PaO}_2/\text{FIO}_2$  ratio occurred in the multiparous plasma group. The mean  $\text{PaO}_2/\text{FIO}_2$  ratio in the multiparous group before transfusion was 254; after receiving multiparous plasma, it was 234, a small difference. The mean  $\text{PaO}_2/\text{FIO}_2$  ratio in the

control group did not change with transfusion of control plasma (246 to 247). Tumor necrosis factor- $\alpha$  concentrations increased after the transfusion of both the control and multiparous plasma. However, the increase in pretransfusion to posttransfusion tumor necrosis factor- $\alpha$  concentrations was greater in the multiparous group than in the control group. Although there was only one documented case of TRALI in this study, it is interesting because multiparous plasma may be causing milder, subclinical injury in the ICU, or producing a systemic inflammatory response syndrome-like state that could predispose to multiorgan damage.

The transfusion of blood products between close relatives can be the ideal set-up for TRALI. For instance, if a mother donated blood products for her child or husband, it is quite possible that HLA antibodies would be present against the paternal antigens of the child and the father. Thus, through the best intentions of protecting a close relative from the blood products of a stranger, the probability of TRALI is potentially increased.

In support of the biologically active lipid theory of TRALI, studies of the association of older blood products with TRALI and organ failure have been published. Silliman et al,<sup>15</sup> in a nested case-control study, found that the transfusion of older whole-blood platelets was associated with a greater incidence of TRALI compared with control subjects (4.5 days vs 4.2 days). From studies<sup>28,29</sup> on the resuscitation of trauma intensive care patients, it was learned that a dose-response relationship existed between early blood transfusions and the later development of multiorgan failure. Could it be that a subset of the transfused blood products, perhaps older blood components, was the real cause of injury in the early resuscitation of these trauma patients? Zallen et al<sup>57</sup> studied a cohort of trauma patients who received 6 to 20 U of PRBCs in the first 12 h after injury. The two cohorts were matched for injury severity score and transfusion requirement, and were classified into two groups: those who did and those who did not develop multiorgan failure. The age of each unit of PRBCs transfused in the first 6 h of resuscitation was determined. The results showed that the mean age of transfused PRBCs in the multiorgan failure group was significantly older (31 days vs 24 days). This relationship persisted on multivariate analysis. Unfortunately, the pulmonary injury was not detailed in these studies, nor was it mentioned if the diagnosis of TRALI was pursued. One would expect, however, that ALI/ ARDS was a significant component of the multiorgan failure.

The risk of older PRBCs has also been shown in patients with sepsis. Although it was a small retrospective study, Purdy et al<sup>58</sup> examined the age of PRBCs

transfused to 31 patients with severe sepsis/septic shock; during the septic episode, the median age of PRBCs transfused to survivors was significantly lower than nonsurvivors (17 days vs 25 days). In another study, Marik and Sibbald<sup>59</sup> reported that septic patients receiving mechanical ventilation who were transfused older PRBCs acquired evidence of splanchnic ischemia as assessed by gastric tonometry.

## DIAGNOSIS

The diagnosis of TRALI requires a high index of suspicion and the exclusion of more common etiologies of posttransfusion respiratory insufficiency. TRALI should be suspected and excluded in all cases of dyspnea and hypoxia temporally related to the transfusion of any blood product. As mentioned earlier, most reactions occur within 1 to 2 h, and almost all reactions occur by 6 h. A careful clinical examination assessing volume overload combined with testing such as echocardiography and possibly pulmonary arterial catheterization should exclude cardiogenic pulmonary edema and volume overload. If present, one should always collect pulmonary edema fluid from the endotracheal tube early in course of the lung injury. Pulmonary edema fluid spontaneously appearing in the endotracheal tube can be collected, or a 14F suction catheter can be wedged and the edema fluid suctioned from the lower airways into a standard specimen trap. Protein measurements of the edema fluid and a matched plasma sample can be diagnostic of increased permeability pulmonary edema. For example, the edema fluid/plasma protein ratio is  $< 0.65$  in hydrostatic pulmonary edema, and  $> 0.75$  with increased permeability pulmonary edema.<sup>53,54</sup> This method is valid only for undiluted pulmonary edema fluid, not BAL.

The only routine laboratory parameter that has been associated with TRALI is leukopenia.<sup>10,19,30,60</sup> This has been an infrequent finding in most of the published cases of TRALI. It is our opinion that the leukopenia is so dynamic that it often goes unrecognized with the infrequency with which the WBC count is measured. In surgical cases with large predicted blood losses and transfusion requirements, the CBC count is often checked every 1 to 2 h. The authors have identified leukopenia in a case of TRALI that would have been completely missed if blood had not been drawn over a 5-h period (Fig 4). The transient leukopenia is presumably due to massive sequestration of the circulating pool of leukocytes in the pulmonary circulation. An appropriate bone marrow response supplies the circulation with new leukocytes a few hours later. This dynamic leukopenia, if observed, could add support to the

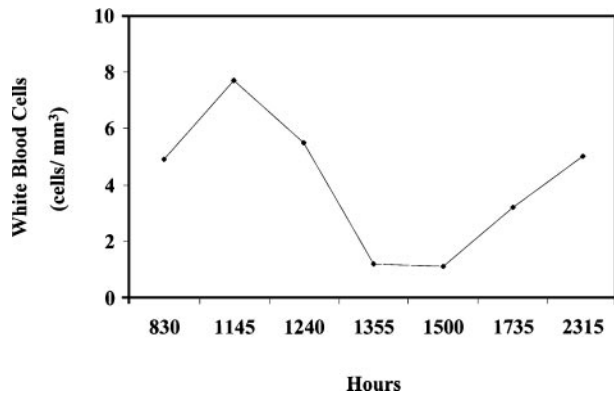


FIGURE 4. Serial WBC counts in a patient undergoing a posterior spinal fusion who acquired intraoperative TRALI. Note the dynamic leukopenia, which began and resolved over a 5-h period. Thrombocytopenia (not shown) also developed and persisted for several days.

diagnosis of TRALI, as it would not be expected to occur in cardiogenic pulmonary edema or volume overload. Thrombocytopenia has also been reported in TRALI and seems to be more durable than the leukopenia.<sup>19,30,60</sup>

Confirmatory and definitive evidence for the diagnosis of TRALI requires investigating the donor and recipient for passively transfused antibodies. A potential algorithm for the hematologic investigation of TRALI is shown in Figure 5.

#### TREATMENT

The first step in the treatment of TRALI is to make the correct diagnosis. Treating TRALI like cardiogenic pulmonary edema or volume overload may lead to adverse outcomes. Levy et al<sup>61</sup> reported a case of confirmed TRALI in which diuretics were empirically administered. The patient became hypotensive, and a pulmonary arterial catheter was inserted. After receiving 1,000 mL of IV crystalloid, the initial pulmonary capillary wedge pressure was 10 mm Hg with a cardiac index of 3.3 L/min/m<sup>2</sup>. Diuretics were discontinued, and further IV fluids were administered. The patient was eventually extubated and survived. Patients with TRALI are often normotensive to hypotensive with normal or low filling pressures. Diuretics may be contraindicated, and IV fluids should be administered as necessary, titrating the arterial BP to a mean pressure of 60 mm Hg with appropriate urine output. Invasive hemodynamic monitoring may be necessary in especially severe cases to guide fluid management.

In the majority of cases, TRALI is a self-limited condition that has a better prognosis than most causes of ALI/ARDS. For mild TRALI cases, sup-

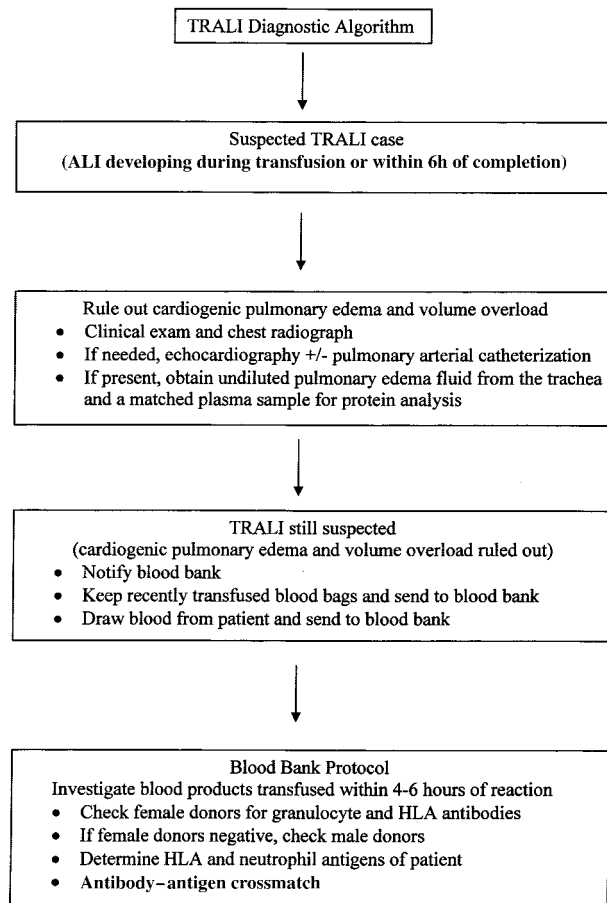


FIGURE 5. Potential algorithm for the hematologic investigation of TRALI.

plemental oxygen and supportive care may be sufficient for treatment. For the more severe case, IV fluids and mechanical ventilation are necessary. A low tidal volume strategy with low plateau pressures should be employed when ventilating TRALI patients, just like other causes of ALI/ARDS.<sup>62</sup> In the majority of patients, the patient will return to baseline status in a few days. Recurrent TRALI cases have been described, so the indications for future transfusions in a TRALI patient should be scrutinized.<sup>14,32</sup> Several case reports<sup>1,60</sup> describe the treatment of TRALI with glucocorticoids. Unfortunately, there has never been a randomized, controlled trial of glucocorticoid therapy in TRALI. Given the potential complications associated with glucocorticoids and the usual self-limited course of lung injury in TRALI, glucocorticoids have no demonstrated role in the treatment of TRALI.

#### PREVENTION

Many cases of TRALI are probably avoidable by adhering to evidence-based transfusion guidelines.

The role of transfusions in the ICU has received increased interest recently, and it has become clear that in selected patients a conservative transfusion threshold improves patient outcomes.<sup>63</sup> Supplementation with recombinant human erythropoietin may also reduce transfusions in the ICU.<sup>64</sup>

Much of the controversy in the prevention of TRALI, however, centers on the multiparous donor. Some would advocate excluding the multiparous donor from the donor pool. Others have found this disconcerting because multiparous donors are often very motivated donors, as evidenced by the look-back study by Kopko et al.<sup>14</sup> In a study<sup>42</sup> of the prevalence of HLA sensitization in female apheresis donors, one third of female plateletpheresis donors had three or more pregnancies. Approximately one fourth of these multiparous donors were HLA sensitized. However, none of their donated platelets had been implicated in a case of TRALI. Since it is impossible to predict *a priori* if a multiparous donor can produce a TRALI reaction, and since the number of blood product donors is already inadequate, it seems extreme at this time to exclude these motivated donors.

Kopko et al<sup>14</sup> provided an excellent example of the utility of a careful investigation in potentially preventing TRALI. A 54-year-old woman was implicated in a fatal case of TRALI involving the transfusion of fresh-frozen plasma. The woman had made 290 previous donations over a 15-year period. She was multiparous, and her plasma was found to be strongly positive for a granulocyte 5b antibody. This fatal case of TRALI was reported to the FDA, as all fatal cases of TRALI should be. The FDA requested that the hospital perform an investigation to see if other recipients of the donor's blood products had acquired TRALI. A retrospective review of the blood product donations made by this donor over the previous 2 years was initiated. This prolific donor had made 73 donations (nearly all plasmapheresis) over the 2-year period, with 54 patients receiving the blood products. Of the 36 patient charts that could be evaluated, 15 cases of TRALI could be identified in 13 patients (2 patients had two separate reactions). Eight of the TRALI cases were severe with pulmonary edema or ALI/ARDS. The other cases were classified as TRALI based on dyspnea and oxygen desaturation temporally related to a transfusion. Disturbingly, only 7 of the 15 cases were reported to the transfusion service of the hospital. By removing the implicated donor and existing blood products from the donor pool, future cases of TRALI were potentially avoided. Thus, a carefully conducted investigation can be crucial to preventing future cases of TRALI.

As explained earlier, the intensive care literature has identified that older, cellular blood products transfused to patients with trauma and severe sepsis/septic shock is a risk factor for multiorgan failure.<sup>57,58</sup> While a prospective, randomized trial of fresher vs older blood product transfusions has not been carried out, a reasonable preventive strategy would be to use fresh blood in the early resuscitation of trauma patients and in the transfusion of patients with severe sepsis/septic shock. An alternative would be to use washed blood components.<sup>55</sup>

Others have proposed that cellular components from implicated TRALI donors be made plasma free by washing with saline solution or frozen/deglycerolized.<sup>1,13</sup> However, some would contend that once a donor has been implicated in a case of TRALI, that donor and the existing blood products should be permanently removed from the donor pool.

Leukocyte reduction is controversial in transfusion medicine. The method of leukocyte reduction can be performed by centrifugation, sedimentation, washing, freeze-thawing, apheresis, or most commonly by filtration. The filtration can be performed prior to storage or prior to transfusion at the patient's bedside.<sup>65</sup> Accepted indications for leukocyte reduction include reduction in HLA alloimmunization, avoidance of febrile nonhemolytic transfusion reactions, and prevention of the platelet refractory state. Leukocyte-reduced blood products can also be used as an alternative to cytomegalovirus-seronegative blood products. Other possible but less accepted indications include reducing perioperative infections and reducing tumor recurrence rates after surgery.<sup>66</sup> A recent study<sup>67</sup> of high-risk surgical patients in Canada showed that prestorage leukoreduction of RBCs decreased mortality and decreased fever episodes and antibiotic use; however, the mortality benefit did not appear to be related to a decrease in infections. In terms of preventing TRALI, leukocyte reduction probably has no role. It is usually the antibody from the donor, not the leukocytes themselves, that is implicated in the TRALI reaction. In theory, leukocyte reduction could reduce the accumulation of biologically active lipids in stored blood products. The WBCs are thought to produce the biologically active lipids by degrading cell membranes through the release of enzymes such as phospholipases. However, an animal model using prestorage leukoreduced whole-blood platelets failed to inhibit TRALI when outdated plasma from these platelets was transfused.<sup>50</sup> In addition, prestorage leukoreduction of PRBCs failed to inhibit the priming of neutrophils exposed to the same PRBCs after storage.<sup>68</sup>

## CONCLUSIONS AND FUTURE DIRECTIONS

TRALI is a serious, potentially life-threatening complication of transfusion therapy that is underdiagnosed and underreported. The key to the diagnosis and treatment of TRALI is a high clinical suspicion and the need to exclude cardiogenic pulmonary edema or volume overload and other more common causes of ALI/ARDS, especially pulmonary or non-pulmonary infection. The pathophysiology of TRALI remains uncertain, although there is evidence for lung injury from both passively transfused antibodies and biologically active lipids. There is sufficient controversy regarding the relative contributions of the antibody theory and the biologically active lipid theory to warrant future studies.

Well-designed prospective trials of TRALI in the ICU could be done, similar to the clinical trials done by the National Institutes of Health ARDS network.<sup>62</sup> It is likely that much could be learned by a prospective trial of the incidence, risk factors, and outcome of TRALI in the ICU. By utilizing the expertise of blood-banking personnel, there would be more insight into the pathophysiology of TRALI. More high-profile, well-designed studies would also increase the awareness of this serious complication of transfusion therapy.

## REFERENCES

- 1 Popovsky MA, Abel MD, Moore SB. Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies. *Am Rev Respir Dis* 1983; 128:185–189
- 2 Thompson JS, Severson CD, Parmely MJ, et al. Pulmonary 'hypersensitivity' reactions induced by the transfusion of non-HLA leukoagglutinins. *N Engl J Med* 1971; 20:1120–1125
- 3 Wolf CFW, Canale VC. Fatal pulmonary hypersensitivity reaction to HL-A incompatible blood transfusion: report of a case and review of the literature. *Transfusion* 1976; 16:135–140
- 4 Kernoff PBA, Durrant IJ, Rizza CR, et al. Severe allergic pulmonary oedema after plasma transfusion. *Br J Haematol* 1972; 23:777–781
- 5 Carilli AD, Ramanamurty MV, Chang YS, et al. Noncardiogenic pulmonary edema following blood transfusion. *Chest* 1978; 74:310–312
- 6 Culliford AT, Thomas S, Spencer FC. Fulminating noncardiogenic pulmonary edema: a newly recognized hazard during cardiac operations. *J Thorac Cardiovasc Surg* 1980; 80:868–875
- 7 Hashim SW, Kay HR, Hammond GL, et al. Noncardiogenic pulmonary edema after cardiopulmonary bypass: an anaphylactic reaction to fresh frozen plasma. *Am J Surg* 1984; 147:560–564
- 8 Ward HN. Pulmonary infiltrates associated with leukoagglutinin transfusion reactions. *Ann Intern Med* 1970; 73:689–694
- 9 Barnard RD. Indiscriminate transfusion: a critique of case reports illustrating hypersensitivity reactions. *N Y State J Med* 1951; 51:2399–2402
- 10 Brittingham TE. Immunologic studies on leukocytes. *Vox Sang* 1957; 2:242–248
- 11 Reese EP Jr, McCullough JJ, Craddock PR. An adverse pulmonary reaction to cryoprecipitate in a hemophiliac. *Transfusion* 1975; 15:583–588
- 12 Suasuna JH, da Costa MA, Faria RA, et al. Noncardiogenic pulmonary edema triggered by intravenous immunoglobulin in cancer-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Nephron* 1997; 77:368–370
- 13 Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. *Transfusion* 1985; 25:573–577
- 14 Kopko PM, Marshall CS, MacKenzie MR, et al. Transfusion-related acute lung injury: report of a clinical look-back investigation. *JAMA* 2002; 287:1968–1971
- 15 Silliman CC, Boshkov LK, Mehdizadehkashi Z, et al. Transfusion related acute lung injury: epidemiology and a prospective analysis of etiologic factors. *Blood* 2003; 101:454–462
- 16 Popovsky MA, Haley NR. Further characterization of transfusion-related acute lung injury: demographics, laboratory features and morbidity [abstract]. *Transfusion* 1999; 39:97
- 17 Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1334–1349
- 18 Wallis JP. Transfusion-related acute lung injury (TRALI): under-diagnosed and under-reported. *Br J Haematol* 2003; 90:573–575
- 19 Ausley MB. Fatal transfusion reactions caused by donor antibodies to recipient leukocytes. *Am J Forensic Med Pathol* 1987; 8:287–290
- 20 Sazama K. Reports of 355 transfusion-associated deaths: 1976–1985. *Transfusion* 1990; 30:583–590
- 21 Lee JH. Transfusion-related fatalities: reports to US FDA, 1990–1998. ABC Newsletter, 1999
- 22 Zoon KC. Transfusion-related acute lung injury (letter). Center for Biologics Evaluation and Research, FDA 2001. Available at: <http://www.fda.gov/cber/ltr/trali101901.htm>. Accessed June 10, 2004
- 23 Kopko PM, Holland PV. Transfusion-related acute lung injury. *Br J Haematol* 1999; 105:322–329
- 24 Silliman CC, Paterson AJ, Dickey WO, et al. The association of biologically active lipids with the development of transfusion-related acute lung injury: a retrospective study. *Transfusion* 1997; 37:719–726
- 25 Ravinovi R, Bugelski PJ, Esser KM, et al. ARDS-like lung injury produced by endotoxin in platelet-activating factor-primed rats. *J Appl Physiol* 1993; 74:1791–1802
- 26 Salzer WL, McCall CE. Primed stimulation of isolated perfused rabbit lung by endotoxin and platelet activating factor induces enhanced production of thromboxane and lung injury. *J Clin Invest* 1990; 85:1135–1143
- 27 Wyman TH, Bjornsen AJ, Elzi DJ, et al. A two-insult *in vitro* model of PMN-mediated pulmonary endothelial damage: requirements for adherence and chemokine release. *Am J Physiol Cell Physiol* 2002; 283:C1592–C1603
- 28 Sauaia A, Moore FA, Moore EE, et al. Early predictors of postinjury multiple organ failure. *Arch Surg* 1994; 129:39–45
- 29 Moore FA, Moore EE, Sauaia A. Blood transfusion: an independent risk factor for postinjury multiple organ failure. *Arch Surg* 1997; 132:620–625
- 30 Leger R, Palm S, Wulf H, et al. Transfusion-related acute lung injury with leukopenic reaction caused by fresh frozen plasma containing anti-NB1. *Anesthesiology* 1999; 91:1529–1532
- 31 Kopko PM, Popovsky MA, MacKenzie MR, et al. HLA class II antibodies in transfusion-related acute lung injury. *Transfusion* 2001; 41:1244–1248
- 32 Win N, Montgomery J, Sage D, et al. Recurrent transfusion-

- related acute lung injury. *Transfusion* 2001; 41:1421–1425
- 33 Win N, Ranasinghe E, Lucas G. Transfusion-related acute lung injury: a 5-year look-back study. *Transfus Med* 2002; 12:387–389
  - 34 Kopko PM, Paglieroni TG, Popovsky MA, et al. TRALI: correlation of antigen-antibody and monocyte activation in donor-recipient pairs. *Transfusion* 2003; 43:177–184
  - 35 Davoren A, Curtis BR, Shulman IA, et al. TRALI due to granulocyte-agglutinating human neutrophil antigen-3a (5b) alloantibodies in donor plasma: a report of 2 fatalities. *Transfusion* 2003; 43:641–645
  - 36 Dykes A, Smallwood D, Kotsimbos T, et al. Transfusion-related acute lung injury (TRALI) in a patient with a single lung transplant. *Br J Haematol* 2000; 109:674–676
  - 37 Wallis JP, Lubenko A, Wells AW, et al. Single hospital experience of TRALI. *Transfusion* 2003; 43:1053–1059
  - 38 Büx J, Becker F, Serger W, et al. Transfusion related acute lung injury due to HLA-A2-specific antibodies in recipient and NBI-specific antibodies in donor blood. *Br J Haematol* 1996; 93:707–713
  - 39 Eastlund DT, McGrath PC, Burkart P. Platelet transfusion reaction associated with interdonor HLA incompatibility. *Vox Sang* 1988; 55:157–160
  - 40 O'Connor JC, Strauss RG, Goeken NE, et al. A near-fatal reaction during granulocyte transfusion of a neonate. *Transfusion* 1988; 28:173–176
  - 41 Virchis AE, Patell RK, Contreras M, et al. Acute non-cardiogenic lung oedema after platelet transfusion. *BMJ* 1997; 314:880–882
  - 42 Densmore TL, Goodnough LT, Ali S, et al. Prevalence of HLA sensitization in female apheresis donors. *Transfusion* 1999; 39:103–106
  - 43 Seeger W, Schneider U, Kreisler B, et al. Reproduction of transfusion-related acute lung injury in an *ex vivo* lung model. *Blood* 1990; 76:1438–1444
  - 44 McCullough J, Clay M, Hurd D, et al. Effect of leukocyte antibodies and HLA matching on the intravascular recovery, survival, and tissue localization of 111-indium granulocytes. *Blood* 1986; 67:522–528
  - 45 Silliman CC, Clay KL, Thurman GW, et al. Partial characterization of lipids that develop during the routine storage of blood and prime the neutrophil NADPH oxidase. *J Lab Clin Med* 1994; 124:684–694
  - 46 Silliman CC, Dickey WO, Paterson AJ, et al. Analysis of the priming activity of lipids generated during routine storage of platelet concentrates. *Transfusion* 1996; 36:133–139
  - 47 Dhainaut JF, Tenaillon A, Le Tulzo Y, et al. Platelet-activating factor receptor antagonist BN 52021 in the treatment of severe sepsis: a randomized, double-blind, placebo-controlled, multicenter clinical trial; BN 52021 Sepsis Study Group. *Crit Care Med* 1994; 22:1720–1728
  - 48 Schuster DP, Metzler M, Opal S, et al. Recombinant platelet-activating factor acetylhydrolase to prevent acute respiratory distress syndrome and mortality in severe sepsis: phase IIb, multicenter, randomized, placebo-controlled, clinical trial. *Crit Care Med* 2003; 31:1612–1619
  - 49 Silliman CC, Voelkel NF, Allard JD, et al. Plasma and lipids from stored packed red blood cells cause acute lung injury in an animal model. *J Clin Invest* 1998; 101:1458–1467
  - 50 Silliman CC, Bjornsen AJ, Wyman TH, et al. Plasma and lipids from stored platelets cause acute lung injury in an animal model. *Transfusion* 2003; 43:633–640
  - 51 Dry SM, Bechard KM, Milford EL, et al. The pathology of transfusion-related acute lung injury. *Am J Clin Pathol* 1999; 112:216–221
  - 52 Yost CS, Matthay MA, Gropper MA. Etiology of acute pulmonary edema during liver transplantation: a series of cases with analysis of the edema fluid. *Chest* 2001; 119:219–223
  - 53 Fein A, Grossman RF, Jones JG, et al. The value of edema fluid protein measurement in patients with pulmonary edema. *Am J Med* 1979; 67:32–38
  - 54 Matthay MA. Pathophysiology of pulmonary edema. *Clin Chest Med* 1985; 6:301–314
  - 55 Popovsky MA, Davenport RD. Transfusion-related acute lung injury: femme fatale? *Transfusion* 2001; 41:312–315
  - 56 Palfi M, Berg S, Ernerudh J, et al. A randomized controlled trial of transfusion-related acute lung injury: is plasma from multiparous blood donors dangerous? *Transfusion* 2001; 41:317–322
  - 57 Zallen G, Offner PJ, Moore EE, et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. *Am J Surg* 1999; 178:570–572
  - 58 Purdy FR, Tweeddale MG, Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. *Can J Anaesth* 1997; 44:1256–1261
  - 59 Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; 269:3024–3029
  - 60 Yomtovian R, Press C, Engman H, et al. Severe pulmonary hypersensitivity associated with passive transfusion of a neutrophil-specific antibody. *Lancet* 1984; 22:244–246
  - 61 Levy GJ, Shabot MM, Hart ME, et al. Transfusion-associated noncardiogenic pulmonary edema: report of a case and a warning regarding treatment. *Transfusion* 1986; 26:278–281
  - 62 ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome: The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301–1308
  - 63 Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; 340:409–417
  - 64 Corwin HL, Gettinger A, Pearl RG, et al. Efficacy of recombinant human erythropoietin in critically ill patients. *JAMA* 2002; 288:2827–2835
  - 65 Sharma AD, Sreeram G, Erb T, et al. Leukocyte-reduced blood transfusions: perioperative indications, adverse effects, and cost analysis. *Anesth Analg* 2000; 90:1315–1323
  - 66 Kopko PM, Holland PV. Universal leukocyte reduction. *Curr Opin Hematol* 2000; 7:397–401
  - 67 Hébert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA* 2003; 289:1941–1949
  - 68 Biffi WL, Moore EE, Offner PJ, et al. Plasma from aged stored red blood cells delays neutrophil apoptosis and primes for cytotoxicity: abrogation by poststorage washing but not prestorage leukoreduction. *J Trauma* 2001; 50:426–432