Transfusion-Related Acute Lung Injury
Report of a Clinical Look-Back Investigation

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Transfusion-related acute lung injury (TRALI) is a syndrome that includes dyspnea, hypotension, bilateral pulmonary edema, and fever. Symptoms may occur during the period between the beginning of transfusion and 4 hours afterward. The severity of symptoms can range from mild to severe. However, in a large series of TRALI cases, 100% required oxygen support, and 72% also required mechanical ventilation. In this same series, symptoms resolved within 96 hours in 80% of patients. The other 20% of patients required longer support, which was associated with persistence of pulmonary infiltrates on chest radiograph.

Pathophysiology
TRALI has been associated with the presence of granulocyte antibodies, HLA class I antibodies, and HLA class II antibodies, and biologically active lipids in donor plasma. All plasma-containing blood components, including red blood cells, platelets, fresh frozen plasma (FFP), and cryoprecipitate, have been implicated in TRALI. Infusion of even small volumes of plasma can trigger the reaction. Intravenous immunoglobulin prepared from a large pool of plasma has also been reported to cause TRALI, but pooled solvent-detergent-treated plasma has not.

Severity of TRALI does not appear to be related to the volume of plasma infused, but may be correlated with the degree of hypoxemia. Infusion of white blood cell antibodies alone is probably not sufficient to induce TRALI. Approximately 20% of women who have had 2 pregnancies have antibodies to leukocytes. Therefore, if infusion of antibodies alone were sufficient to cause TRALI, the reaction would be relatively common. Although it seems natural to assume that the transfusion recipient must possess the corresponding leukocyte antigen for an antibody to cause TRALI, such an association has not been demonstrated. Little is known regarding the effect of antibody titer, antibody avidity, or leukocyte-antigen density on the severity or frequency of TRALI reactions.

Other recipient factors, however, may play a role in TRALI. A 2-event hypothesis of TRALI has been advanced as a possible cause of the syndrome.

Context
Transfusion-related acute lung injury (TRALI) is a syndrome that includes dyspnea, hypotension, bilateral pulmonary edema, and fever. TRALI is the third leading cause of transfusion-related mortality, but it is probably underdiagnosed and underreported.

Objective
To determine if blood products from a frequent plasma donor, whose blood product was implicated in a fatal case of TRALI, caused symptoms of TRALI in other recipients of her plasma.

Design, Setting, and Participants
Retrospective chart review (conducted from November 2000 through April 2001) of 50 patients who received blood components within 2 years (October 1998 through October 2000) from a donor linked to a transfusion-related fatality.

Main Outcome Measure
Occurrence of mild/moderate (dyspnea with fever, chills, hypotension, and/or hypoxemia) or severe (acute pulmonary edema or need for mechanical ventilation) reaction associated with transfusion.

Results
Superimposed illness prevented assessment of TRALI in 14 patients. Of the 36 patient charts that could be reviewed, 7 mild/moderate reactions were reported in 6 patients (16.7%) and 8 severe reactions were reported in 8 patients (22.2%). Of 5 patients who received multiple transfusions from the same donor, 2 experienced 2 reactions: one had 2 mild/moderate reactions and the other had both a mild/moderate and a severe reaction. While 5 of the 7 mild/moderate reactions were reported to the hospital transfusion service, only 2 of the 8 severe reactions were reported. Only 2 reactions (1 mild/moderate and 1 severe) were reported to the regional blood collection facility.

Conclusions
TRALI was frequently underdiagnosed and underreported in recipients of blood products from a donor whose blood products may have caused TRALI in several transfusion recipients. Clinical education and awareness of this often-overlooked diagnosis are imperative for appropriate prevention and treatment.

See also Patient Page.
possible way of explaining why some recipients experience the reaction while others do not. It has been theorized that a transfusion recipient must first have a predisposing condition and then receive plasma that contains leukocyte antibody or biologically active lipid. Conditions thought to predispose transfusion recipients to develop TRALI include infection, cytokine administration, recent surgery, and/or transfusion of large volumes of blood products.

Leukocytes coated with antibodies localize to the pulmonary microvasculature. The release of cytokines by these antibody-coated leukocytes in the vascular space is thought to lead to an increase in vascular permeability and exudation of fluid and protein into the alveolar spaces. The degree of fluid exudation likely determines the severity of the pulmonary reaction and whether oxygen administration or mechanical ventilation is required.

Clinical Aspects
TRALI is fatal in 5% to 10% of cases, and is the third leading cause of transfusion-related mortality. Unfortunately, the signs and symptoms associated with TRALI can easily be attributed to other causes, including fluid overload, pneumonia, and acute respiratory distress syndrome (ARDS). Pulmonary edema, with bilateral “white out” on chest radiograph (Figure), similar to that seen in ARDS, is generally present along with fever and hypotension. The key to distinguishing TRALI from other forms of pulmonary edema is recognition that the pulmonary edema is noncardiogenic and that affected patients do not have volume overload.

This distinction is important because treating patients with TRALI with aggressive diuresis can result in further hypotension, shock, and death. Treatment should consist of maintenance of hemodynamic status and ventilatory assistance. An extensive review of TRALI, including diagnostic criteria, has recently been published.

Although TRALI is often discussed in the transfusion literature, it has received little attention among clinicians. Therefore, it is likely to be underrecognized as a clinical entity. We report a fatal case of TRALI following an FFP transfusion from a frequent plasma donor. Prior transfusions from this frequent plasma donor had not been reported to the regional blood center as causing any transfusion reactions.

Report of a Case
A 54-year-old man was given FFP for reversal of coumadin effect prior to elective knee surgery. Approximately 45 minutes after initiation of the FFP transfusion, the patient experienced respiratory arrest. He died 6 hours later despite aggressive attempts at cardiopulmonary resuscitation.

The blood donor, whose blood component was implicated in this reaction, was a 54-year-old woman who had made 290 previous donations. She had had 3 pregnancies, resulting in 2 births and 1 abortion. The donor’s plasma was found to be strongly positive for granulocyte 5b antibody. Although the granulocyte-specific 5b antigen is present in more than 90% of whites, this was the first time this donor was implicated in a case of TRALI, despite more than 15 years of frequent donation. The donor was permanently deferred from future donations. During the transfusion-related fatality investigation, the Food and Drug Administration (FDA) investigator requested that we perform a look-back study to determine if previous recipients of this donor’s blood components had experienced TRALI or other transfusion reactions.

METHODS
All donations made by the implicated donor in the 2 years prior to the fatality were investigated. Transfusion service medical directors at the facilities that transfused the donor’s FFP units were asked to perform chart reviews, including review of both physicians’ and nurses’ notes, to determine if any other recipients had an adverse reaction to this donor’s blood components. They were asked to determine and report if the recipients experienced fever, chills, hypotension, dyspnea, pulmonary edema, ARDS, or any other untoward event within 6 hours of transfusion.

Reactions were classified as either mild/moderate or severe. Mild/moderate reactions consisted of dyspnea with fever, chills, hypotension and/or oxygen desaturation, but without documented evidence of acute pulmonary edema or need for mechanical ventilation. Severe reactions were defined as any reaction with clinical or radiographic evidence of acute pulmonary edema and/or need for mechanical ventilation within 6 hours of transfusion. Recipients were excluded from the analysis if their underlying clinical condition prevented the reviewer’s ability to determine if a symptomatic reaction was related to the transfusion. These preexisting conditions included pulmonary edema, ARDS, or rapidly deteriorating clinical status resulting in efforts of cardiopulmonary resuscitation prior to transfusion of the blood component.

RESULTS
The donor made 73 donations (72 plasmaphereses and 1 whole blood) in the 2 years prior to her deferral. A total of 54 patients received 63 blood products from this donor. The remaining components were either quarantined when the donor was deferred or not transfused for other reasons. Underlying illness prevented evaluation for evidence of TRALI following transfusion.
in 14 patients. Charts were unavailable for review in 4 patients. 

Of the 36 patient charts that could be evaluated, 13 (36.1%) indicated a transfusion reaction. The clinical scenarios of the patients identified as having had a transfusion reaction are presented in the Table. All reactions were temporally associated with an infusion of FFP. Seven mild/moderate reactions were identified in 6 (16.7%) recipients. Severe reactions were reported in 8 (22.2%) recipients. Of the 5 patients who received multiple transfusions from this donor, 2 experienced 2 reactions each: 1 had 2 mild/moderate reactions, and the other had both a mild/moderate and a severe reaction. Seven (46.7%) of the 15 reactions (5 of 7 mild/moderate, 2 of 8 severe) were reported to the hospital’s transfusion service. Only 2 reactions (13.3%) were reported to the blood collection facility: one was the fatality and the other was a mild/moderate reaction that occurred while the fatality was under investigation.

**COMMENT**

Our findings suggest that TRALI is frequently not diagnosed. Lack of recognition of this syndrome can result in inappropriate treatment, as well as failure to report the reaction to the transfusion service and the blood collection facility. Lack of recognition of TRALI and its reporting in this series of cases led to numerous reactions and, ultimately, a fatality that might have been prevented.

TRALI should be included in the differential diagnosis of respiratory dis-

**Table. Clinical Scenarios of 15 Transfusion-Related Acute Lung Injuries Among 13 Patients**

<table>
<thead>
<tr>
<th>Severity of Transfusion Reaction</th>
<th>Patient Diagnosis</th>
<th>Reason for Transfusion</th>
<th>Clinical Manifestations</th>
<th>Timing of Reaction</th>
<th>Clinical Impression</th>
<th>Transfusion Reaction Suspected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/moderate</td>
<td>Thrombotic thrombocytopenic purpura†</td>
<td>Plasma exchange</td>
<td>Chills, dyspnea</td>
<td>30-min posttransfusion</td>
<td>Febrile reaction</td>
<td>Yes</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>Coumadin reversal</td>
<td>Chills, fever, dyspnea, tachycardia</td>
<td>1-h posttransfusion</td>
<td>Febrile reaction</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Coumadin reversal</td>
<td>Fever, dyspnea, tachycardia</td>
<td>During transfusion</td>
<td>Volume overload</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>HIV, thrombotic thrombocytopenic purpura</td>
<td>Plasma exchange</td>
<td>Chest pain, rigors, tachyplea</td>
<td>20-min posttransfusion</td>
<td>No diagnosis</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>HIV, thrombotic thrombocytopenic purpura</td>
<td>Plasma exchange</td>
<td>Chills, nausea, vomiting, oxygen desaturation</td>
<td>1-h posttransfusion</td>
<td>No diagnosis</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Internal bleeding, automobile crash</td>
<td>Blood loss</td>
<td>Fever, dyspnea</td>
<td>During transfusion</td>
<td>Transfusion-related acute lung injury</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>Gastrointestinal tract bleeding</td>
<td>Fever, hypotension, dyspnea</td>
<td>20-min posttransfusion</td>
<td>Febrile reaction</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Thrombotic thrombocytopenic purpura†</td>
<td>Plasma exchange</td>
<td>Respiratory failure, tachycardia, pulmonary edema</td>
<td>1- to 2-h posttransfusion</td>
<td>Cardiogenic vs noncardiogenic pulmonary edema</td>
<td>No</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>Coumadin reversal</td>
<td>Dyspnea, respiratory failure</td>
<td>During transfusion</td>
<td>No diagnosis</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>Plasma exchange</td>
<td>Tachyplea, tachyplea, chest pain, pulmonary edema</td>
<td>During transfusion</td>
<td>Fluid overload</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Ovarian tumor</td>
<td>Blood loss in operating room</td>
<td>Acute respiratory distress syndrome</td>
<td>1- to 2-h posttransfusion</td>
<td>Multifactorial</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Morbid obesity</td>
<td>Blood loss in operating room</td>
<td>Fever, tachycardia, acute respiratory distress syndrome</td>
<td>During transfusion</td>
<td>Rule-out bleeding/ infection</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Internal bleeding, automobile crash</td>
<td>Blood loss</td>
<td>Fever, chills, hypotension, acute respiratory distress syndrome</td>
<td>2-h posttransfusion</td>
<td>Rule-out bleeding</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Internal bleeding, automobile crash</td>
<td>Blood loss</td>
<td>Fever, acute respiratory distress syndrome</td>
<td>During transfusion</td>
<td>Reaction to foreign proteins in fresh frozen plasma</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Knee replacement</td>
<td>Coumadin reversal</td>
<td>Pulmonary edema, respiratory and cardiac arrest</td>
<td>During transfusion</td>
<td>Transfusion-related acute lung injury</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

*HIV indicates human immunodeficiency virus. †Indicates same patient. ‡Indicates same patient.
tress (with or without pulmonary edema or ARDS) in the setting of blood and component transfusions. To underscore this point, the FDA recently issued an advisory to alert physicians to the characteristics and morbidity of TRALI. We recommend that respiratory symptoms occurring within 2 hours of a transfusion, particularly when combined with fever or hypotension, should be reported to the transfusion service as a possible case of TRALI. An evaluation may then be undertaken and advice regarding treatment provided. Additionally, all confirmed cases of TRALI (both fatal and nonfatal) should be reported to the FDA.

Our investigation was performed at the request of the FDA and was not designed as a prospective clinical study. Therefore, we did not assemble a matched control group for comparison of rates. However, the general rate of transfusion reactions is approximately 1%. The hospital that received the most components involved in our study had transfused 51,792 blood components, which resulted in 229 documented transfusion reactions (0.44%) during the selected 2-year period. The reaction rate in our series of FFP transfusions is much higher. We are unable to determine if plasma transfusions from the implicated donor had a negative impact on the clinical course of the patients who were excluded from the analysis because of the complexity of their underlying illness. We may have thus underestimated the rate of TRALI, since severely ill patients may be especially predisposed to develop it.

Although donor antibodies to white blood cells may be found in about 70% of cases of TRALI, they are of uncertain significance when infused to recipients who do not display signs of TRALI. It is not clear whether a case of TRALI represents an isolated event, or whether an implicated donor (with white blood cell antibodies) can cause multiple cases of TRALI. Our study suggests that donors with leukocyte antibodies who are implicated in a case of TRALI may represent a future transfusion hazard. These findings also support performing a routine look-back investigation if a donor’s blood components are implicated in a TRALI case. The results of a look-back investigation can be used to learn more about this disorder and to determine if reactions are being underdiagnosed and unreported.

TRALI appears to have a spectrum of clinical presentation. Although more than 90% of recipients would be expected to be capable of reacting to granulocyte 5b antibody due to presence of the antigen on their leukocytes, we found only 36% had clinical evidence of a reaction. Prior authors made the diagnosis of TRALI only if there was evidence of pulmonary edema. Our look-back investigation at recipients of blood components from a donor with a granulocyte antibody suggests that TRALI may also present with symptoms that are more subtle. Approximately half of the cases we identified were less severe and involved dyspnea and oxygen desaturation but no pulmonary edema or ARDS.

TRALI has been estimated to occur about once in 5000 transfusions. A recent report suggests it may be higher. The only way to obtain the true frequency of TRALI is to both recognize and report cases to transfusion services and blood collection facilities. Diagnosis and reporting of this syndrome would allow for appropriate treatment and prevent additional reactions in other recipients. Permanent deferral of all future donations may sometimes be warranted. Look-back investigations may provide insight into why some recipients experience severe TRALI with pulmonary edema while others have less severe reactions.

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REFERENCES

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