EDUCATIONAL COMMENTARY – TRANSFUSION-RELATED ACUTE LUNG INJURY

Educational commentary is provided through our affiliation with the American Society for Clinical Pathology (ASCP). To obtain FREE CME/CMLE credits click on Continuing Education on the left side of the screen.

Learning Outcomes
Upon completion of this exercise, the participant should be able to:

- describe the signs and symptoms of transfusion-related acute lung injury (TRALI).
- discuss proposed mechanisms and treatment of TRALI.
- delineate the investigation of possible TRALI.
- formulate strategies to prevent TRALI.

In the 1950s, individual case reports documented transfusion reactions characterized by dyspnea and acute respiratory failure with pulmonary edema in the absence of left ventricular failure. During this time, pulmonary injury related to transfusion was only recognized in conjunction with anaphylaxis and circulatory overload; however, these case reports led to the recognition of transfusion reactions characterized by acute respiratory failure with “noncardiogenic pulmonary edema.” Upon investigation in the 1970s, leukoagglutinating and lymphotoxic antibodies to human leukocyte antigens (HLA) were discovered in 85% to 90% of the transfused components. In 1985, this constellation of findings was coined “transfusion-related acute lung injury (TRALI).” Since then, several mechanisms have been proposed to explain the pathophysiology of these signs and symptoms.

Acute Lung Injury (ALI) and TRALI
Acute lung injury (ALI) was defined in 1994 by the American-European consensus conference as acute hypoxemia with a PaO₂/FiO₂ of ≤300 mmHg and a chest x-ray film demonstrating bilateral pulmonary edema. A Canadian consensus panel, convened in 2004, incorporated the above definition of ALI and added additional criteria to characterize TRALI (see Table I).

<table>
<thead>
<tr>
<th>TABLE I. TRALI Criteria Defined by Canadian Consensus Conference.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute onset</td>
</tr>
<tr>
<td>2. Acute lung injury with hypoxemia: PaO₂/FiO₂ ≤300 or SpO₂ &lt;90% on room air</td>
</tr>
<tr>
<td>3. During or within 6 hours of transfusion</td>
</tr>
<tr>
<td>4. Bilateral alveolar and interstitial infiltrates on chest x-ray film</td>
</tr>
<tr>
<td>5. No evidence of left atrial hypertension or circulatory overload</td>
</tr>
<tr>
<td>6. No preexisting ALI before transfusion</td>
</tr>
<tr>
<td>7. No temporal relationship to risk factor for ALI</td>
</tr>
</tbody>
</table>
EDUCATIONAL COMMENTARY – TRANSFUSION-RELATED ACUTE LUNG INJURY (cont.)

Unlike ALI, which is usually irreversible, the lung injury in TRALI is usually transient. The pulmonary edema is bilateral involving the entire lung and evolves into a characteristic “whiteout” with diffuse fluffy interstitial and alveolar infiltrates on chest x-ray film. Other symptoms associated with this reaction may include: fever with or without chills, dyspnea, cyanosis, tachycardia, and hypotension, which may be preceded by hypertension. Upon auscultation, the patient has diffuse rales and may demonstrate exudative frothy tracheal fluid. These patients lack signs and symptoms associated with circulatory overload such as jugular venous distension and S3 gallop with normal central venous and pulmonary capillary wedge pressures. In addition, they are unresponsive to diuretics.

Unfortunately, laboratory tests in the acute setting of TRALI are not helpful in making the diagnosis. Most recently, a study looked at the usefulness of brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) to distinguish TRALI from transfusion-associated circulatory overload (TACO); however, due to the overlap of test values, these tests have limited diagnostic value.

Pathophysiology

Although the precise mechanism of TRALI has not been determined, there are 2 widely accepted theories regarding its pathophysiology. The first proposed mechanism relies on the formation of antibodies to HLA class I antigens, HLA class II antigens, and human neutrophil antigens (HNA) following exposure to WBC antigens during transfusion, pregnancy, or transplantation. The transfused donor antibodies bind and coat the recipient's neutrophils, which localize within the pulmonary microvasculature. The resultant immune complex activates complement, subsequently damaging the pulmonary endothelium and allowing leakage of proteinaceous fluid into alveolar spaces, accounting for the observed pulmonary edema.

The second model, or “2-hit hypothesis” theory, requires 2 events in which biological response modifiers (BRMs) or leukoagglutinating antibodies play a role. Biological response modifiers are lipophilic compounds or cytokines that accumulate in cellular blood products and are capable of activating and enhancing the oxidative burst in polymorphonuclear (PMN) cells. The first event is a physiological stress that occurs in the patient, such as massive transfusion, surgery, or sepsis, that causes the release of proinflammatory mediators. This leads to activation of the pulmonary vascular endothelium and neutrophils causing sequestration of neutrophils within the pulmonary microvasculature. The second event is the transfusion of BRMs or leukoagglutinating antibodies that activate the already primed neutrophils present in the pulmonary microvasculature. The activated neutrophils release proteolytic enzymes causing pulmonary capillary and endothelial damage resulting in fluid leakage into the alveolar spaces. The patient may experience rapid pulmonary edema, large fluid loss, hypovolemia, and hypotension.
EDUCATIONAL COMMENTARY – TRANSFUSION-RELATED ACUTE LUNG INJURY (cont.)

Transfusion-related acute lung injury has been reported with transfusion of all components containing plasma, including whole blood, RBCs, platelets, granulocytes, and cryoprecipitate. Most implicated components have >60 mL of plasma; however, components with as little as 10 mL of plasma have caused TRALI. A case of TRALI in the setting of intravenous immunoglobulin (IVIG) infusion has been reported.

Treatment and Prevention
The true incidence of TRALI is not known because of diagnosis and reporting inaccuracies. Estimates of TRALI incidence are between 1 in 1,300 to 5,000 transfusion events. Currently TRALI represents the majority of transfusion-related fatalities reported to the Food and Drug Administration (FDA).

Successful treatment of TRALI requires aggressive supportive care with oxygen supplementation that may require mechanical ventilation. Pressor and volume support may also be required for treatment of hypotension. Steroids and other immunosuppressants have not shown any therapeutic benefit. Diuretics are often used for initial treatment of transfusion-associated respiratory distress because distinguishing TRALI from TACO is difficult. While patients with TACO show improvement after diuresis, a lack of response supports a diagnosis of TRALI.

Approximately 80% of patients with TRALI clinically improve within 48 to 96 hours after the adverse event. Because no diagnostic tests are available, TRALI remains a diagnosis of exclusion. The investigating physician must rule out other causes of respiratory distress associated with transfusion. These include circulatory overload, severe allergic reactions with respiratory compromise, sepsis, and myocardial infarction. While the presence of lymphotoxic antibodies to HLA or granulocyte-specific antibodies in the donor or recipient plasma along with a positive reverse lymphocyte crossmatch between the donor’s serum and the patient’s lymphocytes provides support for the diagnosis of TRALI, these tests are usually only available in specialty laboratories and the results are usually not available until well after treatment is initiated. In addition, samples must also be obtained from the donor.

In the other 20% of patients who do not rapidly recover, approximately 2 out of 10 patients will experience slow resolution of symptoms, with persistent hypoxemia and pulmonary infiltrates for >7 days. Death occurs in 5% to 10% of TRALI cases. Death can occur within the first few hours, days, or weeks after transfusion and is most commonly due to the development of acute respiratory distress (ARD). Microscopic examination of tissue from autopsy shows widespread leukocyte infiltration, hyaline membrane formation, destruction of normal lung tissue, and proteinaceous fluid filling alveolar airspaces.

All transfusion reactions should be reported to the transfusion service, and all cases of TRALI must be reported to the collection facility for donor management. The donor center will then trace and quarantine
all other in-date components manufactured from the donor. If additional components have been transfused, the transfusing facility must evaluate the recipients for possible signs or symptoms of a transfusion reaction. The donor center gathers information from the transfusing facility as a part of its evaluation to help determine if donor follow-up is necessary.

Because TRALI is a diagnosis of exclusion, based on a constellation of findings, no consensus on prevention strategies has been developed. Multiple strategies are currently used to minimize the risk. These are listed in Table II. The American Association of Blood Banks (AABB) recommends minimizing the transfusion of components that contain a high volume of plasma from donors who are alloimmunized against leukocyte antigens. In addition, all transfusion services and collection facilities must monitor and report all cases of TRALI. An important means of prevention is to transfuse patients conservatively. Of note, all cases of transfusion-related mortality must be reported to the FDA.

**TABLE II. Strategies To Minimize the Risk of TRALI.**

1. Permanent deferral of donors implicated in a previous case of TRALI or severe respiratory transfusion reaction
2. Divert plasma donations for fractionation from multiparous women (>3 pregnancies)
3. Test donations from multiparous women for HLA or neutrophil antibodies before making plasma
4. Exclusive use of male donors for plasma

**Summary**

Transfusion-related acute lung injury is a noninfectious reaction that is a leading cause of transfusion-related fatalities. Because it is a diagnosis of exclusion, based on clinical signs and symptoms, hospital personnel who administer transfusions must be trained to recognize TRALI. Consensus criteria are guidelines to the diagnosis, but no confirmatory test is available. Although the exact mechanism is not known, TRALI is associated with transfusion of leukocyte antibodies and BRMs initiating a sequence of events leading to cellular activation and leakage of proteinaceous fluid into alveolar spaces. Primary treatment involves aggressive respiratory and volume support while the condition resolves. Multiple strategies proposed to reduce the risk of TRALI involve identifying and deferring leukocyte alloimmunized donors; however, none of these approaches will completely eliminate TRALI. All cases of severe respiratory transfusion reactions must be evaluated by the transfusion service. All cases of TRALI must be reported to the collection facility for product management of in-date products and the implicated blood donor.
EDUCATIONAL COMMENTARY – TRANSFUSION-RELATED ACUTE LUNG INJURY (cont.)

Suggested Reading


© ASCP 2009