Problem-Based Learning Discussion
2009 SCA Annual Meeting

Transfusion Related Acute Lung Injury

Christopher J O’Connor, MD
Director of Cardiothoracic Anesthesia
Rush University Medical Center
Chicago, Il

Antonio Hernandez, MD
Director, Cardiothoracic & Transplant Anesthesiology
Department of Anesthesiology
University of Texas Health Science Center at San Antonio
Director, Surgical Intensive Care Unit
Audie L. Murphy VA Hospital

CASE PRESENTATION

A 49 year-old man with a history of alcohol-induced cirrhosis presented for orthotopic liver transplantation. His medical history is remarkable for mild hypertension treated with metoprolol and aldactone; recent admissions for ascitic fluid drainage, spontaneous bacterial peritonitis and transient episodes of hepatic encephalopathy; and a prior history of an open cholecystectomy. His admission laboratories were remarkable for serum sodium of 132 mEq/L, BUN of 25 mEq/dL, creatinine of 1.9 mg/dL, hemoglobin of 9.8 mg/dL, INR of 2.0 sec, platelet count of 85,000, albumin of 2.0 mg/dL, bilirubin of 4.1 mg/dL, and a normal CXR and ECG. His MELD score was 26. Physical examination revealed a 75 Kg male with obvious ascites, some stigmata of chronic liver disease and decreased breath sounds, but otherwise an unremarkable exam. BP was 118/70 and heart rate of 70 BPM.

Large bore sheaths were placed in both internal jugular veins for rapid blood transfusion; placement of a pulmonary artery catheter (PAC); and the introduction of a 14 Fr infusion catheter for veno-veno bypass. Baseline pulmonary artery and pulmonary artery occlusion (PAP and PAOP, respectively) pressures were normal and the cardiac output was 8.2 L/min. The pre-anhepatic phase was remarkable for significant bleeding due to adhesions. Prior to initiation of VVB, 15 units of PRBC’s and 17 units of FFP had been transfused. The anhepatic phase and reperfusion were otherwise unremarkable. Following reperfusion, however, bleeding was substantial. Hemostatic laboratory values revealed an elevated INR and evidence for mild fibrinolysis. Seven hours into the procedure, 30 units of PRBC’s, 4 units of platelets, 40 units of FFP, 2 units of cryoprecipitate and 2400 mL of cell saver blood had been administered, along with 3,600 units of recombinant Factor VIIa. At this point, the arterial oxygen saturation had decreased to 91% with an FiO2 of 1.0, PEEP of 7 cm H2O, and a tidal volume of 600 ml and respiratory rate of 15. The PAO2 was 85 and extensive clear secretions were suctioned from the endotracheal tube. A CXR, though of poor quality, suggested bilateral pulmonary infiltrates, consistent with pulmonary edema. The patient was taken to the SICU where continuous arterial venous ultrafiltration (CAVH) commenced.

QUESTION:
• What is the differential diagnosis of this patient’s hypoxemia?
• How would you determine the etiology of the pulmonary edema, i.e. heart failure, ARDS, TRALI, transfusion reaction, aspiration, etc.?
• What hemodynamic and respiratory parameters would help in the diagnosis?

The PEEP is increased to 12 cm H₂O, the tidal volume decreased to 500 mL, and the respiratory rate increased to 18 BPM. The peak airway pressures are now 32 cm H₂O (decreased from 50 30” prior) and an ABG reveals a pH of 7.25, PCO₂ of 54 mm Hg, and PAO₂ of 80 mm Hg. The PAOP is 13 mm Hg and the PAP’s are 35/22 mm Hg, with a CVP of 11 mm Hg. The CO is 10.2 L/min and the SVR is 600 dynes/sec/m². A tentative diagnosis of TRALI is made and the procedure expeditiously completed. The patient is taken to the SICU with the above noted ventilatory parameters.

QUESTION:
• What are the risk factors for TRALI? How is it diagnosed?
• What are the treatment options for TRALI? What is the optimal mechanical ventilatory strategy?
• What is the prognosis of TRALI?

DISCUSSION:

Transfusion related acute lung injury (TRALI) is a term that has evolved over time. TRALI has been previously reported as pulmonary hypersensitivity reaction to transfusion (1), pulmonary infiltrates associated with leukoagglutinin in transfusion reactions (2), and pulmonary edema in the course of a blood transfusion without overloading the circulation (3), just to name a few. It is clear through the initial reports, that TRALI is similar yet distinct from other etiologies of pulmonary edema and respiratory failure. As such, we intend to describe aspects of TRALI to include the incidence, definition(s) & clinical presentation, pathophysiology, treatment and strategies for prevention.

Incidence

The incidence of TRALI is truly unknown, due to suspected underreporting and unrecognized respiratory failure related to transfusion of blood products. In October of 2004, the FDA reported that TRALI was the most frequent cause of transfusion-related deaths (4). It is estimated that the incidence of TRALI from transfusion is as follows: 1 in 5,000 units of blood (5), 1 in 2,000 units of plasma, (6) 1 in 7,900 units of FFP (7), and 1 in 432 units of whole blood derived platelets (8). This incidence is based upon the definition established in 2004.

Definition & Clinical Presentation

In 1985, MA Popovsky and SB Moore coined the term “transfusion related acute lung injury”, or TRALI, after reviewing a case series from the Mayo Clinic (9). This case series from 1982 through 1984 included 36 cases, 31 of which included surgical patients and 5 medical patients. The higher incidence of TRALI in surgical patients noted in this series heralds the evolution of the definition of TRALI. TRALI was described as respiratory distress, hypoxemia, and hypotension in the absence of circulatory overload, occurring within 1-2 hours after transfusion of blood products containing plasma. Between 1991 and 1995, the University of Alberta in Canada set forth their criteria for TRALI, based on the review of the
largest report of cases at that time. Their criteria included a) respiratory insufficiency accompanied by significant oxygen desaturation, quantified by pulse oximetry or ABG, b) the degree of respiratory compromise required immediate medical intervention, c) onset of symptoms temporally related to transfusion, and d) no other clinical cause was evident for pulmonary compromise. Keep in mind that TRALI is a form of ALI, for which a definition had not been established.

In 1994, The North American-European Consensus Conference established the description of acute lung injury, which aided in communicating data related to ALI in clinical practice and research (10). This resulted in advancements in educating the medical community with identification and treatment of patients with ALI and ARDS. The criteria for ALI include the following: a) acute setting, b) a lack of clinical evidence of left atrial hypertension, c) chest radiograph demonstrating bilateral infiltrates seen on frontal chest radiograph, d) Hypoxemia — ratio of PaO2/FiO2 <300 mmHg regardless of positive end-expiratory pressure level; <200 mmHg for ARDS. It was in 2004, when The National Heart, Lung and Blood Institute Working Group on TRALI set forth the criteria for TRALI (11). Rather than redefining new criteria for ALI related to transfusion, the Working Group on TRALI adapted the ALI criteria set forth by the American-European Consensus Conference. Therefore, the criteria for TRALI set forth by the Working Group is as follows: a) Criteria for ALI, with the addition of oxygen saturation of <90% on room air, b) there should be no preexisting ALI before transfusion, c) the traditional temporal relationship of onset of symptoms or signs during or within 6 hours of transfusion should be used, d) in patients with an alternative ALI risk factor, TRALI is still possible, e) massive transfusion should not exclude the possibility of TRALI (11). This definition has been adopted as the sole criteria for TRALI, until recently. Recently, PE Marik and HL Corwin described and coined the term “delayed TRALI syndrome” which is distinct from the “classic” TRALI presentation (12). The table below lists and compares the difference between classic versus delayed TRALI. Key differences exist in the time of onset, pathophysiology, course, and most significantly mortality.

<table>
<thead>
<tr>
<th></th>
<th>Classic TRALI</th>
<th>Delayed TRALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset</td>
<td>Within 2 hrs, up to 6 hrs</td>
<td>6-72 hrs</td>
</tr>
<tr>
<td>Rate of development</td>
<td>Rapid</td>
<td>Over several hours</td>
</tr>
<tr>
<td>Cofactors</td>
<td>None</td>
<td>Sepsis, trauma, burns</td>
</tr>
<tr>
<td>Setting</td>
<td>Outside ICU</td>
<td>ICU patient</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Antineutrophil antibodies</td>
<td>Bioactive mediators</td>
</tr>
<tr>
<td>No. units</td>
<td>Usually one</td>
<td>Multiple</td>
</tr>
<tr>
<td>Incidence</td>
<td>Relatively uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>1/5000 RBC transfusions</td>
<td>5%-25% ICU patients</td>
</tr>
<tr>
<td>Fever</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Course</td>
<td>Usually resolves in 48-96 hrs</td>
<td>Resolves slowly</td>
</tr>
<tr>
<td>Resolution</td>
<td>Complete</td>
<td>May progress to fibroproliferative ARDS</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>5-10</td>
<td>35-45</td>
</tr>
</tbody>
</table>

TRALI, transfusion-related acute lung injury; ICU, intensive care unit; RBC, red blood cell; ARDS, acute respiratory distress syndrome.

Pathophysiology

TRALI is but a form of ALI. Pulmonary edema secondary to increased pulmonary endothelial permeability to protein is pathognomonic of ALI & ARDS, regardless of the etiology. There are two proposed mechanisms for the development of TRALI. One involves the presence of antibodies, and the other involves the presence of biologically active substances such as cytokines and lipids.

The first mechanism involves the presence of antibodies present in donor blood or blood products, that bind recipient leukocytes. These antibodies activate recipient neutrophils in pulmonary
capillaries and promote pulmonary capillary endothelial leak (5). Supporting this hypothesis, I refer back to the Mayo Clinic series of TRALI cases, in which 89% of cases had antibodies to granulocytes and 72% had antibodies to lymphocytes.

The second hypothesis involves the transfusion of substances such as cytokines and lipids, that have significant neutrophil priming potential (6). Extensive work by CC Silliman and his associates have gathered data regarding this mechanism. In this mechanism, there is a prerequisite of endothelial priming or injury, such as that noted from surgery, trauma, or sepsis. Next, the transfusion of biologically active substances (lipids and cytokines) prime and activate neutrophils leading to lung damage and capillary leak. Not only does the lung receive ~97% of the entire cardiac output, but it is the vascular bed that first interacts with transfused products. This results in an optimal setup for neutrophil microvascular congestion, endothelial interaction and damage, and not uncommonly neutrophil margination into the alveolar space.

Although these mechanisms are described independently, they are not mutually exclusive and likely occur simultaneously. In the publication by Marik and Corwin, they present information that may aid in the mechanism involved for the different entities of TRALI, classic versus delayed. As noted in the table above, it seems that the antibody mechanism is more likely to occur outside the intensive care unit and non-surgical patients. The delayed type of TRALI is more likely to occur in surgical patients, such as our case of Liver transplantation. The bottom line is that neutrophils are essential for TRALI to develop. Without neutrophils, TRALI would not be possible, regardless of the mechanism involved.

Treatment & Prevention

Management of TRALI is essentially supportive, like for other etiologies of ALI. This includes endotracheal intubation and protective mechanical ventilation (6 mL/kg of ideal body weight), increase in mean airway pressure by adding PEEP, as described by the ARDS Network (13). Using the inflation of a latex balloon as an analogy, when we initially inflate a balloon we need to generate much pressure with little gain in volume. However, after the initial resolution of “atelectasis stent”, it becomes easier to introduce volume into the balloon. The pressure/volume required to overcome the atelectasis stent I will refer to as the lower infection point (LIP). As we continue to introduce air into the balloon, at some point minimal volume into this balloon will result in increased pressure, which represents a state of overinflation and what I will refer to the upper infection point (UIP). Essentially, like a latex balloon, appropriate administration of PEEP will allow the alveoli to remain above the LIP and avoid atelectasis. Protected ventilation will aid in avoiding alveolar over distension by keeping the tidal volume beneath the UIP. Please see the figure below which is adapted from Martin Tobin’s publication in the New England Journal of Medicine (14).
Other strategies in managing ALI include avoiding the use of furosemide, unless treating hypervolemia. Pearl Toy and O Gajic described a sequence of steps to follow when considering the diagnosis of TRALI (15). These steps are summarized in the table listed below which is from their publication. Fatal cases due to TRALI should be reported to the FDA within 72 hours. Since treatment is supportive at best, the key is to prevent the development of TRALI.
The first goal is to avoid unnecessary administration of blood products. When related to blood, L Shore-Lesserson has demonstrated that point of care testing aids in decreasing transfusion therapy in cardiac surgery (16), and P Hebert demonstrated improved survival with conservative transfusion therapy in adult ICU patients (17) as did Jacques Lacroix in pediatric ICU patients (18). In our specific case presentation, de Boer and colleagues demonstrated that both PRBC and platelet transfusion are independent predictors of decreased survival in orthotopic liver transplantation (19). The next step is to choose the appropriate therapy to reduce the risk of TRALI. Of these choices, consider requesting leukoreduced blood, as it has been shown to mildly reduce mortality in patients with existing ALI (20). If plasma is indicated, consider the use of plasma from a non-multiparous female donor(s), since multiparous female donor plasma has been noted to increase the risk of TRALI (21). This practice was adopted in the United Kingdom in 2003, based on recommendations set forth by the UK hemovigilance scheme Serious Hazards of Transfusion, and implemented by the National Blood Service in an effort to reduce TRALI. A recent publication by Chapman CE and colleagues reviewed the results from implementing this practice in the United Kingdom. They noted a reduction in TRALI related to FFP transfusion from 15.5 per million units in 1999 to 3.2 per million units in 2004. Likewise, they noted a reduction in TRALI related to platelet transfusion from 14 per million units in 1999 to 5.8 per million units from 2005-2006 (22).

In conclusion, in an effort to aid our patients that develop TRALI, one must identify if our patient meets the criteria of either classic or delayed TRALI. Presently, we are limited to making the diagnosis based on clinical presentation, and omitting compounding etiologies based on data obtained from invasive monitoring and bedside assessment. Brain natriuretic peptide has been shown to aid in distinguishing hypervolemia associated in massive transfusion (> one blood volume), but its role is moderately reliable at best (23). As we gain more knowledge about TRALI, we may develop better tools for screening, diagnosis, and treatment. Since we are limited with our treatment for TRALI, the best management strategy is to avoid incurring injury. There are various “point of care testing” transfusion algorithms to aid in appropriate transfusion therapy. The key is to adopt a system that is feasible and accepted by the individual institution, based on the multidisciplinary team involved (anesthesiologists, surgeons, blood bank director, and hematologist) and resources available. The key is to abide to performance measures and evidence based practice; first rule of medicine—Do No Harm.

Table 1. Immediate Actions When Considering the Diagnosis of Transfusion-Related Acute Lung Injury

1. Stop the transfusion immediately.
2. Support the patient.
3. If the patient is intubated, obtain undiluted edema fluid as soon as possible (preferably within 15 min), and simultaneous plasma for determination of total protein concentrations.
4. Obtain a complete blood count with differential and chest radiograph.
5. Notify the blood bank of possible transfusion-related acute lung injury, request a different unit, and quarantine other units from the same donor.
6. Follow institutional policies for a transfusion reaction workup, and send to blood bank:
   - A patient blood specimen
   - Bags from units of blood transfused in the last 6 h
   - A copy of transfusion record forms and anesthesia record
   - Indicate the last unit transfused if possible
   - Results of the patient’s human leukocyte antigen type if available
REFERENCES:


Suggested Reading