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ABC Blood Bulletin

TRALI: Transfusion Related Acute Lung Injury

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Transfusion related acute lung injury (TRALI) is best described as a clinical constellation of signs and symptoms including dyspnea, cyanosis, hypotension, fever and chills along with physical findings of bilateral pulmonary edema. The symptoms typically begin within 1-2 hours of transfusion and usually are present by 4-6 hours. The severity can range from mild to severe but is related to the degree of hypoxia.¹

The syndrome is associated with significant morbidity and has been reported as the third most common cause of a fatal transfusion reaction. In a series of 36 patients with TRALI, all required oxygen support for a mean of 40 hours.² Mechanical ventilation was required in 72 percent; TRALI was determined to contribute significantly to mortality in 6 percent.

TRALI most often is associated with transfusion of whole blood, packed red blood cells (pRBCs) and fresh frozen plasma (FFP). There are rare reports of TRALI following transfusion of granulocytes, cryoprecipitate, platelet concentrates and apheresis platelets. Infusion of even very small volumes of blood can trigger this reaction. Estimates of frequency have ranged from 0.014 percent to 0.02 percent per unit transfused and

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from 0.04 percent to 0.16 percent per patient transfused.^{2,3}

Radiographic Findings: The development of bilateral pulmonary infiltrates after transfusion, without evidence of cardiac compromise or acute volume overload, should lead to suspicion of TRALI. The pulmonary infiltrates appear at the time of the reaction and resolve within 96 hours in about 80 percent of affected patients. Arterial blood gas values typically show hypoxemia and respiratory alkalosis paralleling the changes seen on chest x-ray and physical exam. Infiltrates may persist for at least 7 days in the remaining 20 percent. Persistence of infiltrates has been associated with difficulty weaning from mechanical ventilation. The radiographic findings tend to be more remarkable than the physical findings.

Etiology: Classically, the etiology of TRALI has been attributed to the presence of leukocyte antibodies in the plasma of multiparous donors directed against recipient white blood cells (WBCs). Granulocyte or HLA class I antibodies are found in at least one donor in about 70 percent of cases.² In some cases, HLA class II antibodies in donor plasma have been detected against recipient cells.⁴ The exact specificity of the antibody involved and documentation of the presence of the corresponding antigen in the recipient have been determined in only a few cases of TRALI.^{5,6}

TRALI

Clinical Picture:

- Noncardiogenic pulmonary edema
- Dyspnea, cyanosis, hypotension, fever, chills
- Develops within 1-2 hours of transfusion. Usually present by 4-6 hours

- Difficult to distinguish from Acute Respiratory Distress Syndrome

Pathogenesis:

- Sequestration of WBCs in pulmonary microvasculature leads to increased vascular permeability and pulmonary edema

Etiology:

- Antibodies against granulocyte, HLA class I or class II antigens
- Biologically active lipids in stored cellular blood components
- Pulmonary edema arises from capillary injury rather than volume overload

Treatment:

- Supportive ventilatory assistance
- Maintenance of hemodynamic status (e.g., saline infusion)
Diuretics are contraindicated

Less often, leukocyte antibodies, directed against donor white blood cells, are identified in the recipient. Interdonor reactions, caused by the interaction in the recipient of leukocyte antibodies from one donor with the leukocytes of another donor have also been reported. Popovsky et al. have hypothesized that donor antibodies more commonly cause TRALI than recipient antibodies because the former are able to react with the entire circulating and marginating pool of WBCs in the recipient.⁷ Antibodies in the recipient have a much smaller pool of donor WBCs in a blood component with which to react.

The pulmonary edema in TRALI is attributed to WBC-antibody interaction, with subsequent sequestration of WBCs in the pulmonary microvasculature, leading to

increased vascular permeability and accumulation of fluid and protein in the alveoli.

Another hypothesis of the etiology of TRALI is that biologically active lipids in stored blood components enhance polymorphonuclear cell (PMN) NADPH oxidase activity.⁸ This priming activity, however, is not present in non-cellular blood components or fresh cellular blood components.

Silliman et al. advanced a two-event hypothesis to explain the etiology of TRALI.⁹ The first event consists of a predisposing condition. The second is the infusion of biologically active lipids or antibodies to leukocytes in stored cellular blood components. These researchers demonstrated that there was significantly more PMN-priming activity present in post-transfusion samples from 10 patients who had TRALI reactions compared to their pre-transfusion samples or in pre- and post-transfusion samples from 10 control patients with only febrile or urticarial transfusion reactions. Additionally, all 10 patients with TRALI had a predisposing condition including infection, cytokine administration, recent surgery or massive transfusion. Only 2 of the 10 patients with febrile or urticarial reactions had a similar predisposing condition.

Diagnosis: The diagnosis of TRALI is based primarily upon clinical signs and symptoms, not laboratory findings. It is important to determine that the pulmonary edema is noncardiogenic, because it is treated differently than cardiogenic or volume overload types of pulmonary edema. Noncardiogenic pulmonary edema is clinically distinguished from other forms of pulmonary edema based upon normal to decreased pulmonary capillary wedge pressure, normal pulmonary artery pressure, absence of jugular venous distention, absence of murmurs or gallops, normal cardiac silhouette, absence of pulmonary vascular congestion and no

evidence of myocardial infarction by EKG and enzyme testing.

Laboratory confirmation of the clinical diagnosis of TRALI, although important, is performed at a later date. The donors of all components transfused within 6 hours of initiation of the reaction should be screened for the presence of granulocyte and HLA class I antibodies. If a large number of donors are involved, female donors or multiparous female donors can be screened for antibodies first. Then, if those donors are negative for antibody, male donors should be screened. If all of the implicated donors' units are negative, including for HLA class II antibodies⁴, the patient should be tested for leukocyte antibodies. To prove the diagnosis, the antibody present in the donor (or rarely the recipient) should correspond to an HLA or granulocyte antigen present in the recipient (or donor).

Treatment: Corticosteroids, epinephrine and diuretics traditionally have been used to treat TRALI. However, since the pulmonary edema in TRALI is not related to fluid overload or cardiac dysfunction, but to altered vascular permeability in the lungs with exudation of fluid and protein into the alveoli, it is logical that maintenance of adequate circulating volume is the most beneficial and appropriate therapy.¹⁰ Ventilatory assistance and circulatory support are the mainstays of treatment of TRALI; because the disease is self-limited, the majority of patients will respond to these therapies alone. The use of corticosteroids remains controversial. Since the pulmonary edema is due to capillary leak syndrome and is not secondary to volume overload, diuretic use may be detrimental and could lead to hypotension, and decreased cardiac output.

Prevention: Several approaches to the prevention of TRALI have been recommended. Most include limiting the amount of plasma transfused from implicated donors by diverting plasma to

recovered plasma and using pRBCs with either washed or frozen-deglycerolized. Popovsky et al. suggested that implicated donors should be told not to donate again.⁷

Given the rarity of TRALI, a more moderate approach probably is more realistic. The blood center that supplied the blood component should be notified. Any remaining blood product should be returned for studies, such as screening for HLA antibodies in the donor. HLA typing of the recipient will assist in determining specificity. Plasma from implicated donors should be diverted for protein fractionation. Transfusion of pRBCs from such donors when preserved in an anticoagulant-preservative solution like AS-2 probably is acceptable due to the small volume of plasma present in this component.

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