EDUCATIONAL COMMENTARY – TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)

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**Learning Objectives**

On completion of this exercise, the participant should be able to

- understand the definition of TRALI and its importance as the leading cause of transfusion-related fatalities;
- explain the pathophysiology of TRALI; and
- appreciate risk reduction methods.

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related fatalities in the United States, comprising 43% (13) of fatalities reported to the Food and Drug Administration (FDA) in fiscal year 2014. Cases of transfusion-related lung injury have been observed or noted since the 1950s, but it was not until 1983 that TRALI was clearly identified as a syndrome. Further, in 2004, definitions developed by the Canadian Consensus Conference (CCC) differentiated TRALI from possible TRALI. In 2007 the FDA began using the definition criteria for TRALI and possible TRALI and it includes both when reporting fatalities. TRALI generally occurs within six hours following a blood component transfusion, presenting as a new-onset bilateral non-cardiogenic pulmonary edema and hypoxemia. It is believed to be caused by donor antibodies to the human leukocyte antigen (HLA) or the human neutrophil antigen (HNA) and/or biologic response modifiers (BRMs) in the transfused product. The actual incidence of TRALI is unknown and it is suggested that TRALI continues to be overlooked or misdiagnosed owing to compounding complications. A 2012 study by Toy, et al. found that only 45% of TRALI cases were reported to the blood bank.

**Pathogenesis**

All plasma-containing products have been associated with causing TRALI, and it has been documented that as little as 10-20 mL of plasma has been implicated in TRALI reactions. The pathogenesis of TRALI is still not completely understood, but several models have been proposed. Up to 89% of TRALI cases are thought to be antibody-mediated TRALI, which involves the passive infusion of donor HLA or HNA antibodies that bind either neutrophils or monocytes leading to activation and pulmonary edema. It has been demonstrated that antibodies can directly activate neutrophils which release granules leading to vascular endothelium damage. HLA class II antibodies may induce platelets and monocytes to release cytokines and other inflammatory mediators, which subsequently activate neutrophils. One study screened 7920 donors for HLA class I and II antibodies and found antibodies present in 1.7% of
transfused males, 1% of non-transfused males, and 17.2% of females. In the females, the number of pregnancies correlated to the antibody positivity: one pregnancy, 11.2%; two, 22.3%; three, 27.5%; and four or more, 32.2%. Anti-HNA-3a has been implicated in fatal TRALI reactions. A donor look-back of one TRALI fatality due to anti-HNA-3a revealed that out of 36 previous plasma recipients of the same donor, 36% of the recipients had a transfusion reaction. There have also been reports of TRALI occurring in recipients without the presence of donor antibodies. BRMs that accumulate during blood storage have been found to cause antibody-independent neutrophil activation. Examples of BRMs include bioreactive lipids and CD40-Ligand (CD40L).

The two-hit model of TRALI pathogenesis describes two events occurring in the transfusion recipient: predisposition and transfusion. Before transfusion, a multiplicity of physiologic stressors causes sequestration and priming of neutrophils in the recipient’s pulmonary endothelium. Priming of neutrophils can occur in response to priming agents and inflammatory factors such as interleukin 8 (IL-8), infectious agents such as influenza A virus, recent surgery, and massive transfusions. The primed neutrophils enter through narrow capillaries into the endothelium and are sequestered in the lung until activation. Following transfusion of a product containing mediators such as HLA or HNA antibodies or BRMs, the neutrophils and endothelium are activated, resulting in pulmonary endothelial damage, capillary leakage, and pulmonary edema. This model describes events in high-risk patients. Recipient risk factors include positive pressure ventilation, elevated interleukin 8 (IL-8) levels, liver surgery, chronic alcohol abuse, shock, recent history of smoking, and positive fluid balance.

The two-hit model does not explain TRALI in non-critically ill patients, and it is difficult to determine the exact combination of factors required for TRALI to occur. Therefore, the threshold model has been introduced theorizing that a certain threshold must be overcome for a TRALI reaction to occur. In this model the presence of the primed neutrophils alone is below the TRALI threshold and requires activation, which is dependent upon the number of priming agents and their potency. The factors in the transfused product are not always enough to overcome the threshold, but in combination with a certain level of recipient predisposition can meet the TRALI threshold. This model has helped explain TRALI reactions in recipients with varying degrees of risk factors. In recipients with high-risk factors, a transfusion containing relatively low neutrophil-priming activity may be enough to overcome the threshold. In otherwise healthy recipients, all that is needed for TRALI to develop is a higher and stronger neutrophil and endothelial activation from the transfusion; in other words, more antibody or BRMs in the product. Toy, et al. determined that the highest transfusion risk factors include whole blood or plasma from female donors, HLA class II antibodies, and HNA antibodies.

The sufficient cause model, like the threshold model, is a general model that is not necessarily specific to diseases and can be used to explain any multicausal process. The sufficient cause model involves component cause, sufficient cause, and necessary cause. A component cause is any individual
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contributing factor. The sufficient cause is any possible combination of component causes that leads to disease. The necessary cause is the component cause always present in any sufficient cause. For example, the authors suggest that the transfusion is a necessary cause and in combination with other component causes, such as cardiac surgery and hematologic malignancy, will lead to TRALI. That particular combination of causes has now become the sufficient cause. This model does not allow for timing of events. There is no way to represent the timing of risk factors relative to one another or the chronologic order of these contributing factors. This model allows for inclusion of unknown component causes and may allow for further identification of risk factors.

Risk Reduction

It has been well documented that plasma-containing products from immunized donors pose the greatest risk for TRALI. In 2006, AABB recommended the use of low-risk plasma as an attempt to mitigate TRALI reactions. One multihospital study reported a decrease in TRALI incidence from 1 in 4,000 in 2006 to 1 in 12,000 in 2009, and the FDA reported a 63% decrease in TRALI fatalities following the implementation of risk reduction measures. After implementing the use of male-only plasma in 2007, the American Red Cross reported a decrease in nonfatal TRALI cases from 26 cases in 2006 to 7 cases in 2008. In 2014 AABB published a new standard in the 29th edition of Standards for Blood Banks and Transfusion Services requiring that plasma products and whole blood collected for transfusion be from male donors, never-pregnant female donors, or female donors who have been tested since their last pregnancy and found to be negative for HLA antibodies. Most blood centers choose to collect plasma from male donors only and test the female platelet donors for HLA antibodies. HNA antibody testing is not considered cost-efficient and HLA antibody testing can identify the at-risk donors, since donors who have HNA antibodies also often have HLA antibodies.

Diagnosis and Treatment

Some of the symptoms caused by TRALI can mimic other types of transfusion complications. It is important to differentiate between TRALI, anaphylactic reactions, sepsis, and transfusion-associated circulatory overload (TACO) so that proper treatment can be administered. Symptoms present in TRALI include dyspnea, fever, hypotension or sometimes hypertension and hypoxia. Anaphylactic reactions include hypotension and bronchospasms but no signs of fever or pulmonary edema are seen. Hypotension, vascular collapse, fever, and chills are signs of sepsis and TRALI, but respiratory distress occurs infrequently with a septic transfusion reaction. TACO presents very similarly to TRALI with respiratory distress, tachypnea, and cyanosis; however, the pulmonary edema is cardiogenic, and in TACO there is typically an increase in brain natriuretic peptide (BNP). A chest x-ray is helpful in distinguishing these two reactions. However, a comparison chest x-ray prior to transfusion must be present. Once TRALI is suspected, respiratory and circulatory support is necessary. In almost all cases,
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Oxygen supplementation with or without mechanical ventilation is required. The implementation of risk-reduction measures for TRALI has helped tremendously. Approximately 80% of patients recover from TRALI within 96 hours; however, TRALI is fatal in approximately 5-20% of cases.

The Future

Cost will play a role in future TRALI mitigation, but there is hope in further risk reduction methods. These include filters that absorb TRALI-associated antibodies and lipids, broad donor screening for HLA and HNA antibodies, and platelet additive solutions to reduce the plasma from the platelet transfusion. Solvent/detergent-treated plasma (SDP), used as a pathogen-reduction technology, was approved for release in the US in 2013. European studies have shown undetectable levels of TRALI-implicated antibodies, suggesting that the HLA and HNA antibodies are diluted and neutralized as a result of the large donor pools and the BRMs are removed during filtration of the product. Other studies have demonstrated no cases of TRALI with more than 13 million SDP units transfused. Fatalities due to TRALI have reduced drastically since the implementation of risk-reduction measures, but there remains room for improvement. It may be necessary to further identify and focus on the patients with higher risks for TRALI and modify risk factors.

References


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