INTRODUCTION
When a patient develops shortness of breath during or shortly after a blood transfusion, it is wise to ask the question, “Could this be a case of Transfusion Related Acute Lung Injury (TRALI)?” TRALI is the development of non-cardiogenic pulmonary edema occurring during or up to 6 hours after transfusion. Differentiation of TRALI from other causes of acute lung injury, requires evaluation of whether other symptoms, signs, and ancillary test findings associated with TRALI appear in a time-course consistent with TRALI. The diagnosis is initially clinical, as the condition has generally resolved by the time confirmatory testing is completed, however accurate diagnosis is needed to prevent the possibility of further incidents from the same donor.

The primary differential diagnosis includes pulmonary edema from hemodynamic imbalance (volume overload, cardiac dysfunction, oncotic imbalance), and other causes of acute lung injury with inflammatory pulmonary capillary leak (sepsis, aspiration, lung contusion, pneumonia, multiple trauma, drug overdose, burn, cardiopulmonary bypass, inhalation injury, acute pancreatitis). Other causes of dyspnea (pulmonary embolus, general allergic reaction) should also be excluded.

INCIDENCE, MORBIDITY & MORTALITY
The incidence has been estimated at one in 5000 units transfused and up to one in 625 transfused patients. Age, gender, and previous transfusion history are not known risk factors. Due to a lack of consensus as to which features are essential to the diagnosis, the precise incidence of TRALI is unknown.

The FDA Center for Biologics Evaluation and Research, has received reports of TRALI related fatalities in increasing numbers (2001 = 12 of 76 transfusion deaths, 2002 = 16 of 95, and 2003 21 of 94). As such, it represents the most common identified cause of death related to transfusion – more than ABO incompatibility or bacterial contamination – for each of those three years. Most deaths were associated with fresh frozen plasma transfusions; with a lesser number caused by packed red blood cell transfusions and apheresis platelet transfusions. In addition, 26 Non-fatal TRALI events were reported by licensed blood establishments through Med Watch or as Biological Product Deviation between 1999 and 2002.

CLINICAL FEATURES
The onset of TRALI is rapid, occurring during or within an hour of transfusion, but may occur up to 6 hours after transfusion. The most frequent presenting symptoms are: dyspnea, hypoxemia, bilateral pulmonary edema, and fever (1-2 degrees C). Other reported symptoms include: cyanosis, hypertension, and tachycardia. Hypotension is rare. The pulmonary edema in TRALI, is non-cardiogenic, exhibiting features consistent with increased vascular permeability, i.e. normal to decreased capillary wedge pressure, normal pulmonary artery pressure, absence of jugular venous distension, absence of murmurs or gallops, normal cardiac silhouette, absence of pulmonary vascular congestion, and usually >0.7 ratio of protein to fluid ratio in edema fluid. The chest X-ray shows pulmonary infiltrates, usually bilateral with alveolar and/or interstitial patterns without evidence of cardiac enlargement or fluid overload. Infiltrates resolve within 96 hours in about 80% of affected patients but may persist for seven days or more. Radiographic findings tend to be more remarkable than the physical findings. Most cases show significant clinical improvement within the first few hours of onset and generally resolve completely within 24 – 96 hours. In a series of 36 patients with TRALI, mechanical ventilation was necessary in 72% and all required oxygen support (mean duration: 40 hours). TRALI should be diagnosed with caution when pulmonary edema can be explained by an alternative etiology, e.g. myocardial or valvular heart disease, overhydration, or increased vascular permeability due other pathologic, traumatic and/or infectious causes.
**CLINICAL MANAGEMENT**

If the clinical scenario suggests possible TRALI, begin oxygen and supportive care with ventilation support. Saline infusion to improve cardiac output appears to be beneficial. Notify the blood bank and, if indicated, the blood center that supplied the blood component. Diuretics are not effective in treating TRALI, as the edema is from microvascular injury, not volume overload. Corticosteroids and epinephrine have not been shown to be effective.

**IMPLICATED BLOOD PRODUCTS**

TRALI is most often associated with transfusion of fresh frozen plasma, whole blood, and packed red blood cells. Other inciting products reported include: granulocytes, cryoprecipitate, random donor platelet concentrates and single donor platelets obtained by apheresis. Directed donations from mother to child, or from mother to father may present a higher risk due to sensitization of the mother to paternal antigens of the fetus during pregnancy.

**PATHOPHYSIOLOGY**

White blood cell antibodies are frequently identified in donor serum as part of a transfusion reaction evaluation following an episode of TRALI. In a study of 36 cases, 89% showed anti-granulocyte antibodies and 72% showed anti-lymphocyte antibodies in the serum. TRALI is most often associated with blood components obtained from donors sensitized from prior transfusion or pregnancy (especially multiparous females). Most have been found to contain HLA- or granulocyte-specific antibodies (e.g. anti-NA1, anti-NA2, anti-NB1, anti-NB2, anti-5b). Although WBC antibodies are usually found in the donor, TRALI can occasionally occur due to WBC antibodies in the recipient. Some studies suggest that the leukocyte – antibody interaction in TRALI leads to pulmonary microvascular leukocyte sequestration, increased vascular permeability, exudation of fluid and protein into alveolar spaces and minimal pulmonary interstitial inflammation. If the condition persists, there can be hyaline membrane formation.

Additional non-immune mechanisms have been suggested by recent studies in which the largest proportion of patients experiencing transfusion related acute lung injury were without anti-leukocyte antibodies, instead showing increased interleukin 6 and lipid activity. Several studies have suggested other predisposing factors (general anesthesia, infection, exogenous cytokines, recent surgery, massive transfusion, infusion of products with lipid biologically activated by storage conditions) may be necessary for a clinically significant TRALI reaction in addition to the leukocyte – antibody interaction.

---

**LABORATORY CONFIRMATION**

In the appropriate clinical context, the presence of anti-leukocyte antibodies in the donor, followed when feasible, by a demonstration of the corresponding antigen in the recipient confirms the clinical diagnosis. A negative study is not definitive in excluding TRALI.

**REPORTING**

Mandatory reporting of deaths and voluntary reporting of non-fatal TRALI reactions can be done with forms obtained at [http://www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm), by fax at 1-800-FDA-0178, or mail at MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852.

**FURTHER READING**

More in-depth analysis can be found in a recent review article which provided much of the material for this discussion:


Other References:


Holness L, Transfusion Related Acute Lung Injury (TRALI), The FDA current view, Blood Products Advisory Committee July 22-23, 2004


Copyright @2004, Institute for Transfusion Medicine

Editor: Donald L. Kelley, MD, MBA: dkelley@itxm.org.

For questions regarding this TMU, please contact Darrell J. Triulzi, MD at: dtriulzi@itxm.org or 412-209-7304. Copies of the Transfusion Medicine Update can be found on the ITxM web page at [www.itxm.org](http://www.itxm.org).