TRANSFUSION MEDICINE UPDATE

Institute for Transfusion Medicine Issue #3 2006

Transfusion Related Acute Lung Injury (TRALI) Update 2006

Darrell J. Triulzi, MD, Medical Director, The Institute for Transfusion Medicine

INTRODUCTION

Advances in blood safety have greatly reduced the risk of transfusion associated infectious disease transmission. As a result, non-infectious serious hazards of transfusion have come to the forefront as increasingly important blood safety issues. Transfusion associated acute lung injury (TRALI) has emerged as a leading cause of transfusion related morbidity and mortality.[1] This report will summarize recent consensus conferences that have provided practical clinical definitions of TRALI to aid the clinician in diagnosis and to facilitate its study.

DEFINITION

Recent consensus conference groups have defined TRALI as "new acute lung injury (ALI) occurring during or within 6 hours after a transfusion, with a clear temporal relationship to transfusion, in patients without or with risk factors for ALI other than transfusion.[1] (Table 1).

CLINICAL & LABORATORY DIAGNOSIS

TRALI has a clinical presentation mirroring ARDS occurring in the setting of transfusion. Patients present with respiratory distress (dyspnea), hypoxia, pulmonary edema on exam, and bilateral fluffy infiltrates on chest x-ray during or within 6 hours of transfusion. The majority of cases occur during or within one to two hours of transfusion. Signs and symptoms include: tachypnea, frothy pulmonary secretions, hypotension (less commonly hypertension), fever, tachycardia and cyanosis. All patients require supplemental oxygen and the majority of patients require intubation with ventilatory support. Importantly, there is no evidence of circulatory overload with absence of jugular venous distension or an S3 gallop. Central venous pressure and pulmonary wedge pressure is normal**.** B-natriuretic peptide (BNP) may have some value in distinguishing transfusion associated circulatory overload from TRALI.[5] In contrast to ARDS from other causes, patients typically recover with resolution of pulmonary infiltrates within 96 hours. The mortality rate has been reported to be between 5-10%.[6] Laboratory findings in the acute setting are of limited value because they are only suggestive but not diagnostic of TRALI. Such findings include: leucopenia, neutropenia, monocytopenia and hypocomplementemia.[1] Laboratory tests which strongly support the clinical diagnosis of TRALI include the demonstration of HLA class I or class II, or neutrophil specific antibodies in donor plasma and the presence of the cognate (corresponding) antigen on recipient neutrophils. Such testing typically takes days or weeks thus making TRALI primarily a clinical diagnosis with confirmation based on subsequent test results.

Table 1. Canadian Consensus Conference Proposed Criteria for TRALI

Criteria for TRALI:

1. Acute Lung Injury (ALI)
   - Acute onset
   - Hypoxemia
     - Research Setting
       - Ratio of PaO_2/FiO_2 ≤300 or
       - SpO_2 <90% on room air
     - Non-Research Setting
       - Ratio of PaO_2/FiO_2 ≤300 or
       - SpO_2 <90% on room air
       - Other clinical evidence of hypoxia
   - Bilateral infiltrates on chest radiograph
   - No evidence of circulatory overload
2. No preexisting ALI before transfusion
3. During or within 6 hours of transfusion; and
4. No temporal relationship to an alternative risk factor for ALI

Criteria for Possible TRALI:

1, 2, and 3 same as above; and
4. A clear temporal relationship to an alternative risk factor for ALI

From Kleinman S, et al. Transfusion 2004;44:1774-89

INCIDENCE/ IMPLICATED COMPONENTS

The true incidence of TRALI is unknown because a standardized definition has not previously been available. Early reports quoted an incidence of 1:5,000 blood components with subsequent reports ranging from 1:432 whole blood platelets to 1:557,000 red cells.[1] TRALI has been reported from all types of blood components including whole blood, red cells, apheresis platelets, whole blood platelets, fresh frozen plasma, cryoprecipitate, granulocytes, stem cell products and even intravenous immunoglobulin preparations.[8] FFP has been implicated most frequently in TRALI cases and

TRALI related deaths reported to the FDA[9] and UK.[10] Most implicated blood products contain more than 50 ml of plasma.[1]

PATHOPHYSIOLOGY OF TRALI

The exact mechanism of TRALI is not fully understood, but is likely to be multifactorial. An immune antibody mediated mechanism has been implicated in most cases of TRALI. In a minority of reported cases however an antibody is not identified and a non-immune mechanism has been postulated. Data from animal models of TRALI and more recent clinical data have suggested that both mechanisms occur and that TRALI may represent the final common pathway of neutrophil activation and capillary leak which can be triggered by antibodies and/or other biologic response modifiers. In 65-90% of reported clinical cases of TRALI, leukocyte antibodies have been identified in the implicated donor. The cognate antigen can be identified on the recipient's neutrophils in most of these cases. Antibodies which have been implicated in TRALI include donor HLA class I, HLA class II , and/or neutrophil specific antibodies. Although a number of neutrophil specific antibodies have been reported, the most common is directed at the 5b (HNA-3a) antigen. In a small percent of cases, the leukoagglutinating antibody appears to be from the recipient and is directed at the transfused neutrophils. Most of the donors implicated in TRALI have been multiparous women become alloimmunized during pregnancy. Passive transfer of these leukoagglutinating antibodies via transfusion of plasma containing blood components results in binding to recipient neutrophils. Antibody bound neutrophils are activated and sequestered in the lungs where complement activation and release of neutrophil bioactive products results in endothelial damage, capillary leak and ALI.. Despite the strong experimental and clinical evidence supporting an immune mechanism of TRALI, there are inconsistencies. First, antibodies have not been found in 15% or more of cases of TRALI. Second, only a very small proportion of donors with HLA antibodies are implicated in TRALI. Third, donors with known HLA antibodies transfused to patients with the cognate antigen caused lung injury in some patients but not others. Fourth, patient who have experienced TRALI reactions do not always have the cognate antigen to leukocyte antibodies found in the implicated donor. A non-immune mechanism for TRALI has been proposed to explain these limitations. A "two hit" model has been proposed by Silliman et al.[2] which postulates that an initial insult to vascular endothelium results in endothelial activation, release of cytokines, and expression of adhesion molecules. Cytokines attract and prime neutrophils which firmly adhere to the endothelium. Events which could cause the initial pro-inflammatory endothelial activation include: severe infection, surgery, trauma, or massive transfusion. A second "hit" activates sequestered adherent neutrophils to release oxidases and proteases which damage the endothelium causing capillary leak and acute lung injury . The second "hit" may be mediated by transfusion of biologic response modifiers such as leukocyte antibodies, lipid priming molecules, cytokines, CD ligand or endotoxin. One limitation of the "two hit model" is the appearance of TRALI in patients who were apparently healthy prior to transfusion such as in the setting of coumadin reversal for elective surgery. It is possible that such patients have subclinical evidence, or unrecognized risk factors for endothelial activation. Alternatively a transfused component may be able to provide both the mediators of endothelial activation and the second hit bioactive molecules which activate neutrophils triggering ALI.

PREVENTION

the US, measures to prevent TRALI are currently limited to deferral of implicated blood donors. Typically, potentially implicated donors with a history of pregnancy or transfusion are screened for HLA or neutrophil antibodies. The AABB recently issued an interim standard for the 23rd edition of *Standards for Blood Banks and Transfusion Services* requiring that donors implicated in a TRALI case be evaluated for eligibility to donate.[3,4] In practice, donors found to have leukocyte antibodies corresponding to an antigen on the patient leukocytes or exhibiting a positive crossmatch between donor serum and patient leukocytes are deferred from donating plasma containing blood components. The use of fresher platelets or red cells with reduced lipid priming activity or washed components has also been considered. One strategy that is gaining favor is to use plasma exclusively or primarily from male donors and divert plasma from female donors to recovered plasma. A similar strategy for platelets is not feasible due to supply limitations and has recently been addressed in the UK by resuspending platelet pools in male plasma. The use of platelet additive solutions may be another practical way to reduce the plasma content and risk of TRALI from platelet components.

REFERENCES

1. Goldman M, Webert KE, Arnold DM, et al. Proceedings of a consensus conference: Towards and understanding of TRALI. Transfus Med Rev 2005;19:2-31.
2. Silliman CC, Ambruso DR, Boshkov LK. Transfusion-related acute lung injury. Blood 2005;105:2266-73.
3. AABB Association Bulletin #05-06. June 3, 2005.

4. AABB Association Bulletin #05-09. August 11, 2005

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.