inside blood

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CLINICAL TRIALS

Comment on Vlaar et al, page 4218

Tracking TRALI in target populations

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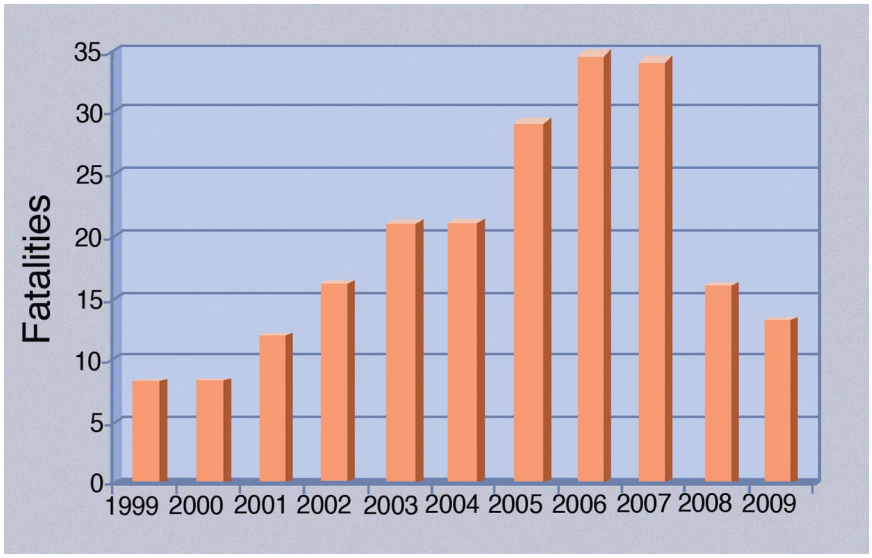
A prospective, case-controlled study in cardiac surgery reveals a high incidence (2.4%) of TRALI despite the introduction of plasma from male donors, indicating a need for additional interventions in susceptible populations.



TRALI fatalities reported to the FDA (1999-2009). In November 2007, blood centers introduced measures to reduce patient exposure to alloreactive antibodies in plasma-rich transfusions. Professional illustration by Marie Dauenheimer.

Transfusion-related acute lung injury (TRALI), first described in 1985 as acute noncardiogenic pulmonary edema occurring soon after transfusion, is under recognized and under reported. Our understanding of the syndrome is based on retrospective case series and passive hemovigilance programs.[1] Incidence risk has generally been described as ~ 1:5000 transfusions but estimates vary by orders of magnitude. With awareness increasing over the past 10 years, TRALI is now the leading life-threatening risk of transfusion, with as many as 35 fatalities reported to the US Food and Drug Administration in 2006 (see figure).[2] The publication of a consensus definition for TRALI in 2004 provided an opportunity to better define the incidence, enumerate risk factors, identify susceptible patient populations and assess the efficacy of preventative measures.[3]

According to the consensus definition, TRALI is a clinical syndrome of acute hypoxemia and bilateral pulmonary infiltrates on chest x-ray occurring within 6 hours of transfusion, in the absence of left atrial hypertension, pre-existing acute lung injury (ALI) or other risk factors for ALI.[4] Intensive care unit (ICU) patients are identified in retrospective analyses as particularly at risk, with incidence as high as 29% in end-stage liver disease.[4] Other studies identify emergency cardiac surgery, hematologic malignancies, massive transfusions, sepsis, and high Acute Physiology and Chronic Health Evaluation II scores as risk factors for TRALI and confirm an association with transfusion of plasma-rich components.[5] One prospective study identifies TRALI in 8% of critically ill, transfused ICU patients and highlights plasma transfusions derived from female donors with a history of multiple pregnancies as a risk.[6]

In this setting, Vlaar et al report the first prospective analysis of the incidence of TRALI in cardiac surgery patients using the consensus definition.[7] Cardiac surgery patients may be particularly susceptible because of a high rate of transfusion, exposure of blood to extracorporeal circuits during cardiopulmonary bypass, and lung deflation with nonventilation. Six hundred sixty-eight consecutive patients were enrolled and 16 TRALI cases (2.4%) identified, including 2 fatalities (13%). Transfused and nontransfused case controls without acute lung injury were selected randomly. After adjustment for patient risk factors, the presence of antibodies against human leukocyte antigens (HLAs) and/or human neutrophil antigens (HNAs) in any transfused component was strongly associated (odds ratio, 14.2; 95% confidence interval, 1.5-132) with TRALI, while the amount of transfused bioactive lipids and the age of transfused red cells were not. Older patients and those that spend longer periods on cardiopulmonary bypass were at increased risk. Seven months into this 28-month study the blood supplier converted to the exclusion of female donors for plasma components, preventing an adequately powered analysis of the risk associated with plasma transfusion from female donors. The authors conclude that cardiac surgery patients are highly susceptible to TRALI and the exclusion of blood products with HLA and HNA antibodies is warranted for all blood components, including platelets and red cells.

The past 10 years have seen a rapid expansion of our understanding of TRALI and the first tentative steps to protect patients. TRALI is a "2 hit" process, requiring a clinical setting of inflammation with activation of neutrophils and/or vascular endothelium, with sequestration of neutrophils in the lungs. Transfusion provides a second insult that triggers neutrophil attack, leading to destruction of the alveolar vascular integrity and the flooding of airspaces with protein-rich fluid.[1] Transfusion-derived "second hits" include HNA antibodies or biologic response modifiers (that accumulate on blood storage, eg, bioactive lipids, cytokines, CD40 ligand, etc) that directly activate neutrophils; HLA class I antibodies that bind to neutrophils, endothelium and other somatic cells; and finally, HLA class II antibodies that act indirectly by stimulating class II antigen-bearing cells such as endothelium or macrophages. TRALI, therefore, has multiple possible etiologies; consequently, prevention requires several different approaches, with each intervention engendering its own cost-benefit decision.

Some decisions are simple and low-cost: avoidance of unnecessary transfusion prevents TRALI and saves resources, while deferral of donors implicated in TRALI reactions may prevent future cases. Alternatively, most severe cases of TRALI are associated with plasma-rich transfusions from female donors containing alloreactive HLA class I and/or II antibodies elicited during pregnancy. After the observation in the United Kingdom that conversion from 50% to > 90% male plasma for transfusion was associated with a substantial drop in TRALI cases,[1] the American Association of Blood Banks (AABB) recommended a similar practice in the US, starting in November 2007. Fatal TRALI cases reported to the FDA (see figure) now document a ~ 60% reduction in 2008-2009 compared with 2006-2007, and a similar reduction in nonfatal cases is reported by the American Red Cross Hemovigilance Program.[8] Absolute exclusion of female blood donors is not feasible for red cell, platelet, or blood group AB plasma donors in the US due to blood availability issues. The alternative approach of screening donors for HLA antibodies has been proposed and adopted for plasma and platelet donors by some blood centers. Approximately 17% of all female blood donors harbor HLA antibodies, with prevalence increasing with the number of prior pregnancies.[9] HLA antibody screening may have less impact on blood availability but increases the cost of all tested components. An effective method to screen donor blood for HNA antibodies is not yet available to blood centers. Likewise, avoidance or elimination of biologic response modifiers may require the use of fresher blood products and/or further processing (washing) before use. None of these interventions are required by FDA regulations or AABB standards, nor are they reimbursed by Medicare or private payors.

Mitigation strategies to further reduce the risk of TRALI will affect the cost and availability of blood products. A more systematic approach promises to identify at-risk populations, design interventions, and perform clinical trials that allow proper cost-benefit analyses. Vlaar et al demonstrate such a need in cardiac surgery and provide a suitable model for randomized controlled studies to test the efficacy of interventions.[7] A commitment to evidence-based transfusion medicine demands no less.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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Comment on Sergeeva et al, page 4262

PR1 on the edge of humoral immunotherapy

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The development of a monoclonal antibody against the PR1/HLA-A2 complex that is aberrantly expressed on myeloid malignancies gives the opportunity to better define the potential benefits and risks of targeting the tumor-associated proteinase 3 and neutrophil elastase-specific PR1 antigen by both cellular and humoral immunotherapeutic approaches.[1]

Previously, Molldrem et al have identified PR1 as a potential target for cellular immunotherapy.[2,3] They and others[3,4] reported the presence of cytotoxic T lymphocytes (CTLs) directed against the PR1 epitope in patients with chronic myeloid leukemia (CML) and acute myeloid leukemia (AML), and demonstrated a correlation with disease outcome. Vaccination studies using synthetic PR1 peptides were able to show the development of biologically relevant immune responses to PR1 in some patients.[4,5] Unfortunately, sustained clinical responses were rare, and ex vivo clonal expansion of high avidity T cells from responding patients directly documenting in vivo expansion of T cells has not been reported.[6] This may indicate that endogenous presentation of PR1 peptide in HLA-A2 molecules could have prevented the in vivo development of high avidity T cells by natural negative selection, thereby impairing successful vaccination strategies.[7] However,