REVIEW

Transfusion-Related Acute Lung Injury

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Transfusion-related acute lung injury (TRALI) is characterized by the sudden development of noncardiogenic pulmonary edema (acute lung injury) after transfusion of blood products. Poor awareness of TRALI outside of the blood transfusion medicine community has led to a serious underestimation of this condition, currently the most important severe complication of blood transfusion. Concern for the transfer of donor antileukocyte antibodies has prompted major changes in the management of the blood supply in some countries; however, recent studies have suggested alternative pathophysiological mechanisms for TRALI related to the shelf life of cellular blood products. Although all blood products have been implicated, most reported cases were associated with fresh frozen plasma, red blood cell, and platelet transfusions. Because many patients have additional predisposing factors for acute lung injury, carefully designed prospective studies are needed to fully assess attributable risk related to transfusion. The treatment of TRALI is supportive, and the prognosis is generally better than for other causes of acute lung injury. As many as one third of all patients who develop acute lung injury have been exposed to blood products. TRALI may be an important and potentially preventable cause of acute lung injury.

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AECC = American-European Consensus Conference; FFP = fresh frozen plasma; IL = interleukin; RBC = red blood cell; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury

With the substantial decrease in the transmission of viral pathogens by blood transfusions during the past decade, transfusion-related acute lung injury (TRALI) has emerged as the most common serious complication of blood transfusion. A lack of awareness of TRALI outside of the transfusion medicine community has led to serious underestimation of this important complication. In some countries, concern for the transfer of donor antileukocyte antibodies has prompted major changes in blood supply management, such as exclusion of women donors in the production of fresh frozen plasma (FFP) in the United Kingdom. Recent studies have suggested alternative pathophysiological mechanisms for TRALI related to the shelf life of cellular blood products. However, for the past 2 decades, most articles about this subject have been published almost exclusively in transfusion medicine subspecialty journals, contributing to a limited awareness of TRALI among general internists and critical care practitioners.

We searched the National Library of Medicine PubMed database (www.pubmed.gov) from 1980 onward using the following search strategy: blood transfusion AND (acute lung injury OR adult respiratory distress syndrome OR pulmonary edema). Cohort and case-control studies, case series, case reports, animal models, and review articles were screened for relevant data regarding epidemiology, pathogenesis, diagnosis, treatment, and prevention of TRALI. Also, we looked up the references of selected articles and consulted experts for additional published or unpublished reports.

The objectives of this review are as follows: (1) to review existing data regarding the incidence, clinical presentation, and outcome of TRALI; (2) to review the latest evidence regarding the 2 leading hypotheses for TRALI pathogenesis: (a) antibody-mediated lung injury associated with passive transfer of donor antileukocyte antibodies and (b) neutrophil-priming activity of biologically active lipid molecules accumulated during storage of cellular blood products; and (3) to propose a hypothesis that TRALI, similar to ventilator-associated lung injury, may be an important and frequently neglected cause of iatrogenic acute lung injury.

EPIDEMIOLOGY

Since the publication of our first case series 20 years ago,[1] TRALI has emerged as one of the most common serious complications of blood transfusion.[2-5] With the reduction of clerical errors and with more effective screening and prevention of the transmission of infectious agents, TRALI has surpassed hemolytic reactions as the leading cause of transfusion-related mortality in developed countries.[3,6] Published incidence of TRALI ranged from 0.02% to 0.05% per blood product unit transfused and from 0.08% to 0.16% per patient who received a transfusion.[1,7-10] In contrast, the incidence of infectious complications varied from 1 in 20,000 blood product units for hepatitis B virus[11] to 1 in 2 million blood product units for human immunodeficiency virus and hepatitis C virus.[12] Although all plasma-containing blood products have been implicated, use of FFP, red blood cells (RBCs), and pooled platelets from several donors seems to have a particularly high risk.[1,8,13-15] Rarely, cryoprecipitate, intravenous immunoglobulin, and stem cell preparations have been implicated.[16-18] In our

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original case series,[1] 31 of 36 patients received blood transfusion products in the perioperative period. In most cases, RBC and FFP transfusions were implicated, with antileukocyte antibodies present in 89% of the donor blood products.[1] In a recent retrospective review of 58 TRALI fatalities during a 5-year period, cardiopulmonary and hematologic disorders were the most common underlying diagnoses.[19] The most common associated blood product was FFP, implicated in 50% of cases.[19] In contrast, Silliman et al[8] found that FFP was implicated in only 1 of 90 cases of TRALI during a 4-year period.

Because of a relative lack of awareness, TRALI almost certainly is underdiagnosed and underreported.[3,14,20,21] A recent "look-back study," requested by the US Food and Drug Administration in response to a fatal TRALI reaction, revealed that 8 additional patients had developed severe acute lung injury after receiving blood donated by the same multiparous donor.[14] Interestingly, TRALI was considered in the differential diagnosis in only 2 of the 8 patients at the time of disease onset. Moreover, in a randomized clinical trial of critically ill patients, a restrictive transfusion threshold (hemoglobin at 7 g/dL vs traditional 10 g/dL) was associated with a decreased incidence of acute lung injury (7.7% vs 11.4%), suggesting that some episodes of acute lung injury may have been TRALI reactions.[22,23]

As many as one third of the 150,000 patients who develop acute lung injury in the United States each year are exposed to multiple blood products near the time of disease onset.[24,25] It is unknown whether this association is causal or merely reflects the severity of the underlying illnesses. It is possible and even probable that current cases of TRALI reported to blood banks represent the "tip of the iceberg" and that transfusion factors play a mechanistic role in many more cases of acute lung injury than previously believed. Although several studies reported the association between blood transfusions and the development of acute lung injury in critically ill patients,[22,24,26,27] until recently the practice of transfusion usually was not characterized in terms of the amount, type, and shelf age of blood products. In a retrospectively studied cohort of patients receiving mechanical ventilation, transfusion of blood products and ventilator settings were identified as major risk factors for the subsequent development of acute lung injury, regardless of underlying severity of illness.[27] To further characterize the specific factors associated with blood transfusion as risk factors for acute lung injury, we evaluated a subgroup of 181 critically ill patients who had received blood transfusion within 48 hours of receiving mechanical ventilation. One third of patients in the subgroup developed acute lung injury within 24 hours of receiving transfusion. Underlying thrombocytopenia and transfusion of FFP but not shelf age of stored RBCs or total number of transfusions were associated significantly with the development of acute lung injury in this patient population.[15] Our observations confirmed that critically ill patients have a high incidence of acute lung injury temporally related to the transfusion of blood products.[24]

ETIOLOGY AND PATHOGENESIS

The exact etiology of TRALI is unknown, but 2 distinct mechanisms have been suggested. The traditional theory proposes an antibody-mediated reaction between recipient granulocytes and antigranulocyte antibodies from donors who were sensitized during pregnancy (multiparous women) or by previous transfusion.[2,14,28,29] In the original case series at our institution, antileukocyte antibodies were present in 89% of implicated donor products.[1] The antibody-mediated increase in pulmonary capillary permeability was reproduced in an ex vivo animal lung model of TRALI.[29] Although most TRALI cases were associated with the presence of antileukocyte antibodies in the *donor* product, a few reports implicated the reaction between the recipient antileukocyte antibodies and donor leukocytes or interdonor incompatibility[30,31]; these 2 reactions are unlikely to play an important role in the future, given the rapid movement toward universal leukoreduction.

Recently, an alternative mechanism was suggested, implicating proinflammatory molecules, predominantly lipid products of cell degradation, known to accumulate during storage of cellular blood product.[8,32-34] This hypothesis was tested in a lipopolysaccharide-primed perfused lung model in which the infusion of biologically active mediators from stored blood resulted in the development of permeability pulmonary edema.[32]

Of note, the 2 hypotheses of TRALI pathogenesis (Figure 1) are not mutually exclusive and even may act synergistically with underlying patient factors to produce acute lung injury. In either theoretical model, an initial "priming" event (first hit) such as sepsis- or trauma-induced endothelial activation usually is required.[1,13,29,30,35]

In the largest clinical series to date, Silliman et al[8] described 90 patients with TRALI treated at the transfusion medicine service at the University of Alberta Hospitals over a 4-year period. Compared with 225 randomly selected controls who received transfusions during the same period, patients with TRALI were more likely to have underlying cardiac disease or hematologic malignancy. The authors evaluated the presence of HLA class I and antigranulocyte antibodies in the donor blood of 28 patients with TRALI and 5 controls and found no significant difference. They described an elevated "neutrophil-priming" activity in the donor blood of patients with TRALI, which increased with the duration of platelet storage. Anti-HLA class II anti-

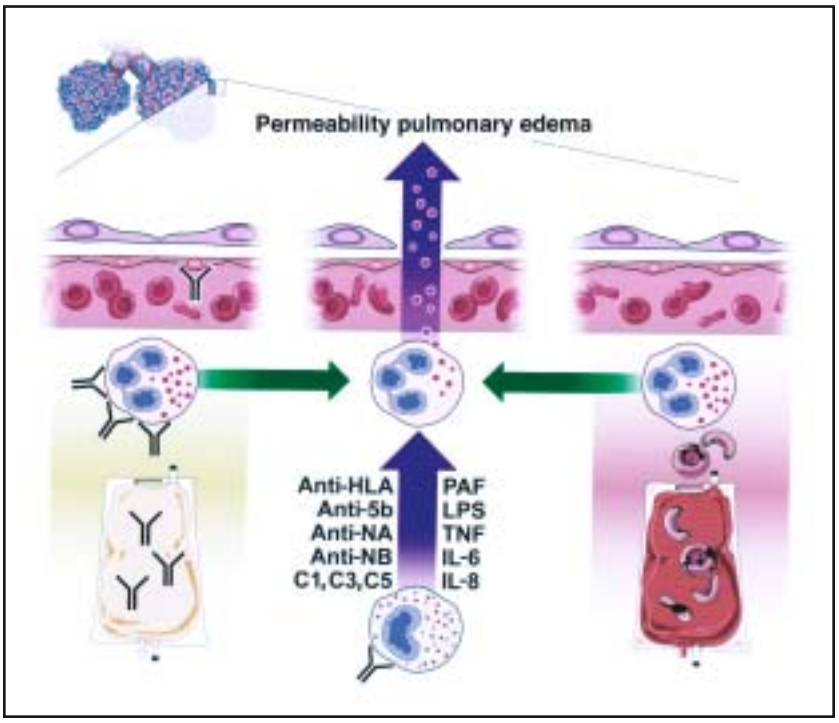

FIGURE 1. Pathogenesis of transfusion-related acute lung injury. The presence of antileukocyte antibodies and/or biologically active lipids from cell membrane fragments in donor blood triggers an inflammatory response, granulocyte activation, and degranulation and injury to the alveolar-capillary membrane. Activated macrophages secrete inflammatory cytokines that further perpetuate the inflammatory reaction. C = complement; HLA = human leukocyte antigen; IL = interleukin; LPS = lysophosphatidil choline; PAF = platelet activating factor; TNF = tumor necrosis factor; 5b, NA, NB = neutrophil antigens.

bodies, interleukin (IL) 6, and IL-8 were measured in patients with TRALI but not in controls. In contrast to previous reports,[1,9,13-15] FFP was implicated in only 1 of 90 TRALI reactions. Moreover, donor antileukocyte antibodies were found in less than 25% of patients compared with 89% in the original series at our institution.[1] Differences in rates of TRALI after FFP transfusion are poorly understood and are likely related to different diagnostic criteria (clinical vs laboratory), varying antibody prevalence in the donor population, and variability in use of FFP in different patient populations.

The duration of blood storage as a risk factor for adverse outcome has been assessed in several human studies with controversial results.[15,31,36-39] Regarding pulmonary complications, an association has been reported between the age of the oldest blood and the development of pneumonia in patients who underwent cardiac surgery.[39] Despite large variability in the duration of RBC storage, in a retrospective cohort of patients receiving mechanical ventilation we found no significant associations between the storage age of RBC transfusions and the development of acute lung injury, onset of pneumonia, or overall outcome.[15] The effect of platelet storage has been difficult to assess, primarily because of the short "shelf life" of platelets; most units are transfused near the end of a brief (5-day) storage period.[8,15] However, inflammatory cytokines are known to accumulate during both platelet (IL-6, tumor necrosis factor [TNF] α, IL-8) and RBC storage (IL-8, TNF-α).[8,40,41] These same molecules (IL-6, TNF-α, IL-8) have been implicated in the initiation and perpetuation of the inflammatory response in acute lung injury of any etiology.[42,43] Prestorage leukoreduction has been successful in reducing febrile reactions caused by proinflammatory cytokines, but whether it prevents TRALI is unknown.[43] Neither leukoreduction nor shorter storage would influence passive transfer of donor antileukocyte antibodies.

The association between exposure to antileukocyte antibodies and TRALI reactions described in our original case series[1] was strengthened recently. In a small randomized trial, blood transfusion from only multiparous women donors produced impaired pulmonary gas exchange, increased plasma concentrations of inflammatory cytokines (TNF-α), and led to one severe and several mild TRALI-like reactions.[28]

Because no previous TRALI study has used a standardized definition of acute lung injury, interpretation of results

across different studies is difficult. Making a distinction between acute lung injury and related conditions such as hydrostatic pulmonary edema (fluid overload and cardiac failure) and lung infection is difficult because of the low specificity of diagnostic criteria.[44-46] Furthermore, infection, pulmonary venous hypertension, and immune-mediated impairments in pulmonary vascular barrier function are not mutually exclusive. Application of the American-European Consensus Conference (AECC) definition[44] has substantially improved the validity of clinical studies of acute lung injury.[47] Recent inclusion of AECC criteria in the TRALI definition will help standardize future clinical studies.[48]

CLINICAL FEATURES

Symptoms of TRALI appear usually within 2 to 6 hours from initiation of transfusion, but cases of presumed TRALI have been described up to 48 hours after transfusion.[5,49] Signs and symptoms of TRALI include dyspnea, tachypnea, frothy sputum, fever, hypotension, or, much more rarely, hypertension.[48] Although application of the AECC definition[44] can help differentiate noncardiogenic from cardiogenic pulmonary edema and fluid overload, distinguishing TRALI solely on clinical grounds from other causes of acute lung injury such as sepsis, trauma, aspiration, disseminated intravascular coagulation, or ventilator-associated lung injury is almost impossible. Laboratory findings for TRALI are inconsistent and include acute transient neutropenia,[50] the presence of matching leukocyte antigen-antibody in the donor and recipient, donor antibody that activates recipient monocytes,[51] and increased neutrophil-priming activity in transfused blood.[8] In patients with an endotracheal tube in place, high protein concentration found in edema fluid sampled within the first hour of intubation may help differentiate TRALI from fluid overload and cardiogenic pulmonary edema.[52]

There is no single test for TRALI; thus, diagnosis is problematic and requires a high index of clinical suspicion. Unfortunately, most cases remain unnoticed or misdiagnosed as fluid overload or acute lung injury of other etiology.[2,14,21] In the previously mentioned look-back study,[14] TRALI was considered in the differential diagnosis in only 2 of 8 patients at the time of disease onset.

TRALI is believed to have a better short-term prognosis than other causes of acute lung injury; less than 70% of patients with TRALI require mechanical ventilation, and hospital mortality is 5% to 15%.[1,4,8,9] Most patients recover within 24 to 48 hours with supportive care. Although less clinically severe than some other causes of acute lung injury, TRALI is costly because patients need intensive care treatment for 2 to 7 days.[4,7]

TREATMENT AND PREVENTION

Management of TRALI is supportive, as it is for any patient with permeability pulmonary edema, and often includes ventilatory support. Lung protective (low tidal volume) ventilatory strategies should be used. Unless there is concomitant fluid overload, diuretics are unlikely to be beneficial and even may be clinically contraindicated.[48] Suspected TRALI reactions should be reported to the blood bank, and a transfusion reaction work-up should be initiated. In addition to acquiring a posttransfusion blood specimen from the patient, bags from units of blood transfused in the last 6 hours should be returned to the blood bank if possible so that residual donor plasma can be tested without necessitating a time-consuming recall of blood donors.[48] Medical records should be reviewed to determine the sequence and timing of transfused units in relation to the clinical manifestations of the disease.[48]

Of note, as many as 25% of multiparous women have circulating antileukocyte antibodies, which also are found in approximately 5% of all plasma-containing blood products.[53] However, most recipients of these transfusion products do not develop TRALI.[4,28] Currently in North America, neither routine exclusion of women donors in the production of FFP, as recently proposed in the United Kingdom,[54] nor changes in duration of storage are recommended.[4,5] Considering the shortage of blood products, the public health implications are obvious if the efficacy of either of these practices is confirmed in a rigorous epidemiological study.[5] Such a study should aim to answer the following fundamental questions:

What is the incidence of clinically defined TRALI in a rigorously conducted prospective clinical study?

Are antileukocyte antibodies, inflammatory cytokines, or biologically active lipids more likely to be present in the donor blood of patients with clinically defined TRALI compared with control patients matched for age, severity of illness, and number of blood transfusions?

What are the most important underlying risk factors (first hit) that increase the probability of TRALI, and what patient population would thus likely benefit from clinical trials of specific interventions, such as washing of cellular products, pretransfusion antibody testing, or avoidance of a specific donor product?

What are the short-term and long-term outcomes of TRALI?

CONCLUSION

Transfusion is a relatively common and important risk factor for acute lung injury. Cases of TRALI reported to blood banks may represent just the tip of the iceberg, and

transfusion may play a mechanistic role in many more cases of acute lung injury than currently realized. To the extent that acute lung injury is related to transfusion factors, it may be a preventable disease.

REFERENCES

1. Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. *Transfusion.* 1985;25:573-577.

2. Popovsky MA, Abel MD, Moore SB. Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies. *Am Rev Respir Dis.* 1983;128:185-189.

3. Williamson LM, Lowe S, Love EM, et al. Serious hazards of transfusion (SHOT) initiative: analysis of the first two annual reports. *BMJ.* 1999;319:16-19.

4. Popovsky MA. Transfusion and lung injury. *Transfus Clin Biol.* 2001; 8:272-277.

5. Kopko PM, Holland PV. Transfusion-related acute lung injury. *Br J Haematol.* 1999;105:322-329.

6. Zoon KC. Transfusion related acute lung injury [letter]. Rockville, Md: US Dept of Health and Human Services, Center for Biologics Evaluation and Research; 2001.

7. Snyder EL. Transfusion reactions. In: Hoffman R, Benz EJ Jr, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, eds. *Hematology: Basic Principles and Practice*. 2nd ed. New York, NY: Churchill Livingstone; 1995:2045-2053.

8. Silliman CC, Boshkov LK, Mehdizadehkashi Z, et al. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. *Blood.* 2003;101:454-462.

9. Wallis JP, Lubenko A, Wells AW, Chapman CE. Single hospital experience of TRALI. *Transfusion.* 2003;43:1053-1059.

10. Ausley MB Jr. Fatal transfusion reactions caused by donor antibodies to recipient leukocytes. *Am J Forensic Med Pathol.* 1987;8:287-290.

11. Dodd RY. Current safety of the blood supply in the United States. *Int J Hematol.* 2004;80:301-305.

12. Goodman JL. The safety and availability of blood and tissues—progress and challenges [editorial]. *N Engl J Med.* 2004;351:819-822.

13. Engelfriet CP, Reesink HW, Brand A, et al. Transfusion-related acute lung injury (TRALI). *Vox Sang.* 2001;81:269-283.

14. Kopko PM, Marshall CS, MacKenzie MR, Holland PV, Popovsky MA. Transfusion-related acute lung injury: report of a clinical look-back investigation. *JAMA.* 2002;287:1968-1971.

15. Gajic O, Rana R, Mendez JL, et al. Acute lung injury after blood transfusion in mechanically ventilated patients. *Transfusion.* 2004;44:1468-1474.

16. Webert KE, Blajchman MA. Transfusion-related acute lung injury. *Transfus Med Rev.* 2003;17:252-262.

17. Reese EP Jr, McCullough JJ, Craddock PR. An adverse pulmonary reaction to cryoprecipitate in a hemophiliac. *Transfusion.* 1975;15:583-588.

18. Suassuna JH, da Costa MA, Faria RA, Melichar AC. Noncardiogenic pulmonary edema triggered by intravenous immunoglobulin in cancer-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome [letter]. *Nephron.* 1997;77:368-370.

19. Holness L, Knippen MA, Simmons L, Lachenbruch PA. Fatalities caused by TRALI. *Transfus Med Rev.* 2004;18:184-188.

20. Wallis JP. Transfusion-related acute lung injury (TRALI)—under-diagnosed and under-reported [editorial]. *Br J Anaesth.* 2003;90:573-576.

21. Popovsky MA, Chaplin HC Jr, Moore SB. Transfusion-related acute lung injury: a neglected, serious complication of hemotherapy. *Transfusion.* 1992;32:589-592.

22. Hebert PC, Blajchman MA, Cook DJ, et al, Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group. Do blood transfusions improve outcomes related to mechanical ventilation? *Chest.* 2001;119:1850-1857.

23. Hebert PC, Wells G, Blajchman MA, et al, Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care [published correction appears in *N Engl J Med.* 1999;340:1056]. *N Engl J Med.* 1999;340:409-417.

24. Hudson LD, Milberg JA, Anardi D, Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1995;151(2, pt 1):293-301.

25. Goss CH, Brower RG, Hudson LD, Rubenfeld GD, ARDS Network. Incidence of acute lung injury in the United States. *Crit Care Med.* 2003;31:1607-1611.

26. Pepe PE, Potkin RT, Reus DH, Hudson LD, Carrico CJ. Clinical predictors of the adult respiratory distress syndrome. *Am J Surg.* 1982;144:124-130.

27. Gajic O, Dara SI, Mendez JL, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med.* 2004;32:1817-1824.

28. Palfi M, Berg S, Ernerudh J, Berlin G. A randomized controlled trial of transfusion-related acute lung injury: is plasma from multiparous blood donors dangerous? *Transfusion.* 2001;41:317-322.

29. Seeger W, Schneider U, Kreusler B, et al. Reproduction of transfusion-related acute lung injury in an ex vivo lung model. *Blood.* 1990;76:1438-1444.

30. Eastlund DT, McGrath PC, Burkart P. Platelet transfusion reaction associated with interdonor HLA incompatibility. *Vox Sang.* 1988;55:157-160.

31. Bux J, Becker F, Seeger W, Kilpatrick D, Chapman J, Waters A. Transfusion-related acute lung injury due to HLA-A2-specific antibodies in recipient and NB1-specific antibodies in donor blood. *Br J Haematol.* 1996;93:707-713.

32. Silliman CC, Voelkel NF, Allard JD, et al. Plasma and lipids from stored packed red blood cells cause acute lung injury in an animal model. *J Clin Invest.* 1998;101:1458-1467.

33. Purdy FR, Tweeddale MG, Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. *Can J Anaesth.* 1997;44:1256-1261.

34. Geelhoed GW, Bennett SH. "Shock lung" resulting from perfusion of canine lungs with stored bank blood. *Am Surg.* 1975;41:661-682.

35. Matthay MA, Zimmerman GA, Esmon C, et al. Future research directions in acute lung injury: summary of a National Heart, Lung, and Blood Institute working group. *Am J Respir Crit Care Med.* 2003;167:1027-1035.

36. Zallen G, Offner PJ, Moore EE, et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. *Am J Surg.* 1999; 178:570-572.

37. Walsh TS, McArdle F, McLellan SA, et al. Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? *Crit Care Med.* 2004;32:364-371.

38. Vamvakas EC, Carven JH. Length of storage of transfused red cells and postoperative morbidity in patients undergoing coronary artery bypass graft surgery. *Transfusion.* 2000;40:101-109.

39. Leal-Noval SR, Jara-Lopez I, Garcia-Garmendia JL, et al. Influence of erythrocyte concentrate storage time on postsurgical morbidity in cardiac surgery patients. *Anesthesiology.* 2003;98:815-822.

40. Heddle NM, Klama L, Singer J, et al. The role of the plasma from platelet concentrates in transfusion reactions. *N Engl J Med.* 1994;331:625-628.

41. Shanwell A, Kristiansson M, Remberger M, Ringden O. Generation of cytokines in red cell concentrates during storage is prevented by prestorage white cell reduction. *Transfusion.* 1997;37:678-684.

42. Pittet JF, Mackersie RC, Martin TR, Matthay MA. Biological markers of acute lung injury: prognostic and pathogenetic significance. *Am J Respir Crit Care Med.* 1997;155:1187-1205.

43. Hebert PC, Fergusson D, Blajchman MA, et al, Leukoreduction Study Investigators. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA.* 2003;289: 1941-1949.

44. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med.* 1994;149(3, pt 1):818-824.

45. Abraham E, Matthay MA, Dinarello CA, et al. Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: time for a reevaluation. *Crit Care Med.* 2000;28:232-235.

46. Meade MO, Guyatt GH, Cook RJ, et al. Agreement between alternative classifications of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2001;163:490-493.

47. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301-1308.

48. Toy P, Gajic O. Transfusion-related acute lung injury. *Anesth Analg.* 2004;99:1623-1624.

49. Levy GJ, Shabot MM, Hart ME, Mya WW, Goldfinger D. Transfusion-associated noncardiogenic pulmonary edema: report of a case and a warning regarding treatment. *Transfusion.* 1986;26:278-281.

50. Yomtovian R, Kline W, Press C, et al. Severe pulmonary hypersensitivity associated with passive transfusion of a neutrophil-specific antibody. *Lancet.* 1984;1:244-246.

51. Kopko PM, Paglieroni TG, Popovsky MA, Muto KN, MacKenzie MR, Holland PV. TRALI: correlation of antigen-antibody and monocyte activation in donor-recipient pairs. *Transfusion.* 2003;43:177-184.

52. Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: a review. *Chest.* 2004;126:249-258.

53. Densmore TL, Goodnough LT, Ali S, Dynis M, Chaplin H. Prevalence of HLA sensitization in female apheresis donors. *Transfusion.* 1999;39:103-106.

54. England bans FFP from female donors to prevent TRALI. *ABC Newslett.* 2003;44:1-5.