PROTOCOLS

Transfusion-related acute lung injury

Principal investigator

France Gauvin, MD, MSc, FRCPC

Department of Paediatrics, Hôpital Ste-Justine, 3175 ch. Côte-Sainte-Catherine, Montréal QC H3T 1C5; tel: (514) 345-4931, ext. 6812; fax: (514) 345-4822; e-mail: france_gauvin@ssss.gouv.qc.ca

Co-investigators

Gilles Delage, MD, Department of Microbiology and Immunology, Université de Montréal; Héma-Québec

Dean A. Fergusson, MHA, PhD, Epidemiologist, University of Ottawa

Norbert Froese, MD, FRCPC, Departments of Anaesthesia and Paediatrics, University of British Columbia

Heather Hume, MD, FRCPC, Department of Paediatrics, Université de Montréal; Transfusion Medicine, Canadian Blood Services

Wendy Lau, MBBS, FRCPC, Department of Paediatric Laboratory Medicine and Pathobiology, University of Toronto

Pierre Robillard, MD, Department of Epidemiology, Biostatistics and Health Care, McGill University

Kathryn Webert, MD, FRCPC, Department of Medicine, Mc Master University

Robin K. Whyte, BSc, MB BS, MRCP (UK), FRCPC, Department of Pediatrics, Dalhousie University

Background

Transfusion of blood products can lead to various transfusion reactions such as circulatory overload, anaphylaxis, bacterial contamination and transfusion-related acute lung injury (TRALI), a rare but life-threatening complication. TRALI was the leading cause of transfusion-related fatalities reported to the American Food and Drug Administration in 2003 representing 22.3% of cases.[1] The incidence of TRALI reported in adult populations varies from 1:1,000 to 1:560,000, depending on the blood product involved.[2,3] In the paediatric population, the incidence is unknown. Currently in Canada, the only way that the incidence of TRALI is determined is through passive voluntary surveillance systems for transfusion reactions. TRALI is certainly under-recognized and under-reported. In fact, knowledge comes from published paediatric case reports and neonatal reports. A recent study in a paediatric intensive care unit reported on 2,505 transfusions in 307 patients and found one possible TRALI case.[4]

Recognized in 1980 as a distinct entity, TRALI occurs after transfusion of plasma-containing products. Most frequently implicated blood products are red blood cells, fresh frozen plasma, apheresis platelets and platelet concentrates. Extremely small volumes of plasma can trigger the reaction.[1] Typical symptoms and signs include acute respiratory distress, hypoxemia, fever, hypotension and tachycardia, and usually occur during or within six hours of the transfusion.

The etiology of TRALI is still uncertain. The acute lung injury is caused by increased permeability of the pulmonary capillary, which leads to pulmonary oedema. Two pathophysiologic mechanisms are proposed: the antibody hypothesis and the neutrophil priming or two-hit hypothesis.

According to the **antibody hypothesis**, TRALI is caused by an antigen-antibody reaction. The granulocyte and/or HLA class I or II antibodies are present in the donor plasma and react with the recipient's white blood cell antigens (or rarely vice versa). The administration of such antibodies could directly cause injury to the lung or could activate neutrophils, monocytes and complements, creating an inflammatory reaction that in turn causes the pulmonary damage. In one series, 89% of donors implicated in TRALI cases had such antibodies.[5] Although likely the explanation in many cases, this hypothesis cannot explain all causes of TRALI because in some cases, no antibodies are detected in either donor blood product or in recipient plasma.[2] Also, considering the high frequency of donors with HLA antibodies (20% of women with two previous pregnancies), the incidence of TRALI would be much higher if this mechanism was the sole explanation of TRALI.

In the **neutrophil priming or two-hit hypothesis**,[2] recipients must first have a predisposing factor which primes the neutrophils; then, the neutrophils are activated by the donor plasma, which contains leucocyte antibody or biologically active lipids. Priming factors could include infection, cytokine administration, recent surgery, and/or transfusion of large volume of blood products. Some conditions are also reported to be associated with an increased risk of TRALI: thrombotic thrombocytopenic purpura, orthotopic liver transplantation, haematologic malignancy and cardiac disease.[5]

Since TRALI is the most common cause of transfusion-related death,[1] it is important to better characterize its incidence and outcome (morbidity and mortality) in the paediatric population. Surveillance will also promote education and increase awareness of this uncommon transfusion reaction among health-care professionals.

Methods

The incidence of TRALI and possible TRALI will be ascertained by determining all newly diagnosed cases in Canada over a two-year period through the CPSP. Each month, the program reaches over 2,400 paediatricians, including paediatric

Transfusion-related acute lung injury (continued)

hemato-oncologists, paediatric intensivists and neonatalogists, who receive an initial reporting form asking them whether they have encountered a new case in the preceding month. Once a participant identifies a new case, a detailed questionnaire designed by the investigators is sent requesting case-specific data.

Objectives

Surveillance of TRALI in the paediatric population is:

1) to determine the incidence using a standardized definition;
2) to describe the characteristics of patients and the associated clinical signs and symptoms;
3) to describe the treatment and outcome;
4) to compare incidence and demographic data with those of the adult population published in the literature;
5) to promote education and awareness of this rare disease among paediatric health-care professionals.

Case definition

The diagnosis of TRALI is a clinical and radiological diagnosis and is not dependent on the results of laboratory tests or any proposed pathophysiologic mechanism. Report any child up to and including 18 years of age with TRALI **or** possible TRALI:

TRALI

Inclusion criteria (all three criteria must be present)

- New onset of acute lung injury (ALI) during or within six hours of transfusion
- Hypoxemia: $PaO_2/FiO_2 = 300$ or $SpO_2 < 90\%$ on room air
- Bilateral infiltrates on frontal chest radiograph

Exclusion criteria

- Evidence of left atrial hypertension (i.e., circulatory overload)
- Pre-existing **acute** lung injury before transfusion
- Temporal relationship to an alternative risk factor for ALI

Possible TRALI

Same TRALI inclusion criteria and same TRALI exclusion criteria, except that a clear temporal relationship to an alternative risk factor for ALI is **present**, such as:

Direct lung injury	**Indirect lung injury**
Aspiration	Severe sepsis
Pneumonia	Shock
Toxic inhalation	Multiple trauma
Lung contusion	Burn injury
Near drowning	Acute pancreatitis
	Cardiopulmonary bypass
	Drug overdose

PROTOCOLS

Duration

September 2005 to August 2007

Expected number of cases

From the transfusion data at Sainte-Justine Hospital, one can extrapolate that approximately 100,000 transfusions are given to Canadian children each year. Using an incidence of 1:5,000, the expected number of new TRALI cases in Canadian children is approximately 20 per year.

Ethical approval

Hôpital Sainte-Justine, University of Montréal

Data analysis and publication

The incidence of TRALI will be calculated as the number of events in the Canadian paediatric population (numerator) divided by the number of units blood products transfused in this population (denominator). The denominator will be approximated using data from Hema-Québec, the Canadian Blood Services and information available from the Public Health Agency of Canada. Data analysis will include demographics, presenting signs and symptoms, diagnostic investigations, management and outcome. The type of blood products will also be specified, if possible, to calculate blood product-specific incidences. The investigators will prepare quarterly reports and annual summaries for distribution. Data will be submitted for publication in a peer-reviewed journal on completion of the study.

References

1. Goldman M, Webert KE, Arnold DM, Freedman J, Hannon J, Blajchman MA. Proceedings of a consensus conference: Towards an understanding of TRALI. *Transfus Med Rev* 2005;19:2-31.
2. Silliman CC, Boshkov LK, Mehdizadehkashi Z. Transfusion-related acute lung injury: epidemiology and a propective analysis of etiologic factors. *Blood* 2003;101:454-62.
3. Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion* 2004;44(12):1774-89.
4. Gauvin F, Lacroix J, Lapointe H, Hume H. Transfusion reactions in pediatric intensive care unit. Unpublished data 2005; Abstract presented to the 6th Annual NATA Symposium, Prague.
5. Webert KE, Blajchman MA. Transfusion-related acute lung injury. *Transfus Med Rev* 2003;17(4):252-62.

More references are available from the principal investigator or the CPSP office.