Transfusion-related acute lung injury in the paediatric population

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Transfusion of blood products can lead to various transfusion reactions. Transfusion reactions that can cause pulmonary complications are: circulatory overload, anaphylactic reactions, bacterial contamination and transfusion-related acute lung injury (TRALI). TRALI is a rare but life-threatening complication of transfusion. TRALI is now the leading cause of transfusion-related fatalities reported to the US FDA[1] and to the Transfusion-Transmitted Injuries Surveillance System (TTISS) in Canada (unpublished results).

Even though TRALI is becoming recognized more frequently in clinical practice and has received greater attention and description in the literature, it likely remains under-diagnosed and under-reported. This article will review the epidemiology, pathophysiology, clinical presentation, diagnosis and treatment of TRALI as well as present a brief discussion of possible strategies for TRALI prevention.

What is the incidence of TRALI?

The incidence of TRALI reported in adult populations varies from 1:1000 to 1:560 000, depending on the blood product involved.[2-5] The wide range of reported incidence figures is due to different definitions used in studies or surveillance systems, different diagnostic criteria, different quality of denominator data used (products issued vs. products transfused) and most importantly whether the figures were derived from prospective studies or from surveillance systems and in the latter case by the quality of the surveillance system. There is no reliable literature addressing the incidence of TRALI in the paediatric population; evidence of TRALI in children is only supported by published case reports.[6-8] Cases have also been reported in neonates.[9,10] In a recent study done at the paediatric intensive care unit of UHC Sainte-Justine, the incidence was 1:2500.[11] The Canadian Paediatric Surveillance Program is therefore currently targeting TRALI to help estimate the incidence of TRALI in children.

What are the clinical aspects of TRALI?

Since 1950, several names, including pulmonary hypersensitivity reaction, pulmonary leukoagglutinin reaction and allergic pulmonary oedema, have been given to this transfusion reaction.[12] Typical symptoms and signs include acute respiratory

distress, hypoxemia, fever, hypotension, and tachycardia. Symptoms can be mild or very severe. New bilateral pulmonary infiltrates, usually alveolar and interstitial, are present on chest X-ray.[13] This condition should be consistent with non-cardiogenic pulmonary oedema; there must be no evidence of circulatory overload or cardiac dysfunction.

Since 1983, TRALI has been recognized as a distinct entity, occurring 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] In one case series, TRALI appeared to be increased with the administration of older units of blood.[13] Symptoms usually occur early in transfusion and almost always within six hours of completion of transfusion.

What is the pathophysiology of TRALI?

The etiology of TRALI is unknown and its exact pathophysiologic mechanism 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 currently proposed: 1) the antibody hypothesis and 2) the neutrophil priming or two-hit hypothesis.[14,15] Both hypotheses are supported by animal studies.[16] According to the first hypothesis, TRALI is caused by an antigen-antibody reaction.[4,12,17,18] The antibodies (granulocyte antibodies 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 complement, creating an inflammatory reaction that in turn causes the pulmonary damage.[18] In one series, 89% of donors implicated in TRALI cases had such antibodies.[13] Although likely the explanation in many cases, this hypothesis cannot explain all cases of TRALI because in some instances, no antibodies are detected in either donor or recipient.[2,17] 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.

Another hypothesis, the "two-hit" or "neutrophil priming" hypothesis, was proposed by Silliman et al.[2,4,19] According to this hypothesis, 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 massive transfusion.[15,20] 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.[13]

How to confirm the diagnosis of TRALI?

The diagnosis is made on the basis of clinical signs and symptoms, chest X-ray, and the time relation with transfusion of blood product (within six hours). Other causes of pulmonary oedema also have to be excluded (fluid overload or cardiac

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dysfunction). A consensus definition for TRALI was reached in 2004 (see table 1).[5] TRALI is defined as a new ALI that occurs within six hours of transfusion and for which no other risk factor can be found. When another risk factor that can be temporally related to the ALI is also present, the reaction is defined as a possible TRALI. The presence of TRALI cannot be confirmed in patients with pre-existing ALI.

Since TRALI is a clinical syndrome, no laboratory test can confirm its presence; i.e., no laboratory test is pathognomonic for TRALI. Laboratory investigations can be performed to confirm the presence of HLA and/or neutrophil antibodies in the donor plasma.[14] However, the absence of such antibodies does not exclude the presence of TRALI. Rarely, antibodies reactive for donor granulocytes are found in the recipient.[13]

Table 1: Recommended criteria for TRALI and possible TRALI[5]

1. TRALI criteria
   a. ALI
      i. Acute onset
      ii. Hypoxemia
      $PaO_2/FiO_2 = 300$ or
      $SpO_2 < 90\%$ on room air
      iii. Bilateral infiltrates on frontal chest radiograph
      iv. No evidence of left atrial hypertension (i.e. circulatory overload)
   b. No pre-existing ALI before transfusion
   c. During or within 6 hours of transfusion
   d. No temporal relationship to an alternative risk factor for ALI

2. Possible TRALI
   a. ALI
   b. No pre-existing ALI before transfusion
   c. During or within 6 hours of transfusion
   d. A clear temporal relationship to an alternative risk factor for ALI (table 2)

Table 2: Risk factors for ALI[5]

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

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What is the treatment of TRALI?

Treatment of TRALI consists of ventilatory and hemodynamic support.[21] Oxygen administration is necessary in 100% of cases, and mechanical ventilation in 72% of cases.[12] The hypotension may be unresponsive to fluid administration and may require the use of inotropes/vasopressors.[13] Diuretics are not useful and are contraindicated in patients who present hypotension.[21] Many treatment modalities have been suggested, including corticosteroids, prostaglandin E1, antiendotoxin antibodies, nonsteroidal anti-inflammatory medications, anti-TNF antibodies, pentoxiphylline and surfactant, yet there is no evidence-based data supporting the effectiveness of these interventions.[13]

What is the prognosis of patients with TRALI?

TRALI patients usually have a good prognosis; however, the mortality rate is approximately 6%.[12] In patients that survive, resolution is usually rapid (within 96 hours) and there are no long-term sequelae.[21] In some patients (20%), hypoxemia and pulmonary infiltrates persist for more than seven days.[13]

Can we prevent TRALI?

It is unlikely that TRALI can ever be entirely prevented, but its frequency may be reduced by measures taken both by hospitals transfusing blood components and by blood suppliers. As in the reduction of any complication associated with blood transfusion, the first step is to assure the judicious use of blood components only for indications that are justified based on sound medical evidence. Hospitals should have procedures in place (e.g., blood utilization guidelines, blood conservation programs) which aim to minimize unnecessary transfusions. Hospital medical staff should be aware of the signs and symptoms of all transfusion reactions, including those of TRALI, and should have a high index of suspicion in the presence of a reaction, in order to diagnose TRALI appropriately. All cases of TRALI or possible TRALI should be reported to the surveillance system in place in the hospital's jurisdiction as well as to the blood supplier.

When a TRALI reaction is reported to the blood supplier, the blood supplier will determine the identity of all donors whose donations were associated with the TRALI reaction. These donors are then either deferred from future donation of plasma containing blood components for transfusion or are investigated to determine if they have anti-HLA/neutrophil antibodies. If the latter approach is used, donors with antibodies considered to be implicated or possibly implicated in the reaction are deferred, while donors without such antibodies are able to continue as blood donors. Blood suppliers are now also evaluating more proactive prevention strategies that would further decrease the risk of TRALI by restricting the use of high-plasma volume containing components from donors with anti-HLA/neutrophil antibodies or from donors at high likelihood of having anti-HLA/neutrophil antibodies (i.e., donors who have previously been pregnant or transfused).

It is important to mention that directed donation from a mother to her infant is a particular high risk set up for TRALI, even though only a few cases have been recognized.[7]

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Why is it important to recognize TRALI and to report it?

When you suspect a TRALI or a possible TRALI in a paediatric patient, it is important to report it to your hospital blood bank and to the Canadian Paediatric Surveillance Program. The blood bank will inform the blood supplier who, as described above, will determine the suitability of the associated donors with respect to continuing blood donation. As well, the blood supplier will determine if there are other blood components from the same donor that are still in inventory and, if so, remove these components, thus potentially preventing TRALI in other patients.

Reporting this syndrome to the Canadian Paediatric Surveillance Program is also important for the following reasons:

1) Since TRALI is the most common cause of transfusion-related death (at least in adults)[1], it is important to better characterize its incidence and outcome (morbidity and mortality) in the paediatric population.
2) We need to determine if TRALI truly occurs less frequently in neonates and children or if the reason there are so few paediatric cases are reported is that TRALI is not being recognized and distinguished from other pulmonary pathologies in this patient population.
3) Characterising patients with TRALI could help understanding the patho-physiology of this clinical syndrome and help researchers focus on specific mechanisms, elaborate experimental models and create new diagnostic tools.
4) Data on transfusions associated with TRALI could inform strategies to avoid this complication and eventually evaluate the efficacy of any preventive measures that may be introduced.

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Quiz

1) Which of the following criteria is not included in the definition of TRALI?

a. Hypoxemia
b. Bilateral infiltrates on frontal chest radiograph
c. Evidence of left atrial hypertension or cardiac dysfunction
d. No pre-existing ALI before transfusion
e. Occurs during or within six hours of completion of transfusion

2) TRALI has been implicated in all these blood products except:

a. red blood cells
b. plasma
c. albumin
d. platelets

3) Treatment of TRALI includes all these measures except:

a. oxygen
b. fluid ressucitation
c. mechanical ventilation
d. diuretics
e. vasopressors

4) Which of the following is right concerning the evolution and prognosis of TRALI?

a. mortality rate is 25%.
b. resolution occurs generally within 96 hours.
c. long-term sequelae are frequent.
d. mechanical ventilation is necessary in 100% of patients.

5) Which of the following statements is false?

a. TRALI is a clinical syndrome for which no specific diagnostic test exists.
b. TRALI can be caused by biologically active substances present in the blood component transfused.
c. Absence of HLA or HNA antibodies in donor excludes TRALI.
d. TRALI can be caused by an antibody-antigen interaction between a blood recipient and the blood component transfused.

Answers:
1-c, 2-c, 3-d, 4-b, 5-c