18a Transfusion-Related Acute Lung Injury (TRALI) n=3

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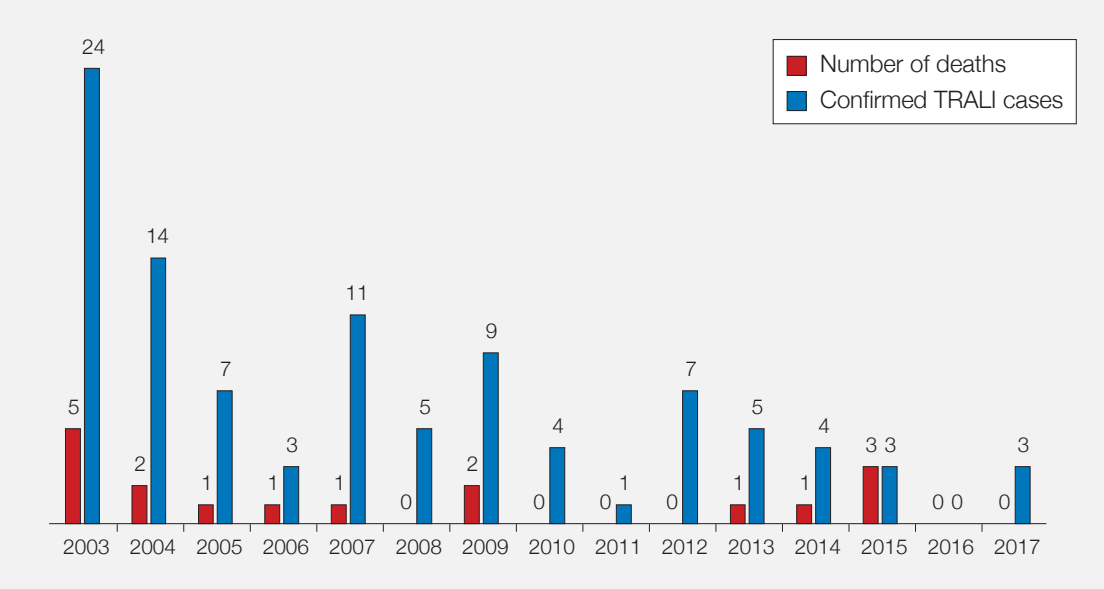
Definition:

Transfusion-related acute lung injury (TRALI) is defined as acute dyspnoea with hypoxia and bilateral pulmonary infiltrates during or within 6 hours of transfusion, in the absence of circulatory overload or other likely causes, or in the presence of human leucocyte antigen (HLA) or human neutrophil antigen (HNA) antibodies cognate with the recipient.

There were 3 confirmed cases of TRALI this year. Eleven cases were reported as suspected TRALI, 4 cases were transferred to transfusion-associated dyspnoea (TAD), 1 case to transfusion-associated circulatory overload (TACO) and 3 cases were withdrawn.

Figure 18a.1: Number of suspected TRALI cases and deaths at least possibly related to TRALI by year of report



TRALI=transfusion-related acute lung injury

Figure 18a.1 shows TRALI cases from 2003 to 2017, reclassified using the criteria introduced in the 2016 Annual SHOT Report. The use of male donors only for fresh frozen plasma (FFP) was implemented in 2003. Cases are recorded as deaths if death was at least 'possibly' related to transfusion (imputability 1 or greater).

Assessment of TRALI

The classification criteria are outlined in Table 18a.1 below. A mapping of how the revised criteria compare to the widely used Canadian Consensus definitions for TRALI is given in Table 18a.3, in order to help international comparison.

Classification	Definition	Mapping to Canadian Consensus definition
Highly likely	Cases with a convincing clinical picture and positive serology	TRALI + positive serology
Probable	Cases with positive serology but other coexisting morbidity which could independently cause acute lung injury or fluid overload	Possible TRALI (pTRALI) + positive serology
Equivocal	Cases with positive serology in the clear presence of lung injury due to other causes or fluid overload	not TRALI [excluded because of other morbidity but meets positive criteria] + positive serology
Antibody-negative TRALI	Cases with a convincing clinical picture where serology is not available or negative	TRALI + absent or negative serology
Unlikely- reclassify as TAD	Cases where the picture and serology was not supportive of the diagnosis. These cases are transferred to TAD	pTRALI or not TRALI + negative or absent serology

Table 18a.1: Revised SHOT criteria for assessment of TRALI cases

Probability	Number of cases
Highly likely	0
Probable	1
Equivocal	1
Antibody-negative	1
Unlikely (transferred to TAD/TACO)	5

Table 18a.2: TRALI case probability (SHOT criteria) 2017 cases

Table 18a.2 includes notified cases which have been transferred to other categories but not cases which have been withdrawn.

Canadian Consensus classification	Number of cases
TRALI	1
Possible TRALI	1
Not TRALI	1

Table 18a.3: Classification using Canadian Consensus definitions

Table 18a.3 includes only cases classified as TRALI - withdrawn or transferred cases would by definition be classified as 'Not TRALI'.

Case histories

Case 18a.1: Antibody-negative TRALI - a possible role for HLA cross-reactivity?

A <10-year-old girl with acute lymphocytic leukaemia (ALL) attended as an outpatient for a prophylactic platelet transfusion. Thirty minutes after transfusion of a unit of pooled platelets, the patient suffered acute vomiting, abdominal pain, acute tachypnoea, and desaturated to 70% on air. The chest X-ray showed a complete white-out. The patient required intubation and ventilation but subsequently made a complete recovery. The patient had previously been well and there were no clinical features of fluid overload or additional fluids.

One male donor had HLA antibodies against HLA-A25, -A34, -A66, -A68; the recipient typed as HLA-A2;A26.

This case has been classified as 'antibody-negative TRALI' based on a classical history and absence of alternative explanations. However, although the antibodies are not cognate with the recipient it is noted that they are in the same 'cross-reactive group'. Cross-reactive groups (CREG) denote operationally monospecific HLA antisera that react with two or more HLA antigens due to public epitopes that are differentially shared among HLA class I gene products (Focosi 2014). In this case, A2 (recipient) and A68 (donor antibody) are in the same CREG group and A26 (recipient) is in the same group as A25, A34 and A66 (donor).

HLA cross-reactivity has not been reported as having an association with TRALI but has a moderate effect on platelet refractoriness. It is therefore feasible that there could be a causative relationship for TRALI.

Case 18a.2: Probable TRALI

A female teenager developed acute respiratory deterioration, hypoxia and bilateral patchy air space shadowing 4 hours after transfusion of red cells. The transfusion was given for anaemia 2 days after a liver transplant for Alagille syndrome. She had a positive fluid balance and impaired renal and cardiac function secondary to the underlying syndrome although these had not caused functional compromise. She required ventilation but made a complete recovery.

The red cell donor had HNA-1a antibodies which were cognate with the recipient.

The case was classified as 'probable TRALI' in view of the positive serology and the treating clinician's impression that fluid overload was unlikely, however the patient also had coexisting risk factors for fluid overload which therefore cannot be ruled out.

Case 18a.3: Equivocal TRALI

A female patient in her 60s was already under prolonged ventilation following oesophageal surgery complicated by a perforated oesophagus and splenic rupture and she was also recovering from postoperative sepsis. She developed increased oxygen requirements and deterioration in the chest X-ray (CXR) following a transfusion of two units of red cells. There was pre-existing pulmonary oedema on a CXR prior to the transfusion, but this was worse after transfusion and a computerised tomography (CT) scan showed patchy ground-glass shadowing within the lung fields in keeping with acute respiratory distress syndrome (ARDS).

Investigation of the donors showed that both red cell donors had HLA class 1-specific antibodies, in particular to HLA-A2. The patient also had the cognate HLA-A2 antigen.

This case has been classified as 'equivocal TRALI' - it is practically impossible to assign causation retrospectively in the presence of pre-existing lung injury, infection and fluid overload but the presence of cognate antibodies in both donors raises the possibility of TRALI as a causative or contributory factor.

Cumulative serological data

Since 1996, 207/327 (63.3%) reported cases have had full laboratory investigation for TRALI. Concordant antibodies were identified in 118/207 (57.0%) of these. The most frequently identified antibody specificities (either alone or in combination with other concordant antibodies) have been HLA-DR4 (22/118 cases, 18.6%), HLA-DR52 (17/118, 14.4%) and HLA-A2 (19/118, 16.1%). All other HLA antibody specificities have been identified in less than 10% of cases. Concordant HNA specific antibodies, alone or in combination, have been found as follows: HNA-1a (10/118 cases, 8.5%); HNA-2 (2/118, 1.7%); HNA-3a (2/118, 1.7%).

Analysis of reports of 187 complete TRALI investigations between 2001 and 2017 inclusive has shown that the specificities of concordant antibodies were as follows:

Table 18a.4: Concordant donor antibodies 2001 to 2017 inclusive

Concordant donor antibodies 2001 to 2017 inclusive				
HLA class I alone	HLA class II alone	Both HLA class I and HLA class II	Granulocyte-specific antibody (+/- HLA antibodies)	None identified
21/187 (11.2%)	36/187 (19.3%)	27/187 (14.4%)	19/187 (10.2%)	84/187 (44.9%)

Commentary

Three confirmed cases of TRALI were reported this year, including 1 delayed report of a case from 2016. This number is comparable to the annual incidence over the last decade. The revised classification, as intended, gives a better proportion of cases where TRALI is thought to be at least a possible explanation for the clinical picture.

Part of the motivation for including the presence of leucocyte antibodies in the definition used by SHOT is to be able to monitor the effectiveness of TRALI prevention measures. In the 3 confirmed cases, all components transfused were consistent with TRALI-reduction measures (male donor FFP and screening of parous female platelet donors). Case 18a.1 is a reminder that male donors can have HLA antibodies and that it is worthwhile testing male donors for antibodies if there is a high clinical suspicion of TRALI.

The question raised by Case 18a.1 of whether HLA cross-reactivity could cause TRALI needs further investigation. The most direct way of demonstrating that antibodies in the donor are reactive with the recipient would be to perform a lymphocyte crossmatch. While this is logistically difficult to arrange, it is suggested that this would be a useful addition to the investigation of suspected TRALI cases. For the moment, it is proposed to continue classifying cases with cross-reactive but not matching antibodies in the 'antibody-negative TRALI' category so that they can receive additional scrutiny.

Blood Centres should consider performing a lymphocyte crossmatch in suspected transfusion-related acute lung injury (TRALI) cases where donors are found to have human leucocyte antigen (HLA) antibodies in the same cross-reactive group as the recipient.

References

Focosi D. HLA nomenclature 2014. http://www.ufrgs.br/imunovet/molecular_immunology/hla.html#CREG [accessed 15 April 2018].