18a Transfusion-Related Acute Lung Injury (TRALI) n=0

Author: Tom Latham

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 no confirmed cases of TRALI this year. Six cases were reported as suspected TRALI; 4/6 cases were transferred to transfusion-associated dyspnoea (TAD), 1/6 case to unclassifiable complications of transfusion (UCT) and one was withdrawn.

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

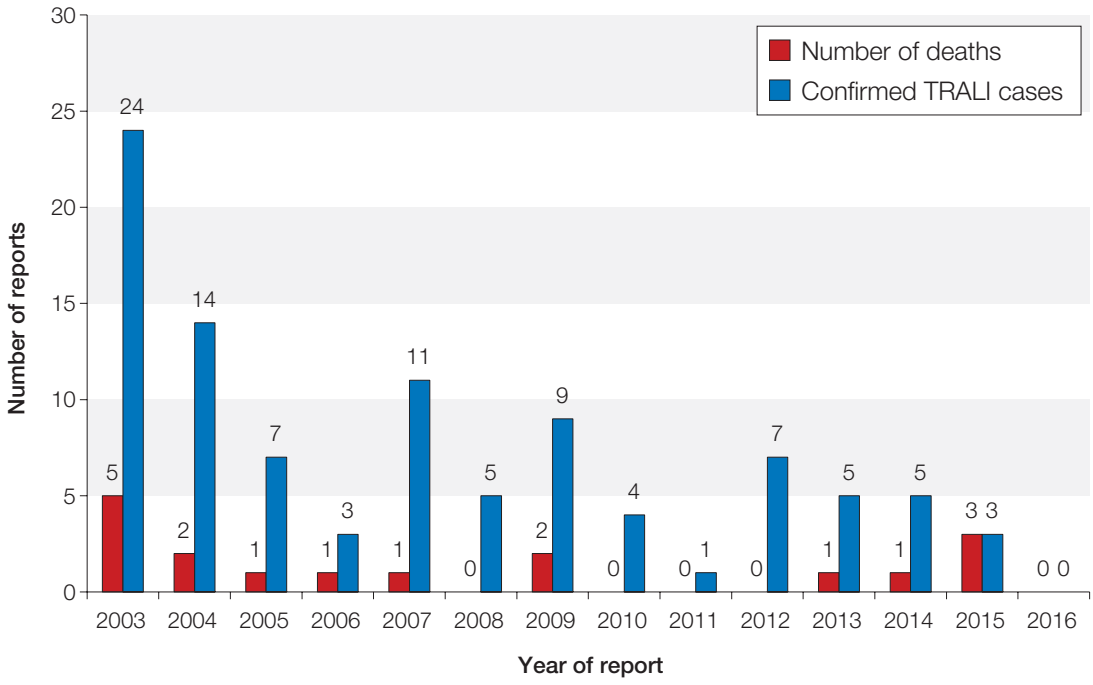

Figure 18a.1 shows TRALI cases from 2003-2016 reclassified using the new criteria. The use of male donors only for fresh frozen plasma (FFP) was implemented in 2003. Cases are recorded as deaths if death was at least 'possibly' related to transfusion (imputability 1 or greater).

Assessment of TRALI

In this year's report revised criteria for classifying TRALI are used. These give greater emphasis to the finding of leucocyte antibodies and use the presence of alternative explanations for respiratory compromise to determine imputability. The 'possible TRALI' (pTRALI) category is divided in to two categories, clarifying whether the uncertainty in diagnosis is due to the existence of alternative explanations or due to the absence of antibodies. Cases with negative serology and a dubious clinical history for TRALI have been transferred to the TAD category.

The revised criteria are outlined in Table 18a.1 below. Mapping showing how the revised criteria compare to the widely-used Canadian Consensus definitions (CCD) for TRALI is given in Table 18a.1 in order to help international comparison and Table 18a.3 shows how the 6 cases reported in 2016 would be classified by CCD.

Table 18a.4 compares the classification of historical and current cases between the two SHOT classification systems. This shows good concordance. The main difference relates to the handling of cases thought unlikely to be TRALI. It also shows that cases of 'antibody-negative TRALI' with a clear clinical history are rare.

Classification	Definition	Mapping to previous SHOT classification	Mapping to Canadian Consensus definition
Highly likely	Cases with a convincing clinical picture and positive serology	Highly likely	TRALI +positive serology
Probable	Cases with positive serology but other coexisting morbidity which could independently cause acute lung injury or fluid overload	Probable with positive serology	pTRALI +positive serology
Equivocal	Cases with positive serology in the clear presence of lung injury due to other causes or fluid overload	Possible with positive serology	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	Probable/possible with negative/absent serology	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	Unlikely	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	0
Equivocal	0
Antibody negative	0
Unlikely (transferred or withdrawn)	6

Table 18a.2: TRALI case probability (SHOT criteria) for cases reported in 2016

Canadian Consensus classification	Number of cases
TRALI	0
Possible TRALI	2
Not TRALI	4

Table 18a.3: Classification using Canadian Consensus definitions

Table 18a.4: Comparison of previous and revised classification: TRALI cases 2012-2016

Revised classification	Previous SHOT classification			
	Highly likely	Probable	Possible	Unlikely
Highly likely	3			
Probable		12		
Equivocal			2	
Antibody negative			3	
Unlikely				17

Illustrative case histories

In order to illustrate the revised classification, and compare assignment with the previous classification, some case histories from previous SHOT reports and this year's submissions are presented.

Case 18a.1: Highly likely (from the 2014 Annual SHOT Report)

A healthy 22-year-old woman had a 3L postpartum haemorrhage (PPH) after an elective caesarean section. She was transfused with four units of red blood cells in optimal additive solution (RBCOA), four FFP and two cryoprecipitate pools. Within 10 minutes of starting the cryoprecipitate transfusion she developed difficulty breathing and became cyanosed. Her oxygen saturation was 64%, respiratory rate 30 breaths per minute, pulse 125 beats per minute and her blood pressure (BP) increased. She was treated with 80mg furosemide and had a 2L diuresis but her condition worsened. Her chest X-ray showed patchy consolidation throughout both lungs. On the next day her respiratory function deteriorated further and she required intubation. She was ventilated for one day and then made a full recovery. Laboratory investigation identified multiple HLA antibody matches between donors and this patient: three female cryoprecipitate donors had concordant antibodies and one female RBCOA donor had concordant antibodies.

This case was classified as 'highly likely' and this remains unchanged - there is a classical history and multiple concordant antibodies.

Case 18a.2: Probable (from the 2015 Annual SHOT Report)

This patient was already on oxygen for pneumonia post autologous haemopoietic stem cell transplant (HSCT) but deteriorated rapidly 20 minutes after transfusion of two units of red cells and died of respiratory failure seven days later. Serology showed HLA class I antibodies cognate with the recipient.

This case was originally classified as probable TRALI. In the current classification this would also be classed as probable TRALI: there was severe deterioration with clear temporal relationship to transfusion and cognate antibodies, but it was not possible to rule out a coincidental worsening of the underlying pneumonia.

Case 18a.3: Equivocal - due to comorbidity (from the 2015 Annual SHOT Report)

This patient developed breathlessness 40 minutes following six units of red cells, four units of FFP and one pool of cryoprecipitate for a variceal bleed. There was pre-existing fluid overload before transfusion and a chest X-ray before transfusion suggested pneumonia. However antibodies cognate with the recipient were present in one red cell unit and two donors to the cryoprecipitate pool.

This case was originally classified as 'possible TRALI'. This case would be classed as 'equivocal TRALI' in the revised classification because there is large volume transfusion in the clear presence of pre-existing fluid overload and pneumonia, however the presence of antibodies cognate with the recipient cannot be ruled out as contributing to the respiratory deterioration.

Case 18a.4: Antibody-negative TRALI (from the 2012 Annual SHOT Report)

A 3-year-old boy undergoing vinblastine chemotherapy for astrocytoma became pyrexial, tachypnoeic and hypoxic 1 hour into transfusion after 140mL of a unit of RBCOA. Chest X-ray showed bilateral ground glass shadowing. He required admission for oxygen and made a full recovery after 2 days. The red cell donor was male with no antibodies on testing.

This case was originally classified as 'possible TRALI' in view of the clinical history and lack of other explanations but considering the absence of antibodies.

Case 18a.5: Unlikely - transfer to TAD (2016)

A 70-year-old woman with pre-existing evidence of infection on chest X-ray, and echocardiographic evidence of pulmonary hypertension and left atrial enlargement became hypoxic 5 hours after transfusion of a single pool of apheresis platelets. Bilateral interstitial disease was shown on computerised tomography (CT) scan of her lungs. She recovered with oxygen therapy and there was some improvement after diuretics. Serology was negative.

This case was transferred to TAD due to the negative serology and existence of multiple alternative explanations for her hypoxia, although the timing of the event would be compatible with TRALI.

Cumulative serological data

Since 1996, 204 of 324 (63.0%) reported cases have had full laboratory investigation for TRALI. Concordant antibodies were identified in 116/204 (56.9%) of these. The most frequently identified antibody specificities (either alone or in combination with other concordant antibodies) have been HLA-DR4 (22/116 cases, 19.0%), HLA-DR52 (17/116, 14.7%) and HLA-A2 (18/116, 15.5%). 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 (9/116 cases, 7.8%); HNA-2 (2/116, 1.7%); HNA-3a (2/116, 1.7%).

Analysis of reports of 184 complete TRALI investigations between 2001 and 2016 inclusive has shown that the specificities of concordant antibodies were as follows:

Table 18a.5: Concordant donor antibodies 2001 to 2016 inclusive

Concordant donor antibodies 2001 to 2016 inclusive				
HLA class I alone	HLA class II alone	Both HLA class I and HLA class II	Granulocyte-specific antibody (+/- HLA antibodies)	None identified
20/184 (10.9%)	36/184 (19.5%)	27/184 (14.7%)	18/184 (9.8%)	83/184 (45.1%)

Commentary

The definition of TRALI used by SHOT has been unchanged since 1995, and 12 years have passed since the Canadian Consensus definition was agreed (Kleinman et al. 2004). We consider that a revised definition is now appropriate in order to serve haemovigilance needs better, and to clarify the classification of pulmonary complications of transfusion. While the classical definition of 'hypoxia and chest X-ray abnormalities within 6 hours not due to other causes' is still valid, the difficulty from a classification point of view is that it is not possible to prove causation. The revised definition is a working definition which avoids the need to make a judgement on whether the event is caused by any morbidity present. Table 18a.4 shows that there is good consensus between current and previous classifications.

The association between leucocyte antibodies and TRALI is well established both in animal models and human studies, although there remain questions regarding pathogenetic mechanisms (Peters et al. 2015a). Most importantly, the success of TRALI prevention strategies, such as the use of male donor-only plasma, aimed at reducing the risk of transfusion of leucocyte antibodies supports a causative relationship (Müller et al. 2015). Antibody-mediated TRALI should therefore now be considered as a potentially preventable complication of transfusion. From a haemovigilance point of view, the practical need is to monitor antibody-associated cases in order to assess the effectiveness of prevention strategies. From this perspective, a purely clinical definition, where the presence of comorbidity excludes TRALI is unsatisfactory: there is no reason, for example, why fluid overload should offer protection from antibody-mediated damage.

In contrast, the nature of antibody-negative TRALI remains poorly understood (Peters et al. 2015b). While acute lung injury can be produced by manipulation of blood components in animal models, the relevance of these artificial models to lung injury in humans is unclear. Similarly, biological mediators

such as bioactive lipids which can cause lung injury in animal models have not, so far, been definitively demonstrated in human cases of TRALI. The practical need for these cases is for further research to identify possible mechanisms and preventive strategies. Given that there is no diagnostic test it is most helpful at this stage to restrict diagnosis of antibody-negative TRALI to cases which have a typical clinical history.

What is clear however, is that respiratory deterioration following transfusion is not uncommon. Many of the cases are multifactorial with several contributory factors coexisting; it is difficult in many cases to establish whether there was a causative relationship with transfusion at all. This is an important area for ongoing research but it is unhelpful for the monitoring of antibody-mediated TRALI to count cases thought unlikely to be TRALI in the TRALI statistics. Reassigning these 'unlikely TRALI' cases to the TAD classification will allow a broader approach to be taken to respiratory deterioration associated with transfusion.

There are certainly difficulties with defining TRALI based on antibody detection, and it is certainly not proposed that the demonstration of antibodies can yet be considered either a necessary or sufficient definition for TRALI. No serological test is completely sensitive and indeed assays such as Luminex bead assays are able to detect antibodies at lower levels than may have been possible in earlier reports. In addition, the difficulty of obtaining samples from both the recipient and all implicated donors means that some cases will not have complete serological investigation. It is certainly possible that some of the cases of 'antibody-negative TRALI' in fact relate to cases where antibodies are responsible but below limits of detection. Continuing to monitor the incidence of 'antibody-negative TRALI' may help to investigate this possibility, as the incidence would be expected to respond to preventive measures in parallel with the antibody-mediated cases.

Conversely, it is clear that the majority of donations with leucocyte antibodies do not cause TRALI. The risk of finding an antibody by chance increases with the number of donations received and thus the likelihood ratio of antibody testing for diagnosing TRALI decreases with the number of units transfused. In practice this will not affect the validity of classification, as patients with major haemorrhage are unwell almost by definition, thus having alternative explanations for respiratory deterioration and being assigned to lower imputability categories.

A final difficulty with revising the classification relates to international and historical comparison. As shown in the mapping above, it is fairly straightforward to translate between different classifications. The terminology 'equivocal TRALI' has thus been chosen for cases with positive antibodies but unclear history to avoid confusion with the 'possible TRALI' category in the Canadian Consensus classification.

In summary, we propose that the revised classification based on serology provides better separation between the haemovigilance need to monitor preventable antibody-associated cases and the investigative need to identify how to prevent pulmonary complications of transfusion. We also propose that the use of a pathologically-defined classification of TRALI gives a more objective basis for international comparison.

References

Kleinman S, Caulfield T et al. (2004) **Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel.** Transfusion 44, 1774-1789

Müller M, van Stein D et al. (2015) **Low-risk transfusion-related acute lung injury donor strategies and the impact on the onset of transfusion-related acute lung injury: a meta-analysis.** Transfusion 55(1), 164-175

Peters A, van Stein D, Vlaar AP (2015a) **Antibody-mediated transfusion-related acute lung injury; from discovery to prevention.** Br J Haematol 170, 597–614

Peters A, van Hezel M et al. (2015b) **Pathogenesis of non-antibody mediated transfusion-related acute lung injury from bench to bedside.** Blood Reviews 29, 51–61