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

17a

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.

Key SHOT message

- An updated terminology and criteria for redefinition of transfusion-related acute lung injury (TRALI) has been proposed by an international collaborative group in 2019, focussing on TRALI as a clinical diagnosis and does not consider the underlying pathophysiology. Work is ongoing to investigate whether the proposed changes will be suitable for use in haemovigilance practice

Abbreviations used in this chapter

CT	Computerised tomography
ECMO	Extracorporeal membrane oxygenation
FAHR	Febrile, allergic and hypotensive reactions
FFP	Fresh frozen plasma
HLA	Human leucocyte antigen
HNA	Human neutrophil antigen
NT-BNP	N-terminal-pro B-type natriuretic peptide
TACO	Transfusion-associated circulatory overload
TAD	Transfusion-associated dyspnoea
TRALI	Transfusion-related acute lung injury
UCT	Uncommon complications of transfusion

Recommendation

- Reporters should include an assessment of whether respiratory status was stable in the 12 hours prior to transfusion for all pulmonary complications of transfusion, to aid classification according to the revised consensus definitions

Action: All SHOT reporters

Introduction

There were 3 confirmed cases of antibody-positive TRALI this year. In total, 18 cases were reported as suspected TRALI. Of these, 5 cases were transferred to transfusion-associated dyspnoea (TAD), 5 cases to transfusion-associated circulatory overload (TACO), 2 cases to febrile, allergic and hypotensive reactions (FAHR) and 1 to uncommon complications of transfusion (UCT). In the remaining 2 cases, 1 has been deferred to the next Annual SHOT Report as serology results are in progress and 1 was withdrawn.

The cases in this year's Annual SHOT Report are primarily classified using the SHOT nomenclature (Table 17a.1), which takes into account both the clinical history and the presence of leucocyte antibodies. In

2019, the consensus redefinition of TRALI (Vlaar et al. 2019) was proposed by an international working group, to which SHOT provided representation (Table 17a.2). This redefinition was intended to update the earlier Canadian consensus criteria. A mapping between the SHOT nomenclature and the redefinition is provided in Table 17a.1.

Table 17a.1: SHOT criteria for assessment of TRALI cases

Classification	Definition	Mapping to consensus redefinition
Highly likely	Cases with a convincing clinical picture and positive serology	TRALI type I + positive serology
Probable	Cases with positive serology but other comorbidities which could independently cause acute lung injury or fluid overload	TRALI type II + positive serology
Equivocal	Cases with positive serology in the clear presence of lung injury due to other causes or fluid overload	ARDS or 'TRALI/TACO cannot be distinguished' + positive serology
Antibody-negative TRALI	Cases with a convincing clinical picture where serology is not available or negative	TRALI type I + absent or negative serology
Unlikely - reclassify as TAD	Cases where the history and serology were not supportive of the diagnosis. These cases are transferred to TAD	TRALI type II or 'TRALI/TACO cannot be distinguished' + negative or absent serology

Table 17a.2: Consensus redefinition criteria for TRALI

TRALI Type I—Patients who have no risk factors for ARDS and meet the following criteria:

a. i. Acute onset
   ii. Hypoxemia (P/F ≤ 300* or SpO_2 < 90% on room air)
   iii. Clear evidence of bilateral pulmonary edema on imaging (e.g., chest radiograph, chest CT, or ultrasound)
   iv. No evidence of LAH† or, if LAH is present, it is judged to not be the main contributor to the hypoxemia
b. Onset during or within 6 hr of transfusion‡
c. No temporal relationship to an alternative risk factor for ARDS

TRALI Type II—Patients who have risk factors for ARDS (but who have not been diagnosed with ARDS) or who have existing mild ARDS (P/F of 200-300), but whose respiratory status deteriorates§ and is judged to be due to transfusion based on:

a. Findings as described in categories a and b of TRALI Type I, and
b. Stable respiratory status in the 12 hr before transfusion

* If altitude is higher than 1000 m, the correction factor should be calculated as follows: [(P/F) × (barometric pressure/760)].
† Use objective evaluation when LAH is suspected (imaging, e.g., echocardiography, or invasive measurement using, e.g., pulmonary artery catheter).
‡ Onset of pulmonary symptoms (e.g., hypoxemia—lower P/F ratio or SpO_2) should be within 6 hours of end of transfusion. The additional findings needed to diagnose TRALI (pulmonary edema on a lung imaging study and determination of lack of substantial LAH) would ideally be available at the same time but could be documented up to 24 hours after TRALI onset.
§ Use P/F ratio deterioration along with other respiratory parameters and clinical judgment to determine progression from mild to moderate or severe ARDS. See conversion table in Appendix S2 to convert nasal O_2 supplementation to FiO_2.

Table 2. New consensus TRALI definition from Vlaar et al. (2019)

Death n=0

There were no deaths this year. Figure 17a.1 shows TRALI cases from 2003-2019, classified using the criteria introduced in the 2016 Annual SHOT Report (Bolton-Maggs et al. 2017). 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).

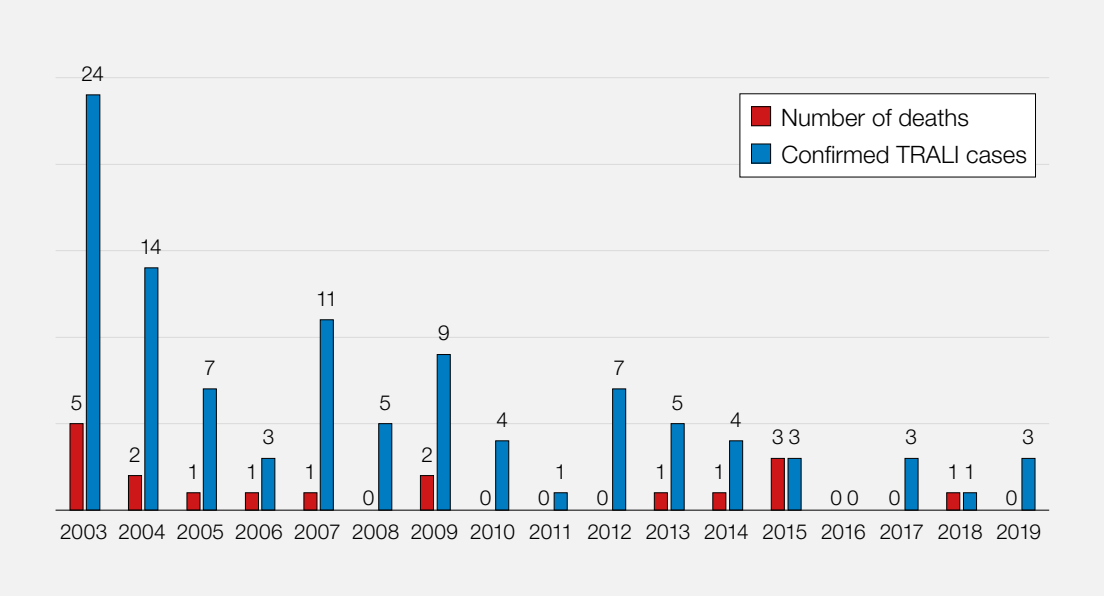

Figure 17a.1: Number of confirmed TRALI cases and deaths at least possibly related to TRALI by year of report

Major morbidity n=3

There were 3 cases of major morbidity, all related to the need for ventilation. Cases are presented in detail below in order to illustrate application of the consensus redefinition criteria and show how they relate to the SHOT nomenclature.

Case 17a.1: Probable TRALI - Acute lung injury following cardiac surgery with cognate antibodies in red cells from a female donor without history of pregnancy

A female patient in her 20s, undergoing cardiac surgery was transfused four units of red cells and two pools of platelets for intraoperative bleeding. 30 minutes after coming off bypass, she became hypoxic with increased difficulty ventilating. Pink frothy fluid was aspirated on bronchoscopy and chest X-ray showed severe pulmonary oedema. There was no respiratory improvement with diuretics. She required extracorporeal membrane oxygenation (ECMO) and 15 days ventilation.

Serological investigation identified HLA antibodies cognate with recipient HLA A2, DR11 and DR17 in one red cell donor. It is notable that the donor had no history of pregnancy. The case has been classified as 'probable TRALI' as it is impossible to rule out major haemorrhage as a cause of the lung injury. In the consensus redefinition this would fit 'TRALI type II' as timing and acute lung injury criteria are met, but there is an alternative risk factor for lung injury present (cardiac surgery).

Case 17a.2: Probable TRALI - Acute deterioration in a patient with sepsis with cognate antibodies in both red cell units

A female patient in her 60s with myelodysplasia was admitted with fever and weight loss and had bronchopneumonia on a computerised tomography (CT) scan on admission, treated with intravenous antibiotics. She received a two-unit red cell transfusion for anaemia and was found unconscious 15 minutes after the second unit started with hypoxia and hypotension. Chest X-ray showed florid pulmonary oedema; post-transfusion N-terminal-pro B-type natriuretic peptide (NT-BNP) was borderline at 200pg/mL. She required 48 hours of ventilation and inotropic support but subsequently made a full recovery. Echocardiogram showed good left ventricular function but a vegetation on her mitral valve; she was subsequently confirmed as having infective endocarditis, for which she received an extended course of antibiotics.

Serological investigation showed multiple HLA class II antibodies in the donor of the first unit (HLA DR 4,15, 51; cognate with recipient) and class I antibody (HLA B60; cognate with recipient) in the second unit. The case has been classified as 'probable TRALI' as she had pre-existing lung disease and it is impossible to rule out sepsis or endocarditis compromising her ability to handle the volume of transfusion. In the consensus redefinition this would fit 'TRALI type II' as there are alternative risk factors for lung injury present (sepsis).

Case 17a.3: Equivocal TRALI - Cognate antibodies from female platelet donors in a patient with multiple possible reasons for lung injury

A male patient in his 50s, 40 days post allogeneic transplant for myelofibrosis had had a complicated admission with influenza, suspected pneumocystis pneumonia and bacteraemia, but was clinically improving on the day of reaction though still on oxygen. He was transfused two pooled units of platelets prior to Hickman line insertion and then became acutely hypoxic and breathless immediately after the procedure. CT scan was reported as 'There is widespread mixed interstitial and intra-alveolar air space shadowing suggesting an evolving bilateral pneumonic process. The appearances are more confluent, than on the previous chest X-ray. The appearances are not typical of acute pulmonary oedema.' He required ventilation for 48 hours and was treated with multiple antibiotics but made a full recovery.

Serological investigation of the female donors contributing to the platelet pools revealed HLA A2 antibodies in one platelet donor and HLA Bw4 in the second platelet donor cognate with both the recipient's original HLA type and the stem cell donor's HLA type. One donor had no history of pregnancy or transfusion. The case has been classified as 'equivocal TRALI' as the timing and serology are compatible but there are other possible causes (which the imaging favours). The case arguably does not meet the criteria for TRALI in the consensus redefinition as it does not meet the criterion of 'clear evidence of bilateral pulmonary edema on imaging.'

Analysis of cases

Classification of cases using SHOT and revised consensus nomenclature

Table 17a.3: Classification of 2019 cases referred as suspected TRALI

Probability	Number of cases
Highly likely	0
Probable	2
Equivocal	1
Antibody-negative	0
Unlikely - transferred to other categories	15

Table 17a.3 includes notified cases which have been transferred to other categories but not cases which have been withdrawn or deferred.

Table 17a.4: Classification of 2019 cases using revised consensus definitions

Consensus redefinition classification	Number of cases
TRALI type I	0
TRALI type II	2
Not TRALI	1

Table 17a.4 includes only cases classified as TRALI. There may be cases in both TAD and TACO categories which could be classified as TRALI type II or 'TRALI/TACO cannot be distinguished' under the consensus definition.

Cumulative serological data

Analysis of reports of 191 complete TRALI investigations between 2001 and 2019 inclusive has shown that the specificities of concordant antibodies were as follows:

Table 17a.5: Concordant donor antibodies 2001 to 2019 inclusive

HLA class I alone	HLA class II alone	Both HLA class I and HLA class II	Granulocyte specific antibody (+/- HLA antibodies)	None identified
22/191 (11.5%)	36/191 (18.9%)	29/191 (15.2%)	19/191 (9.9%)	85/191 (44.5%)

Commentary

The number of cases due to antibody-mediated TRALI in this year's Annual SHOT Report remains relatively stable. All cases this year had antibodies which could not have been prevented by existing TRALI reduction measures. The occurrence of HLA antibody-associated TRALI associated with red cell transfusion from female donors with no history of pregnancy or transfusion demonstrates that targeting screening to females with history of pregnancy or restricting donors with antibodies to red cell donation is unlikely to completely prevent antibody transmission.

The publication of the revised consensus criteria is the major change this year. How do the revised criteria contribute to haemovigilance? The new criteria do appear workable in terms of being able to classify cases, and the 'TRALI type II' concept does group together an identifiable clinical phenomenon of unwell patients who develop a respiratory deterioration following transfusion. It remains unsatisfactory that TRALI is defined purely as a syndrome of clinical features based on arbitrary cut-off points.

Underlying the new diagnostic criteria, the authors offer a fundamental concept of TRALI as 'post-transfusion pulmonary oedema caused by increased endothelial permeability.' This is certainly a well-defined concept, but is a true redefinition which fundamentally alters the haemovigilance implications of TRALI. There is a difference in terms of preventative approaches between cases where biologically active agents in the transfusion contributed to endothelial injury (which are thus in the domain of safety of blood components), and cases where pre-existing endothelial permeability reduced the ability to tolerate the fluid load associated with the transfusion (which is a clinical matter for prevention).

The long-term aim would be a classification of post-transfusion lung injury based on aetiology, but this is not currently possible. Leucocyte antibodies are an established causative agent, although neither necessary nor sufficient for a TRALI diagnosis. It remains important to consider the presence of leucocyte antibodies and the imputability of their relationship with the reaction to monitor the effectiveness of preventative strategies based on antibody reduction.

Nevertheless, it will be important to align case reporting with the new definitions to aid international comparison. The initial priority is to formally review how the redefinition is applicable in practice; a review of historical pulmonary complication cases is proposed both for SHOT and internationally. It is proposed that SHOT will continue to report antibody-associated cases as a sub-category.

References

Bolton-Maggs PHB (Ed), Poles D, et al. (2017) on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2016 Annual SHOT Report. https://www.shotuk.org/shot-reports/ [accessed 08 June 2020].

Vlaar APJ, Toy P, Fung M, et al. (2019) A consensus redefinition of transfusion-related acute lung injury (TRALI). *Transfusion* 2019;**59**:2465-2476.