Pulmonary Complications n=163 17

Author: Puneet Malhotra with contributions from members of the pulmonary Working Expert Group (WEG)

Key SHOT messages

- Pulmonary complications of transfusion remain a leading cause of transfusion-related mortality and morbidity, contributing to over 50% of transfusion-related deaths reported to SHOT from 2010 to 2019
- When compared to blood use in various National Health Service (NHS) Trusts/Health Boards, a degree of under-reporting is apparent

Abbreviations used in this chapter

ARDS	Acute respiratory distress syndrome	**NBTC**	National Blood Transfusion Committee
BNP	Brain natriuretic peptide	**NT-Pro BNP**	N-terminal-pro brain natriuretic peptide
IHN	International Haemovigilance Network	**TACO**	Transfusion-associated circulatory overload
ISBT	International Society of Blood Transfusion	**TAD**	Transfusion-associated dyspnoea
LAH	Left atrial hypertension	**TRALI**	Transfusion-related acute lung injury
NHS	National Health Service	**WEG**	Working Expert Group

Recommendations

- All cases with pulmonary complications up to 24 hours post transfusion should be reported to SHOT with as much information as possible to ensure adequate inference and effective learning

Action: All SHOT reporters, National Blood Transfusion Committee (NBTC), hospital transfusion teams

- Risk assessment of all patients needing transfusions will help institute appropriate, timely mitigating actions to prevent or reduce the severity of pulmonary complications. Prompt recognition with appropriate investigations and accurate diagnosis will help improve morbidity and mortality

Action: All staff involved in transfusion

Introduction

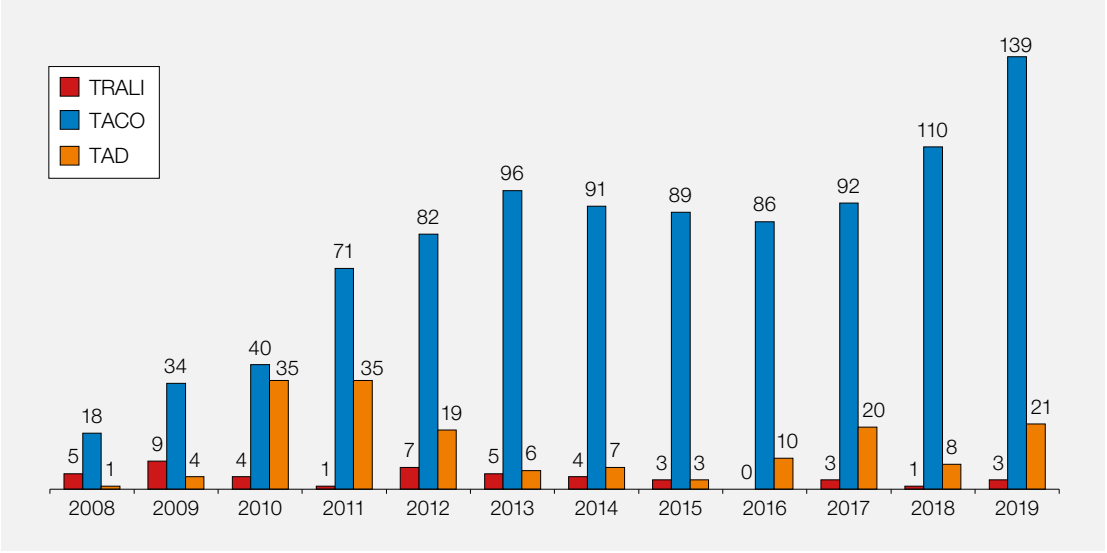
Pulmonary complications of transfusion remain a leading cause of transfusion-related mortality and morbidity, contributing to over 50% of transfusion-related deaths reported to SHOT from 2010 to 2019 (Narayan et al. 2019). There are two well-recognised pulmonary complications of transfusion: transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). In 2019, updated consensus criteria for the definition of both these conditions were published (Vlaar et al. 2019, Wiersum-Osselton et al. 2019). Cases submitted to SHOT that do not meet these criteria, but where there is a temporal relationship between the patient's respiratory deterioration and blood transfusion are included in the transfusion-associated dyspnoea (TAD) category.

The TAD category serves as an important repository for cases of uncertain cause, highlighting potential challenges distinguishing clinically between TACO and TRALI. An important contributing factor in some cases is a lack of adequate clinical information to confidently categorise patients as either TACO or TRALI. Therefore, for the purposes of data analysis, the pulmonary WEG of SHOT has decided in 2020 to sub-classify TAD cases as:

- TAD-C: cases where adequate clinical information was available
- TAD-IC: cases where clinical information was inadequate

SHOT accepted 163 reports of pulmonary complications in 2019; this was the highest annual number received to date. The majority of pulmonary complication reports are of TACO (139 in 2019), a year on year increase (92 in 2017, 110 in 2018) which may be due to enhanced awareness following the recommendation from SHOT to implement a TACO checklist (Bolton-Maggs et al. 2016), together with publicity from the 2017 UK national comparative audit of TACO (Morton et al. 2017). The number of confirmed TRALI cases has reduced since 2003 following the change to production of frozen plasma exclusively from males as a risk-reduction measure. The number of reported TAD cases has varied over recent years and this probably reflects a combination of incomplete submitted data for individual cases and revisions of the definitions for the pulmonary complications. All categories are explored in detail in the next three chapters.

Figure 17.1: Reports of pulmonary complications by year 2008-2019



TRALI=transfusion-related acute lung injury; TACO=transfusion-associated circulatory overload; TAD=transfusion-associated dyspnoea

Updated definition of TRALI

The 2004 consensus definition of TRALI was revised in 2019 (Vlaar et al. 2019) based on current evidence, and to harmonise with the updated Berlin definition of acute respiratory distress syndrome (ARDS) (Ferguson et al. 2012). In the redefinition, the term 'possible TRALI' was dropped to remove the ambiguity of whether 'possible' meant the extent to which the symptoms met the case definition, or the extent to which the blood transfusion was responsible for the reaction (imputability). New terminology was proposed: TRALI type 1 (without an ARDS risk factor), and TRALI type II (with an ARDS risk factor or with mild existing ARDS). In cases with an ARDS risk factor and respiratory deterioration over the 12 hours preceding the transfusion, if the ARDS risk factor was deemed as causative (rather than the transfusion), the cases were classified as ARDS. In this revision, TRALI is a clinical diagnosis not requiring the detection of cognate white blood cell antibodies. The authors recommended adoption into haemovigilance systems for international standardisation, however this will require validation and further collaborative work with international haemovigilance organisations.

Updated definition of TACO

Application of the International Society of Blood Transfusion (ISBT) definition for TACO (ISBT/IHN 2011),

led to recognition that several cases categorised as TACO by clinicians and endorsed by haemovigilance systems did not meet the ISBT criteria (Wiersum-Osselton et al. 2019). This prompted the development of a standardised surveillance definition for TACO by a joint working group from the ISBT haemovigilance working party, the International Haemovigilance Network (IHN) and AABB with wide international consultation. SHOT was a key contributor and collaborator in this work.

Circulatory overload is associated with left atrial hypertension (LAH) and the presence of LAH is a discriminator between TACO and TRALI but demonstrating evidence of this is difficult. Both echocardiography and serum brain natriuretic peptide (BNP) or NT-pro brain natriuretic peptide (NT-Pro BNP) are potentially useful investigations but are currently infrequently performed. BNP/NT-Pro BNP can often be performed on the same sample type as that used for compatibility testing, allowing convenient retrospective testing of pre- and post-transfusion blood samples.

Recent data from SHOT show that only 9.1% (10/110) of reported cases of TACO had an echocardiography report provided, and only 2.7% (3/110) had a NT-Pro BNP performed (Narayan et al. 2019). BNP or NT-Pro BNP is a potentially useful surrogate for LAH: a normal level excludes TACO and is therefore a valuable negative predictor. An increase to 1.5 times the pre-transfusion level supports TACO (Li et al. 2009; Zhou et al. 2005). The pre-transfusion level is often raised as heart failure is a risk for TACO, and therefore the extent of change is important. However, there are some limitations: NT-Pro BNP levels are unreliable in critically ill patients and in renal failure due to impaired renal clearance and hypoxic vasoconstriction (Klanderman et al. 2019), limiting its usefulness in this population.

The new TACO haemovigilance definition relies on the 'additional criteria' to demonstrate features of circulatory overload and this is important when echocardiography and BNP/NT-Pro BNP may not be available to provide evidence of LAH. The additional criteria (excluding BNP/NT-Pro BNP) rely on demonstrating indirect evidence of circulatory overload by the presence of unexplained cardiovascular changes (hypertension, tachycardia, enlarged cardiac silhouette (if reported), and new peripheral oedema), or evidence of fluid overload. These parameters also have limitations in delineating pulmonary complications of transfusion. Unanticipated changes in cardiovascular status can occur in both TRALI and TACO, though hypotension is more commonly seen in TRALI. Changes in blood pressure and heart rate are non-specific and may be confounded by the patient's underlying condition. Fluid balance and response to diuretics (especially volume of diuresis, which may be impaired by renal failure) are generally not well recorded. Fever has been shown to be present in both TACO and TRALI in approximately 30% of TACO cases (Bolton-Maggs et al. 2017; Parmar et al. 2017), suggesting an inflammatory component in both, and is therefore also a non-discriminatory clinical sign.

Most patients classified as TAD are very unwell with multiple ongoing issues. Some cases had features suggestive of TACO or TRALI but not enough reported detail to meet the SHOT criteria and hence included under TAD. International collaborative work is essential to help improve our understanding of the pathophysiology of this group of complications and that may help identify appropriate risk reduction measures in the future. SHOT is also evaluating the impact of the recent updated definition of TRALI on the reporting strategy for pulmonary complications and the potential for re-categorisation of cases previously classified as TAD.

Conclusion

National reporting of transfusion complications and annual publication of the data is a valuable resource enabling better recognition, production of guidelines and safer transfusion practice. SHOT recommends reporting any cases where patients develop respiratory distress during or up to 24 hours after transfusion. It is important to differentiate a 'surveillance definition' from a 'clinical diagnosis'. A combination of diagnostic testing and the patient's response to treatment may suggest a clinical diagnosis. A surveillance definition is used in haemovigilance and provides a standardised method of categorising the reaction in the patient. While they are based on similar data, they fulfil different purposes.

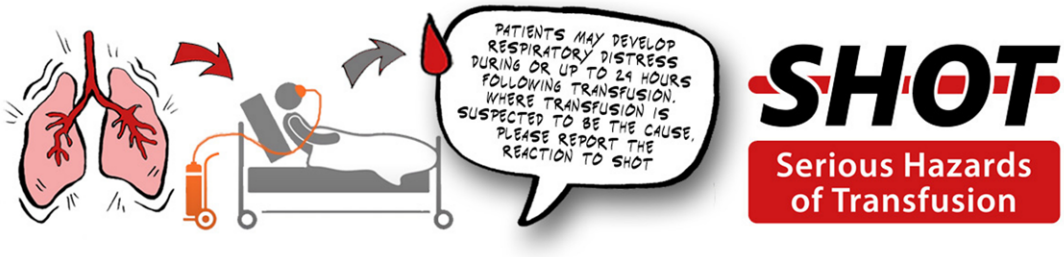
There is an urgent need to ensure international harmonisation of classifying pulmonary transfusion reactions, especially TRALI and TAD, to allow for uniform comparisons, improve understanding of these complications and enhance transfusion safety. An international collaborative including representatives

from SHOT is planning to develop a universal reporting form for respiratory transfusion reactions which will help to make comparisons of reaction rates between various haemovigilance systems.

Recommended resources

SHOT Bite No. 11: Respiratory symptoms during transfusion
https://www.shotuk.org/resources/current-resources/shot-bites/

SHOT educational video about pulmonary complications post transfusion can be accessed at this link:
https://www.shotuk.org/resources/current-resources/videos/



References

Bolton-Maggs PHB (Ed), Poles D et al. (2016) on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2015 Annual SHOT Report. https://www.shotuk.org/shot-reports/ [accessed 09 June 2020].

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].

Ferguson ND, Fan E, Camporota L, et al. (2012) The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012;**38**:1573-82.

ISBT/IHN (2011) Haemovigilance Working Party of the ISBT: Proposed standard definitions for surveillance of non-infectious adverse transfusion reactions. http://www.isbtweb.org/fileadmin/user_upload/Proposed_definitions_2011_surveillance_non_infectious_adverse_reactions_haemovigilance_incl_TRALI_correction_2013.pdf [accessed 09 June 2020].

Klanderman RB, Bosboom JJ, Migdady Y, et al. (2019) Transfusion-associated circulatory overload-a systematic review of diagnostic biomarkers. *Transfusion* 2019;**59(2)**:795-805.

Li G, Daniels CE, Kojicic M, et al. (2009) The accuracy of natriuretic peptides (brain natriuretic peptide and N-terminal pro-brain natriuretic) in the differentiation between transfusion-related acute lung injury and transfusion-related circulatory overload in the critically ill. *Transfusion* 2009;**49**:13-20.

Morton S, Grant-Casey J, Bolton-Maggs P, et al. (2017) Skating on Thin Ice: National Audit of TACO Demonstrates Poor Recognition of Risk Factors. *Blood* 2017;**130(1)**:2406.

Narayan S (Ed), Poles D, et al. (2019) on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2018 Annual SHOT Report. https://www.shotuk.org/shot-reports/ [accessed 08 June 2020].

Parmar N, Prendergast J, Lieberman L, et al. (2017) The association of fever with transfusion-associated circulatory overload. *Vox Sang* 2017;**112(1)**:70-78.

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

Wiersum-Osselton J, Whitaker BL, Grey S, et al. (2019) Revised international surveillance case definition of transfusion associated circulatory overload (TACO): a classification agreement validation study. *Lancet Haematol* 2019;**6(7)**:e350-e8 doi:10.1016/ S2352-3026(19)30080-8.

Zhou L, Giacherio D, Cooling L, et al. (2005) Use of B-natriuretic peptide as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload. *Transfusion* 2005;**45(7)**:1056-63.

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).

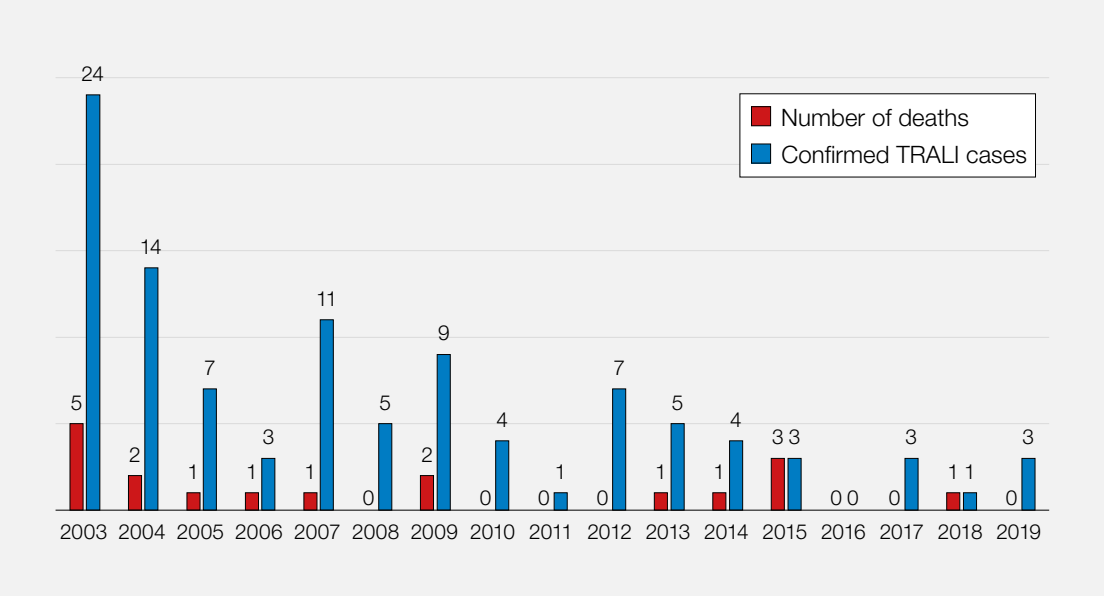


Figure 17a.1: Number of confirmed TRALI cases and deaths at least possibly related to TRALI by year of report

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.

17b Transfusion-Associated Circulatory Overload (TACO) n=139

Author: Sharran Grey

With thanks to Harriet Lucero for case assessments January-August 2019

Definition:

TACO is defined as acute or worsening respiratory compromise and/or acute or worsening pulmonary oedema during or up to 12 hours[†] of transfusion, with additional features including cardiovascular system changes not explained by the patient's underlying medical condition; evidence of fluid overload and a relevant biomarker[¥].

[†]SHOT accepts cases up to 24 hours
[¥]see Table 17b.2 for details of required and additional criteria for a surveillance diagnosis

Key SHOT message

- Patients who develop respiratory distress during or up to 24 hours following transfusion where transfusion is suspected to be the cause must be reported to SHOT. The transfusion-associated circulatory overload (TACO) definition criteria can be used as guidance but this should not be restrictive. SHOT experts can transfer cases between categories

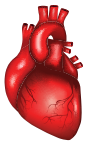
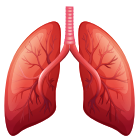
Abbreviations used in this chapter

CPAP	Continuous positive airway pressure	**IHN**	International Haemovigilance Network
Hb	Haemoglobin	**ISBT**	International Society for Blood Transfusion
NT-BNP	N-terminal-pro B-type natriuretic peptide	**TACO**	Transfusion-associated circulatory overload

Recommendations

- A formal pre-transfusion risk assessment for transfusion-associated circulatory overload (TACO) should be undertaken whenever possible for all patients receiving blood transfusion (especially if older than 50 years or weighing less than 50kg) and mitigating actions taken, as TACO is the most commonly reported cause of transfusion-related mortality and major morbidity
- Use weight-adjusted red cell dosing to guide the appropriate number of units required for all non-bleeding adult patients, ideally using tools which also highlight inappropriate transfusion (Grey et al. 2018, NCA 2017)

Action: All staff authorising transfusion

TACO Checklist	Red cell transfusion for non-bleeding patients	If 'yes' to any of these questions
	Does the patient have a diagnosis of 'heart failure' congestive cardiac failure (CCF), severe aortic stenosis, or moderate to severe left ventricular dysfunction? Is the patient on a regular diuretic? Does the patient have severe anaemia?	1 • Review the need for transfusion (do the benefits outweigh the risks)?
	Is the patient known to have pulmonary oedema? Does the patient have respiratory symptoms of undiagnosed cause?	2 • Can the transfusion be safely deferred until the issue can be investigated, treated or resolved?
	Is the fluid balance clinically significantly positive? Is the patient on concomitant fluids (or has been in the past 24 hours)? Is there any peripheral oedema? Does the patient have hypoalbuminaemia? Does the patient have significant renal impairment?	3 • Consider body weight dosing for red cells (especially if low body weight) • Transfuse one unit (red cells) and review symptoms of anaemia • Measure the fluid balance • Consider giving a prophylactic diuretic • Monitor the vital signs closely, including oxygen saturation

Due to the differences in adult and neonatal physiology, babies may have a different risk for TACO. Calculate the dose by weight and observe the notes above.

TACO=transfusion-associated circulatory overload

Figure 17b.1: TACO pre-transfusion checklist

Introduction

A new surveillance definition for TACO was published in 2019 (Wiersum-Osselton et al. 2019) which was the culmination of several years of collaborative work between the International Haemovigilance Network (IHN), AABB, and the International Society of Blood Transfusion (ISBT). The new definition identifies a higher percentage of cases previously designated as TACO by haemovigilance systems compared to the former ISBT definition (ISBT/IHN 2011). This work represents a significant advance in this area and is intended to form the basis for internationally consistent reporting of TACO. It is also intended to promote the clinical recognition of TACO, while recognising the need for further research into preventative measures and mitigations and aspires to the improved understanding of patho-aetiology, and methods to distinguish the pulmonary complications of transfusion.

SHOT experts were key participants in this work, and early adopters of the new definition. The criteria for the new definition have been used to assess the TACO cases reported to SHOT in 2019 (Table 17b.2).

Death n=9

TACO resulted in patient death in 9 reported cases (all adults).

Major morbidity n=33

TACO remains the leading cause of transfusion-related combined mortality and major morbidity. There was 1 paediatric patient this year that suffered major morbidity.

Table 17b.1: Demographic overview of cases reported in 2019

Demographic	Number of reports
Deaths (imputability 3 - certain)	0
Deaths (imputability 2 - probable)	6
Deaths (imputability 1 - possible)	3
Major morbidity outcome	33
Age*	Range: 27 days to 103 years Median: 76 years
Gender	Female=75 Male=64
Medical specialties with highest number of cases*	Haematology=26 Acute medicine=23, general medicine=23 Emergency medicine=9, trauma and orthopaedics=9
Bleeding patients (indication code R1 or 'massive bleeding' indicated)	20
Non-bleeding patients (other indication codes or not stated)	119

**Data provided in 138/139 cases*

Commentary

TACO is more commonly reported in elderly, non-bleeding patients, but is seen across all age groups and is consistent with the data from previous years. There were 4 cases in the under-18 age group: 1 neonate and 3 paediatric cases (age 1-3 years). Haematology and adult medical specialties are again the most common specialties where TACO is reported and this should be considered when delivering TACO education and mitigation plans.

Analysis by definition criteria

Cases reported in 2019 were assessed using the surveillance criteria in Table 17b.2. It should be noted that the criteria are for the purposes of reporting and surveillance, and do not constitute a clinical diagnosis for the purpose of real-time interventions for the medical management of a patient presenting with respiratory compromise during or following transfusion. However, the surveillance criteria should promote recognition of TACO.

Table 17b.2: TACO surveillance definition (adapted from Wiersum-Osselton et al. 2019)

Patients classified with TACO (surveillance diagnosis) should exhibit at least one required criterion* with onset during or up to 12 hours after transfusion (SHOT continues to accept cases up to 24 hours), and a total of 3 or more criteria i.e. *A and/or B, and total of at least 3 (A to E)

*** Required criteria (A and/or B)**

A. Acute or worsening respiratory compromise and/or
B. Evidence of acute or worsening pulmonary oedema based on:
– clinical physical examination, and/or
– radiographic chest imaging and/or other non-invasive assessment of cardiac function

Additional criteria

C. Evidence for cardiovascular system changes not explained by the patient's underlying medical condition, including development of tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette and/or peripheral oedema
D. Evidence of fluid overload including any of the following: a positive fluid balance; clinical improvement following diuresis
E. Supportive result of a relevant biomarker, e.g. an increase of B-type natriuretic peptide levels (BNP) or N-terminal-pro brain natriuretic peptide (NT-pro BNP) to greater than 1.5 times the pre-transfusion value

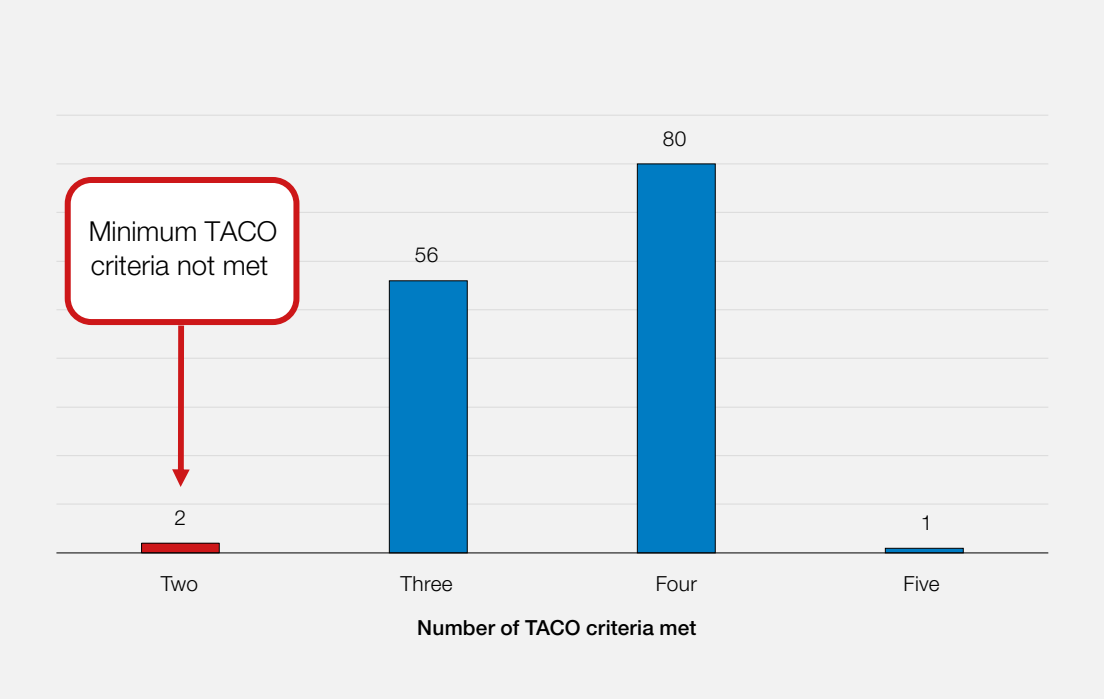


Figure 17b.2: Number of surveillance criteria versus number of accepted TACO cases

TACO=transfusion-associated circulatory overload

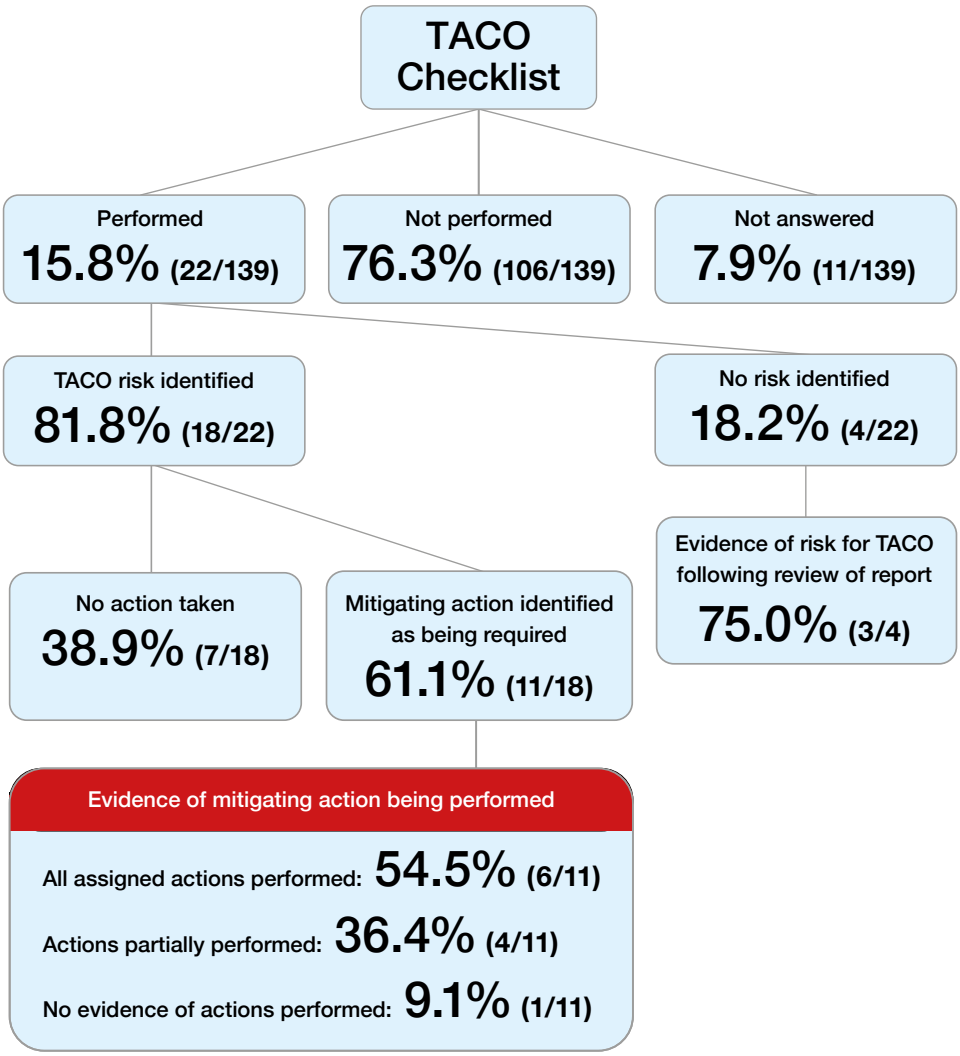
There were 2 cases that scored only two criteria but were nevertheless accepted into the TACO category as a pulmonary complication as they were otherwise clinically persuasive cases. One case had developed pulmonary oedema with temporal association with transfusion but lacked cardiovascular system changes and data relating to fluid balance and diuretic therapy was not available. The other case had worsening of respiratory symptoms following transfusion but due to lack of vital sign observation data and as diuretic therapy was withheld in this dying patient, some data for the assessment were not available. Only 1 case had all five criteria as NT-pro BNP had been tested. See the 2018 Annual SHOT Report, p.143 (Narayan et al. 2019) for further information on the utility of this test in demonstrating left atrial hypertension in the differential assessment of pulmonary complications of transfusion.

Use of the TACO checklist

The TACO risk assessment recommendation was introduced in the 2015 Annual SHOT Report (Bolton-Maggs et al. 2016). A question regarding the use of the TACO risk assessment and mitigating actions was added to the SHOT reporting questionnaire for the 2019 reporting year. An overview is shown in Figure 17b.3. The analysis shows that a TACO risk assessment was only performed in 22/139 (15.8%) cases of reported TACO. A TACO risk factor was identified in 18/22 (81.8%) of cases but only 11/18 (61.1%) of these cases had mitigating actions assigned.

Further review of these cases showed that in 1 case there was no evidence of the mitigating actions being performed and in 4 cases they were only partially performed, with only 6 having evidence of being performed in full. Of these 6 cases there was evidence that additional mitigations could have been taken: 2 improved with diuretic treatment indicating that pre-transfusion prophylactic diuretics may have prevented the TACO episode; 1 case could have had weight-adjusted red cell dosing/a single unit; and 1 case had iron deficiency anaemia with TACO developing during the second unit and therefore a single unit of red cells with intravenous iron could have prevented TACO. In 4/22 (18.2%) cases where a TACO risk assessment was performed, no risks were reported and therefore no mitigating actions assigned. However, on review of these cases there was evidence in the report that in 3 cases there were clear risk factors for TACO (positive fluid balance in 2 cases and heart failure in 1) resulting in a missed opportunity to assign mitigating actions.

Figure 17b.3: Use of the TACO checklist to identify patients at risk of TACO and implementation of mitigations



TACO cases with evidence of excessive red cell volume to meet the target haemoglobin (Hb)

The recommendation for weight-adjusted red cell dosing for non-bleeding patients was introduced in the 2017 Annual SHOT Report (Bolton-Maggs et al. 2018). Analysis of the 2019 data shows that this is not implemented in practice and is contributing to a significant level of overtransfusion in reported cases of TACO.

There were 61 cases where the patient was not bleeding and both the body weight and pre-transfusion Hb level were reported. Thirty-two of these cases also had a post-transfusion Hb level reported. In 10/32 (31.3%) cases their post-transfusion Hb target was exceeded (post-transfusion Hb range 103-150g/L). The number of red cell units transfused was reported in 35 cases. There were 23/35 (65.7%) cases that received more than the calculated weight-adjusted dose resulting in 6/23 (26.1%) exceeding their post-transfusion Hb target.

Case 17b.1: Omitted TACO checklist leading to overtransfusion and TACO

A female patient in her 70s weighing 54kg developed anaemia following orthopaedic revision surgery (Hb 67g/L). She had a number of risks for TACO: positive fluid balance (1215mL), and the pre-transfusion chest X-ray report was suggestive of possible infection and heart failure, however a TACO checklist was not performed before the transfusion. She was transfused two units of red cells. Following the second unit she developed shortness of breath, crackles on chest auscultation, hypoxia, tachycardia and an increase in blood pressure. The post-transfusion chest X-ray report confirmed findings were consistent with heart failure, fluid overload and possible infection.

She was transferred to the critical care unit for continuous positive airway pressure (CPAP) ventilation. Her respiratory status improved following treatment with diuretics, nitrates and fluid restriction. Her post-transfusion Hb was 108g/L.

This case highlights a missed opportunity to identify this patient as being at risk of TACO and to take mitigating actions. If the checklist had been performed before the transfusion it would have identified possible heart failure and positive fluid balance as risks for circulatory overload. Although a fluid balance measurement was already in place, albeit not identified as a risk, other mitigations could have been considered such as prophylactic diuretics and weight-adjusted red cell dosing. Based on a post-transfusion target Hb of 80-100g/L, this patient with low body weight only required 280mL (one unit) to meet her target Hb. A weight-adjusted dose may have avoided TACO and overtransfusion in this case.

Learning points

- In non-bleeding patients an excessive volume of red cell transfusion to meet a target haemoglobin (Hb) level remains a significant factor in cases of transfusion-associated circulatory overload (TACO). This can be minimised by weight-adjusted red cell dosing, and medical management of anaemia where possible

  [target Hb (g/L) - pre-transfusion Hb (g/L)] x weight (kg) x 0.4mL red cells = volume of red cells (mL) required to meet target Hb
  (The volume of a unit of adult-specification red cells is 220-340mL)

  Calculation taken from Norfolk (2013)

- A significant number of reported TACO cases do not appear to have had a TACO checklist performed, and/or TACO risk reduction measures were not implemented where risk was identified. This should be embedded into the procedure for the request and authorisation of transfusion

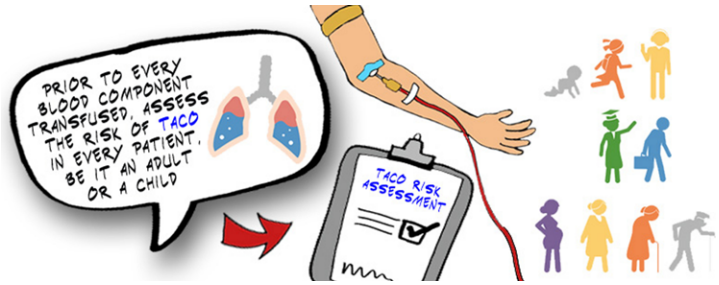
Conclusion

TACO is in many cases a preventable complication of transfusion but remains the leading cause of transfusion-related mortality and major morbidity. More cases than ever were reported to SHOT in 2019, but TACO continues to be under-reported. The majority of TACO cases have a recognised risk factor for circulatory overload and although there are now well-established recommendations and tools to mitigate TACO in patients with risk factors, analysis of the data unfortunately shows these are not being implemented in clinical practice, and opportunities are being missed to protect patients. There is more to learn about the pulmonary complications of transfusion which will undoubtedly advance patient safety in the future, but in the meantime we should improve practice with what we already know and have available now.

Recommended resources

Example of weight-adjusted red cell dosing implemented in clinical practice
www.rcdcalculator.co.uk

SHOT Bite No. 11: Respiratory symptoms during transfusion
https://www.shotuk.org/resources/current-resources/shot-bites/



SHOT
Serious Hazards of Transfusion

References

Bolton-Maggs PHB (Ed), Poles D et al. (2016) on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2015 Annual SHOT Report. https://www.shotuk.org/shot-reports/ [accessed 09 June 2020].

Bolton-Maggs PHB (Ed), Poles D, et al. (2018) on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2017 Annual SHOT Report. https://www.shotuk.org/shot-reports/ [accessed 08 June 2020].

Grey S, Farrar K, Kinsella P, et al. (2018) A web-App for weight-adjusted red cell dosing: post-development implementation and clinical effectiveness. *B J Haem* 2018;**181(1)**:146.

ISBT/IHN (2011) Haemovigilance Working Party of the ISBT: Proposed standard definitions for surveillance of non-infectious adverse transfusion reactions. http://www.isbtweb.org/fileadmin/user_upload/Proposed_definitions_2011_surveillance_non_infectious_adverse_reactions_haemovigilance_incl_TRALI_correction_2013.pdf [accessed 09 June 2020].

Narayan S (Ed), Poles D, et al. (2019) on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2018 Annual SHOT Report. https://www.shotuk.org/shot-reports/ [accessed 08 June 2020].

NCA (2017) National Comparative Audit of Blood Transfusion: Transfusion associated circulatory overload audit 2017 https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/14909/2017-taco-national.pdf [accessed 09 June 2020].

Norfolk D (ed) (2013) Handbook of Transfusion Medicine (5th edn). The Stationery Office, London URL https://www.transfusionguidelines.org/transfusion-handbook [accessed 09 June 2020].

Wiersum-Osselton J, Whitaker BL, Grey S, et al. (2019) Revised international surveillance case definition of transfusion associated circulatory overload (TACO): a classification agreement validation study. *Lancet Haematol* 2019;**6(7)**:e350-e8 doi:10.1016/ S2352-3026(19)30080-8.

Transfusion-Associated Dyspnoea (TAD) n=21

17c

Author: Shruthi Narayan

Acknowledgements: All members of the pulmonary Working Expert Group (WEG)

Definition:

TAD is characterised by respiratory distress within 24 hours of transfusion that does not meet the criteria for transfusion-related acute lung injury (TRALI) or transfusion-associated circulatory overload (TACO) or allergic reaction. Respiratory distress in such cases should not be adequately explained by the patient's underlying condition (International Society of Blood Transfusion (ISBT) definition).

Key SHOT messages

- Pathophysiology of transfusion-associated dyspnoea (TAD) is still not known and with no definite diagnostic criteria, our understanding is evolving
- Cases submitted are reviewed by SHOT experts including pulmonologists to determine imputability, causality and categorisation
- Further international collaboration in this area will help identify causal and contributory factors and identify appropriate risk reduction measures

Abbreviations used in this chapter

AML	Acute myeloid leukaemia	**ISBT**	International Society of Blood Transfusion
ARDS	Acute respiratory distress syndrome	**NIDDM**	Non-insulin dependent diabetes mellitus
COPD	Chronic obstructive pulmonary disease	**TACO**	Transfusion-associated circulatory overload
CPAP	Continuous positive airway pressure	**TAD**	Transfusion associated dyspnoea
CXR	Chest X-ray	**TRALI**	Transfusion-related acute lung injury
FAHR	Febrile, allergic and hypotensive reactions	**WCC**	White cell count
IHN	International Haemovigilance Network	**WEG**	Working Expert Group

Recommendation

- Patients who develop respiratory distress during or up to 24 hours following transfusion where transfusion is suspected to be the cause must be reported to SHOT

Action: All staff involved in transfusion

Introduction

TAD is a pulmonary complication post transfusion that cannot be classified as TACO or TRALI, nor can it be ascribed to patient's pre-existing diseases. The underlying risk factors and aetiopathogenesis

are still unknown. Although such reactions are not very common, knowledge about them can prevent serious complications. Early recognition and prompt supportive treatment is beneficial. Appropriate risk reduction strategies are only possible once we understand these reactions better.

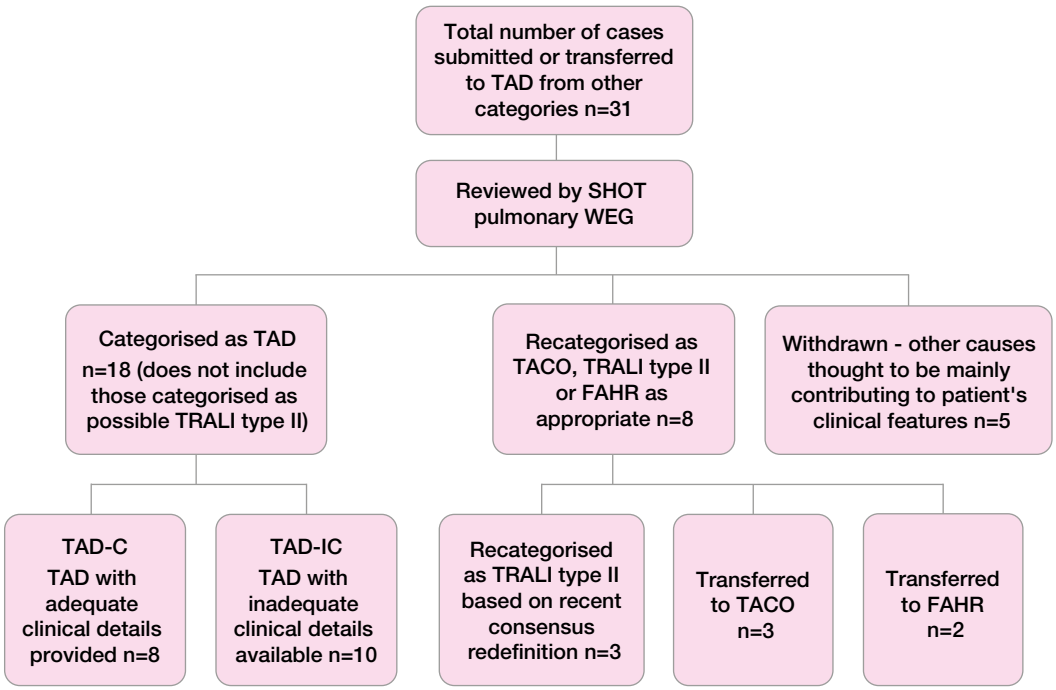
There has been significant international collaborative work relating to pulmonary complications post transfusion, most notably with TACO and TRALI. A new surveillance definition for TACO, published in 2019 (Wiersum-Osselton et al. 2019), was the culmination of several years of collaborative work between the International Haemovigilance Network (IHN), AABB, and the ISBT. The new proposed revised consensus criteria for TRALI (Vlaar et al. 2019), the term 'possible TRALI' has been dropped. The terminology of TRALI type I (without an acute respiratory distress syndrome (ARDS) risk factor) and TRALI type II (with an ARDS risk factor or with mild existing ARDS) has been proposed. It suggests that cases with an ARDS risk factor that meet ARDS diagnostic criteria and where respiratory deterioration over the 12 hours before transfusion implicates the risk factor as causative should be classified as ARDS. According to this, TRALI remains a clinical diagnosis and does not require detection of cognate white blood cell antibodies. While this may help in clinical differentiation, this needs validating with real-life case scenarios to understand the implications to haemovigilance especially from the perspective of appropriate risk reduction preventative measures.

SHOT has recruited two experts from pulmonary medicine as part of the pulmonary WEG and all reported cases from 2019 were reviewed by the group. Interpretation was limited in several cases by the available clinical information including results from relevant investigations. The group applied the new proposed TRALI consensus definitions to those cases reported under TAD to see if it helped re-categorise these reactions. There were 3 cases categorised as TRALI type II which were non-immune TRALI. They are detailed below.

Those that are included under TAD were subdivided based on adequacy of the clinical information available, TAD-C (those with complete or adequate clinical information) and TAD-IC, those with inadequate information. As is usual, there were a few transfers between categories (febrile, allergic and hypotensive reactions (FAHR), TACO, TRALI, etc.) reflective of the challenges involved in interpreting these complex cases. All cases are included in order to build up the series of cases over time. A deep dive into all cases of TAD reported to SHOT over the years is being planned soon to identify common themes. TAD represents cases with atypical or overlapping entities with varying severity of reaction and impact on patients, and with currently unexplained pathophysiology.

The following figure summarises the categorisation and transfer of these cases.

Figure 17c.1: Summary of transfers and categorisation of cases included under TAD



Death n=1

Case 17c.1: TAD-IC

A man with known chronic obstructive pulmonary disease (COPD) in his 80s admitted with suspected sepsis with leucocytosis (white cell count (WCC) >30x10^9/L) developed acute dyspnoea with no wheeze/rash and deteriorated suddenly during red cell transfusion with tachypnoea and tachycardia, hypoxia (O_2 saturations 78%) temperature 37.7°C with bilateral transmitted sounds. He was not reported to have any concomitant cardiac or renal disease. Due to sudden deterioration, investigations could not be completed to ascertain cause.

In view of sudden onset dyspnoea, paucity of clinical information and temporal correlation with transfusion, this has been included in the TAD-IC category.

Major morbidity n=4

In 2019 there were 4 cases included as major morbidity. These include 1 case categorised as TAD-C (Case 17c.2), and the 3 cases of TRALI type II described below were admitted to intensive care as a result of the transfusion.

Case 17c.2: TAD-C

A patient in her 80s was admitted with symptomatic anaemia and a 3-week history of worsening breathlessness and leg oedema. Other co-morbidities included acute on chronic renal failure (stage 3), non-insulin dependent diabetes mellitus (NIDDM), hypertension, cardiac failure with oedema. She was reported to have become more breathless 3 hours after the start of a unit of packed red cells with tachypnoea and desaturation: her oxygen saturation (on 10L O_2) dropped from 91% to 87%. Chest X-ray (CXR) showed an area of developing consolidation.

While there were clinical risk factors for TACO, she was in a negative fluid balance, on regular diuretics with minimal or no response to repeat diuretics and bronchodilators. Chest infection could be contributory and has been included here to highlight the need to monitor such complex patients during transfusions due to the potential for sudden deterioration in clinical status necessitating prompt supportive measures and appropriate treatment. The patient needed continuous positive airway pressure (CPAP) and oxygen support and recovered from this episode.

TRALI type II as per redefinition consensus criteria n=3

Case 17c.3: Imputability-2 (Probable)

A young patient in his 30s diagnosed with acute myeloid leukaemia (AML) on induction chemotherapy developed rigors within 2 hours of platelet transfusion, with a rise in temperature of 2.4°C, tachycardia, desaturation, and wheeze. The CXR showed ARDS with progression from the previous one.

This case was initially reported under TRALI and investigated for antibodies but not all donors responded when contacted. The patient had haemoptysis on the morning of the incident and eventually died due to non-transfusion related causes.

Case 17c.4: Imputability-1 (Possible)

A woman in her 70s with pre-existing COPD and asthma became hypoxic, tachypnoeic and tachycardic within 1.5 hours of platelet transfusion. Cultures were negative, serology was negative and CXR showed bilateral ground glass appearance. The patient recovered following treatment with steroids, antihistamines and supportive measures.

Case 17c.5: Imputability-1 (Possible)

A patient in her 40s following surgery for breast carcinoma required massive transfusion, needing several blood components desaturated to 68% with hypotension, no evidence of fluid overload and bilateral patchy infiltrates on CXR. There was no evidence of cardiac, renal or respiratory disease and the donor antibody screen was negative. The patient needed CPAP support and recovered.

Learning point

- Clinicians should report all cases of post-transfusion pulmonary complications to the transfusion service so that further investigation can allow for further classification of such cases. There are cases where such distinction may not always be possible

Conclusion

Most patients classified as TAD are very unwell with multiple ongoing issues. Some of these had features suggestive of TACO or TRALI but not enough reported detail to meet the SHOT criteria and hence included here. The pathophysiology of this group of complications requires further elucidation (Badami et al. 2015). There is some evidence that patients with sepsis are more at risk of respiratory complications following transfusion (Roubinian 2018), a reminder that every transfusion, particularly of platelets, a rich source of biological response modifiers, (Garraud et al. 2013; Garraud et al. 2016), should be reviewed to ensure it is indicated. There is still much work that needs to be done to understand cases reported under TAD, this is limited by the clinical information available and co-morbidities.

References

Badami KG, Joliffe E and Stephens M. (2015) Transfusion-associated dyspnea: shadow or substance? *Vox Sang* 2015;**109(2)**:197-200.

Garraud O, Cognasse F, Hamzeh-Cognasse H, et al. (2013) [Blood transfusion and inflammation]. *Transfus Clin Biol* 2013;**20(2)**:231-238.

Garraud O, Cognasse F, Tissot JD, et al. (2016) Improving platelet transfusion safety: biomedical and technical considerations. *Blood Transfus* 2016;**14(2)**:109-122.

Roubinian N. (2018) TACO and TRALI: biology, risk factors, and prevention strategies. *Hematology Am Soc Hematol Educ Program* 2018;**2018(1)**:585-594. doi:10.1182/asheducation-2018.1.585.

Wiersum-Osselton J, Whitaker BL, Grey S, et al. (2019) Revised international surveillance case definition of transfusion associated circulatory overload (TACO): a classification agreement validation study. *Lancet Haematol* 2019;**6(7)**:e350-e8 doi:10.1016/ S2352-3026(19)30080-8.

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