18 Pulmonary Complications n=188

Author: Shruthi Narayan 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 65.9% of transfusion-related deaths reported to SHOT from 2010 to 2020

Abbreviations used in this chapter

ADU	Avoidable, delayed and under/overtransfusion	**NM**	Near miss
ALICT	Acute lung injury caused by transfusion	**TACO**	Transfusion-associated circulatory overload
ARDS	Acute respiratory distress syndrome	**TAD**	Transfusion-associated dyspnoea
FAHR	Febrile, allergic and hypotensive reactions	**TRALI**	Transfusion-related acute lung injury
HTR	Haemolytic transfusion reactions	**UCT**	Uncommon complications of transfusion
NBTC	National Blood Transfusion Committee	**WEG**	Working Expert Group

Recommendations

- All cases with pulmonary complications occurring during or up to 24 hours post transfusion should be reported to SHOT with as much information as possible, to ensure adequate inference and effective learning. The clinical status (especially cardiac, respiratory status and other significant co-morbidities) of the patients prior to the transfusion episode helps in understanding the pulmonary reaction and contributing factors and should be included in the submitted reports

Action: All SHOT reporters, hospital transfusion teams

- A transfusion-associated circulatory overload (TACO) checklist should be utilised whenever possible prior to every transfusion, especially in vulnerable patients. This would also help provide further insight into cases reported as transfusion-associated dyspnoea (TAD) or transfusion-related acute lung injury (TRALI)

Action: All clinical staff involved in transfusion

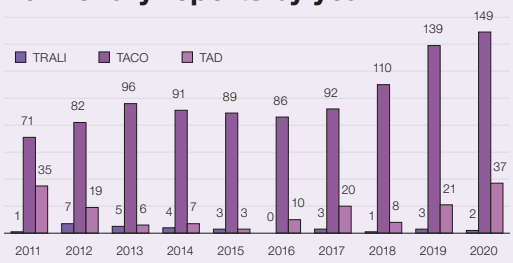
- A thorough post-event investigation should be carried out in all cases with severe complications following transfusion to identify improvements locally with respect to identification and mitigation of risks, patient monitoring and management

Action: All staff involved in investigation of transfusion incidents

Headline data 2020

Number of reports n=188
Deaths n=23
Major morbidity n=33

Pulmonary reports by year



Demographic data

Male n=91
Female n=97
Adults n=185
Paediatric n=3

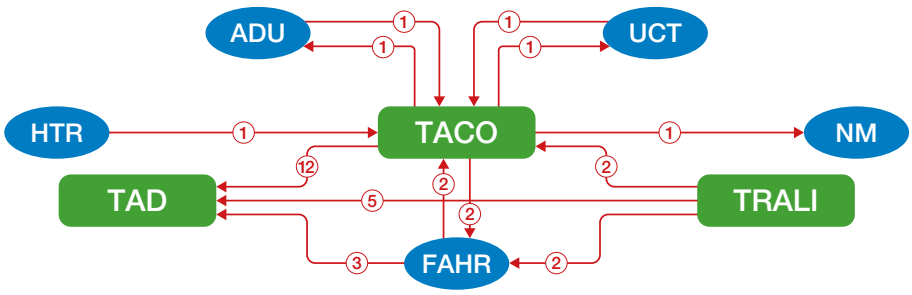
Blood component data

Red cells n=154
Platelets n=6
Plasma n=13
Multiple Components n=15
Other n=0

Introduction

Pulmonary complications continue to be the leading cause of transfusion-related mortality and morbidity, contributing to 114/173 (65.9%) of transfusion-related deaths reported to SHOT from 2010 to 2020. The total number of cases continue to increase year on year and in 2020, 188 reports were analysed under the 'pulmonary complications' categories. Three of the cases in 2020 were in children and pulmonary complications contributed to 23 deaths and 33 cases of major morbidity. These are discussed in detail in the respective chapters.

With sparse new evidence in relation to pulmonary complications post transfusion since the 2019 Annual SHOT Report, the categorisation of these reactions remains complex. There is ongoing international collaboration for harmonisation of definitions and data collection. The interpretation and categorisation of the cases remains challenging and is also limited by the available information included in the reports submitted to SHOT (clinical, radiological, and other investigations results). The respiratory and cardiovascular status of patients in the 12 hours prior to the transfusion episode helps in understanding the factors contributing to the patient's respiratory deterioration post transfusion but is often not available. Figure 18.1 shows the case transfers in 2020 when the SHOT WEG have reviewed all the cases submitted. This highlights the complexity and challenges in categorisation of pulmonary complications. Reporters are strongly encouraged to report all cases with respiratory deterioration up to 24 hours following transfusion. Focus must be placed on analysing the actual phenomena in these patients and what actions were performed to prevent reactions rather than trying to fit the clinical/radiological/laboratory picture into a single category. All relevant information must be included in the report to SHOT. The pulmonary WEG review the submitted cases, deliberate based on the information available and will assign the appropriate category.



TACO=transfusion-associated circulatory overload; TRALI=transfusion-related acute lung injury; TAD=transfusion-associated dyspnoea; HTR=haemolytic transfusion reactions; ADU=avoidable, delayed or under/overtransfusion; FAHR=febrile, allergic and hypotensive reactions; UCT=uncommon complications of transfusion; NM=near miss

Figure 18.1: Case transfers to and from the pulmonary categories in 2020 (n=34)

COVID-19 patients

A particular challenge faced by the pulmonary WEG members in 2020 was the interpretation of the clinical and radiological picture in patients with COVID-19 pneumonia who developed worsening respiratory status <24 hours after convalescent plasma administration under approved trials. Multiple factors could contribute to the deterioration in these patients, ranging from worsening of the COVID-19 pneumonitis (sudden respiratory deterioration with ARDS is well recognised in these patients), to other factors such as thromboembolism and cardiac effects of COVID-19. Secondary bacterial infections and other rare events such as pneumothorax and pneumomediastinum can also cause respiratory deterioration (Pooni et al. 2020). These cases are detailed further in the following chapters.

TRALI

The definition of TRALI continues to be under review. There were 2 confirmed cases of antibody-positive TRALI this year. The cases in this year's Annual SHOT Report are primarily classified using the SHOT nomenclature, which considers 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 which is more a clinical diagnosis not requiring the detection of cognate white cell antibodies making application of imputability from a haemovigilance perspective challenging.

It is imperative that the diagnosis of TRALI should not be applied loosely under different classification systems to refer to different entities. A new concept of 'acute lung injury caused by transfusion' (ALICT) has been proposed which could potentially be useful until the debate about terminology settles as it considers the aetiopathological and clinical elements of TRALI. ALICT as a concept refers to a reaction caused by something in the blood (which may include antibodies or other, perhaps undiscovered mediators). The relationships between the existing nomenclature/categories and the presence or absence of cognate antibodies has been explored further in the TRALI chapter. The authors hope that this helps define the questions for further research and validation.

TACO

The 2020 reporting year recorded 149 TACO cases which is the highest ever reported to SHOT. Cases were analysed using the same surveillance criteria as last year (Wiersum-Osselton et al. 2019). There continues to be suboptimal use of the pre-transfusion TACO risk assessment and weight-adjusted red cell dosing is not sufficiently implemented.

It is critically important that all TACO cases are used as a learning opportunity to prevent or mitigate TACO in other patients. A new recommendation for this year is the use of the TACO investigation and preventive action guidance tool, to ensure a structured and comprehensive review of cases to support effective preventive actions (see recommendations and recommended resources sections in Chapter 18b, Transfusion-Associated Circulatory Overload (TACO)).

TAD

TAD remains a diagnosis of exclusion and has no defining criteria. Some of the cases included as TAD had features suggestive of TACO or TRALI but due to insufficient information available to meet the SHOT criteria, have been included under TAD.

There is still much work that needs to be done to understand cases reported under TAD and this is limited by the clinical information available and co-morbidities. International collaborative work to help improve understanding of the epidemiology, pathophysiology in this group of complications is vital and will help identify risk factors and appropriate mitigating measures in the future.

Conclusion

TRALI, TACO and TAD are all potentially fatal complications of blood transfusion. The mechanisms for pulmonary deterioration in transfusion recipients are multifactorial and complex, involving both transfusion-specific and patient-specific factors. All staff dealing with transfusions must be vigilant for

these complications especially in vulnerable patients and must assess risk, initiate mitigating measures where possible and manage complications promptly. Thorough investigations of these complications will help identify any areas for improvement locally with respect to risk assessment of patients, clinical care provided and escalation policies.

Patients must be informed about these risks as part of their consent discussion. This is especially important in vulnerable patients with risk factors for pulmonary complications from transfusion. Patients having transfusions as day cases must receive information on when to seek urgent medical help, as these could be delayed and manifest when patients are back home after their transfusions. Blood components should be administered only after careful consideration of the risks of transfusion versus the potential physiologic benefit of the planned transfused blood component. Unnecessary blood transfusions must be avoided.

Work is ongoing to improve international harmonisation of the classification of 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 are working 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
https://www.shotuk.org/resources/current-resources/videos/

References

Pooni R, Pandey G, Akbar S. Broadening the differential: pneumomediastinum and COVID-19 infection. *BMJ Case Reports CP* 2020;**13**:e237938.

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

Wiersum-Osselton J, Whitaker BL, Grey S, et al. Revised international surveillance case definition of transfusion associated circulatory overload (TACO): a classification agreement validation study. *Lancet Haematol* 2019;**6(7)**:e350-e358. doi: 10.1016/S2352-3026(19)30080-8.

18a Transfusion-Related Acute Lung Injury (TRALI) n=2

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

- The definition of transfusion-related acute lung injury (TRALI) is currently under review. It is essential to be explicit about what is understood by the term 'TRALI' when comparing data and literature between different sources

Abbreviations used in this chapter

ALICT	Acute lung injury caused by transfusion	**HNA**	Human neutrophil antigen
ARDS	Acute respiratory distress syndrome	**IRC**	International revised consensus
CT	Computerised tomography	**LAH**	Left atrial hypertension
ECG	Electrocardiogram	**TACO**	Transfusion-associated circulatory overload
FAHR	Febrile, allergic and hypotensive reactions	**TAD**	Transfusion-associated dyspnoea
HLA	Human leucocyte antigen	**TRALI**	Transfusion-related acute lung injury

Recommendation

- Reporters should report all cases of suspected pulmonary complications. Cases should initially be reported using existing SHOT definitions and can be re-categorised by the SHOT experts if required

Action: All SHOT reporters

Introduction

There were 2 confirmed cases of antibody-positive TRALI. In total 16 cases were reported as suspected TRALI. Of these, 5 cases were transferred to TAD, 2 cases to TACO, 2 cases to FAHR and 5 were withdrawn.

The cases in this Annual SHOT Report are primarily classified using the SHOT nomenclature (Table 18a.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 18a.2). This redefinition was intended to update the earlier Canadian Consensus criteria (Kleinman et al. 2004). An approximate mapping between the SHOT nomenclature and the redefinition is included in Table 18a.1.

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 coexisting morbidity 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 18a.1: SHOT criteria for assessment of TRALI cases

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 18a.2: Consensus redefinition criteria for TRALI

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

Note: The P/F ratio equals the arterial pO2 ("P") from the ABG divided by the FIO2 ("F") – the fraction (percent) of inspired oxygen that the patient is receiving expressed as a decimal (40% oxygen = FIO2 of 0.40). SpO2 =oxygen saturation. O2 = oxygen. For information on appendix S2 see original paper by Vlaar et al. 2019.

Category	TRALI type I		TRALI type II	
	Antibody-positive	Antibody-negative	Antibody-positive	Antibody-negative
Highly likely	1	-	-	-
Probable	-	-	-	-
Equivocal	-	-	1	-
Antibody-negative	-	-	-	-

Table 18a.3: Summary of 2020 TRALI cases

Deaths n=1

Case 18a.1: Possible TRALI

A woman in her 80s was readmitted 4 hours after an outpatient two-unit red cell transfusion, with sudden onset of cough and breathlessness. Chest X-ray showed bilateral pulmonary oedema but also dense consolidation in the right upper lobe. A COVID-19 test was negative, and she had normal

C-reactive protein and ECG. She died on the night of admission. Investigation of donors showed a HNA 1b (auto)antibody in one donor which was cognate with the recipient however this was not detectable on the archive sample from the time of donation. The history appeared fairly classical, possibly with pneumonia acting as a 'first hit'. The case has been classified as 'TRALI type II' in the consensus redefinition due to the presence of another risk factor for lung injury (consolidation on chest X-ray). In the SHOT classification scheme the case has been classified as 'equivocal TRALI'. We are unable to exclude the pneumonia being the sole cause; the significance of the late detected antibody is unclear but should be considered as possibly causative given that it is not uncommon in other contexts, particularly neonatal alloimmune thrombocytopenia, for morbidity to occur with an antibody becoming subsequently detectable.

Major morbidity n=1

Case 18a.2: Highly likely TRALI

A dialysis-dependent man in his 70s received a two-unit transfusion while on dialysis, with fluid removal taking account of the transfusion volume. He developed acute pulmonary oedema around the time of the second unit. Fluid overload was suspected but he deteriorated following further ultrafiltration. Echocardiogram was normal. He improved after 24 hours of supportive care. Multiple HLA class I and class II antibodies cognate with the recipient were identified in the donor of the first unit. The features are consistent with a classical antibody-mediated TRALI, and thus has been classified as 'highly likely TRALI'. The case has been classified as 'TRALI type I' in the consensus redefinition schema because of the absence of other risk factors for acute lung injury.

Commentary

The pattern of cases reported as suspected TRALI this year is much the same as previous years. However, the understanding of what is meant by the term 'TRALI' is in a state of evolution in the light of the IRC definition of TRALI. International work is being performed to validate the IRC criteria; however, this has been slowed because of other priorities arising from the COVID-19 pandemic.

IRC (Table 18a.2) has not yet been universally implemented at an international level. It defines TRALI as an empirical syndrome of clinical features. This is a valid position to take, and a syndromic definition has the advantage of easy categorisation, cases either meet the criteria or do not. The IRC criteria do identify a recurrent pattern of pulmonary deterioration seen in association with transfusion, and thus a group of patients deserving analysis.

However, the informal usage of the term TRALI, for example the monitoring of TRALI cases as a performance indicator for Blood Services and the clinical requests for investigation 'to rule out TRALI', indicate that TRALI is commonly understood as implying a causative role for the transfused product. Causation is also implicit in the SHOT nomenclature which classifies cases as 'highly likely', 'probable', or 'equivocal' corresponding to the plausibility that the detected antibody caused the reaction. Additionally, the proposal by the IRC authors that 'in TRALI, the primary physiologic abnormality resulting in pulmonary oedema is an increase in capillary permeability.' This is certainly a valid viewpoint but perhaps extends the scope of TRALI, for example encompassing a recipient who is unable to tolerate the fluid load of the transfusion because of underlying sepsis. IRC thus represents a true redefinition rather than a simple refinement of criteria.

A concept of pulmonary complications based on causation remains useful to help identify appropriate risk-reduction strategies. Measures to prevent recurrent reactions due to leucocyte antibodies or other mediators in transfused components are distinct from identifying patients unable to tolerate fluid, as their underlying condition may affect endothelial permeability. It is currently impossible to provide objective criteria because of the multifactorial nature of pulmonary reactions with several possible contributing causes, and the absence of a gold standard diagnostic test. It is however possible to infer the plausibility that biologically active factors in the blood caused the reaction by taking in to account the clinical features and presence of leucocyte antibodies, in a similar manner to estimating imputability.

All classifications are artificial constructs, and thus their usefulness is context dependent. Haemovigilance systems need to classify adverse events into discrete categories which are internationally comparable,

so there is utility in strict empirical criteria. However, Blood Services need to be able to monitor the safety of products and have workable guidelines to identify which donors to investigate or defer, and for this purpose a classification based on the causative role of the product and the presence of antibodies is more useful. Treating clinicians need to understand what has caused adverse events in order to provide treatment and prevent adverse events in patients at risk, and also therefore have a need for a model based on causation, but with a wider scope than simply the transfused component.

What can be agreed is that it is unhelpful for different groups to use the same terminology to refer to different entities. Until universal definitions and criteria have been agreed, there may be value in specifying terminology to illustrate the concepts for these pulmonary reactions. One approach may be to use the nomenclature 'acute lung injury caused by transfusion' (ALICT) to refer to the concept of a reaction caused by something in the blood (which may include antibodies or other, perhaps undiscovered mediators).

The three related concepts suggested are as follows:

TRALI: *Hypoxaemia with clear evidence of bilateral pulmonary oedema on imaging and no evidence of left atrial hypertension, with onset within 6 hours of transfusion where the respiratory state has been stable in the 12 hours prior to transfusion.* This refers to the purely empirical clinical syndrome as defined by the IRC. Cases either meet or do not meet TRALI criteria, and therefore phrases such as 'probable TRALI' are no longer applicable.

Antibody-positive: *HLA or HNA antibodies are present in the donor of the transfused component which are cognate with the recipient*. This refers to objective presence or absence and carries no causative implication.

ALICT: *Acute lung injury caused by biologically-active agents in the transfused component.* This represents the 'causative/pathophysiological' concept understood by 'TRALI'. This cannot be objectively assigned but can be assigned a 'level of plausibility', similar to the current SHOT classification as 'highly likely, probable or equivocal,' taking into account all clinical and laboratory features of the case. The assignment of 'ALICT plausibility' is similar to the concept of imputability but is not identical because it excludes fluid in the transfusion as the causative principle.

Figure 18a.1 illustrates how these three concepts overlap. The intersection between all three categories 'classical antibody-mediated TRALI' is thus the common ground of understanding; the remainder of the diagram offers a model for defining the questions for further research and validation.

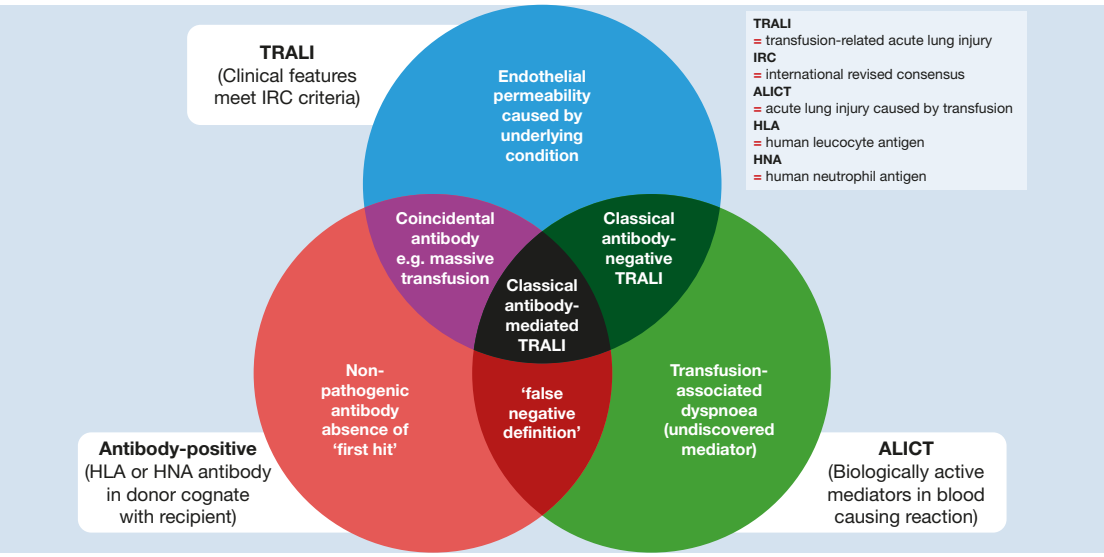


Figure 18a.1: Conceptual relationship between TRALI, ALICT and donor antibody

References

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

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

18b Transfusion-Associated Circulatory Overload (TACO) n=149

Author: Sharran Grey

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 18b.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. The SHOT Working Expert Group can transfer cases between categories

Abbreviations used in this chapter

Hb	Haemoglobin	**TACO**	Transfusion-associated circulatory overload
NT pro-BNP	N-terminal-pro B-type natriuretic peptide		

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

Action: All staff authorising transfusions

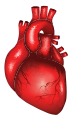
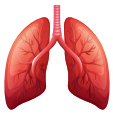
- A structured incident review should be undertaken for every case of TACO. This will ensure optimal organisational and individual patient safety measures are in place to protect patients from TACO as far as possible (see recommended resources)

Action: Trust/Health Board governance and clinical risk departments, all staff investigating transfusion incidents

- Weight-adjusted red cell dosing should be used to guide the appropriate volume required for all non-bleeding adult patients. Ideally tools which also highlight inappropriate transfusion should be used (Grey et al. 2018, NCA 2017)

Action: All staff authorising transfusions

The TACO pre-transfusion assessment infographic has been re-drafted as a checklist (Figure 18b.1) that can be incorporated as part of the transfusion care pathway in healthcare.

TACO Checklist	Patient Risk Assessment	YES	NO
	Does the patient have any of the following: 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?		
	Is the patient known to have pulmonary oedema?		
	Does the patient have respiratory symptoms of undiagnosed cause?		
	Is the fluid balance clinically significantly positive?		
	Is the patient receiving intravenous fluids (or received them in the previous 24 hours)?		
	Is there any peripheral oedema?		
	Does the patient have hypoalbuminaemia?		
	Does the patient have significant renal impairment?		

If Risks Identified	YES	NO
Review the need for transfusion (do the benefits outweigh the risks)?		
Can the transfusion be safely deferred until the issue is investigated, treated or resolved?		

If Proceeding with Transfusion: Assign Actions	TICK
Body weight dosing for red cells	
Transfuse a single unit (red cells) and review symptoms	
Measure fluid balance	
Prophylactic diuretic prescribed	
Monitor vital signs closely, including oxygen saturation	

Name (PRINT):	
Role:	
Date:	**Time (24hr):**
Signature:	

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 18b.1: TACO pre-transfusion checklist

Introduction

The 2020 reporting year has recorded the highest number of TACO cases ever reported to SHOT. COVID-19 has complicated the assessment of some cases and the overall increase in number of reports received has been affected by patients on convalescent plasma trials. The increasing number of cases where preventive actions include the TACO pre-transfusion checklist being incorporated into documents and processes, including electronic systems and training programmes, is a welcome and positive change in practice. It is critically important that all TACO cases are used as a learning opportunity to prevent or mitigate TACO in other patients. A new recommendation for this year is the use of the TACO investigation and preventive action guidance tool, to ensure a structured and comprehensive review of cases to support effective preventive actions (see recommendations and recommended resources sections).

Deaths n=18

TACO resulted in the death of a patient in 18 reported cases. Although the imputability level was 1 (possibly related to transfusion) in most cases, this is a significant increase in the number of cases of TACO where patients died, and the transfusion was judged to be contributory. This may reflect the severity of underlying illness and in particular those with COVID-19 as such patients were unfortunately more likely to die.

Major morbidity n=25

There were fewer cases resulting in major morbidity than in the previous reporting year but again this may reflect the severity of underlying illness in some patients, in that they were possibly more likely to die than they were to survive following major morbidity. TACO remains the leading cause of transfusion-related combined mortality and major morbidity.

Table 18b.1: Demographic overview of cases

Demographic	Number of reports
Deaths (imputability 3)	0
Deaths (imputability 2)	2
Deaths (imputability 1)	16
Major morbidity outcome	25
Age†	Range: 9 days to 97 years Median: 73 years
Top 3 medical specialties†	Haematology, acute medicine, general medicine
Bleeding patients (indication code R1 or 'massive bleeding' indicated†	24
Non-bleeding patients (other indication codes or not stated)	125

† where data was provided

TACO is more commonly reported in the elderly, non-bleeding patients but is seen across all age groups and is consistent with the data from previous years. There were 2 cases in the under-18 age group both of which were neonates. 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 of cases

Analysis by definition criteria

Cases reported in 2020 were assessed using the surveillance criteria in Table 18b.2. It should be noted that the criteria are for the purposes of reporting and surveillance. They 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.

Figure 18b.2 shows the number of accepted TACO cases versus the number of TACO surveillance criteria met. One accepted case only met two TACO surveillance criteria but was otherwise a clinically compelling scenario. A patient with a positive fluid balance developed respiratory distress and increased oxygen requirement during transfusion, which improved following treatment with a diuretic. A chest X-ray was not performed and therefore the presence of pulmonary oedema could not be confirmed, and there were no cardiovascular changes reported. There was a slightly increased number of patients meeting all five criteria due to a slight increase in NT pro-BNP testing, which is a useful indicator of left atrial hypertension in patients with circulatory overload.

Table 18b.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

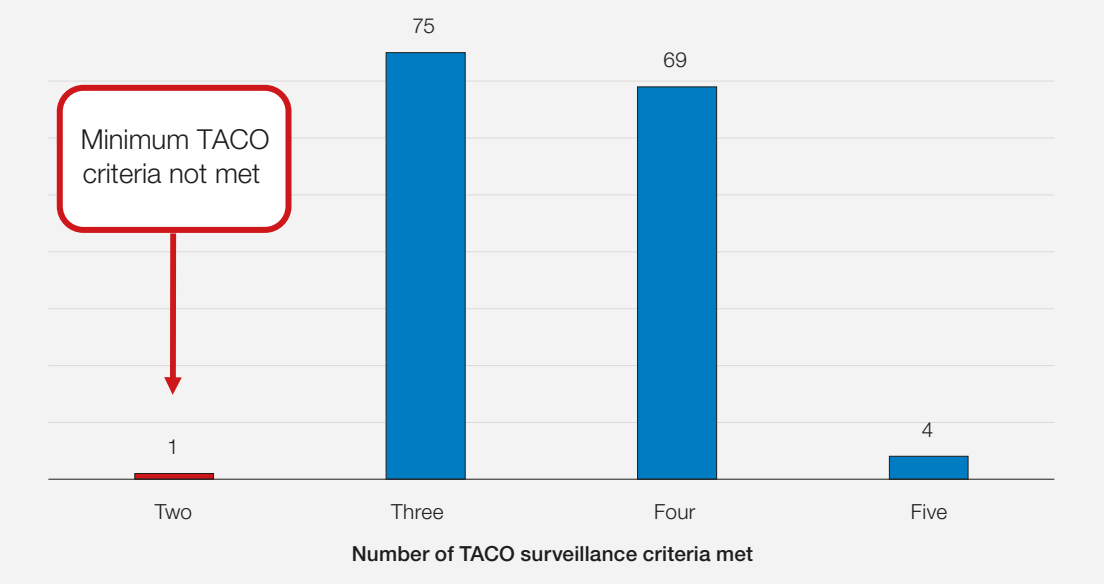


Figure 18b.2: Number of TACO surveillance criteria versus number of accepted TACO cases

Use of the TACO checklist

The TACO risk assessment recommendation was introduced in 2016 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 18b.3.

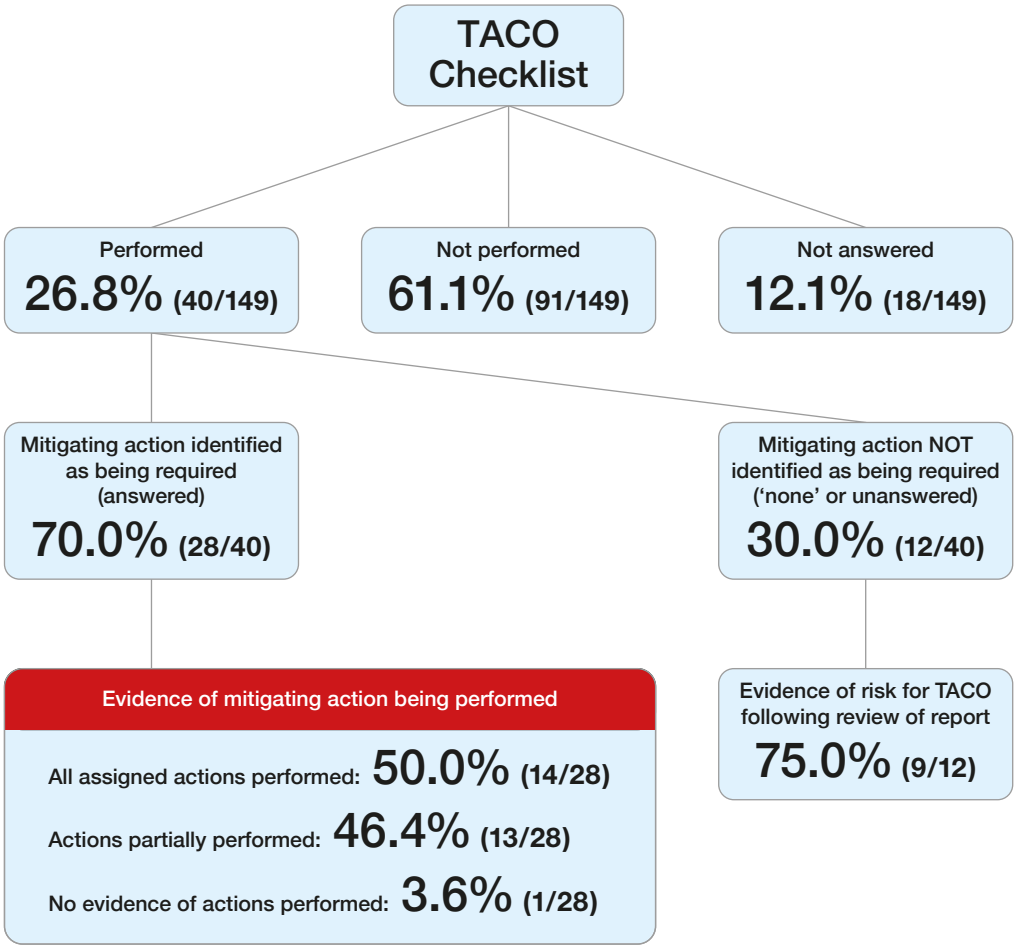


Figure 18b.3: Use of the checklist to identify patients at risk of TACO and implementation of mitigations

The TACO checklist had only been reported as performed in 40/149 (26.8%) of cases, resulting in missed opportunities to mitigate the risk of TACO. Where it had been performed, 28/40 (70.0%) of those cases were identified as requiring a TACO risk-reduction measure. This was performed in 14/28 (50.0%) of cases, with the majority of the remainder partially performed, or not fully assessable from the data available. A TACO risk-reduction measure was not identified as required in 12/40 (30.0%) of cases, but on review 9/12 (75.0%) of these cases had clear risk factors for TACO, suggesting the checklist had not been accurately performed.

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

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

In 2020 there were 73 cases where the patient was not bleeding, and body weight and pre-transfusion Hb level was reported. Thirty-four of these cases also had a post-transfusion Hb level reported. In 7/34 (20.6%) of cases their post-transfusion Hb target was exceeded. The number of red cell units transfused was reported in 28 cases. In 12/28 (42.9%) of cases the patient received more than the calculated weight-adjusted dose resulting in 5/12 (41.2%) exceeding their post-transfusion Hb target. This suggests that weight-adjusted red cell dosing is not sufficiently implemented, and this continues to result in excessive red cell transfusion.

Learning points

- 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) in non-bleeding patients. This can be minimised by weight-adjusted red cell dosing, and medical management of anaemia where possible. The red cell calculation shown below helps estimate the volume of red cells required to meet the target haemoglobin (Norfolk 2013)

  [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 in the UK is 220 - 340mL)

  This volume calculation will help inform the number of units to be requested

- A significant number of reported TACO cases do not appear to have had a TACO checklist performed, and/or TACO risk-reduction measures not implemented where risk was identified. This should be embedded into the procedure for the request and authorisation of transfusion
- Every case of TACO is an opportunity to improve practice and reduce risk for other patients. Structured investigation and root-cause analysis allows implementation of effective preventive actions

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 2020, but cases of TACO continue to be under-recognised and under-reported. Most TACO cases have a recognised risk factor for circulatory overload. Although there are now well-established recommendations and tools to mitigate TACO in patients with risk factors, analysis of the data shows these are not being implemented in clinical practice, and opportunities are being missed to protect patients. It is critically important that every case of TACO is used as an opportunity to improve practice and reduce risks for other patients. Structured investigation and root cause analysis allows implementation of effective preventive actions for the future protection of patients.

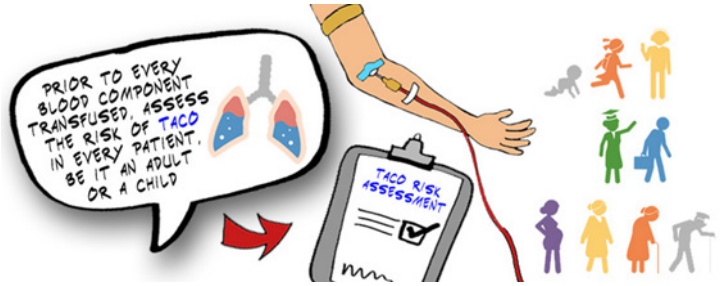
Recommended resources

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

TACO investigation and preventive action guidance tool
https://www.shotuk.org/resources/current-resources/

TACO checklist: in risk assessment/checklist alternative format for incorporation into clinical documents
https://www.shotuk.org/resources/current-resources/

SHOT Bite number 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. on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2015 Annual SHOT Report (2016). https://www.shotuk.org/shot-reports/ [accessed 28 April 2021].

Bolton-Maggs PHB (Ed), Poles D, et al. on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2017 Annual SHOT Report (2018). https://www.shotuk.org/shot-reports/ [accessed 28 April 2021].

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

NCA. 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 28 April 2021].

Norfolk D (ed). Handbook of Transfusion Medicine (5th edn) (2013). The Stationery Office, London URL https://www.transfusionguidelines.org/transfusion-handbook [accessed 28 April 2021].

Wiersum-Osselton J, Whitaker BL, Grey S, et al. Revised international surveillance case definition of transfusion associated circulatory overload (TACO): a classification agreement validation study. *Lancet Haematol* 2019;**6(7)**:e350-e358. doi: 10.1016/S2352-3026(19)30080-8.

18c Transfusion-Associated Dyspnoea (TAD) n=37

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Acknowledgements: All members of the Pulmonary 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 message

- 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 verify imputability, causality and categorisation. International collaborative work in this area will help identify causal and contributory factors and identify appropriate risk-reduction measures

Abbreviations used in this chapter

ARDS	Acute respiratory distress syndrome
CCU	Critical care unit
CP	Costophrenic
CT	Computed tomography
CXR	Chest X-ray
ECMO	Extracorporeal membrane oxygenation
FAHR	Febrile, allergic and hypotensive reactions
FFP	Fresh frozen plasma
Hb	Haemoglobin
HDU	High dependency unit
HLA	Human leucocyte antigen
ICU	Intensive care unit
PPH	Postpartum haemorrhage
PRES	Posterior reversible encephalopathy syndrome
WEG	Working Expert Group
TACO	Transfusion-associated circulatory overload
TAD	Transfusion-associated dyspnoea
TAD-C	TAD with adequate clinical information
TAD-IC	TAD with inadequate clinical information
TRALI	Transfusion-related acute lung injury

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 with as much detail (clinical and laboratory aspects) as possible

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 a patient's pre-existing disease. This entity is useful for the surveillance function of haemovigilance systems, but little is known that ties all the cases included in this category other than the temporal correlation between respiratory deterioration and transfusion. The pathophysiology of this group of complications remains unclear (Badami et al. 2015). Appropriate risk-reduction strategies are only possible once we have a better understanding of these reactions. There is some evidence that patients with sepsis are more at risk of respiratory complications following transfusion (Roubinian 2018), a reminder that every transfusion should be reviewed to ensure it is indicated, particularly platelets, which are a rich source of biological response modifiers (Garraud et al. 2013; Garraud et al. 2016).

Categorisation of pulmonary complications following transfusion remains a complex area with ongoing international collaboration for harmonisation of definitions and data collection. Often, the interpretation of the cases submitted is limited by the available clinical information including results of relevant investigations. The SHOT pulmonary WEG continue to attempt to apply the new proposed TRALI consensus definitions (Vlaar et al. 2019) to those cases reported under TAD to assess whether it helped re-categorise these reactions. There were 2 cases categorised as TRALI type II with risk factors for ARDS, and these are detailed below.

Cases included under TAD have been 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). Transfers of cases submitted between categories (FAHR, TACO, TRALI, etc.) reflect the challenges involved in interpreting these real-life cases. 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 these cases.

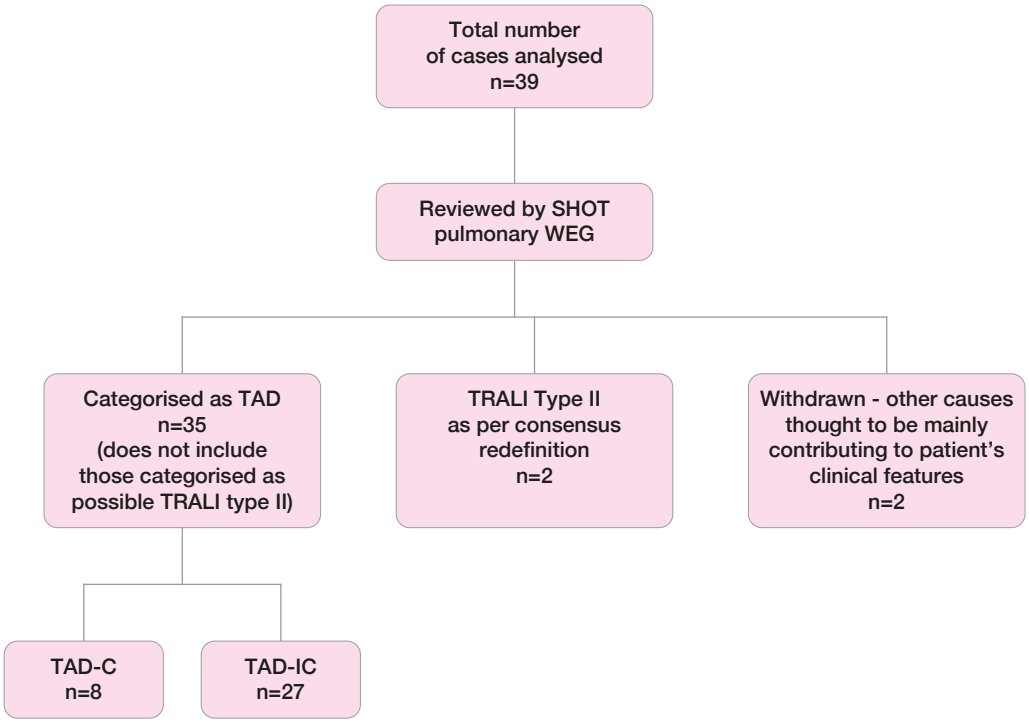

Figure 18c.1: Summary of cases included under TAD

TAD=transfusion-associated dyspnoea; TAD-C=TAD with adequate clinical information; TAD-IC=TAD with inadequate clinical information; TRALI=transfusion-related acute lung injury; WEG=working expert group

Deaths n=4

All 4 deaths were possibly related to the transfusion (imputability 1).

Case 18c.1: Severe shortness of breath and agitation

A patient in her 70s admitted with suspected acute coronary syndrome had multiple co-morbidities: lung cancer, chronic kidney disease, paroxysmal atrial fibrillation, and hypertension. The patient had a deterioration in her respiratory status in the 12 hours prior to transfusion. During a red cell transfusion, the patient developed severe shortness of breath and agitation. Hydrocortisone, chlorphenamine and diuretics were given with no effect and the patient went into cardiac arrest.

Case 18c.2: Cardiac arrest following transfusion

A man in his 70s was admitted with shortness of breath and suspected community acquired pneumonia. He had acute kidney impairment, congenital isolated hyperinsulinism, right bundle branch block, hypertension and had clinical evidence of fluid overload prior to transfusion. Whilst being transfused a unit of red cells, the patient's condition deteriorated quickly leading to cardiac arrest. The patient was resuscitated, admitted to ICU following arrest, but died 4 days later.

Case 18c.3: Respiratory distress and tachycardia following a platelet transfusion

A man in his mid-70s with metastatic prostate cancer and bone marrow failure was admitted following collapse for further evaluation and treatment. During transfusion of irradiated apheresis platelets, the patient developed acute respiratory distress and tachycardia. There was no clinical evidence of circulatory overload. No information regarding input/output was available. He had received two red cell units in the 24 hours prior to this. He was given steroids, diuretics and O_2. The diuresis response was not recorded. The patient worsened, was reviewed by the critical care team, and a decision was made for no escalation in care and to remain on the ward for palliative care. The CXR post transfusion showed patchy consolidation in the right lower zone.

Case 18c.4: TRALI type II

A patient in his 70s, with metastatic lung adenocarcinoma, was admitted with community acquired pneumonia and suspected sepsis. He was transfused two units of red cells for Hb 54g/L, 5 hours and 40 minutes later the patient went into respiratory failure requiring non-invasive ventilation and admission to ICU. He later deteriorated and died. The case was discussed with the Blood Service consultant and investigated for TRALI. A CXR done post transfusion showed bilateral ground-glass opacities with relative sparing of lung apices. Blunting of the CP angles was seen, more on the left suggestive of pleural effusion. Findings were consistent with pulmonary oedema. TRALI investigations revealed HLA class I antibodies in the donor of this unit, but not cognate to the patient. No HLA class II antibodies or granulocyte-specific antibodies were found. These results do not support a diagnosis of antibody-mediated TRALI. This case has been included in TAD and would qualify for TRALI type II under the consensus redefinition.

Major morbidity n=7

All cases included here are those where patients needed admission to HDU/ICU/CCU following respiratory deterioration post transfusion. In 1 case, a patient needed to be admitted briefly following respiratory distress after transfusion as a day case. All patients subsequently recovered.

TRALI type II as per redefinition consensus criteria n=2

Cases included here were originally submitted under TRALI, but investigations did not reveal cognate antibodies and the patients had risk factors for ARDS, had stable respiratory parameters prior to the transfusion episode but deteriorated significantly following transfusions. These would qualify as TRALI type II under the consensus redefinition but considered under TAD due to a lack of positive serology with cognate antibodies. These cases are described separately here in trying to map to the new consensus redefinition criteria, one resulted in death and one in major morbidity. Both are included in the numbers above.

Case 18c.5: Imputability 1 (possible)

A woman in her mid-20s was admitted to the maternity unit having suffered an eclamptic seizure at home at 27+5 weeks gestation. Intrauterine fetal demise was diagnosed due to a large abruption. She then underwent an emergency caesarean section, was coagulopathic and developed severe PPH. She received several blood components: four units of FFP, four pools of cryoprecipitate, four units of packed red cells and one unit of platelets. After leaving theatre, she was transferred to ICU. At this point a positive bacterial culture (BactAlert) from the platelets had been reported to the Blood Service consultant who then contacted the clinical area to inform them of potential contamination. There were no infective issues reported at the time. The organism was later identified as Propionibacterium acnes. The patient did not recover as would be expected postoperatively. Her CXR showed non-specific diffuse ground glass shadowing consistent with ARDS. There were no positive blood cultures from the patient. A head CT 4 days after surgery showed changes consistent with PRES. The chest CT showed ARDS. She deteriorated and was increasingly difficult to ventilate so was transferred for ECMO and improved slowly. A possible diagnosis of TRALI was considered 4 days after the transfusions. HLA A2 Antibody detected not cognate to the patient.

This was originally reported as possible 'equivocal TRALI' to SHOT due to the finding of antibodies, onset within 6 hours and a plausible clinical history but with many other possibilities. But as only immune TRALI cases are included in the SHOT TRALI category, this has been moved to TAD. This fits in the TRALI type II category according to the consensus redefinition as risk factors for ARDS, not clinically overloaded prior to transfusion; developed hypovolaemic shock after PPH; CXR changes consistent with ARDS; no respiratory infection symptoms prior to transfusion.

The second case was Case 18c.4 described above under the section 'Deaths'. The case was submitted to SHOT in the TRALI category. Investigations revealed HLA class I antibodies in the donor of this unit, but not cognate to the patient. No HLA class II antibodies or granulocyte-specific antibodies were found. These results did not support a diagnosis of antibody-mediated TRALI. They are included in TAD and would qualify for TRALI type II under the consensus redefinition.

COVID-19 convalescent plasma related cases n=4

Four cases were reported in 2020 where patients with COVID-19 pneumonia enrolled onto the RECOVERY trial and developed worsening in their respiratory status <24 hours after convalescent plasma administration. The imputability is difficult to assess in these patients as deterioration could be related to worsening of the COVID-19 pneumonitis. Sudden respiratory deterioration with ARDS is well recognised in these patients and other factors such as thromboembolism and cardiac effects of COVID-19 could also be contributory. Secondary infections, sepsis and rarely pneumothorax and pneumomediastinum could complicate the clinical picture as well (Pooni et al. 2020). All cases have been included for analysis with an imputability of 1 (possible).

Learning point

- Clinicians should report all cases of post-transfusion pulmonary complications to the Blood Service so that further investigation can allow for further classification of such cases. There are cases where such distinction may not always be possible. This is in addition to SHOT reporting

Conclusion

Pulmonary complications following transfusions account for the majority of morbidity and mortality associated with transfused blood components in hospitalised patients. The 'terrible T's': TRALI, TACO, and TAD primarily damage the lung, leading to respiratory failure. The differential diagnosis for patients who develop respiratory distress during or within a few hours after transfusion include TRALI, TACO, an anaphylactic transfusion reaction, and transfusion of contaminated (bacteria) blood components. Often these are in patients with multiple ongoing clinical issues, many of which may also be contributing to the deterioration. TAD with no definitive criteria remains a diagnosis of exclusion. Information about

pre-transfusion clinical state of the patient especially the respiratory status in the preceding 12 hours prior to the transfusions help in categorisation along with results of investigations. Reporters are encouraged to provide as detailed a report as possible to increase understanding of these complications from a haemovigilance perspective. This would also help identify how healthcare providers can risk-stratify individual patients or patient populations to determine whether a given transfusion is more likely to benefit or harm the patient based on the transfusion indication, risk, and expected outcome.

References

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

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

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

Pooni R, Pandey G, Akbar S. Broadening the differential: pneumomediastinum and COVID-19 infection. *BMJ Case Reports CP* 2020;**13**:e237938.

Roubinian N. 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.

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