Pulmonary Complications of Transfusion n=212

17

Author: Shruthi Narayan

With contributions from the SHOT Pulmonary Working Expert Group members

Abbreviations used in this chapter

ARDS	Acute respiratory distress syndrome
BNP	B-type natriuretic peptide
BP	Blood pressure
BSH	British Society for Haematology
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CT	Computed tomography
CXR	Chest X-ray
ECG	Electrocardiogram
FFP	Fresh frozen plasma
GI	Gastrointestinal
GP	General practitioner
Hb	Haemoglobin
HLA	Human leucocyte antigen
HNA	Human neutrophil antigen
ICU	Intensive care unit
ISBT	International Society of Blood Transfusion
IRC	International revised consensus
LV	Left ventricle
MHRA	Medicines and Healthcare products Regulatory Agency
NBTC	National Blood Transfusion Committee
RLL	Right lower lobe of the lung
TACO	Transfusion-associated circulatory overload
TAD	Transfusion-associated dyspnoea
TRALI	Transfusion-related acute lung injury
WEG	Working expert group

Key SHOT messages

- Pulmonary complications of transfusion remain a leading cause of transfusion-related mortality and morbidity, contributing to more than 50% of transfusion-related deaths reported to SHOT from 2013 to 2022
- Categorising pulmonary complications can be challenging. Staff need to be precise in clarifying what is meant when the various terms are used
- Preventable risk factors, in particular fluid overload, are often identifiable regardless of the final classification. Structured incident investigation may be useful to ensure that risk factors and preventative actions are identified

The recommendations from previous years continue to be relevant and specific recommendations are also covered in the individual chapters.

Recommendations (repeat from previous years)

- 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, 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

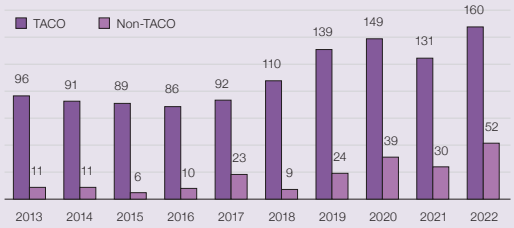
Pulmonary complications post transfusion continue to contribute significantly to death and major morbidity. Patients with respiratory complications are often elderly with multiple co-morbidities which could all contribute to the complication post transfusion. Pulmonary complications present diagnostic and therapeutic challenges with mainly supportive measures available and paucity of specific therapies.

There is an increasingly upward trend in the number of pulmonary complications reported to SHOT in the last decade.

Headline data 2022

Number of reports n=212
Deaths n=15
Major morbidity n=37

Pulmonary reports by year



Demographic data

Male n=98
Female n=114
Adults n=198
Paediatric n=8
Unknown n=6

Blood component data

Red cells n=162
Platelets n=13
Plasma n=7
Granulocytes n=3
Cryoprecipitate n=1
Multiple components n=26

All cases included in the TACO chapter are those that meet the validated ISBT TACO surveillance definition (Wiersum-Osselton et al. 2019). In this year's Annual SHOT Report, all the pulmonary reactions which do not meet the ISBT TACO criteria are covered in a single chapter similar to last year (Narayan et al. 2022). These cases have been primarily classified using the IRC TRALI classification (Vlaar et al. 2019). Categorisation of these reactions is challenging as is evident from the extensive reclassification of cases following submission and has been explained further in the subsequent chapters. A recent Australian study looking at the impact of revised definitions of TACO and TRALI on haemovigilance reporting found that while the revised TACO definition appears to capture more cases than the former definition, there was no significant difference in the number of TRALI cases using the IRC TRALI classification as compared to the Canadian Consensus Conference definition (Yuan et al. 2021).

As has been highlighted previously and evident in most cases, mechanisms for post-transfusion pulmonary complications are multifactorial and complex, involving both transfusion-specific and patient-specific factors. The respiratory deterioration is a common end point for multiple pathophysiological mechanisms. Unwell patients therefore have the highest risk of transfusion but may also have the highest need for transfusion. Reported TACO cases are increasing and most patients with pulmonary complications were at risk of fluid overload or had features of fluid overload even if TACO criteria were not met.

It is important that the relative risks and benefits of transfusion should be weighed up carefully in all patients receiving a transfusion but particularly those with other morbidities. Pre-transfusion TACO risk assessment should be used sincerely rather than as a tick box exercise as this can prompt appropriate actions to mitigate the risk. While the evidence for effectiveness of this pre transfusion is still awaited, it is clear from some of the cases that the checks were not done properly, with missed opportunities for mitigating interventions.

A systematic review of safety checklists concluded 'safety checklists appear to be effective tools for improving patient safety in various clinical settings by strengthening compliance with guidelines, improving

human factors, reducing the incidence of adverse events, and decreasing mortality and morbidity. None of the included studies reported negative effects on safety' (Thomassen et al. 2014).

There is of course work to do in identifying patients at risk of pulmonary complications prior to transfusion, in particular patterns of comorbidity. It will not be possible to prevent all respiratory deteriorations with a temporal relationship to transfusion but at least those that can be prevented may be identified through pre-transfusion checks. Future goals might be to improve understanding of which patients with inflammation are sensitive to fluid, how to prevent any adverse impact, effectiveness of measures currently advocated and identify which reactions to investigate for leucocyte antibodies.

Blood components should be administered only after careful consideration of the patient's unique risk of a transfusion complication versus the physiologic benefit of the planned transfused blood component. Staff need to be vigilant when transfusing critically ill patients. At least some of these pulmonary complications are potentially preventable and early recognition with prompt treatment is vital. Patient education and awareness are also important, especially if transfused as day cases or in the community.

Less is often more with regards to transfusion.

References

Narayan S (Ed), Poles D, et al. on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2021 Annual SHOT Report (2022). https://www.shotuk.org/shot-reports/ [accessed 27 April 2023].

Thomassen Ø, Storesund A, Søfteland E, et al.. The effects of safety checklists in medicine: a systematic review. *Acta Anaesthesiol Scand*. 2014;**58(1)**:5-18. doi: 10.1111/aas.12207. Epub 2013 Oct 10. PMID: 24116973.

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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.

Yuan Y, Dennington P, Daly J, et al. The Impact of Revised Definitions for TACO and TRALI on Hemovigilance Reporting. Blood 2021; Volume 138, Supplement 1, Page 3252 https://www.sciencedirect.com/science/article/pii/S0006497121051831 [accessed 02 May 2023].

17a Transfusion-Associated Circulatory Overload (TACO) n=160

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 17a.1 for details of required and additional criteria for a surveillance diagnosis

Key SHOT messages

- The number of TACO cases reported in 2022 is the highest to date. Although cases continue to increase, there is likely to be a level of under-reporting
- The continued adoption of the TACO checklist is encouraging although analysis of the data shows it is still under-used or used ineffectively
- TACO continues to be a major cause of transfusion-related mortality and morbidity

Recommendations (new)

- 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 TACO definition criteria can be used as guidance, but this should not be restrictive. SHOT experts can transfer cases between categories

Action: All staff involved in transfusion

Recommendations (ongoing)

- A formal pre-transfusion risk assessment for 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 transfusion

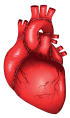
- A structured incident review should be undertaken for every case of TACO to ensure optimum organisational and individual patient safety measures are in place to protect patients from TACO as far as possible (see 'Recommended resources')

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

- 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, National Comparative Audit 2017)

Action: All staff authorising transfusion

The TACO pre-transfusion risk assessment infographic (Figure 17a.1) was updated in the 2020 Annual SHOT Report to make it suitable for incorporation into clinical documents. No further update was required this year.

TACO Checklist	Patient Risk Assessment	TICK
	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?	
	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 can be 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 17a.1: TACO pre-transfusion checklist

TACO Surveillance Definition
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 BNP levels or NT-pro BNP to greater than 1.5 times the pre-transfusion value

Table 17a.1: TACO surveillance definition (adapted from Wiersum-Osselton et al. 2019)

Introduction

The number of cases reported in 2022 is the highest to date and is an increase of 29 cases from 2021 (n=131). Although the pathophysiology of the pulmonary complications of transfusion is not fully understood, the evolving understanding of risk factors for TACO and the development of tools to mitigate

risks has advanced significantly in recent years. This chapter describes the demographics of patients reported to have TACO, the adoption of risk-reduction strategies, and highlights areas for further focus based on signals from the data and ongoing trends.

Deaths related to transfusion n=8

There were 8 deaths related to the transfusion, of which 1 was definitely related (imputability 3), 1 was probably related (imputability 2) and 6 were possibly related (imputability 1) (Table 17a.2).

Major morbidity n=25

There were 25 cases of major morbidity cases in 2022, this is similar to 2021 when there were 23 cases reported.

Table 17a.2: Demographic overview of cases

Demographic	Number of reports
Deaths (imputability 3, definite)	1
Deaths (imputability 2, likely)	1
Deaths (imputability 1, possible)	6
Major morbidity outcome	25
Age	Range: newborn – 97 years (3 aged under 18 years) Median: 72 years
Gender	91 female: 69 male
Body weight (adults)	Female (n=56): average 66.6kg (range: 33.1-105kg) Male (n=33): average 77.9kg (range: 63-125kg)
Top 4 medical specialties	Haematology=32, general medicine=19, acute medicine=18, gastroenterology=10
Bleeding patients (indication code R1 or 'massive bleeding' indicated)	19
Non-bleeding patients (other indication codes or not stated)	141

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 3 cases in the under-18 age group, (newborn to age 17 years). TACO was reported more in adult female patients compared to male. Weight was provided in 33 adult female cases, with an average of 66.6kg (33.1-105kg). Weight was provided in 34 adult male cases, with an average of 77.9kg (63-125kg). This difference may account for the apparent higher incidence of TACO in female patients and underlines the risk of TACO in lower-weight patients and the importance of weight-adjusted red cell dosing. Adult medical specialties and haematology continue to be the most common specialties where TACO is reported, and this should be considered when targeting TACO education and mitigation plans.

Use of the TACO risk assessment

The recommendation for a formal pre-transfusion TACO risk assessment 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 questionnaire for the 2019 reporting year. An overview is shown in Figure 17a.2. The TACO risk assessment was not used in 60.6% (97/160) cases. This is a similar level compared to 2021.

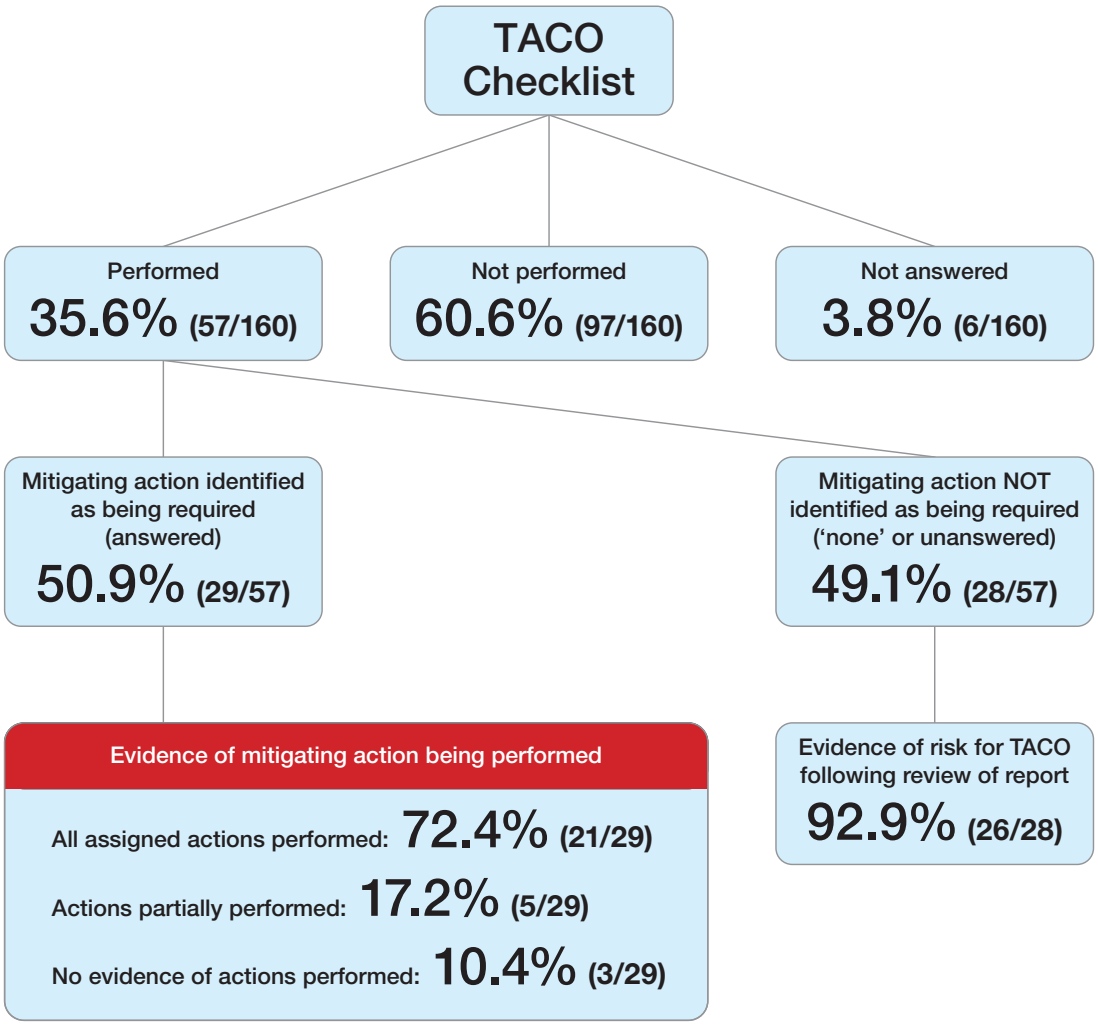


Figure 17a.2: Use of the checklist to identify patients at risk of TACO and implementation of mitigating actions

The TACO checklist was reported to have been used in only 57/160 (35.6%) cases. It is disappointing that the checklist is not universally utilised as there may have been missed opportunities to reduce the risk of TACO. This has been a SHOT recommendation since 2016 and is also highlighted in the BSH guideline on the administration of blood components (BSH Robinson et al. 2018). Where a TACO checklist was performed 29/57 (50.9%), it demonstrated the need for a mitigating action and in most cases, these were taken. In some cases, additional measures could also have been instigated. There were 3 cases where assigned actions had not been carried out and 5 where the actions were only partially completed. Where a TACO checklist was performed and it was determined a mitigating action was not required, a review of these reports showed that 26/28 (92.9%) did in fact have at least one risk factor for TACO. It is important to recognise that while the TACO risk assessment does not guarantee avoidance of TACO, it can provide a means of identifying patients at risk. This helps apply strategies to reduce risk and help make safe transfusion decisions. It is not clear from the data whether this is due to improper use of the TACO checklist or whether this reflects lack of clinical knowledge to perform the risk assessment.

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

There were 68 cases where a pre-and post-transfusion Hb was provided. In 18/68 (26.5%) cases there was evidence of excessive red cell transfusion to meet the Hb target. Of these 17/18 (94.4%) had a Hb above 100g/L. In 2 cases these were inappropriate transfusions based on the pre-transfusion Hb level.

The number of units transfused, and body weight were provided in 10/68 (14.7%) of these cases. Excluding the two inappropriate transfusions the number of units transfused was excessive based on the patient's weight and pre-transfusion Hb level in 6/10 cases. In 2/10 cases patients with severe chronic

anaemia only required minimal transfusion to alleviate the symptoms of anaemia. Three and six units of red cells were transfused in these cases. This underlines the importance of weight-adjusted red cell dosing to avoid the risks of overtransfusion.

Cases involving severe chronic anaemia

Severe anaemia was added to the TACO checklist following a signal previously observed in the data (Narayan et al. 2019). Non-bleeding adult patients with severe chronic anaemia are particularly vulnerable to TACO even in the absence of additional risk and comorbidities that are known to predispose TACO.

In 39/160 cases there was a Hb <60gL. Of these, 7/39 cases were severe anaemia due to haemorrhage or erroneous Hb measurement. The remaining 32/39 cases were severe chronic anaemia and 7 had clear evidence of iron deficiency. There is still evidence that iron replacement (including intravenous iron) is not being administered to patients with iron deficiency anaemia. Transfusion of excessive volumes of red cells, lack of consideration of patients with low body weight, and evidence of aiming for a Hb target that is intended for the correction of acute anaemia increase the risk of TACO in these patients. Patients with severe chronic anaemia should receive only minimal red cell transfusion with the aim of alleviating symptoms as opposed to aiming for Hb correction to meet a target Hb level.

Case 17a.1: Severe chronic iron deficiency anaemia in a patient with low body weight

A female patient in her 80s with a low body weight (49kg) was asymptomatic and haemodynamically stable with severe microcytic hypochromic anaemia (Hb44g/L) with no clinical signs of pulmonary oedema on the chest X-ray or clinical examination. Three units of red cells were transfused over a period of 15 hours because the attending doctor was aiming for a post-transfusion Hb of 70-90g/L. The patient developed respiratory compromise (desaturation from 100% on room air to 71%, with dyspnoea, wheeze, and tachypnoea). There were new cardiovascular changes: tachycardia (heart rate 131bpm) and hypertension (blood pressure 204/96mmHg). Fluid balance was not clearly documented. Additional fluid was not involved. A diuretic was given but the patient deteriorated and died, therefore a diuretic response could not be evaluated. There was clear evidence of overtransfusion as the post-transfusion Hb was 111g/L. The patient did not otherwise have comorbidities predisposing circulatory overload. The post-transfusion chest X-ray showed pulmonary oedema.

This was a complex case which was referred to the coroner. The post-mortem examination report described pulmonary oedema and congestion of the lungs. The histopathology findings on the lung tissue were interpreted as TRALI by the histopathologist due to the presence of fibrinous exudate and neutrophil polymorphs in the alveoli which is indicative of an inflammatory process. The symptoms, signs and the clinical context met the haemovigilance criteria for TACO and was reported as such by the hospital to SHOT and per legal obligations to the MHRA. As TRALI had been cited in the post-mortem report there was an obligation to report this to the Blood Service. A clinical assessment for TRALI was performed and it was agreed the case met the TACO criteria, not TRALI. Blinded opinion was sought from the two other members of the SHOT Pulmonary Complications of Transfusion WEG who also agreed this was TACO. All agreed that a TRALI investigation (involving the testing of recipient and donors) was not indicated based on the clinical assessment criteria for pulmonary complications of transfusion. A TRALI assessment had only been initiated based on the interpretive comments in the histopathology and the post-mortem reports.

The purpose of considering a TRALI investigation was not to differentiate TACO and TRALI for the purpose of determining the cause of death, rather a potential public health concern should any of the donors have a clinically significant HLA or HNA antibody that could potentially cause a similar reaction in another recipient. A TRALI investigation would normally require testing of the recipient to demonstrate a match between donor antibody and recipient tissue-type. The only biological specimen available were paraffin blocks of lung tissue. As testing procedures are validated on blood samples (not tissue in paraffin histology blocks), any results would be unvalidated and reliability unknown. The absence of HLA/HNA antibodies in the donors would exclude antibody-mediated TRALI, however if present it could not be excluded if recipient typing was not possible.

The conclusions regarding the type of pulmonary complication of transfusion differed as haemovigilance criteria and histopathology are each based upon different evidence however it was agreed the patient had a pulmonary complication of transfusion. The understanding of the pathogenesis of TACO is incomplete and it is widely agreed that there may be an inflammatory aspect, and therefore the presence of fibrinous exudate and neutrophil polymorphs in the alveoli of the lung does not exclude TACO. A negative TRALI investigation would not exclude 'antibody-negative' TRALI, and indeed TACO and TRALI may co-exist (Bosboom et al. 2019).

The patient was at risk of TACO due to her low body weight and severe anaemia. A TACO risk assessment would have identified this and should have prompted single unit/weight-adjusted red cell dosing, prophylactic diuretic etc. Despite this, the attending doctor was aiming for a significantly higher target Hb as would have been appropriate if the patient had stable acute anaemia. The patient had asymptomatic severe chronic iron deficiency and therefore a small volume red cell transfusion (to improve any symptoms of anaemia and minimise risk of cardiac ischaemia), followed by intravenous iron replacement was indicated.

Cases with evidence of a structured investigation

Previous data suggested there was a lack of structured investigation following cases of TACO, resulting in missed opportunities to mitigate the risk of TACO and to improve transfusion safety for all patients. The TACO structured investigation tool was first launched in the 2020 Annual SHOT Report and continues to be a recommendation this year. The pulmonary reactions questionnaire in the SHOT database (Dendrite) has been updated to include a question as to whether it was performed. The template was used by only 37/160 (23.1%) of reporters in 2022. A structured review and incident investigation should be undertaken for every case of TACO to optimise organisational and individual patient-safety measures.

Learning points

- Severe chronic anaemia (asymptomatic or minimally symptomatic) requires only minimal transfusion (usually a single unit) followed by pharmacological treatment where appropriate
- Non-bleeding adult patients with severe chronic anaemia are particularly vulnerable to TACO even in the absence of other risk factors and comorbidities that predispose to TACO

Conclusion

The continued adoption of the TACO checklist is encouraging though analysis of the data shows it is still under-used or used ineffectively. There has been some uptake of the TACO structured assessment tool, but the data suggest that there is significant lack of structured investigation following cases of TACO and this results in missed opportunities to mitigate the risk of TACO and to improve transfusion safety for all patients. Overtransfusion of red cells also remains an issue which could be minimised by weight-adjusted or single unit transfusion in non-bleeding patients. The transfusion management of patients with severe chronic anaemia is concerning and resulted in a patient death this year due to excessive transfusion. There are several strategies now available to mitigate the risk of TACO based on many years of haemovigilance data. Everyone involved in the transfusion process has a professional duty to protect patients from TACO wherever possible.

With an increasing number of TACO cases reported to SHOT year-on-year, including instances of preventable deaths, a TACO safety alert is being planned to be released UK-wide by SHOT through the MHRA. This will help promote implementation of measures to enhance safety and facilitate appropriate transfusion decisions. The NBTC indication codes are also being reviewed currently and an updated version is expected to be released soon. Identifying risk-factors for TACO in vulnerable patients prior to transfusion helps initiate appropriate mitigating measures. Some TACO deaths are preventable.

Recommended resources

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

TACO Incident Investigation 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 No. 11: Respiratory Symptoms During Transfusion
https://www.shotuk.org/resources/current-resources/shot-bites/

SHOT Video: TACO
https://www.shotuk.org/resources/current-resources/videos/

Patient Blood Management - Blood assist app
Apple (https://apps.apple.com/gb/app/blood-assist/id1550911130)
Google play (https://play.google.com/store/apps/details?id=uk.nhsbt.bloodassist)
Web based (https://www.bloodassist.co.uk/)

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Pulmonary complications of transfusion (non-TACO) n=52

17b

Author: Tom Latham

With contributions from the Pulmonary WEG members

Definition:

Cases where there is a respiratory deterioration within 24 hours of transfusion which does not meet ISBT TACO criteria, and which is not explained by the recipient's underlying condition.

Key SHOT messages

- Pulmonary complications are often multifactorial, and classification of these cases is challenging
- Fluid overload is often suspected as a contributing factor even if cases do not meet TACO criteria
- Classification of a case as TRALI using international criteria does not imply or depend on the presence of leucocyte antibodies in the donor

Recommendation

- A structured TACO investigation tool should be used for all pulmonary complications

Action: All staff involved in investigating transfusion reactions

Introduction

Pulmonary reactions which do not meet the ISBT TACO criteria are discussed in this chapter. Cases have been primarily classified using the IRC TRALI classification (Table 17b.1) (Vlaar et al. 2019). Due to the complexity of these reactions, there was extensive reclassification of cases following submission and review by the pulmonary WEG members. Further details can be found in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2022/).

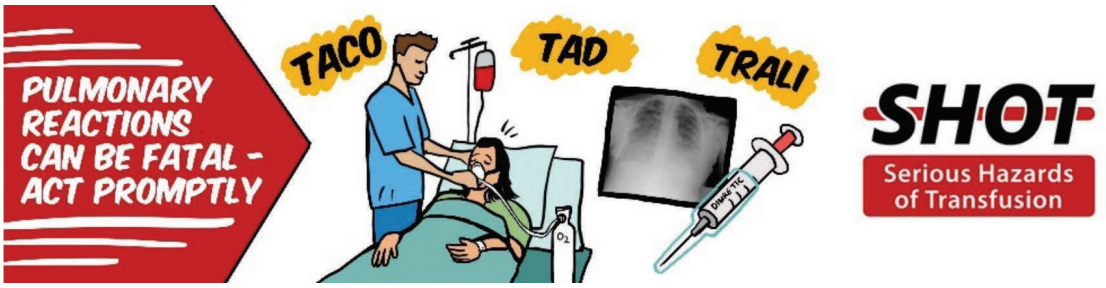


Table 17b.1 International classification of pulmonary complications

Table 7 Comparison table to assist with pulmonary reaction classification

	TRALI Type I	TRALI Type II	ARDS	TRALI/TACO	TACO	TAD
Hypoxemia	Present	Present	Present	Present	May be present but not required	May be present but not required
Imaging evidence of pulmonary edema	Documented	Documented	Documented	Documented	May be present but not required	May be present but not required
Onset within 6 hr	Yes	Yes	Yes	Yes	Yes*	No*
ARDS risk factors	None	Yes—with stable or improving respiratory function in prior 12 hr	Yes—with worsening respiratory function in prior 12 hr	None, or if present, with stable or improving respiratory function in prior 12 hr	Not applicable	Not applicable
LAH†	None/mild	None/mild	None/mild	Present or not evaluable	Present	May be present but not required

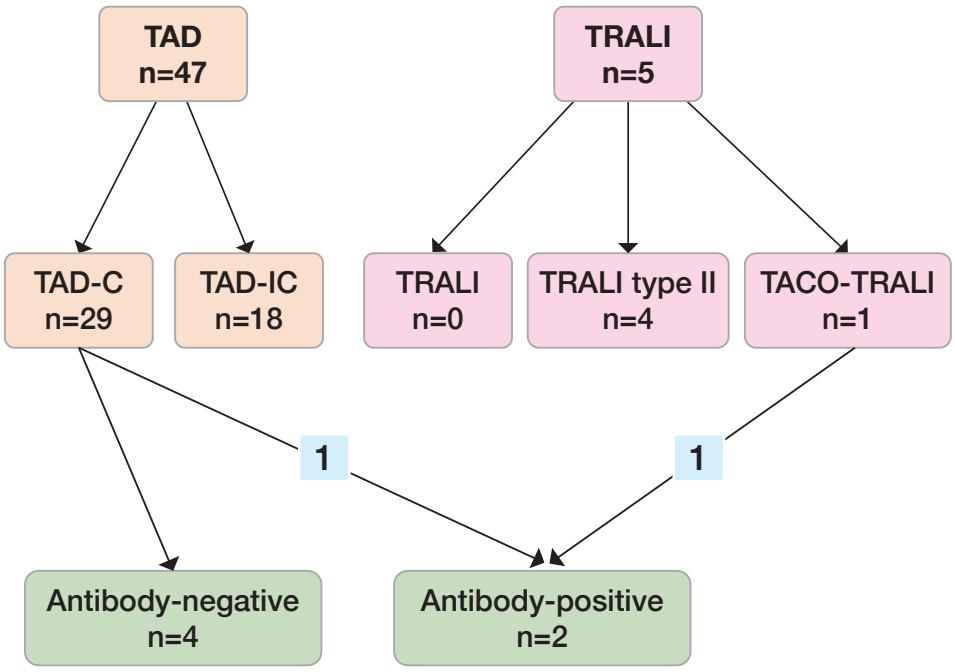
*Some definitions of TACO allow onset up to 12 hours posttransfusion. However, our current recommendation is that 6 hours be used. If pulmonary edema occurs greater than 6 hours following the transfusion and is clinically suspicious for a temporal association with transfusion, the case should be classified as TAD as is currently done in many hemovigilance systems.

†LAH is difficult to assess. When LAH is suspected, we recommend using objective evaluation to determine if it is present. Objective criteria include imaging (e.g., echocardiography) or invasive measurement (e.g., pulmonary artery catheter pressure measurement). However, clinical judgment is often required and, if this is needed, should be used for case classification as follows: TRALI and/or TACO = respiratory insufficiency at least partially explained by hydrostatic lung edema resulting from cardiac failure or fluid overload or unable to fully assess the contribution of hydrostatic lung edema resulting from cardiac failure or fluid overload; TACO = respiratory insufficiency explained by hydrostatic lung edema resulting from cardiac failure or fluid overload.

Reproduced from Vlaar et al. 2019

The final classification of cases is summarised in Figure 17b.1. The TAD category is subclassified into TAD-IC, the cases which could not be classified because of incomplete information reported, and TAD-C, the cases where there was sufficient information to judge that the case did not meet either TACO or TRALI criteria.

Figure 17b.1: Final classification of non-TACO cases



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

Deaths related to transfusion n=7

There were 7 deaths reported this year. A summary is presented in Table 17b.2. All patients were unwell prior to transfusion, and it is not clear how much the transfusion contributed to the reaction. The cases classed as definitely related (imputability 3), or probably related (imputability 2), were both classified as TAD-IC but were suggestive of fluid overload. There were no deaths due to antibody-associated TRALI.

Table 17b.2: Summary of pulmonary complication deaths

Case	Category	Imputability	Products transfused	Explanatory features	Underlying disease	Imaging	Difficulty classifying
1	TAD-IC	1, possible	2 red cell units	Cardiac failure, peripheral, aspiration pneumonia, low albumin, liver impairment, renal impairment. Crackles on chest examination	Fall/anaemia	Not performed	Absent imaging. Insufficient criteria for TACO
2	TAD-C	1, possible	2 red cell units	Cardiac failure, lung infection, COPD, low albumin	Terminal malignancy	L basal shadowing	Insufficient criteria for TACO.
3	TAD-C	1, possible	1 apheresis platelets	Neutropenic sepsis, pneumonia, low albumin, peripheral oedema	Lymphoma	Bilateral worsening	Donor antibody negative. Does not fit TRALI as deteriorating state.
4	TAD-IC	3, definite	2 red cell units	Low albumin. Rise in BP and crackles on chest examination	Multiple sclerosis, Hb68g/L	Not performed	Insufficient criteria for TACO, absent imaging
5	TAD-IC	2, probable	4 FFP, 2 cryoprecipitate	Liver disease, ascites, low albumin, pre-existing lung abnormality (collapse, ground glass shadowing)	Liver disease	Bilateral pulmonary oedema	Insufficient criteria for TACO, hypoxia likely but not reported
6	TAD-IC	1, possible	3 red cell units	Decompensated liver disease, low albumin, COPD, infection, cardiac ischaemia	GI bleed	Not performed	Absent imaging
7	TRALI type II	1, possible	13 red cell units, 12 FFP, 4 cryoprecipitate 2 pooled platelets	Decompensated liver disease, ascites, renal failure, low albumin, COVID-19, lobar pneumonia	Massive haemorrhage-traumatic arterial puncture	Bilateral pulmonary oedema	Meets TRALI type II criteria but multiple explanations. Not investigated for donor antibody in view of large number of donors

Case 17b.1: Major haemorrhage in a patient with multiple comorbidities, meeting TRALI criteria

A male patient in his 50s with decompensated liver disease, renal failure, ascites, COVID-19 and RLL pneumonia was transfused 13 red cell units, 12 FFP, 4 cryoprecipitate, and 2 platelets following a puncture of the inferior epigastric artery during ascites drainage. There was sudden development of 'very high ventilation requirements' with 'ARDS like picture' on CXR. He was mechanically ventilated for 18 days but died as result of respiratory compromise.

This case is representative of the difficulty in classifying pulmonary complications. The case met the IRC criteria for TRALI type II since there was hypoxia, bilateral chest imaging changes rapidly after transfusion and the pre-transfusion respiratory state was described as 'stable'. There were multiple other risk factors for developing ARDS even if the transfusion had not occurred. Causation was almost impossible to establish; investigating the donors for antibodies was unlikely to be helpful since there would be a high chance of finding leucocyte antibodies if over 40 random donors were investigated. Prolonged ventilation does not favour a classical antibody-mediated TRALI as the sole cause of death since antibody-mediated TRALI is normally self-limiting.

Case 17b.2: Suspected fluid overload in an outpatient transfusion

A female patient in her 50s with multiple sclerosis attended for an outpatient red cell transfusion. The reason for the Hb of 68g/L was not recorded. During the second unit of red cells, she developed severe respiratory distress, with systolic blood pressure 196mmHg, flushing, wheeze and crepitations. There was no improvement with diuretics and adrenaline. Care was not escalated because of a pre-existing resuscitation order. The case was reported as TACO, with 'death directly and solely caused by transfusion'.

The case remains strongly suggestive of fluid overload but there was insufficient clinical information to meet ISBT TACO or TRALI criteria. The reporters recognised that a TACO checklist was not part of their transfusion policy and awareness of TACO was poor. These issues were addressed following an investigation. Low albumin and low Hb were identifiable risk factors for fluid overload, but the severity of the reaction was unexpected given the pre-transfusion risks. It was not clear whether the preventative actions were commensurate with the identifiable risks and would have prevented the reaction.

Major morbidity n=12

There were 12 cases (2 TRALI, 9 TAD-C and 1 TAD-IC) associated with major morbidity as they required ICU admission or ventilation. Of these, 5 were considered to be probably related to the transfusion (imputability 2). A summary can be found in the supplementary information on the SHOT website (https://www.shotuk.org/report-summary-and-supplement-2022/). Two cases with leucocyte antibodies are detailed in the following section.

A similar picture is seen of recipients with multiple comorbidities. The case below is described since it demonstrates a specifically identifiable risk for transfusion despite classification as TAD.

Case 17b.3: Rapid transfusion of patient with megaloblastic anaemia

A female in her 30s was admitted with megaloblastic anaemia and a Hb31g/L, undetectable folate levels and low B12 levels. She was transfused three units of red cells, the second unit over 20 minutes. Desaturation was noted during the second unit and the transfusion was stopped during the third unit. The CXR showed features of fluid overload, but the case did not meet TACO criteria. The patient was admitted to ICU but made a full recovery.

This case was classified as TAD as there were insufficient features to meet TACO criteria but appears to be the classical picture of overtransfusion in megaloblastic anaemia. Patients with B12 or folate deficiency can have impaired myocardial function and may not tolerate transfusion well. Transfusion can often be avoided since the haemoglobin typically responds rapidly to haematinic replacement. There were 2 similar cases in this year's Annual SHOT Report.

Learning point

- Patients with megaloblastic anaemia are at risk of fluid overload and transfusion should be avoided if possible. If transfusion is necessary because of severe features of anaemia, a single unit or weight-adjusted red cell dosing should be given with close monitoring

TRALI and leucocyte antibody cases

In 2022, cases have been classified as TRALI using the IRC definition. In contrast to previous SHOT classifications, the presence of leucocyte antibodies plays no part in this definition. Antibodies however remain an established cause of TRALI, and one which is potentially preventable. Cases which were positive for antibodies (HLA or HNA) are therefore presented in parallel. The terminology 'plausibility' used in Table 17b.3 indicates whether it is plausible that the features of the reaction were caused by leucocyte antibodies.

Cases meeting TRALI criteria n=5

Table 17b.3: Cases meeting TRALI criteria

Case	Category	Plausibility	Products transfused	Explanatory features	Underlying disease	Antibody	Outcome
1	TRALI type II	Plausible	1 apheresis platelets	Unexplained breathlessness prior to transfusion	Neuroblastoma	Not tested	Mechanical ventilation, full recovery
2	TRALI type II	Implausible	1 red cell unit	Cardiac failure, sepsis, consolidation on CXR	Surgery for perianal abscess	Not tested	Symptoms resolved within 30 minutes
3	TRALI/TACO	Plausible	1 red cell unit	Low albumin, cardiac failure (LV assist device), positive fluid balance	GI bleed	HLA I and II	CPAP, improved after 6 hours
4	TRALI type II	Equivocal	Pooled granulocyte	Pre-existing bilateral consolidation	Neutropenic sepsis	Not tested	Increased oxygen, full recovery
5	TRALI type II	Equivocal	13 red cell units, 12 FFP, 4 cryoprecipitate 2 pooled platelets	Decompensated liver disease, ascites,renal failure, low albumin COVID-19, lobar pneumonia	Massive haemorrhage - traumatic arterial puncture	Not tested	Death possibly related to transfusion

Case 17b.4: Reaction to granulocytes fulfilling TRALI criteria

A male patient in his 40s with neutropenic sepsis and ALL developed acute breathlessness, fever, and hypoxia 6 hours after a granulocyte transfusion. Diffuse bilateral shadowing was reported on CXR. The patient made a full recovery with increased oxygen provision only.

There were 3 cases of pulmonary reactions to granulocytes reported this year. In many cases the reaction represents the therapeutic effect of granulocytes responding to underlying infection, for example with rapid development of unilateral consolidation. This case meets TRALI criteria, but the distinction seems arbitrary, and the rapid subsequent recovery would favour a therapeutic effect rather than a classical antibody-mediated TRALI reaction. Febrile and pulmonary reactions are very common after granulocyte transfusion. Investigating donors for antibodies is unlikely to be helpful in establishing causation because of the large number of donors involved, and the need to consider antibody cross-reacting with any of the donations in the pool, not only the recipient (who by definition is not likely to have circulating neutrophils).

Case 17b.5: Antibody-positive case at high risk for TACO

A male recipient in his 60s with a left ventricular assist device, renal impairment and low albumin experienced dyspnoea, wheeze, hypoxia, and an increase in temperature approximately 1 hour into transfusion of red cells for anaemia due to GI bleeding. He had also received 1L crystalloids and had a 1.2L positive fluid balance. The CXR showed bilateral pulmonary congestion and there was no initial improvement with diuretic. He was transferred to ICU and received CPAP and a furosemide infusion. He had improved after 6 hours and was transferred back to the ward the following day. HLA class I and II antibodies were found in a female donor.

The case does meet TRALI criteria, but the patient was clearly at high risk of fluid overload and had established heart failure. The relatively short period of hypoxia is not typical of an antibody-mediated TRALI. The case was classified in the IRC scheme as 'TACO and TRALI cannot be distinguished'.

Cases with leucocyte antibodies n=2

Six cases reported this year were tested for antibodies, 2 of these had donors with antibodies that matched the recipient. Both were classed as 'major morbidity'. One case, Case 17b.5 is described under TRALI above, the 2nd did not meet TRALI criteria.

Case 17b.6: Antibody-positive case which does not fit TRALI criteria

A female in her 60s who was post allogeneic transplant attended for an outpatient red cell transfusion. She had recently been started on antibiotics by her GP and was slightly breathless prior to transfusion. She became hypoxic during transfusion, developed atrial fibrillation and had a small troponin rise. There was an improvement within 2 hours following administration of diuretics, and she needed non-invasive ventilation. The chest CT scan showed peribronchial ground glass shadowing in keeping with bronchopneumonia. Subsequent investigations showed she was positive for influenza A. A female red cell donor was positive for HLA A2 and B27 which matched the recipient.

The case was classified as TAD-C since the imaging features and clinical course were not those of TRALI. The HLA antibodies were likely to be incidental; HLA class I antibodies are thought to have a weaker association with TRALI than HLA class II and HNA antibodies.

Commentary

The pattern of pulmonary complication reports is similar to previous years, with many recipients having multiple possible explanations for a respiratory deterioration. Figure 17b.2a summarises the presence of alternative factors in the cases reported. The median number of explanatory factors in this year's cases was 3. Figure 17b.2b shows that many patients had pre-existing cardio-respiratory disturbance identifiable on pre-transfusion observations or had pre-existing features of fluid overload. Control data for general transfusion recipients would be needed to investigate whether any of these factors are risk factors for pulmonary deterioration, but as a general principle the benefits of transfusion should be carefully considered against the risks when transfusing unwell patients.

Features on imaging and features of the reaction itself are summarised in Figures 17b.2c and 17b.2d. Unsurprisingly, increased respiratory rate and fall in oxygen saturation were present in the majority of cases, however it is notable that there was an improvement with diuretics in a majority of cases where it was reported, supporting the idea that fluid overload is a contributory factor in many cases which do not satisfy formal TACO criteria.

There is clearly an unmet need for explanation, as 38% of cases were referred as 'likely' or 'certain' that 'the blood product caused the reaction'. Classification appears difficult as there are many transfers between categories. Classifying cases as TAD, and particularly TAD-IC arguably does not meet this need. Table 17b.4 shows the proportion of reports which supplied information necessary to provide a TRALI classification or which could help to support a TACO classification, showing that these data are often difficult for reporters to supply. Use of a structured TACO investigation tool as suggested in previous Annual SHOT Reports may help improve classification accuracy (Narayan et al. 2021).

Classification of reactions is not an end, but a means to aid understanding. There does not seem to be any easily apparent difference either in terms of underlying factors or reaction features between cases classified as TRALI or TAD. The distinction between TACO, TRALI and TAD often seems dependant on the interpretation of the wording of the IRC, rather than reflecting genuine differences in pathophysiology. Given that it seems likely that many of these cases are multifactorial, it is perhaps unrealistic to expect that fitting cases into a small number of categories provides sufficient information capacity to capture the important features of interest.

The key aim of haemovigilance remains one of prevention, and the approach of 'preventing what we know can be prevented' still applies. The number of antibody-associated TRALI cases remains very

low and there are even fewer cases which unambiguously seem to be transfusion reactions. Fluid overload is the other well-defined mechanism which is potentially preventable, and there is still work to do in identifying at risk cases. Only 33% of cases had a TACO checklist performed prior to transfusion (Table 17b.5) despite previous SHOT recommendations. Perhaps more concerning are cases where the checklist did not identify a patient as at risk despite gross features of fluid overload, suggesting the checklist may simply be being completed as a tick box exercise in some cases. Further work is required to establish whether the presence of multiple risk factors, in particular fever or inflammation, should warrant additional intervention to prevent fluid overload.

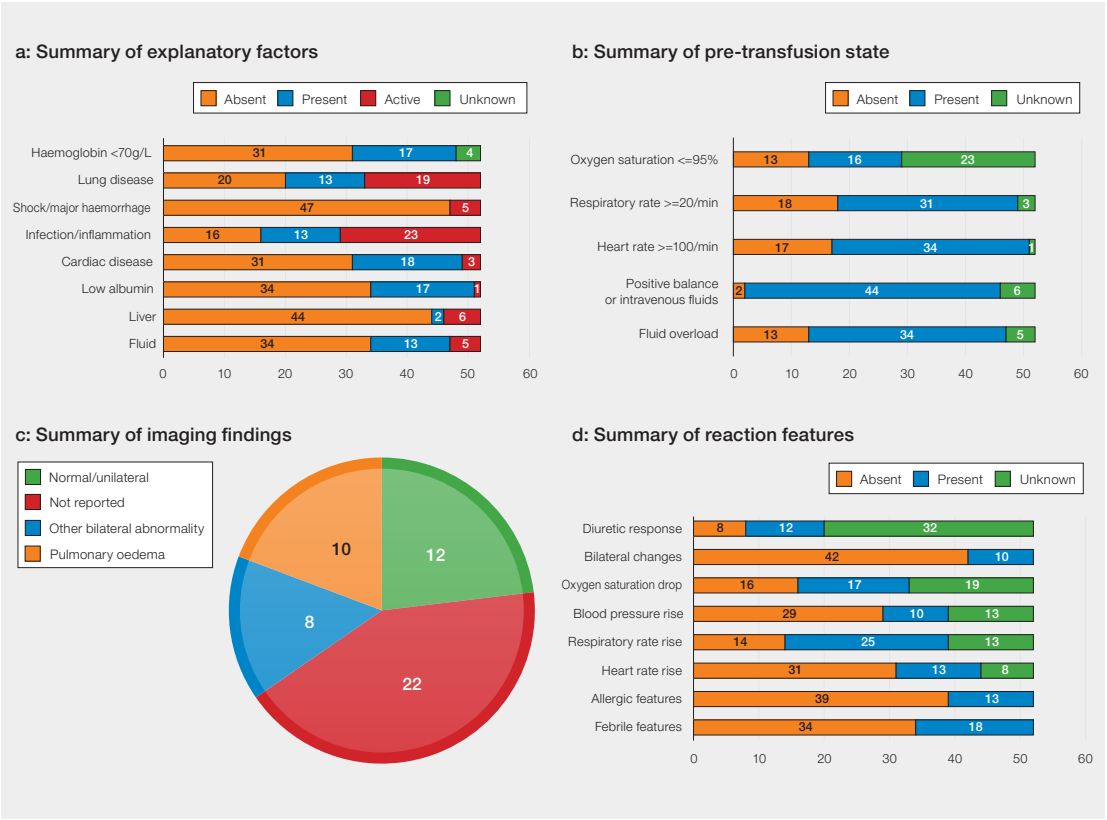


Figure 17b.2: Clinical features of pulmonary cases

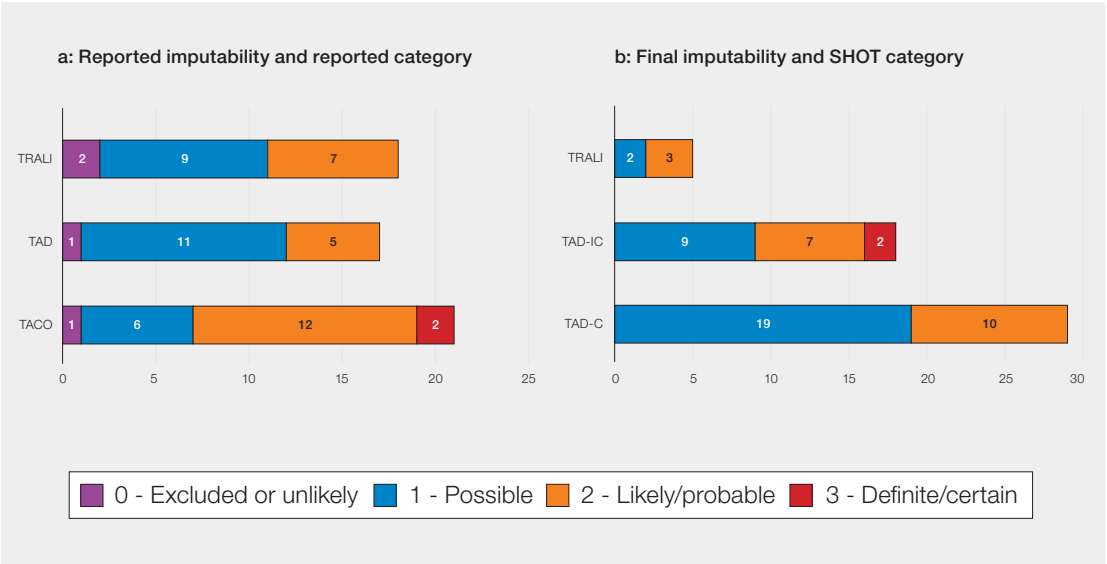


Figure 17b.3: Imputability of pulmonary cases

Table 17b.4: Submission rates for criteria necessary for classification

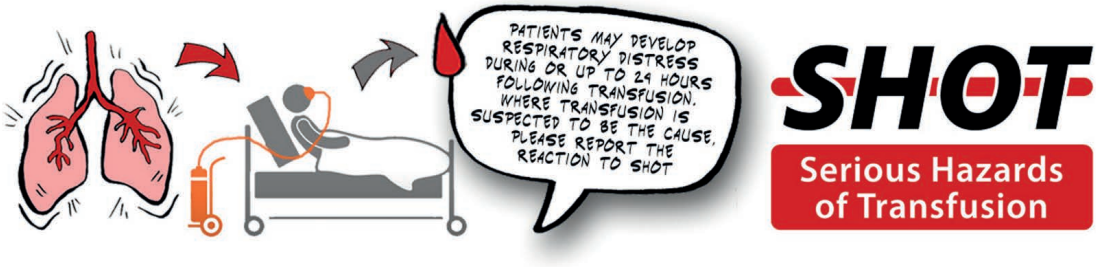
Necessary for classification	% responses submitted
Respiratory state	34%
Timing	100%
Post-transfusion SaO2	77%
Post-transfusion CXR	52%
Helpful for classification	
BNP	3%
Fluid balance	24%
Post-transfusion BP	82%
ECG	13%
Echo	8%
Name, dose and timing of diuretic	50%
Volume of diuresis	48%
Effect on respiratory systems	50%

Table 17b.5: Concordance with previous SHOT recommendations

SHOT recommendations	% reported	% 'yes'
TACO checklist	92%	33%
Risks identified	32%	40%
TACO investigation	89%	20%
Features identified	11%	0%

Conclusion

Pulmonary deterioration following transfusion remains common. The implications of the recently introduced international definitions of TRALI and TACO are still under investigation, and it appears difficult for reporters to supply information necessary to classify cases using these definitions. Preventable factors, particularly risk factors for fluid overload, can often be identified and offer opportunities for further preventative interventions.



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