

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

17b

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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/>).

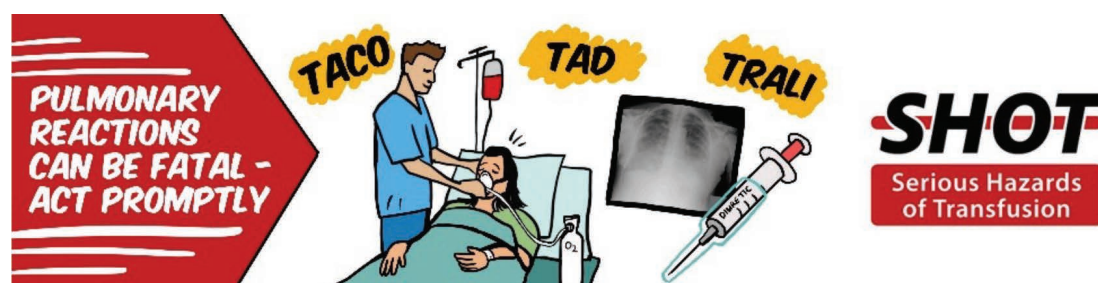


Table 17b.1
International classification of pulmonary complications

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

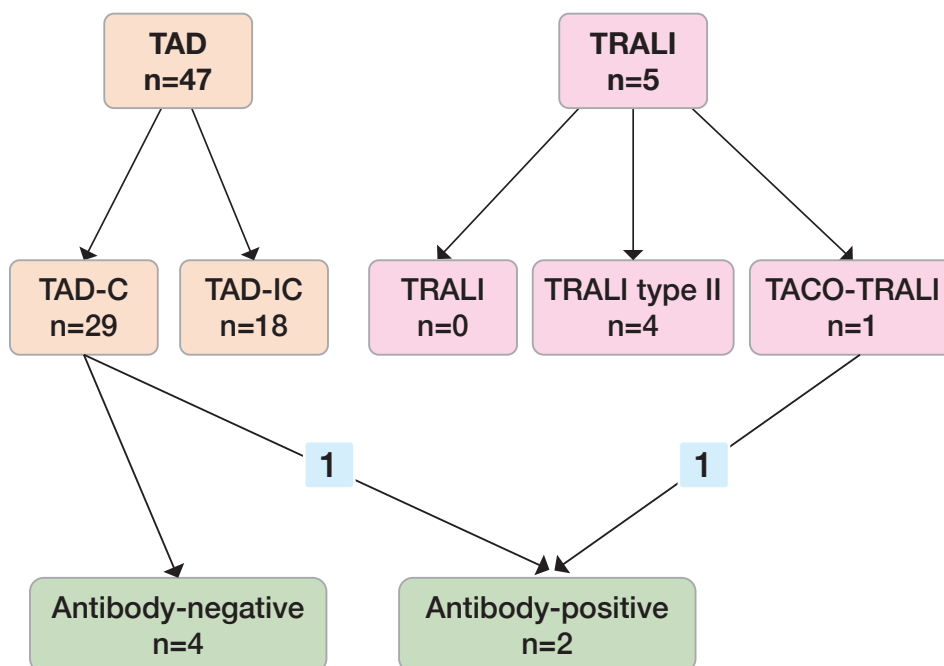
*Some definitions of TACO allow onset up to 12 hours posttransfusion. However, our current recommendation is that 6 hours be used. If pulmonary edema occurs greater than 6 hours following the transfusion and is clinically suspicious for a temporal association with transfusion, the case should be classified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

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

Table 17b.2:
Summary of pulmonary complication deaths

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

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

Table 17b.3:
Cases meeting
TRALI criteria

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.

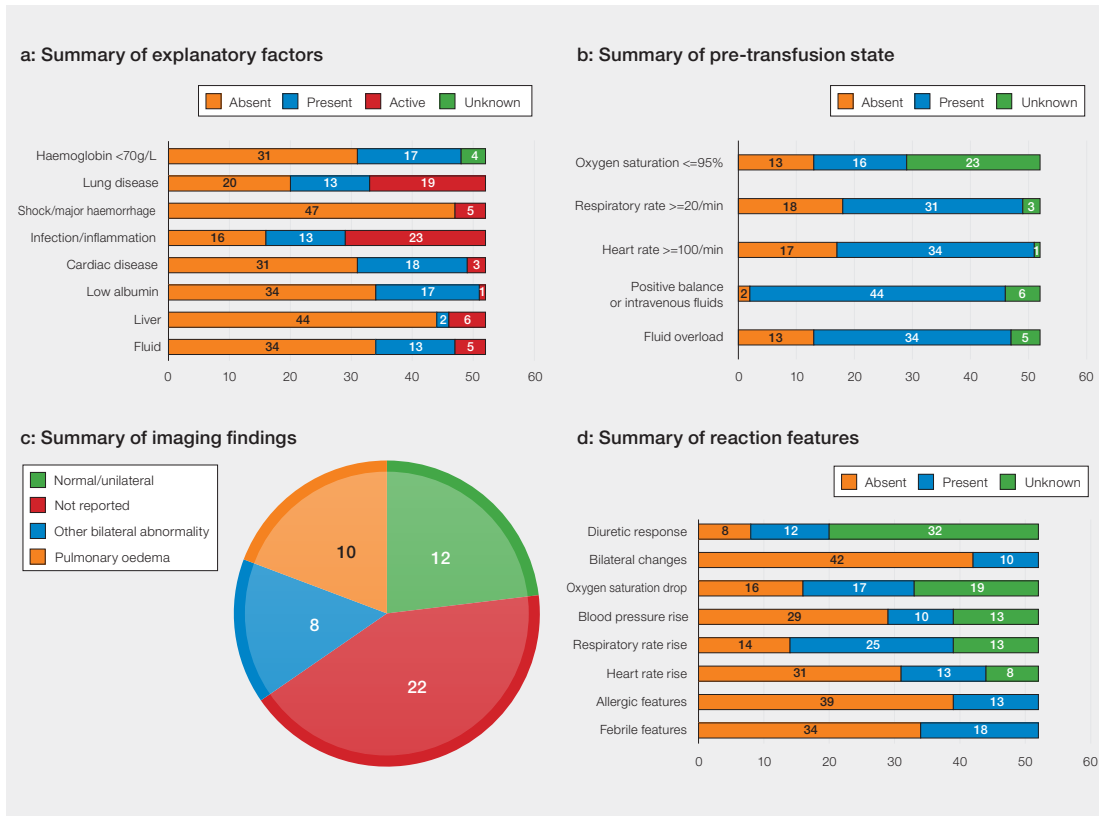


Figure 17b.2: Clinical features of pulmonary cases

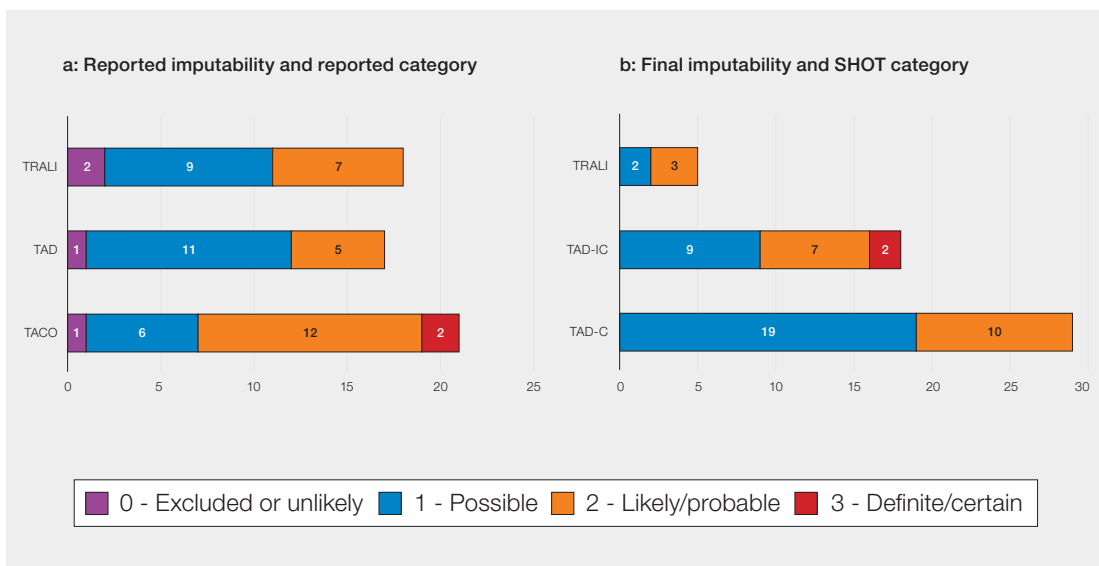


Figure 17b.3: Imputability of pulmonary cases

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

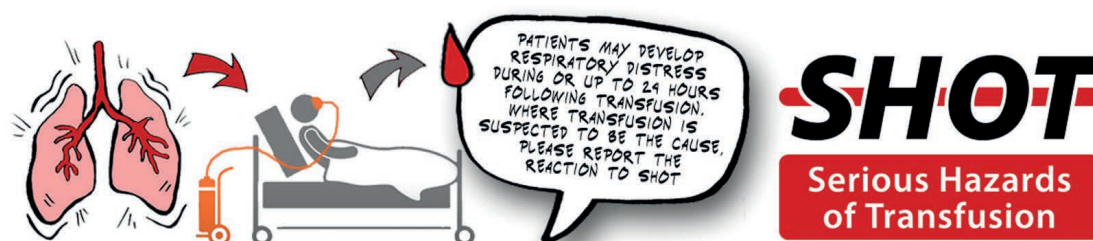
Necessary for classification	% responses submitted
Respiratory state	34%
Timing	100%
Post-transfusion SaO ₂	77%
Post-transfusion CXR	52%
Helpful for classification	
BNP	3%
Fluid balance	24%
Post-transfusion BP	82%
ECG	13%
Echo	8%
Name, dose and timing of diuretic	50%
Volume of diuresis	48%
Effect on 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.



References

Narayan S (Ed), Poles D, et al. on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2020 Annual SHOT Report (2021). <https://www.shotuk.org/shot-reports/> [accessed 27 April 2023].

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