17 Pulmonary Complications n=161

Author: Tom Latham

Abbreviations used in this chapter

ISBT	International Society of Blood Transfusion	**TAD**	Transfusion-associated dyspnoea
RC	Revised consensus (TRALI criteria)	**TRALI**	Transfusion-related acute lung injury
TACO	Transfusion-associated circulatory overload	**WEG**	Working expert group

Key SHOT messages

- Classification and nomenclature of pulmonary complications are evolving. When using these terms, staff need to be precise in clarifying what is meant when the terminology is 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

Classification of pulmonary reactions: clear reflection or confusing rabbit hole?

> 'When I use a word,' Humpty Dumpty said, in rather a scornful tone, 'it means just what I choose it to mean-neither more nor less.' 'The question is,' said Alice, 'whether you can make words mean so many different things.' 'The question is,' said Humpty Dumpty, 'which is to be master-that's all. – Lewis Carroll

The overview chapter this year focuses on current challenges and controversies in classifying pulmonary complications of transfusion and discusses the rationale for the decision to consolidate non-TACO pulmonary complication cases into a single chapter in the Annual SHOT Report.

Pulmonary complications of transfusion contribute significantly to transfusion-related morbidity and mortality. In this year's Annual SHOT Report, there were 18 deaths in patients who were reported to have pulmonary complications thought to be at least possibly due to the transfusion. Gaining a better understanding of why some patients develop respiratory deterioration after transfusion is therefore a priority for transfusion safety. Patients with pulmonary complications post transfusion are often complex with multiple pathologies being present simultaneously, and it is difficult to disentangle the contribution of the underlying disease, the fluid load of the transfusion, and biologically active mediators in the transfusion (including leukocyte antibodies but with the possibility of other undiscovered agents).

Organisation into categories is a natural approach to understanding complex phenomena, aiming to reduce cognitive load by grouping together cases with features of interest in common and to provide a concise terminology for discourse and record keeping. The generally accepted approach for pulmonary reactions is to classify as either TACO, TRALI or TAD. In recent years there has been much work internationally to standardise definitions. The ISBT TACO criteria have undergone international validation and have been found to be useful, perhaps underpinned by the idea that fluid overload is a pathologically defined concept even though clinical recognition may be challenging. The RC TRALI criteria have been more controversial and yet to be validated. It remains to be seen whether they will be adopted

internationally, but it does not appear that the goal of reaching a consensus of what is understood by 'TRALI' has yet been achieved. TAD remains a diagnosis of exclusion for cases which do not meet TACO or TRALI criteria, and thus does not represent a pathologically defined entity. A classification as TAD is dependent on the definition chosen for TRALI and TACO and whether there is sufficient clinical information available to apply the definitions.

All categorisations are to some extent artificial constructs, and this is particularly evident for pulmonary complications, where there is no naturally apparent dividing line and no gold standard diagnostic investigation. The usefulness of categorisations to a user depends on whether they preserve the features which the user is interested in. However, different users have different needs. For example, *haemovigilance practitioners* need to identify trends which could identify emerging safety concerns and monitor the effectiveness of preventative recommendations. *Blood Services* need to identify concerns with blood products and to identify donors who may need deferral in order to preserve safety of the blood supply. *Clinicians* need simple indicators based on clinically measurable or observable features to identify prevention and treatment interventions. *Researchers* need objective and precisely defined criteria so that work is reproducible and which either maximises the probability of including phenomena of interest or minimises the probability of including cases where the object of study is not present. There is a conflict between a precisely defined classification losing information which is of interest to a particular group, or a more conceptual categorisation leading to unclear communication because of differences of interpretation.

In this year's Annual SHOT Report, the pulmonary WEG have attempted to escape between the horns of the dilemma by consolidating pulmonary cases which do not meet ISBT TACO criteria into a single chapter and accepting that it is probably most helpful to view a complex object from multiple angles rather than to force cases into mutually exclusive classes in a single classification system. The approach is to acknowledge that all factors that could have contributed to the reaction probably interact rather than trying to work out which was the most important factor. Classification of cases using the RC TRALI schema will be important for international comparison. There does not seem to be a clear separation between cases classified using this schema but perhaps this will become clearer with larger numbers of cases either through international collaboration or historical review of cases. The number of cases with leukocyte antibodies remains low, with only 1 case this year, but it remains important to continue to monitor leukocyte antibodies to monitor the effectiveness of TRALI prevention strategies.

The technical details of classification can sometimes seem arbitrary and of little interest to non-specialists. By consolidating cases and returning the focus to identifying preventable factors, it is hoped that it will be easier to see the bigger picture. One message does emerge from the new approach, which illustrates the benefit of using parallel approaches. The strict application of ISBT TACO criteria ensures that fluid overload was present in cases included in the TACO chapter with high confidence. The recurring conclusion from this year and previous reports is that recognition and prevention of fluid overload is often incomplete. Complementary to this conclusion is the finding from the non-TACO chapter that risk factors or features suggesting fluid overload were present in over half of the remaining pulmonary cases, and therefore preventative messages could potentially be extended more widely. Cases may often be difficult to classify because of missing information or subjectivity of interpreting definitions, but preventative actions may nevertheless be identifiable.

TACO is still the main cause of death from transfusion and much work is being done on prevention. This should be extended to all pulmonary complications. Use of TACO checklists and structured investigation of incidents remains the main focus of prevention, although there is further work needed on assessing whether mitigating actions were sufficient. Only 12/40 cases where a checklist was completed had all mitigating actions performed. 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, and identify which reactions to investigate for leukocyte antibodies.

17a Transfusion-Associated Circulatory Overload (TACO) n=131

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.2 for details of required and additional criteria for a surveillance diagnosis

Abbreviations used in this chapter

BSH	British Society for Haematology	**NCA**	National comparative audit
CT	Computed tomography	**NT-pro BNP**	N-terminal-pro B-type natriuretic peptide
Hb	Haemoglobin	**TACO**	Transfusion-associated circulatory overload
HDU	High dependency unit	**TRALI**	Transfusion-related acute lung injury
WEG	Working expert group		

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

Recommendations

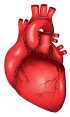
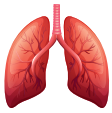
- A formal pre-transfusion risk assessment for TACO should be undertaken whenever possible for all patients receiving blood transfusion (especially if older than 50 years or weighing less than 50kg) and appropriate mitigating actions taken
- Use weight-adjusted red cell dosing to guide the appropriate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

Action: All staff authorising transfusion

- A structured review and incident investigation should be undertaken for every case of TACO to optimise organisational and individual patient-safety measures

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

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

Introduction

The traditional hypothesis for the pathophysiology of TACO is increased hydrostatic pressure in the pulmonary capillaries which surround the alveoli which results in a transudate and increased interstitial pressure. This is forced into the alveoli causing pulmonary oedema which compromises normal lung function, leading to hypoxia. Other mechanisms have been proposed. These include a TRALI-like response where inflammatory cells disrupt the endothelial barrier resulting in the passage of transudate and exudate. The interstitium becomes widened and epithelial layer of the alveolus is disrupted allowing the passage of inflammatory cells and exudate resulting in pulmonary oedema. Mechanical destruction (barotrauma) may cause increased permeability and dysfunction of the capillary endothelial layer. The increased intra-capillary pressure disrupts the endothelial glycocalyx of the capillary allowing transudate and exudate to penetrate the epithelial barrier of the alveolus. Storage lesions such as the presence of microparticles or cell-free haemoglobin may induce vasoconstriction of the capillary resulting in transudate and exudate which disrupts the epithelial barrier of the alveolus (Bosboom et al. 2019). The emerging complexity of the mechanism of transfusion-related pulmonary oedema creates significant difficulties for definitive categorisation for haemovigilance purposes, and increasingly strengthens the hypothesis that pulmonary complications of transfusion may not be mutually exclusive.

Although the pathophysiology of TACO is not fully understood, the evolving understanding of risk factors for TACO and the development of tools to mitigate risks has been a significant advance in recent years. This chapter describes the demographics of patients reported to have TACO, haemovigilance categorisation, and the adoption of TACO risk-reduction strategies, and highlights areas requiring further focus.

Deaths related to transfusion n=11

TACO resulted in the death of a patient in 11 reported cases. With exception of 1 case the imputability level was low (possibly related to transfusion). There were fewer deaths compared to the previous reporting year (18 in 2020) which was significantly affected by COVID-19. This was likely to have been influenced by the severity of underlying illness of those with COVID-19 and as such were more likely to die.

Major morbidity n=23

There were a similar number of cases that resulted in major morbidity compared to the previous reporting year (25 in 2020). This may reflect a continued increased number of patients with severe respiratory comorbid disease due to COVID-19 but fewer that resulted in the patient's death, as COVID-19 related deaths began to fall. TACO remains the leading cause of transfusion-related combined mortality and major morbidity.

Table 17a.1: Demographic overview of cases

Demographic	Number of reports
Deaths (imputability 3)	0
Deaths (imputability 2)	1
Deaths (imputability 1)	10
Major morbidity outcome	23
Age	Range: 2 months-97 years (five age under 18 years) Median: 74.5 years
Gender	76 female: 55 male
Body weight (adults)	Female (n=38): average 65.2kg (38.0-118kg) Male (n=33): average 75.2kg (51.0-125.6kg)
Top four medical specialties where TACO was reported	Acute medicine 16.0% (21), haematology 14.5% (19), emergency medicine 12.2% (16), general medicine 10.7% (14)
Bleeding patients (indication code R1 or 'massive bleeding' indicated	28
Non-bleeding patients (other indication codes or not stated)	103

Commentary

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 5 cases in the under-18 age group, (age 2 months to 16 years). TACO was reported more in adult female patients compared to male. Weight was provided in 38 adult female cases, with an average of 65.2kg (38.0-118kg). Weight was provided in 33 adult male cases, with an average of 75.2kg (51.0-125.6kg). 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 delivering TACO education and mitigation plans.

Analysis by definition criteria

Cases reported in 2021 were assessed using the surveillance criteria in Table 17a.2. It should be noted that the criteria are for the purposes of reporting and surveillance and do not constitute a clinical diagnosis for the purpose of real-time interventions for the medical management of a patient presenting with respiratory compromise during or following transfusion. However, the surveillance criteria should help promote recognition of TACO.

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

Figure 17a.2 shows the number of accepted TACO cases versus the number of TACO surveillance criteria met. The majority of cases met four criteria. Only 2 cases met all five criteria where a pre- and post-transfusion BNP sample had been taken. This is a useful biomarker to demonstrate left atrial hypertension. In previous years, cases were accepted that did not fully meet the criteria due to missing data but were otherwise clinically compelling cases. A decision has now been taken to not include these cases and instead transfer them to the non-TACO category for separate analysis.

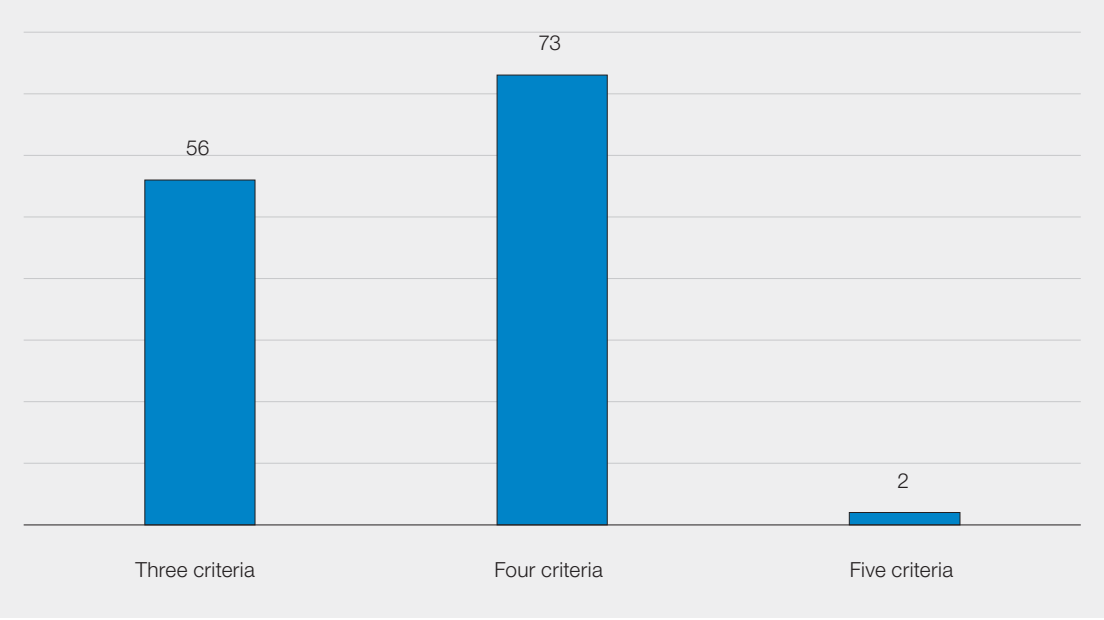
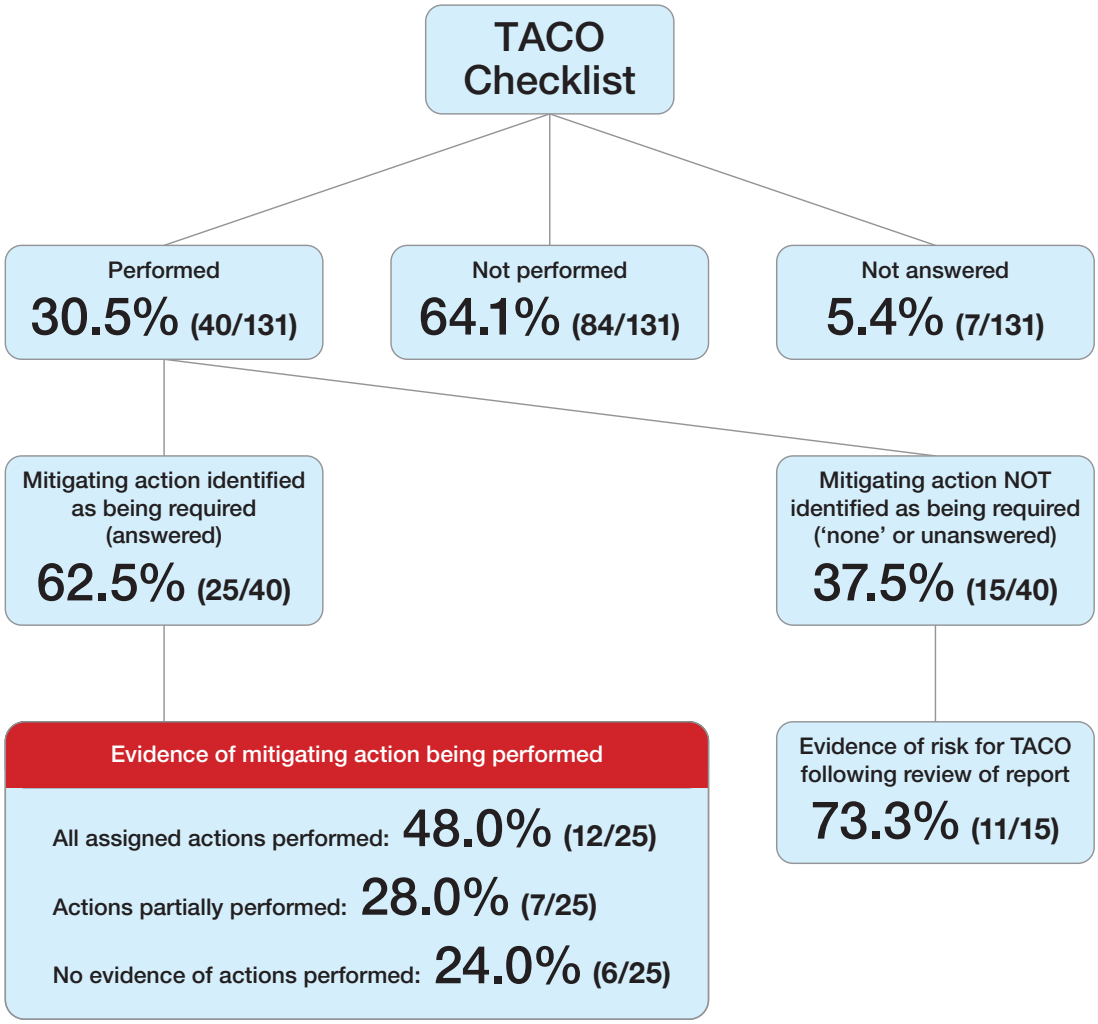


Figure 17a.2: Number of surveillance criteria versus number of accepted TACO cases

Use of the TACO checklist

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.3.

Figure 17a.3: Use of the checklist to identify patients at risk of TACO and implementation of mitigating actions



TACO=transfusion-associated circulatory overload

The TACO checklist was reported to have been used in only 40/131 (30.5%) 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 25/40 (62.5%) this demonstrated the need for a mitigating action and in most cases appropriate actions were taken. There were 6 cases where assigned actions had not been performed and 7 where the actions were only partially complete. Where a TACO checklist was performed and it was determined a mitigating action was not required, a review of these reports showed that 11/15 (73.3%) 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 it and help make safe transfusion decisions.

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

The recommendation for weight-adjusted red cell dosing with tools to identify inappropriate transfusion for non-bleeding patients was introduced in the 2017 Annual SHOT Report (Bolton-Maggs et al. 2018). Analysis of the 2021 data shows that this is not sufficiently implemented in practice and is contributing to overtransfusion in some reported cases of TACO. There were 20 cases involving red cell transfusions that reported a body weight, a pre- and post-transfusion Hb level and the number of units transfused. In 3/20 (15.0%) of cases transfusion was not required because the Hb was already within the target range. There were 2/20 (10.0%) cases that received more than the calculated weight-adjusted dose, and in 3/20 (15.0%) cases, the post-transfusion Hb target was exceeded.

Case 17a.1: Omitted TACO risk assessment led to overtransfusion and TACO, with no structured investigation performed

*A male patient in his 70's weighing **64kg** was admitted to a medical ward with **severe symptomatic microcytic hypochromic anaemia (Hb 47g/L).** His pre-transfusion CT scan showed some pulmonary fibrosis and a small pleural effusion. He had **severe left ventricular systolic dysfunction**, **renal impairment**, **peripheral oedema** and was on a **regular diuretic**. He was initially transfused uneventfully with two units of red cells. A TACO risk assessment was not performed and a fluid balance chart was not in place. His post-transfusion Hb was 65g/L. He was then given a third unit of red cells. There were no signs of active bleeding. He became wheezy, hypertensive, tachycardic, pyrexial and had rigors. His oxygen saturations reduced to 75% and he had peripheral pitting oedema. His post-transfusion chest X-ray showed consolidation thought to be caused by aspiration pneumonia and new bilateral infiltrates consistent with pulmonary oedema. He received oxygen via continuous positive airway pressure, a diuretic, hydrocortisone, bronchodilator and antibiotics. He was transferred to HDU and later recovered. The local procedural review identified single unit with review and not transfusing blood for iron deficiency as preventative actions.*

This patient had multiple risks for TACO (in **bold** above). A TACO risk assessment/checklist was not performed but would have identified these, and there were no reported mitigations put in place. A single unit red cell transfusion followed by intravenous iron would have sufficed to treat this patient's severe symptomatic anaemia. Three units of red cells was excessive in a relatively low weight patient with no active bleeding. TACO was almost inevitable in this scenario. Although a local review took place it did not identify all strategies to avoid TACO. The TACO structured investigation tool (see recommended resources) would have also highlighted the need for single unit transfusion and review, weight-adjusted red cell dosing, fluid balance chart, increased measurement of oxygen saturation, a prophylactic diuretic in addition to his regular medication (if not contraindicated). These measures would have helped mitigate the risk for this transfusion episode and help in planning future transfusions. It also represents an opportunity to improve practice and reduce risk for all future patients.

Learning points

- Excessive volume of red cell transfusion to meet a target Hb level remains a significant factor in cases of TACO, in non-bleeding patients. This can be minimised by weight-adjusted red cell dosing, and medical management of anaemia where possible. The calculation below helps estimate the volume of red cells required to meet the target Hb (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)

- 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 incident investigation allows implementation of effective corrective and preventative actions

Conclusion

The continued adoption of the TACO checklist is encouraging though analysis of the data shows it is still under-utilised. The data suggests that there is 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. The TACO structured investigation tool was launched last year 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

and what gaps and preventative actions were identified. This will inform the degree to which it is being adopted and will also provide important data regarding the implementation of risk-reduction measures.

Recommended resources

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

TACO Incident Investigation Guidance Tool

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/

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Pulmonary Complications of Transfusion: Non-TACO (n=30)

17b

Authors: Tom Latham and Shruthi Narayan

Acknowledgements: All members of the pulmonary WEG

Definition:

Cases where there was respiratory deterioration temporally related to transfusion which may not be due to the patient's condition and which do not meet SHOT surveillance criteria for TACO.

Abbreviations used in this chapter

AF	Atrial fibrillation
ARDS	Acute respiratory distress syndrome
ATD	Adult therapeutic dose
ATRA	All-trans-retinoic acid
BNP	B-type natriuretic peptide
CCU	Critical care unit
CLL	Chronic lymphocytic leukaemia
COPD	Chronic obstructive pulmonary disease
CXR	Chest X-ray
FAHR	Febrile, allergic and hypotensive reactions
FFP	Fresh frozen plasma
GI	Gastrointestinal
Hb	Haemoglobin
HDU	High dependency unit
ISBT	International Society of Blood Transfusion
ICU	Intensive care unit
IV	Intravenous
RC	Revised consensus (TRALI criteria)
TACO	Transfusion-associated circulatory overload
TAD	Transfusion-associated dyspnoea
TRALI	Transfusion-related acute lung injury
UCT	Uncommon complications of transfusion
WEG	Working expert group

Key SHOT message

- The understanding and nomenclature of pulmonary complications is evolving. Cases submitted are reviewed by the SHOT pulmonary WEG (which includes pulmonologists) to assess the reports for imputability, causality and categorisation.
- Regardless of final categorisation, preventable risk factors for established causes such as fluid overload are identifiable in many cases

Recommendations

- 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

- A structured incident review should be undertaken for all cases of respiratory deterioration after transfusion. This will ensure optimum organisational and individual patient safety measures are in place to protect patients from TACO as far as possible

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

Introduction

As noted in the overview chapter, all pulmonary complication reports which do not meet the ISBT TACO criteria have been consolidated into a single chapter this year. Categorisation of pulmonary complications following transfusion remains a complex area with ongoing international collaboration for validation of definitions and data collection. Often, the interpretation of the cases submitted is limited by the available clinical information including results of relevant investigations. Transfers of cases submitted between categories (FAHR, TACO, TRALI, UCT etc.) reflect the challenges involved in interpreting these real-life cases. By consolidating cases together, it is hoped that preventable factors can be identified regardless of the final classification, which will always to some extent be arbitrary.

The SHOT pulmonary WEG continues to attempt applying the new proposed RC TRALI definitions to those cases reported under TAD to see if it helps categorise these reactions (Table 17b.1). As there are have been few cases with positive leukocyte antibodies for many years, these cases have been reported as 'antibody-positive' in addition to the RC classification. There was 1 case classified as TRALI type II with risk factors for ARDS and 1 case with worsening respiratory status in the 12 hours prior to transfusion, categorised as transfused ARDS.

Cases classified as TAD represent cases which do not fit TRALI or TACO criteria, either because clinical features do not meet criteria or because there was insufficient information to classify. As in the previous years, 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 insufficient clinical information).

Figure 17b.1 summarises the categorisation and transfers of pulmonary complication cases submitted this year.

Table 17b.1 Summary of classification using the revised consensus criteria

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

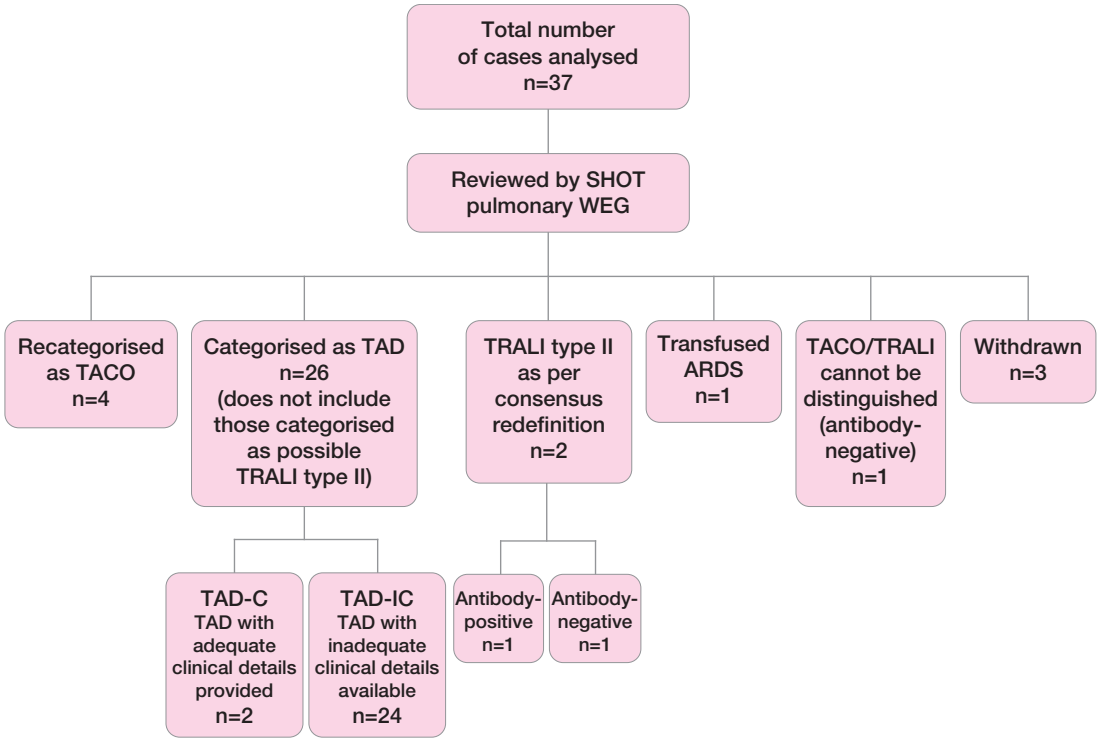


Figure 17b.1: Summary of transfers and categorisation of cases included under TAD

WEG=working expert group; TACO=transfusion-associated circulatory overload; TAD=transfusion-associated dyspnoea; TRALI=transfusion-related acute lung injury; ARDS=acute respiratory distress syndrome

Most cases included as TAD had incomplete clinical and laboratory information (TAD-IC). This could either be due to lack of availability or accessibility of the information when the reporter was submitting the case or that all the relevant investigations were not done as part of patient management.

Many cases had identifiable factors which could explain the respiratory deterioration. These are summarised in Figure 17b.2.

There was only 1 case of antibody-associated TRALI, which was considered as probably contributing to the patient's death.

There were 3 patients with COVID-19 pneumonitis. Interpretation of the clinical and radiological picture in patients with COVID-19 pneumonia who developed worsening respiratory status <24 hours after administration of any blood component continues to be a challenge. 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). Imputablity has been attributed as being 'possible' in these cases.

Figure 17b.2: Summary of possible explanatory factors for non-TACO pulmonary complications

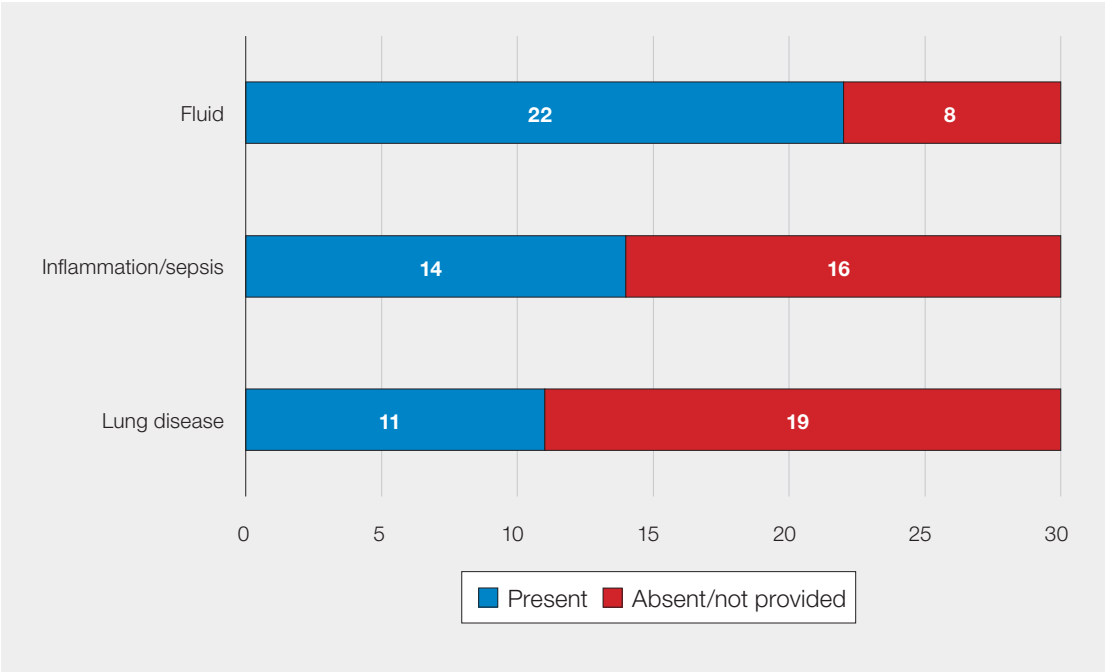
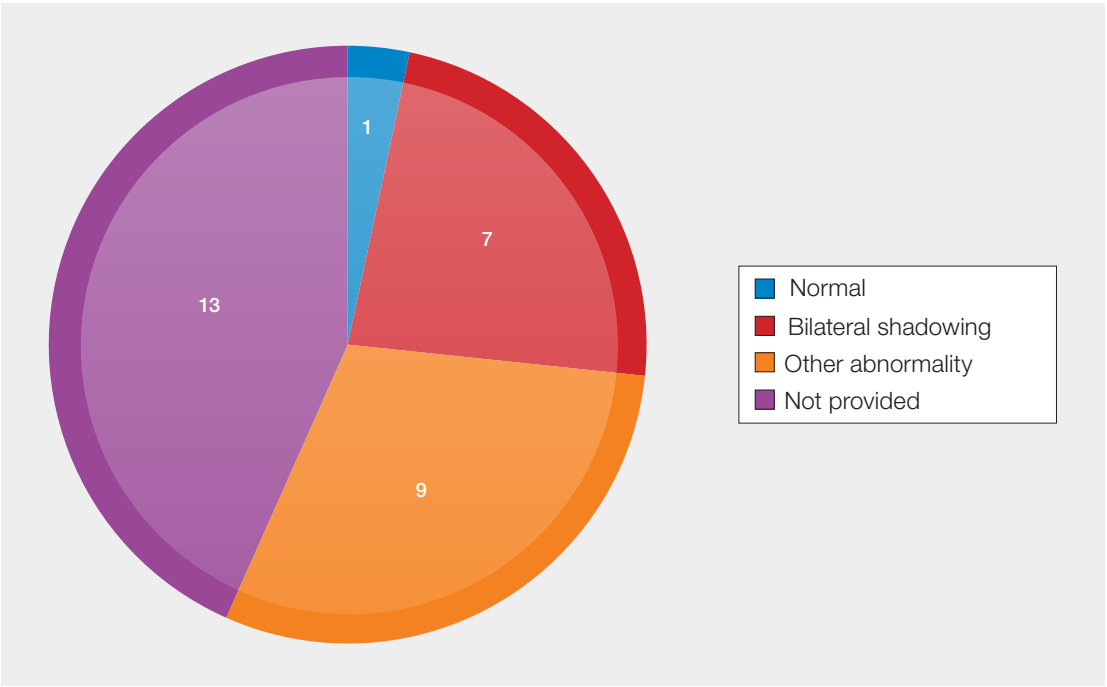


Figure 17b.3: Summary of imaging findings for non-TACO pulmonary complications



Deaths related to transfusion n=7

There were 7 transfusion-related deaths, 2 were categorised as having an imputability of probable, and the other 5 were all possibly related to the transfusion.

Pulmonary complications contribute significantly to transfusion-related deaths reported in the UK. Table 17b.2 summarises all pulmonary complication deaths this year. In particular, the table summarises features (pre-existing patient factors, aspects of the transfusion and features of the reaction) which could support fluid or the underlying disease causing a respiratory deterioration. The table also notes the challenges in applying definitions.

It is notable that in all cases where death occurred, patients had some risk factors for, or features of, fluid overload. In 3 cases, the patients had advanced liver disease. Pulmonary complications are common

in liver disease, with multiple underlying mechanisms, many of which, including fluid overload, may be exacerbated by transfusion.

A full narrative description of all cases which caused death can be found in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/).

Table 17b.2: Summary of pulmonary complication deaths

Case	Category	Imputability	Blood components transfused	Feature or risks for fluid overload	Underlying disease	Imaging	Difficulty classifying
1	TACO/ TRALI antibody-negative	2	3 red cell units	Rise in BNP, heart failure on 200mg frusemide	Autoimmune haemolysis	Bilateral CXR changes	Imputability of heart disease, between RC and SHOT class
2	TRALI type II antibody-positive	2	2 red cell units, 4 FFP, 1 ATD platelet	Large volume transfusion over 3 hours	Myelodysplasia, sepsis	Bilateral CXR changes	Imputability of antibody
3	TRALI type II	1	1 red cell unit	Cirrhosis, anaemia Hb 47g/L	Cirrhosis, anaemia Hb 47g/L	Bilateral pulmonary oedema, effusions	Difference between SHOT and RC class
4	TAD-IC	1	1 red cell unit	History of AF, heart failure, cirrhosis	Cirrhosis, COPD	Perhilar consolidation	Does not fit TRALI/ TACO
5	TAD-IC	1	3 FFP	Alcoholic liver disease	COVID-19, GI bleed	Not supplied	Limited clinical detail
6	TAD-IC	1	1 red cell unit	Decompensated heart failure anaemia Hb 79g/L	COVID-19	Not supplied	Limited clinical detail
7	TAD-IC	1	1 red cell unit	Renal impairment, cardiac impairment, low albumin, positive fluid balance	GI bleed	Not supplied	Limited clinical detail

Major morbidity n=2

Both cases included here are those where patients needed admission to HDU/ICU/CCU following respiratory deterioration post transfusion. They subsequently recovered.

Table 17b.3: Summary of pulmonary complication major morbidity cases

Case	Category	Imputability	Blood components transfused	Features or risks for fluid overload	Underlying disease	Imaging	Difficulty classifying
1	TAD-C	1	2 ATD platelets, 1 red cell unit	Cardiac and renal impairment, IV fluid, response to diuretic	Lymphoma, sepsis	Unilateral consolidation	Does not meet TACO/ TRALI criteria
2	TAD-C	1	4 red cell units		GI bleed, CLL, COVID-19	Bilateral pulmonary oedema	Antibody-negative, definition of 'stable respiratory state'

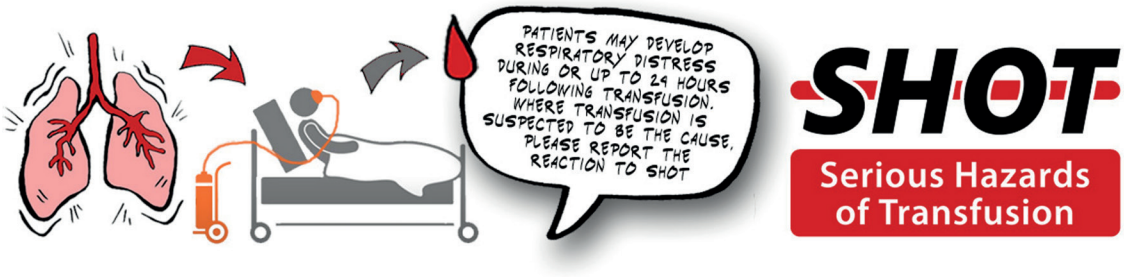
Learning point

- All cases with post-transfusion pulmonary complications must be reported to the Blood Service so that further investigation can be done as appropriate to help classify these cases. Regardless of final classification, many cases have identifiable risk factors which may have compromised the ability of the patient to tolerate the transfusion

Conclusion

As illustrated in the cases included here, most patients with pulmonary complications are very unwell with multiple ongoing issues and it is often difficult to establish whether the transfusion contributed to the deterioration or whether the deterioration was coincidental. Consolidation of cases into one chapter and incorporating the RC TRALI criteria has led to a proliferation of classes, which will be helpful for international comparison but there is not always a clear dividing line between cases assigned to different classifications.

There is still much work that needs to be done to understand pulmonary complications, and identify common themes which will inform future preventative and management strategies. Some of the uncertainty revolves around whether there may be undiscovered mediators in the transfusion which contributed to the reaction, which will always be impossible to rule out. What is apparent however is that there are often identifiable features, particularly for fluid overload that could indicate patients at higher risk of transfusion. These factors are identifiable across categories and it is probably more helpful to acknowledge that all factors coexist and interact rather than to make subjective decisions about which was the most important in order to assign cases to a single category. It is hoped that consolidating cases in to a single chapter will help to assess pulmonary complication cases holistically, and a retrospective review of cases is planned for this year.



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