18 Pulmonary Complications

Author: Paula Bolton-Maggs

Pulmonary complications remain a serious outcome of transfusion, particularly for elderly patients with comorbidity. The distinction between the three categories, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and transfusion-associated dyspnoea (TAD) remains fluid, as demonstrated by the number of reports that were moved between these categories. Ten cases were moved from TACO to TAD, 4 from TRALI to TAD, 2 from TAD to TACO and 1 from TRALI to TACO. An international group, including representatives from SHOT, the International Society of Blood Transfusion (ISBT), the International Haemovigilance Network (IHN) and the American Association of Blood Banks (AABB), has continued to review reporting criteria for TACO. A revised definition of these has progressed with validation studies, and these were reviewed at a 1-day meeting in November 2017. The pathophysiology of the pulmonary complications of transfusion is not well understood. In parallel with this, another group is reviewing the definition of TRALI. A workshop is planned for autumn 2018 to review the state of knowledge of TRALI, TACO and TAD accepting that there are gaps in knowledge and overlap between these three entities. There is great interest in the role of the glycocalyx (Brettner et al. 2017). Other relevant references: (Force et al. 2012, Juffermans and Vlaar 2017, Morsing et al. 2018, Toy et al. 2016).

The refined SHOT definitions for TRALI and TACO have resulted in an increase of cases moved to TAD. Reporters are strongly encouraged to keep notifying cases of respiratory distress even when it is not clear to which category these belong, but also to record as much detail as possible. Reporting of dyspnoea in the febrile, allergic and hypotensive reactions (FAHR) category triggers additional questions which request information about fluids, whether there is a history of lung, renal or cardiac disease together with other factors which may help to understand the pathology of this particular reaction. Advice is given in the British Society for Haematology (BSH) guidelines on action to take in the event of acute transfusion reactions (BSH Tinegate et al. 2012). These are not only allergic/febrile reactions but incorporate any adverse reactions that occur in the first 24 hours.

A national comparative audit of TACO was undertaken in the UK in 2017 with collection of data from more than 4000 patients over 60 years of age. More than 80% of these patients had additional risk factors for TACO (other than their age) but less than 1% were identified as such (Morton et al. 2017). Awareness needs to be improved and the use of the TACO checklist is encouraged.

If a patient develops a reaction, or becomes breathless, stop the transfusion, maintain venous access with saline, undertake rapid clinical assessment and call for assistance if necessary. For patients at risk of TACO careful clinical assessment of cardiac status and fluid balance should be documented before the transfusion is started. The respiratory rate should be monitored throughout transfusion (NICE 2015, BSH Robinson et al. 2018). The oxygen saturations should also be measured in patients identified at risk of TACO. Patients with renal dysfunction and those with positive fluid balance prior to transfusion are also at risk of TACO. Measurement of B-natriuretic peptide (BNP) before and after a transfusion reaction may be helpful in establishing a diagnosis of TACO (Zhou et al. 2005) and has been considered as one of the diagnostic criteria for TACO but this is not widely performed or available in the UK.

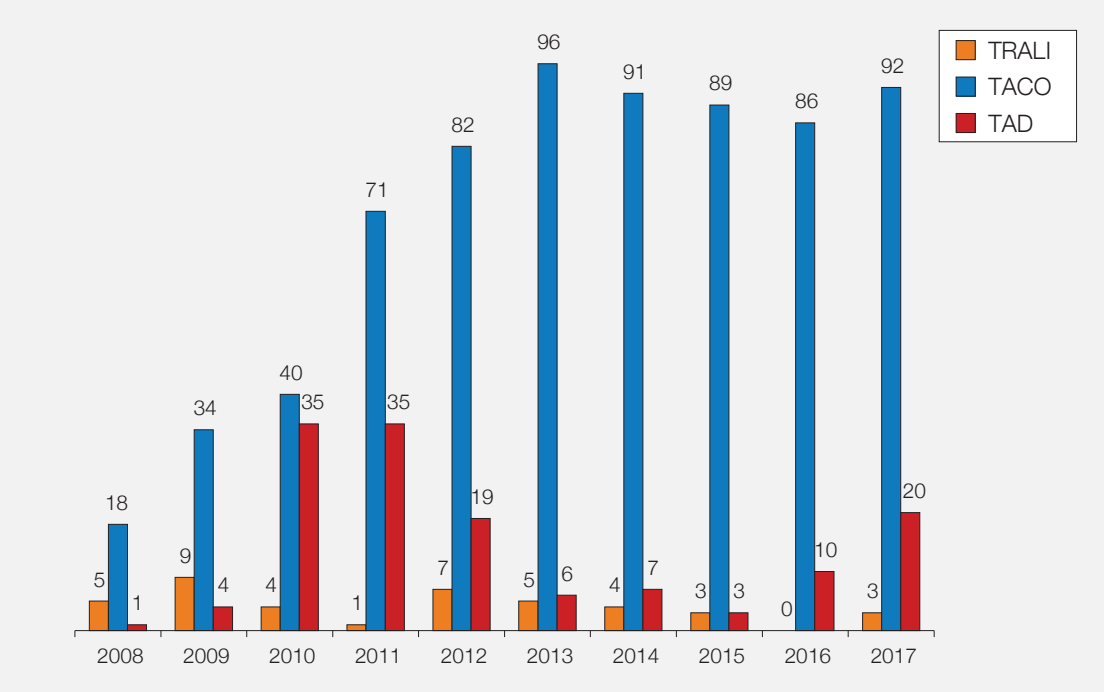


Figure 18.1: Reports of pulmonary complications by year 2010-2017

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

References

Brettner F, von Dossow V and Chappel D. The endothelial glycocalyx and perioperative lung injury. *Curr Opin Anaesthesiol* 2017;**30:**36-41.

BSH Robinson S, Harris A et al. The administration of blood components: a British Society for Haematology Guideline. *Transfus Med* 2018;**28(1):**3-21. http://onlinelibrary.wiley.com/doi/10.1111/tme.12481/pdf [accessed 23 March 2018].

BSH Tinegate H, Birchall J et al. Guideline on the investigation and management of acute transfusion reactions Prepared by the BCSH Blood Transfusion Task Force. *Br J Haematol* 2012;**159:**143-153.

Force ADT, Ranieri VM et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;**307:**2526-2533.

Juffermans NP and Vlaar AP. Possible TRALI is a real entity. *Transfusion* 2017;**57:**2539-2541.

Morsing KSH, Peters AL et al. The role of endothelium in the onset of antibody-mediated TRALI. *Blood Rev* 2018;**32:**1-7.

Morton S, Grant-Casey J et al. Skating on thin ice: national audit of TACO demonstrates poor recognition of risk factors. *Blood* 2017;**130 Suppl 1:**2406.

NICE Guideline NG24 Blood transfusion 2015 https://www.nice.org.uk/guidance/ng24/chapter/Recommendations#alternatives-to-blood-transfusion-for-patients-having-surgery-2 [accessed 19 March 2018].

Toy P, Kleinman SH and Looney MR. Reply to concerns regarding dropping the term 'possible TRALI'. *Transfusion* 2016;**56:**2394-2395.

Zhou L, Giacherio D et al. Use of B-natriuretic peptide as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload. *Transfusion* 2005;**45:**1056-1063.

18a Transfusion-Related Acute Lung Injury (TRALI) n=3

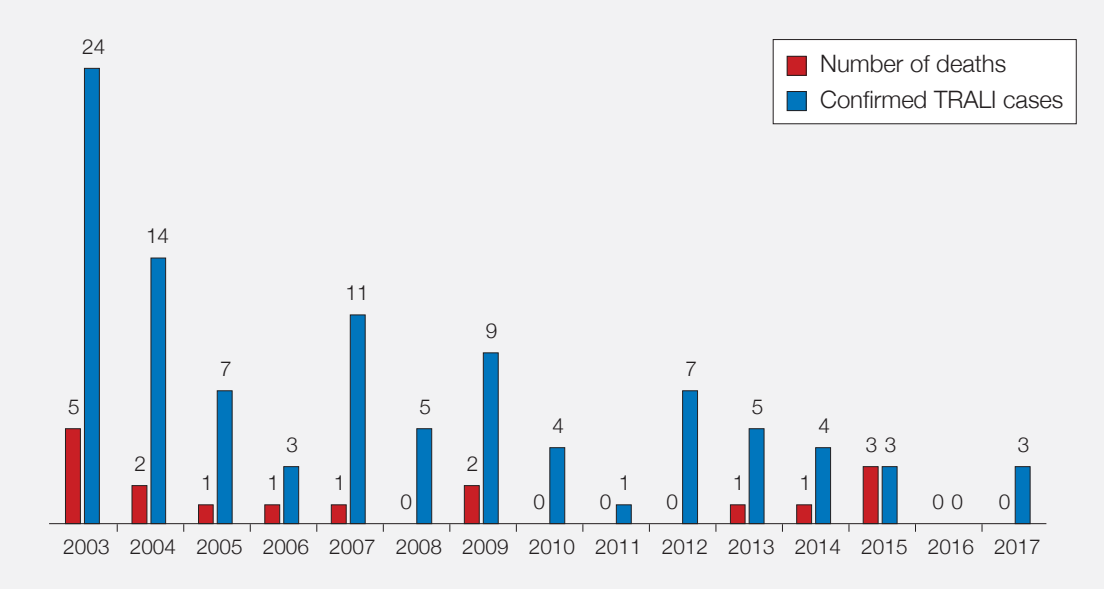
Author: Tom Latham

Definition:

Transfusion-related acute lung injury (TRALI) is defined as acute dyspnoea with hypoxia and bilateral pulmonary infiltrates during or within 6 hours of transfusion, in the absence of circulatory overload or other likely causes, or in the presence of human leucocyte antigen (HLA) or human neutrophil antigen (HNA) antibodies cognate with the recipient.

There were 3 confirmed cases of TRALI this year. Eleven cases were reported as suspected TRALI, 4 cases were transferred to transfusion-associated dyspnoea (TAD), 1 case to transfusion-associated circulatory overload (TACO) and 3 cases were withdrawn.

Figure 18a.1: Number of suspected TRALI cases and deaths at least possibly related to TRALI by year of report



TRALI=transfusion-related acute lung injury

Figure 18a.1 shows TRALI cases from 2003 to 2017, reclassified using the criteria introduced in the 2016 Annual SHOT Report. The use of male donors only for fresh frozen plasma (FFP) was implemented in 2003. Cases are recorded as deaths if death was at least 'possibly' related to transfusion (imputability 1 or greater).

Assessment of TRALI

The classification criteria are outlined in Table 18a.1 below. A mapping of how the revised criteria compare to the widely used Canadian Consensus definitions for TRALI is given in Table 18a.3, in order to help international comparison.

Classification	Definition	Mapping to Canadian Consensus definition
Highly likely	Cases with a convincing clinical picture and positive serology	TRALI + positive serology
Probable	Cases with positive serology but other coexisting morbidity which could independently cause acute lung injury or fluid overload	Possible TRALI (pTRALI) + positive serology
Equivocal	Cases with positive serology in the clear presence of lung injury due to other causes or fluid overload	not TRALI [excluded because of other morbidity but meets positive criteria] + positive serology
Antibody-negative TRALI	Cases with a convincing clinical picture where serology is not available or negative	TRALI + absent or negative serology
Unlikely- reclassify as TAD	Cases where the picture and serology was not supportive of the diagnosis. These cases are transferred to TAD	pTRALI or not TRALI + negative or absent serology

Table 18a.1: Revised SHOT criteria for assessment of TRALI cases

Probability	Number of cases
Highly likely	0
Probable	1
Equivocal	1
Antibody-negative	1
Unlikely (transferred to TAD/TACO)	5

Table 18a.2: TRALI case probability (SHOT criteria) 2017 cases

Table 18a.2 includes notified cases which have been transferred to other categories but not cases which have been withdrawn.

Canadian Consensus classification	Number of cases
TRALI	1
Possible TRALI	1
Not TRALI	1

Table 18a.3: Classification using Canadian Consensus definitions

Table 18a.3 includes only cases classified as TRALI - withdrawn or transferred cases would by definition be classified as 'Not TRALI'.

Case histories

Case 18a.1: Antibody-negative TRALI - a possible role for HLA cross-reactivity?

A <10-year-old girl with acute lymphocytic leukaemia (ALL) attended as an outpatient for a prophylactic platelet transfusion. Thirty minutes after transfusion of a unit of pooled platelets, the patient suffered acute vomiting, abdominal pain, acute tachypnoea, and desaturated to 70% on air. The chest X-ray showed a complete white-out. The patient required intubation and ventilation but subsequently made a complete recovery. The patient had previously been well and there were no clinical features of fluid overload or additional fluids.

One male donor had HLA antibodies against HLA-A25, -A34, -A66, -A68; the recipient typed as HLA-A2;A26.

This case has been classified as 'antibody-negative TRALI' based on a classical history and absence of alternative explanations. However, although the antibodies are not cognate with the recipient it is noted that they are in the same 'cross-reactive group'. Cross-reactive groups (CREG) denote operationally monospecific HLA antisera that react with two or more HLA antigens due to public epitopes that are differentially shared among HLA class I gene products (Focosi 2014). In this case, A2 (recipient) and A68 (donor antibody) are in the same CREG group and A26 (recipient) is in the same group as A25, A34 and A66 (donor).

HLA cross-reactivity has not been reported as having an association with TRALI but has a moderate effect on platelet refractoriness. It is therefore feasible that there could be a causative relationship for TRALI.

Case 18a.2: Probable TRALI

A female teenager developed acute respiratory deterioration, hypoxia and bilateral patchy air space shadowing 4 hours after transfusion of red cells. The transfusion was given for anaemia 2 days after a liver transplant for Alagille syndrome. She had a positive fluid balance and impaired renal and cardiac function secondary to the underlying syndrome although these had not caused functional compromise. She required ventilation but made a complete recovery.

The red cell donor had HNA-1a antibodies which were cognate with the recipient.

The case was classified as 'probable TRALI' in view of the positive serology and the treating clinician's impression that fluid overload was unlikely, however the patient also had coexisting risk factors for fluid overload which therefore cannot be ruled out.

Case 18a.3: Equivocal TRALI

A female patient in her 60s was already under prolonged ventilation following oesophageal surgery complicated by a perforated oesophagus and splenic rupture and she was also recovering from postoperative sepsis. She developed increased oxygen requirements and deterioration in the chest X-ray (CXR) following a transfusion of two units of red cells. There was pre-existing pulmonary oedema on a CXR prior to the transfusion, but this was worse after transfusion and a computerised tomography (CT) scan showed patchy ground-glass shadowing within the lung fields in keeping with acute respiratory distress syndrome (ARDS).

Investigation of the donors showed that both red cell donors had HLA class 1-specific antibodies, in particular to HLA-A2. The patient also had the cognate HLA-A2 antigen.

This case has been classified as 'equivocal TRALI' - it is practically impossible to assign causation retrospectively in the presence of pre-existing lung injury, infection and fluid overload but the presence of cognate antibodies in both donors raises the possibility of TRALI as a causative or contributory factor.

Cumulative serological data

Since 1996, 207/327 (63.3%) reported cases have had full laboratory investigation for TRALI. Concordant antibodies were identified in 118/207 (57.0%) of these. The most frequently identified antibody specificities (either alone or in combination with other concordant antibodies) have been HLA-DR4 (22/118 cases, 18.6%), HLA-DR52 (17/118, 14.4%) and HLA-A2 (19/118, 16.1%). All other HLA antibody specificities have been identified in less than 10% of cases. Concordant HNA specific antibodies, alone or in combination, have been found as follows: HNA-1a (10/118 cases, 8.5%); HNA-2 (2/118, 1.7%); HNA-3a (2/118, 1.7%).

Analysis of reports of 187 complete TRALI investigations between 2001 and 2017 inclusive has shown that the specificities of concordant antibodies were as follows:

Table 18a.4: Concordant donor antibodies 2001 to 2017 inclusive

Concordant donor antibodies 2001 to 2017 inclusive				
HLA class I alone	HLA class II alone	Both HLA class I and HLA class II	Granulocyte-specific antibody (+/- HLA antibodies)	None identified
21/187 (11.2%)	36/187 (19.3%)	27/187 (14.4%)	19/187 (10.2%)	84/187 (44.9%)

Commentary

Three confirmed cases of TRALI were reported this year, including 1 delayed report of a case from 2016. This number is comparable to the annual incidence over the last decade. The revised classification, as intended, gives a better proportion of cases where TRALI is thought to be at least a possible explanation for the clinical picture.

Part of the motivation for including the presence of leucocyte antibodies in the definition used by SHOT is to be able to monitor the effectiveness of TRALI prevention measures. In the 3 confirmed cases, all components transfused were consistent with TRALI-reduction measures (male donor FFP and screening of parous female platelet donors). Case 18a.1 is a reminder that male donors can have HLA antibodies and that it is worthwhile testing male donors for antibodies if there is a high clinical suspicion of TRALI.

The question raised by Case 18a.1 of whether HLA cross-reactivity could cause TRALI needs further investigation. The most direct way of demonstrating that antibodies in the donor are reactive with the recipient would be to perform a lymphocyte crossmatch. While this is logistically difficult to arrange, it is suggested that this would be a useful addition to the investigation of suspected TRALI cases. For the moment, it is proposed to continue classifying cases with cross-reactive but not matching antibodies in the 'antibody-negative TRALI' category so that they can receive additional scrutiny.

Blood Centres should consider performing a lymphocyte crossmatch in suspected transfusion-related acute lung injury (TRALI) cases where donors are found to have human leucocyte antigen (HLA) antibodies in the same cross-reactive group as the recipient.

References

Focosi D. HLA nomenclature 2014. http://www.ufrgs.br/imunovet/molecular_immunology/hla.html#CREG [accessed 15 April 2018].

18b Transfusion-Associated Circulatory Overload (TACO) n=92

Authors: Sharran Grey and Paula Bolton-Maggs

The reporting criteria for TACO have been revised by a joint working group from the International Society of Blood Transfusion (ISBT) haemovigilance working party, the International Haemovigilance Network (IHN) and American Association of Blood Banks (AABB) with wide international consultation. SHOT has continued to be a key contributor and collaborator in this work. Validation of the revised criteria took place throughout 2017.

An international consensus conference was the ultimate objective of the working party following validation of the reporting criteria. The working party recognised that the revised reporting criteria are an important improvement and will likely be further revised as research advances. The revision group is planning to finalise the validation and publish the criteria to make them available for use in due course. The validation process and expert discussions highlighted significant gaps in knowledge of TACO pathogenesis and diagnosis, and for this reason a consensus conference will be deferred until these issues can be more satisfactorily addressed. However, it was recognised that a workshop to appraise current and ongoing research would be valuable for future planning.

Experts agreed that delineating the current categories of pulmonary complications is problematic and there is likely considerable overlap. It is important this does not act as a barrier in reporting to SHOT. Transfusion-associated dyspnoea (TAD) is an essential category for capturing these cases.

Key SHOT message

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

Recommendation

- A formal pre-transfusion risk assessment for transfusion-associated circulatory overload (TACO) should be undertaken whenever possible, as TACO is the most commonly reported cause of transfusion-related mortality and major morbidity

Action: All staff authorising transfusion

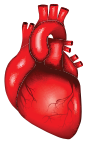
TACO Checklist	Red cell transfusion for non-bleeding patients	If 'yes' to any of these questions
	Does the patient have a diagnosis of 'heart failure' congestive cardiac failure (CCF), severe aortic stenosis, or moderate to severe left ventricular dysfunction? Is the patient on a regular diuretic?	1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

Figure 18b.1: TACO pre-transfusion checklist

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.

Recommendation

- 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)

Action: All staff authorising transfusion

Deaths n=7

Two of the 7 deaths were clearly related to transfusion. One of these cases had major gastrointestinal haemorrhage while anticoagulated. Serial full blood counts showed the patient was overtransfused/over-resuscitated with red cells and died following development of pulmonary oedema. The patient in the other case had a history of left ventricular failure and received two units of red cells for symptomatic relief of anaemia. The patient developed pulmonary oedema during the second unit and died within an hour of transfusion. The remaining deaths were in patients who all had pre-existing comorbidities that are known risks for circulatory overload.

Major morbidity n=20

Sixteen of the 20 cases of major morbidity had evidence of pre-existing fluid overload, pulmonary oedema, comorbidities predisposing to circulatory overload and/or were also receiving significant volumes of non-blood fluids and were therefore at risk of TACO. Two cases had no apparent risk factors for TACO but had received large volumes of blood components, and in 1 case there was evidence of over-estimation of haemorrhage. There were only 2 cases where TACO developed with no apparent risk factors reported.

Demographic overview of cases

Table 18b.1: Demographics of reported TACO cases

Demographic	Number of reports
Deaths (imputability 3)	2
Deaths (imputability 2)	4
Deaths (imputability 1)	1
Major morbidity (serious sequelae)	0
Major morbidity (minor sequelae)	3
Major morbidity (signs and symptoms with risk to life with full resolution/unknown outcome)	17
Age	Range 3-97 years Median 77 years
Specialties	Haematology=18 Acute medicine=17 Intensive therapy unit (ITU)/anaesthetics=6 Adult surgical specialties=13 Other adult medical specialties=31 Paediatrics=1 Obstetrics=1 Other specialties/unknown=5
Bleeding patients (indication code R1 or 'massive bleeding' indicated)	15
Non-bleeding patients (other indication codes or not stated)	77

In agreement with previous years, the demographic analysis shows that TACO is more commonly reported in the older population and where transfusion is given for anaemia rather than bleeding. Haematology and adult medical specialties are again the most common specialties where TACO is reported.

Analysis by definition criteria

This year's data have been analysed using the draft TACO reporting criteria developed by the joint working group described in the introduction (ISBT 2017). These criteria are summarised below:

Patients classified as having TACO (surveillance diagnosis) should have acute or worsening respiratory compromise during or up to 12 hours after transfusion (SHOT accepts cases up to 24 hours after transfusion) and should exhibit two or more of the criteria below:

- 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 e.g. echocardiogram
- Evidence of 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
- Evidence of fluid overload including any of the following: a positive fluid balance; response to diuretic therapy combined with clinical improvement; and change in the patient's weight in the peri-transfusion period
- Elevation in B-type natriuretic peptide (BNP) levels (e.g. BNP or N-terminal (NT)-pro BNP) to greater than 1.5 times the pre-transfusion value. A normal post-transfusion BNP level is not consistent with a diagnosis of TACO; serial testing of BNP levels in the peri-transfusion period may be helpful in identifying TACO

These criteria establish a surveillance definition based on a complete description of an event, including information that becomes available well after onset. This is for reporting and tracking purposes and the criteria do not constitute clinical diagnosis for the purpose of real-time clinical interventions.

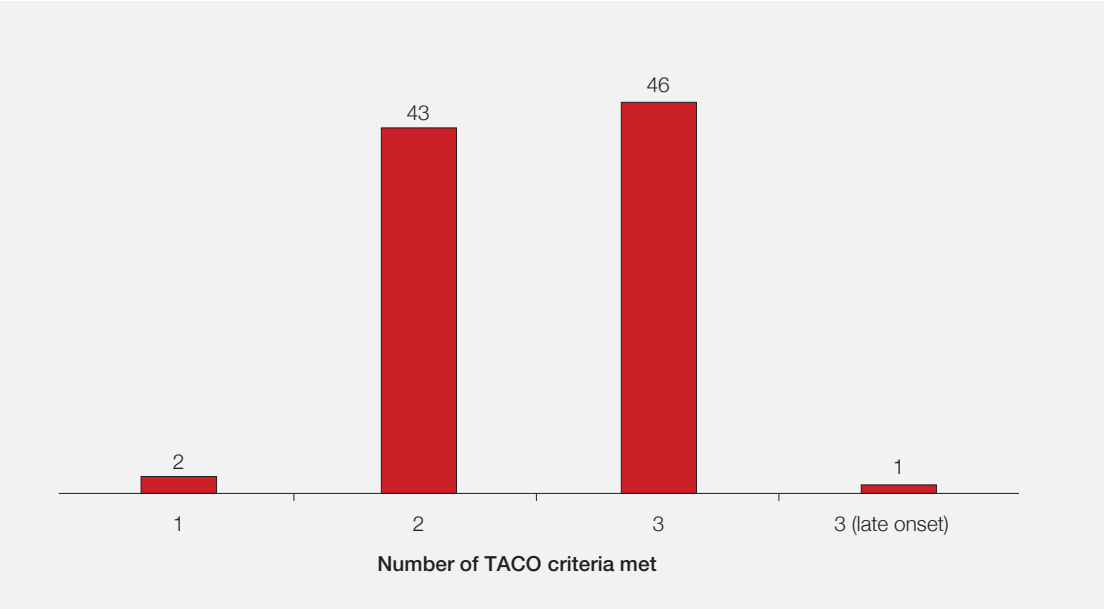


Figure 18b.2: Analysis of reports by the revised surveillance diagnosis criteria

TACO=transfusion-associated circulatory overload

Ninety-two reports were accepted into the TACO category. Eighty-nine (96.7%) met the revised surveillance criteria for TACO (89/92). In 1 of the 3 cases that did not strictly meet the criteria the timing of onset of symptoms was reported as 12-24 hours after transfusion. On review of the case the patient had received a large volume transfusion over a long period of time, which highlights the need for standardisation of the timing of symptom onset in relation to transfusion and is discussed further below. The 2 other cases scored only one criterion. One patient had pulmonary oedema following a large volume transfusion for haemorrhage, however due to lack of unanticipated cardiovascular parameter changes, no fluid balance record, no record of diuretic therapy and BNP not tested, only one criterion was met in an otherwise clinically compelling scenario. The other patient had received only a single unit of red cells and developed pulmonary oedema. In the absence of fluid balance measurement, lack of unanticipated cardiovascular parameter changes, failure to improve with diuretic therapy and BNP not tested, this case did not fully meet the new criteria. Although the patient had chronic underlying pulmonary pathology, the clinical scenario suggested that on balance the pulmonary oedema was probably precipitated by transfusion in this patient with risk factors for circulatory overload (renal impairment and requirement for regular diuretic medication).

The new criteria focus on the pathophysiology of circulatory overload based on the effects on cardiovascular and pulmonary systems. Pro-inflammatory features are being increasingly recognised in cases of pulmonary complications of transfusion. Whether these are purely circulatory overload, an overlapping syndrome or another unidentified entity is not understood. The two previous years' data have been analysed in the context of fever to explore this further.

Fever in cases reported and categorised as TACO

Author: Harriet Lucero

There is a recognised association between TACO and fever. The incidence was reported as 45/107 (42.1%) cases of TACO in a retrospective review (Parmar et al. 2017). Fever was defined as a temperature rise >1°C to reach >38°C and/or rigors or chills. Another study reported febrile or inflammatory symptoms in 65/97 (67.0%) cases of TACO (Andrzejewski et al. 2012).

A review of cases reported to SHOT in 2015 and 2016 showed that fever was a symptom in 34/164 (20.7%) cases reported as TACO. 'Fever' is not defined in the TACO questionnaire; it is a yes/no answer. In 15/34 (44.1%) cases with fever no alternative explanation for the fever was provided. In the cases where potential alternative explanations existed the patients were already on antibiotics or were being treated for infection prior to the transfusion.

If there are respiratory signs or symptoms suggestive of TACO, then the presence of fever does not exclude the diagnosis. This is reflected in the revised TACO surveillance diagnosis criteria (ISBT 2017). Research continues into the potential inflammatory processes involved in pulmonary oedema associated with transfusion.

Timing of TACO symptoms

Author: Harriet Lucero

TACO is generally considered to occur within 6 hours of transfusion, but SHOT has accepted cases within 24 hours of transfusion. Part of the revision work on the international surveillance criteria for TACO includes the timing of the reaction. The revised ISBT surveillance definition (ISBT 2017) is 'during or up to 12 hours after transfusion'.

All cases reported to SHOT between 2010 and 2016 where the timing of reaction was reported to be greater than 6 hours have been reviewed (Table 18b.2). A total of 83/555 (15.0%) of TACO cases were reported as being 6 hours or more after transfusion by the reporting organisation. Review of these shows that the 'time of transfusion' is often recorded as the time the first unit was started.

Certainly, in the case of multiple red cell transfusions, the total transfusion time will be more than 6 hours. Many of the cases analysed experienced a reaction during the transfusion or shortly after completion. Cases categorised as 'unclear' are where the data submitted were insufficient to reach a firm conclusion.

Table 18b.2: Timing of reported TACO cases

Time given for symptom onset by reporting hospital		Time of symptom onset from end of transfusion following review of the full data set				
		<6 hours	6-12 hours	12-24 hours	unclear	>24 hours
6-12 hours	**53**	31	16		6	
12-24 hours	**30**	10	4	8	5	3

A small number of patients experienced delayed reactions beyond 12 hours and 3 cases occurred beyond 24 hours, 2 of which were following outpatient transfusions and the timing of symptom onset was therefore potentially prior to the time of presentation to hospital.

The analysis demonstrates the need for an internationally agreed standard for the timing of the onset of TACO in relation to the transfusion episode.

Illustrative cases

Case 18b.1: An inappropriate transfusion leading to TACO and cancelled elective surgery

A patient in their 90s was admitted for an elective total knee replacement. The patient's haemoglobin (Hb) was 95g/L and weight was 73kg. Two units of red cells were prescribed for preoperative Hb optimisation. A Hb check was not performed between units and a fluid balance chart was not in place. At the end of the second unit the patient had dyspnoea and was hypoxic, with hypertension and tachycardia. The chest X-ray was suggestive of pulmonary oedema and the post-transfusion Hb was 128g/L. The patient responded to diuretic therapy. The patient's surgery was cancelled due to TACO.

Preoperative Hb optimisation should take place prior to admission where anaemia is identified, investigated and treated following surgical pre-assessment. Red cell transfusion is rarely appropriate except in occasional circumstances, for example where a patient has chronic bleeding or marrow impairment leading to anaemia that cannot be controlled medically.

Notwithstanding this, the patient in this case had a pre-transfusion Hb level that exceeded the trigger for transfusion and transfusion resulted in an excessive Hb level. The development of TACO then unfortunately led to the patient being discharged following recovery without having their surgery.

Case 18b.2: Lack of attention to appropriate red cell dose leads to TACO

A patient in their 90s weighing 75kg with a newly diagnosed haematological condition was admitted with sepsis and a Hb level of 79g/L. The patient was known to have heart failure, renal impairment and peripheral oedema and therefore had risk factors for circulatory overload. Two units of red cells were prescribed with prophylactic diuretics. During transfusion of the second unit the patient became breathless, began coughing up frothy sputum, developed bilateral crackles, tachycardia and hypertension. The chest X-ray was consistent with pulmonary oedema.

The root-cause analysis and preventive actions decided by the reporting hospital focused on future slow-rate transfusion, prophylactic diuretics and improved fluid balance measurement. Although these are important factors, the rate of transfusion in this case was not excessive (2-4 hours per unit) and diuretics were administered, suggesting TACO would not have been avoided in this scenario. However, the dose of red cells prescribed was not questioned as part of the root-cause analysis. Based upon a calculation of 0.4mL/kg raising the Hb level by 1g/L, this patient required less than a single unit of red cells to meet their target Hb. A weight-adjusted dose may have avoided TACO in this patient which developed during transfusion of the second unit.

Case 18b.3: Inappropriate and excessive transfusion causing TACO in a patient without risk factors for circulatory overload

A patient in their 50s weighing 67kg was prescribed six units of red cells for iron deficiency anaemia after being admitted with Hb 37g/L. The patient had no risk factors for TACO except for profound anaemia. During the fifth unit the patient became dyspnoeic, hypoxic and hypertensive. The patient recovered after diuretic therapy and had a post-transfusion Hb level of 100g/L.

Blood transfusion in iron deficiency anaemia is only appropriate as initial treatment if the patient is symptomatic. This patient was likely to be symptomatic with profound anaemia however the dose should have been limited to one or two units to resolve symptoms. The decision-making for this case appears to be aimed at a 'back to normal' Hb level with no attempt to treat the iron deficiency. Although a root-cause analysis was undertaken by the reporting hospital, much of the preventive action was focused on national education for junior medical staff and local implementation of the TACO checklist. Although these are important measures this case of TACO could have been avoided by a local policy of single unit or weight-adjusted red cell dosing. The transfusion laboratory has an important role in identifying and avoiding excessive and/or inappropriate transfusion.

References

Andrzejewski C Jr, Popovsky M et al. Hemotherapy bedside biovigilance involving vital sign values and characteristics of patients with suspected transfusion reactions associated with fluid challenges: can some cases of transfusion-associated circulatory overload have pro-inflammatory aspects? *Transfusion* 2012;**52(11):**2310-20.

Grey S, Farrar K et al. A web-App for weight-adjusted red cell dosing: post-development implementation and clinical effectiveness. *Br J Haematol* 2018;**181 Suppl 1**:146.

ISBT (2017). TACO reporting criteria (April 2017) draft for validation. http://www.isbtweb.org/fileadmin/user_upload/TACO_reporting_criteria_April_2017_draft_for_validation.docx [accessed 4 January 2018].

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

18c Transfusion-Associated Dyspnoea (TAD) n=20

Author: Paula Bolton-Maggs

Definition:

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

Twenty cases are included, 8 males and 12 females. Five were reported as TAD, 10 transferred from TACO, 1 from febrile, allergic and hypotensive reactions (FAHR) and 4 from TRALI. Two cases were transferred from TAD to TACO. Four patients suffered major morbidity defined by admission to intensive therapy units (ITU). Seven patients died, and in 5 cases the reaction was considered contributory. The age range was 15 to 93 years with a median age of 71 years. In 6 cases (30.0%) 'sepsis' was flagged and it is likely that this contributed to the reaction. Most reactions occurred in relation to red cells either alone, n=15, or with other components n=2. One reaction each was reported for platelets, granulocytes and plasma.

Key SHOT messages

- Pulmonary reactions to transfusion are difficult to classify, often because these occur in elderly patients with significant comorbidity. They may have features to suggest transfusion-associated circulatory overload (TACO) but cannot be classified as TACO if the data are incomplete (particularly missing information about fluid balance, and post-reaction chest X-ray (CXR) to confirm presence or absence of pulmonary oedema)
- TRALI is considered within 6 hours of transfusion in the absence of circulatory overload or other likely causes, or in the presence of human leucocyte antigen (HLA) or human neutrophil antigen (HNA) antibodies cognate with the recipient. Some cases of acute lung injury will therefore be reported as, or transferred to TAD

TACO and TAD have been included in SHOT reporting from 2008 together with a pulmonary questionnaire intended to capture as much information as possible about the event. This followed the introduction of TAD as a category by ISBT.

There is no clear international agreement on what TAD is, and the definitions of both TACO and TRALI are currently under international review. The use of more stringent criteria for both TACO and TRALI, and the absence of data in many fields contributes to the increase in number accepted as TAD compared to previous years.

The cases of TAD resulting in death and major morbidity are summarised below. The other 11 cases are available in the supplementary information provided for this Annual Report (by chapter) on the SHOT website www.shotuk.org.

Deaths n=5

Case 18c.1: Acute severe reaction to transfusion

A lady in her 80s was transfused for anaemia after a fall and minor head injury resulting in bleeding from the scalp (on a background of iron deficiency anaemia). The plan was to give a single unit of red cells then follow this with an iron infusion the next day. She was being treated for an infective exacerbation of chronic obstructive pulmonary disease. She had renal impairment and a low albumin. Within 5 minutes of transfusion starting she developed a worsening wheeze and became agitated, had an increase in respiratory rate from 24 to 44 breaths per minute (/min), and was immediately treated for anaphylaxis with adrenaline, hydrocortisone and chlorphenamine, and intravenous (IV) fluids with some improvement, and later given furosemide with further improvement. She died 2 days later.

The clinicians were unable to decide if this was an allergic reaction or circulatory overload but in view of the clinical history she was more likely to have overload, but there was not enough evidence to classify this as TACO. The patient was already acutely unwell before the transfusion started (history of deterioration since starting treatment for a chest infection at home with increased confusion culminating in a fall). They considered that transfusion may have contributed to her death.

Case 18c.2: A frail elderly woman developed pulmonary symptoms related to transfusion

A woman in her 90s received regular red cell transfusions for myeloproliferative disease. She had community-acquired pneumonia with acute kidney injury. She was already very frail, and was drowsy on admission with Hb 59g/L. The respiratory rate was 25-26/min, oxygen saturation was 94-95% on 2L of oxygen. Blood pressure (BP) was 110/60mmHg and she had tachycardia 100-105/min. At the end of the second unit the respiratory rate increased to 30/min with a fall in oxygen saturation to 76% but no significant change in BP or pulse. She was reviewed by the doctor who reported peripheral oedema and raised jugular venous pressure. Furosemide treatment did not give any benefit. She died the following day and transfusion was considered as a possible contributing factor.

Case 18c.3: A man with leukaemia and fungal chest infection died after transfusion

An elderly man with acute myeloid leukaemia (AML) received a unit of red cells and a unit of platelets as part of a regular transfusion regime. He had received six cycles of chemotherapy. He also had interstitial lung disease was very unwell with pulmonary aspergillosis with a progressive cavity, new consolidation, poor left ventricular function (ejection fraction 22%) with a pericardial effusion and cardiac failure. He went home after the transfusion, and 9 hours after the end of the transfusion (01:25) the patient became breathless and was coughing. He arrested and was pronounced dead in hospital at 03:09.

The case was reported to the coroner who decided that the death was from 'natural causes and rare complications from necessary treatment'.

Case 18c.4: A man with liver disease reacted to cryoprecipitate (transfer from TRALI)

A man in his 40s with a known history of alcohol abuse and liver cirrhosis was admitted to the intensive therapy unit with a variceal bleed. His Hb was 71g/L and platelet count was 43x10^9/L with coagulopathy. He received several blood components (three units of red cells, two units of platelets, four units of fresh frozen plasma (FFP)) prior to two units of cryoprecipitate (cryo). Before he received the cryo he was self-ventilating on room air, respiratory rate was 25/min and oxygen saturation was >94%. After starting the cryo there was an abrupt deterioration in his gas exchange resulting in emergency intubation and ventilation. His post-intubation CXR showed marked (new) bilateral interstitial infiltrates. Prior to the transfusion of cryo the central venous pressure (CVP) was 13mmHg and his fluid balance was 3L positive over 36 hours. He had received a total of 1.4L of crystalloid in the 24 hours prior to his intubation. The remainder of his positive fluid balance represented blood component support. An echocardiogram performed later in his admission showed a normal left ventricle with an estimated ejection fraction of 60% and normal right ventricular function. He received a total of 300mg of furosemide in bolus doses over the 24 hours after intubation. This had

no appreciable effect on his gas exchange and he continued to require very high levels of ventilatory support with FiO_2 consistently greater than 60% with mean airway pressures around 20cm of water.

Advice was sought from the TRALI panel with the following response: 'There is very significant liver impairment and big bleed with massive transfusion (and almost certainly a lot of crystalloid infusion as well). These patients are notoriously volume- and sodium ion-intolerant and this is TACO with extremely low possibility of TRALI'. It appears that no antibody investigations were performed. The clinical team remained of the view that this was TRALI. He remained on the ventilator and died 8 days after this event. The reporters concluded that death was 'possibly related' to the transfusion of cryoprecipitate.

Case 18c.5: A complex case with sudden deterioration in relation to transfusion requiring admission to ITU and ventilation

A man in his 60s with peripheral vascular disease received a postoperative (debridement of necrotic foot) transfusion for anaemia (Hb 76g/L). He was already on antibiotics and was a known diabetic. Transfusion of the first unit was uneventful. Three hours after starting the second unit his heart rate rose from 125 to 142/min, blood pressure increased from 120/65 to 154/83 and oxygen saturation fell from 98% to 95% with increase in respiratory rate from 20 to 29/min. His temperature increased from 36.5 to 37.5°C. A doctor found him to be breathless, with audible wheeze, no crepitations on auscultation but pulse irregularly irregular and vomiting. Electrocardiogram (ECG) confirmed fast atrial fibrillation. Critical care outreach review took place and blood tests including cultures were taken. Portable CXR: consolidation of right middle lobe. He had a metabolic acidosis. IV fluids were given, 1000mL over 4 hours, together with IV chlorphenamine, IV paracetamol, and salbutamol nebuliser. He was transferred to the high dependency unit (HDU) for haemofiltration and noradrenaline infusion and was put onto nasal high flow the following day. He was treated for diabetic ketoacidosis. He was noted to be struggling with breathing. At 07:30 he was started on continuous positive airway pressure (CPAP). At 11:20 he needed intubation; during this his cardiac output stopped and he could not be resuscitated. He died 3 days after the transfusion reaction which was considered contributory.

The CXR was normal preoperatively. After the reaction 'there are florid ground-glass changes affecting both lungs with upper zone predominance. There is relative sparing of the lung bases. No pleural effusion or obstructing endobronchial lesion. Conclusion: Florid pulmonary abnormalities are visible. These could represent infection, adult respiratory distress syndrome, or possibly other entities such as drug reaction or other rarer causes of interstitial lung disease. These may well be contributing to the patient's metabolic instability'.

This was initially escalated as a potential TRALI. Staff contacted the Blood Service and information was submitted to the expert panel. The expert panel believed the pulmonary symptoms were due to TACO. The report was reviewed by the TACO expert who noted: 'difficult to attribute TACO as although pulmonary oedema is mentioned, the post-transfusion CXR report does not confirm this. There is no fluid balance record, the heart rate at time of reaction is lower than baseline and the mean arterial pressure (MAP) is normal. Given the inflammatory symptoms, suggest consider transferring to TAD or withdraw'.

Local case review: the doctors now think this was possibly pneumonia alongside a diabetic ketoacidosis episode and septic shock with the transfusion being a contributory factor. Note that the blood culture taken at the time of reaction was negative.

Major morbidity n=4

Case 18c.6: Transfusion reaction on a background of autoimmune disease

A woman in her 70s underwent insertion of a permanent pacemaker for heart block. She had a background of autoimmune disease (systemic lupus erythematosus, immune thrombocytopenia and autoimmune haemolytic anaemia). She developed a transfusion reaction resulting in admission to the ITU. She became clammy with increasing shortness of breath (respiratory rate increased from 18 to 32/min), wheeze and tachycardia of 129/min. She improved with diuretic treatment.

There was not enough information to classify this as TACO.

Case 18c.7: Acute hypoxia follows transfusion (transfer from TRALI)

A woman in her 60s received a blood transfusion without complications following coronary artery bypass surgery and observations were stable during transfusion. She had diabetes and known ischaemic heart disease. She developed rigors (but no measurable increase in temperature) after blood transfusion with a tachycardia of 199/min, BP 175/77 and decreased oxygen saturation. The CXR showed bilateral alveolar infiltration, and she was readmitted to intensive care shivering and shaking uncontrollably. IV fluid and antibiotics were started. This was thought to be TRALI because of acute hypoxia and bilateral infiltrates seen on CXR after one unit of blood with normal echocardiogram and no suggestion of fluid overload. A Blood Centre was informed but no TRALI investigations were suggested.

Case 18c.8: Breathlessness after transfusion (transfer from TRALI)

A woman in her 50s was receiving a course of chemotherapy for myelodysplasia in leukaemic transformation and was also on IV antibiotics for infection (but she was not neutropenic). These had been started earlier on the same day as her transfusion when she had fever 38.3°C associated with a fall in oxygen saturation to 86% requiring oxygen. She recovered from this. Later the same day she started feeling breathless following the end of the red cell transfusion and this increased over the following 6 hours with worsening hypoxia and increasing oxygen requirement. She required admission to the ITU. Her antibiotics and other drugs were given in a total infusion volume of about 1600mL plus blood components to 700mL during the same day. The CXR showed clear evidence of opacification which was not present before transfusion. She did not improve after treatment with diuretics. The TRALI panel considered TACO more likely but this reaction did not meet the TACO criteria.

Case 18c.9: Bronchospasm under anaesthetic (transfer from TRALI)

A young woman underwent emergency caesarean section at around 03:30 for placental abruption under general anaesthesia. She was difficult to ventilate and she developed respiratory failure with profound bronchospasm. It was not clear what the cause was and she was initially treated for possible acute exacerbation of asthma, but an acute reaction to blood transfusion was possible (she had received four units of red cells, two units of FFP and one unit of platelets) or an allergic reaction. Postoperatively she was transferred to ITU and remained intubated and ventilated. She improved after a few hours and was extubated. Overnight she was stable and was discharged to the labour ward at 07:00 for removal of uterine packs and tamponade balloon. Following removal of the balloon she started to complain of difficulty breathing. She was coughing and her saturation dropped to 88%. Her oxygen requirement continued to increase and she required transfer back to the critical care unit for nasal high flow oxygen therapy and CPAP. Acute respiratory distress syndrome (ARDS) was noted, but the clinicians were unsure whether this was from treatment or the smoking history that predisposes to this, or this might be TRALI or TACO (her mast cell tryptase was normal). She made a full recovery.

Additional cases are available in the supplementary information for this Annual Report by chapter on the SHOT website www.shotuk.org.

Commentary

As can be seen from the cases above, some might have been classified as TACO had there been more information, particularly evidence of pulmonary oedema or details of fluid balance. Others might be classified as TRALI if non-antibody cases of acute lung injury (ALI) were included in that category. The international consensus on both these categories will help to clarify how the pulmonary complications are reported. A review of transfusion reactions classified as TAD 2011-2013 was published from the New Zealand haemovigilance scheme (Badami et al. 2015). The authors examined 37 reactions that had been reported as TAD. With additional information from the case notes 34 initially classified as TAD by reviewer 1 were reduced to 16, and from 33 to 15 by the second reviewer. Several were reclassified as TACO, from initial 1 to 8 by the first reviewer, and 0 to 6 by the second reviewer. None were reclassified as TRALI. These authors 'renew the call' for better diagnosis and reporting of TACO.

Reference

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