Pulmonary Complications of Transfusion n=119

17

Author: Paula Bolton-Maggs

Reports of pulmonary complications continue to make the greatest contribution to death and major morbidity after transfusion. Transfusion-related acute lung injury (TRALI) is defined by SHOT as those patients with lung infiltrates during or within 6 hours of transfusion in the absence of other causes or in the presence of human leucocyte antigen (HLA) or leucocyte antibodies cognate with the recipient. This remains an uncommon complication of transfusion. The cases that do not meet these criteria, nor satisfy the updated criteria for transfusion-associated circulatory overload (TACO) are included in the transfusion-associated dyspnoea (TAD) category. As can be seen from the section on TAD, it is possible that some of these cases were TRALI or TACO, but the details and/or investigations were insufficient to include them in those categories.

Patients with respiratory complications are often elderly with multiple co-morbidities which makes it more difficult to classify them into one or another of these three groups. Surveillance criteria for TACO have now been significantly updated and the evolution of this process has been in evidence in the Annual SHOT Reports over the past three years. The criteria used for analysis of reports in 2018 are now published and it is hoped that this will result in improved case definition and reporting of this important complication. As shown in Figure 17.1 the number of TACO case reports has increased in 2018, perhaps linked to publicity associated with the National Comparative Audit of TACO (NCA 2017).

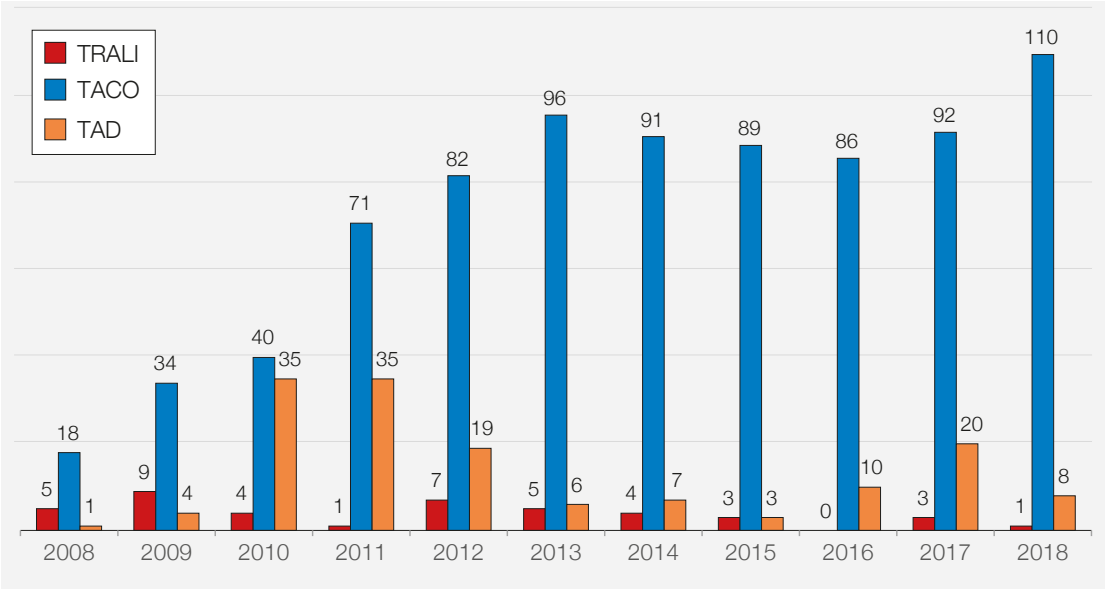


Figure 17.1: Reports of pulmonary complications by year 2008-2018

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

Over the past two years a great deal of discussion has taken place about TACO and TRALI, with the recognition that the pathophysiology of both these conditions is poorly understood, that both may occur together, and that further research is warranted. TACO may have an inflammatory component (a proportion of cases demonstrate fever). For both conditions 2-hit theories are suggested, the first being patient-related factors and the second some property of the infused blood component. TACO is a clinical diagnosis with no clear biomarker although B-type natriuretic peptide (BNP) (or N-terminal-pro brain natriuretic peptide (NT-pro-BNP), a more stable molecule) levels may be useful (Klanderman et al. 2019) and these are now incorporated into the surveillance definition. Following updated definitions for

acute lung injury (the Berlin definition, Ferguson et al. 2012) a reassessment of the diagnostic criteria for TRALI suggests that confirmatory leucocyte antigen-antibody data should be sought but are not essential for diagnosis (Vlaar et al. 2019) since there are other factors which provoke TRALI (Toy et al. 2012). This is a major change from the principles of TRALI case definition for SHOT. It is likely that many cases classified in the past as TAD may be TRALI under these revised criteria. SHOT needs to consider the impact of these recent updates on the reporting strategy, and whether in the first instance all the pulmonary complications are gathered under a single heading. In 2019 SHOT has recruited two pulmonary experts to assist in the analysis and classification of the pulmonary complications.

Some significant research findings include:

- TRALI patients have reduced levels of interleukin (IL)-10 (Kapur et al. 2017a)
- TRALI is associated with raised levels of C-reactive protein (CRP) in mice (Kapur et al. 2015)
- T-regulatory and dendritic cells may protect from TRALI through IL-10 (murine model) (Kapur et al. 2017b)
- Gastrointestinal microbial flora may affect susceptibility to TRALI (murine model) (Kapur et al. 2018)

These findings may suggest options for treatment such as IL-10 or down-modulation of CRP (Semple et al. 2018).

At least some of these pulmonary complications are potentially preventable and early recognition with prompt treatment is vital. Patient education and awareness are also important, especially if transfused as day cases or in the community.

References

Ferguson ND, Fan E, Camporota L, et al. (2012) The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012;**38(10)**:1573-82.

Kapur R, Kim M, Rebetz J, et al. (2018) Gastrointestinal microbiota contributes to the development of murine transfusion-related acute lung injury. *Blood Adv* 2018;**2(13)**:1651-1663.

Kapur R, Kim M, Aslam R, et al. (2017b) T regulatory cells and dendritic cells protect against transfusion-related acute lung injury via IL-10. *Blood* 2017b;**129(18)**:2557-2569.

Kapur R, Kim M, Rebetz J, et al. (2017a) Low levels of interleukin-10 in patients with transfusion-related acute lung injury. *Ann Transl Med* 2017a;**5(16)**:339.

Kapur R, Kim M, Shanmugabhavananthan S, et al. (2015) C-reactive protein enhances murine antibody-mediated transfusion-related acute lung injury. *Blood* 2015;**126(25)**:2747-51.6

Klanderman RB, Bosboom JJ, Migdady Y, et al. (2019) Transfusion-associated circulatory overload-a systematic review of diagnostic biomarkers. *Transfusion* 2019;**59(2)**:795-805.

Semple JW, McVey MJ, Kim M, et al. (2018) Targeting transfusion-related acute lung Injury: the journey from basic science to novel therapies. *Crit Care Med* 2018;**46(5)**:e452-e458.

Toy P, Gajic O, Bacchetti P, et al. (2012) Transfusion-related acute lung injury: incidence and risk factors. *Blood* 2012;**119(7)**:1757-67.

Vlaar APJ, Toy T, Fung M, et al. (2019) A consensus redefinition of transfusion-related acute lung injury. *Transfusion* 2019 doi.org/10.1111/trf.15311.

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

Transfusion-Related Acute Lung Injury (TRALI) n=1

17a

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 was 1 confirmed case of TRALI this year, with a further 11 cases reported as suspected TRALI. Of these, 3 cases were transferred to transfusion-associated dyspnoea (TAD), 2 cases to transfusion-associated circulatory overload (TACO) and 4 cases were withdrawn. The final 2 cases have been deferred to the next Annual SHOT Report as serology results are in progress. The 1 confirmed case was transferred to TRALI from TAD.

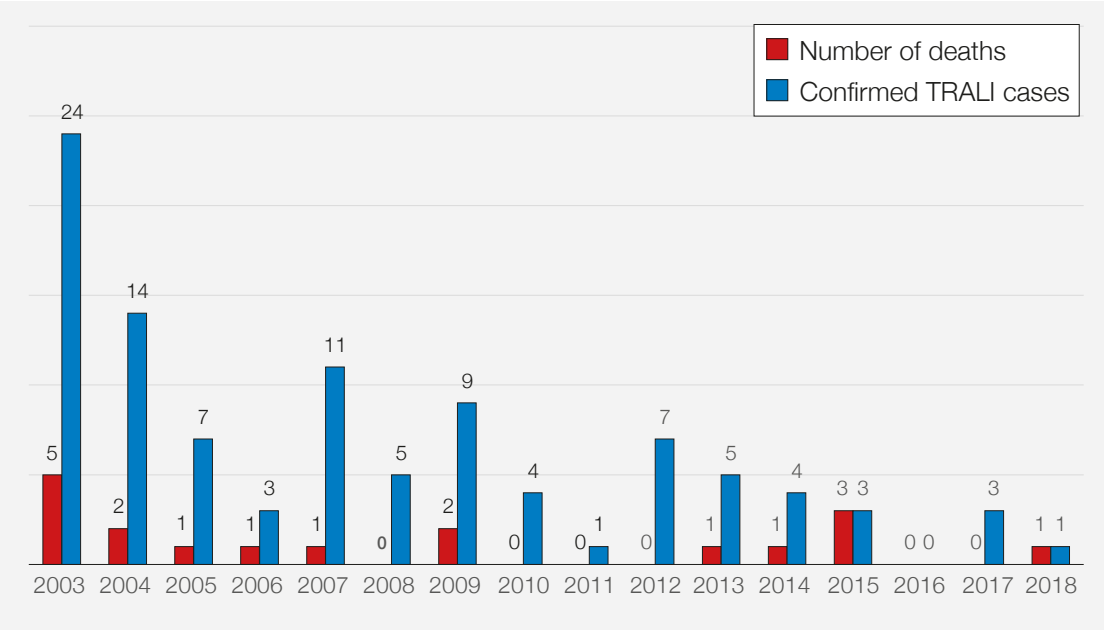


Figure 17a.1: Number of confirmed TRALI cases and deaths at least possibly related to TRALI by year of report

TRALI=transfusion-related acute lung injury

Figure 17a.1 shows TRALI cases from 2003-2018, classified 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 the death was at least 'possibly' related to the transfusion (imputability 1 or greater).

Assessment of TRALI

The classification criteria are outlined in Table 17a.1 below. A mapping of how the revised criteria compare to the widely used Canadian Consensus definitions for TRALI is given in Table 17a.3, in order to help international comparison.

Table 17a.1: Revised SHOT criteria for assessment of TRALI cases

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 17a.2: TRALI case probability (SHOT criteria) - 2018 cases

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

Table 17a.2 includes notified cases which have been transferred to other categories but not cases which have been withdrawn or deferred.

Table 17a.3: Classification using Canadian Consensus definitions

Canadian Consensus classification	Number of cases
TRALI	0
Possible TRALI	1
Not TRALI	0

Table 17a.3 includes only cases classified as TRALI, withdrawn or transferred cases would by definition be classified as 'Not TRALI'.

Deaths n=1

Case 17a.1: Antibody-negative TRALI - post mortem diagnosis without serology

A male patient in his late 60s, with recent diagnoses of advanced myelodysplasia and prostate cancer presented to the emergency department (ED) with abdominal pain, hypotension and a platelet count of 6. He had a raised C-reactive protein, metabolic acidosis with raised lactate, low albumin and renal impairment prior to transfusion and received two units of red cells and a unit of platelets on the day of admission uneventfully. Over 24 hours later, 10 minutes after starting a platelet transfusion, he became acutely breathless and hypoxic with a further fall in blood pressure and deterioration in renal function. In view of his underlying diagnoses, a decision was made not to escalate care further and he suffered a cardiac arrest shortly afterwards.

Post-mortem findings showed pleural effusions and gross pulmonary oedema, with no evidence of infection, infarction or injury, and the coroner gave 'transfusion lung injury' as the primary cause of death. Serological investigations were not performed as the National Health Service Blood and Transplant (NHSBT) expert panel felt that the picture was one of terminal decline rather than a transfusion reaction.

The case was initially reported to SHOT as TAD, however we have included the case as 'antibody-negative TRALI' in view of the coronial diagnosis. We considered imputability as 'death probably due to transfusion' as the transfusion does appear to have been a major contributor even though the patient was clearly very unwell before the transfusion.

Cumulative serological data

Since 1996, 207 of 328 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 2018 inclusive has shown that the specificities of concordant antibodies were as follows:

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%)

Table 17a.4: Concordant donor antibodies 2001 to 2018 inclusive

Commentary

Numbers of confirmed and reported TRALI cases are similar to previous years. The confirmed case this year was difficult to classify. It would not strictly meet SHOT TRALI definitions as there are other plausible explanations for the reaction (as was considered by the NHSBT expert panel), and there is no serological evidence; nevertheless the case was included as TRALI as the death certificate has recorded this as the cause of death. The case highlights the difficulty in making decisions on whether to investigate serologically, especially as recalling donors for investigation does have an associated harm in terms of donor anxiety and temporary deferral. Cases in England are reviewed by an expert panel of intensivists independent of NHSBT and cases are investigated if they meet criteria of timing, hypoxia and lack of alternative diagnoses; however, the basis for the decision is not available to SHOT when reviewing. It is probably prudent to have a lower threshold for investigating donors where there is a patient death or long term harm which appears attributable to transfusion, even though other pulmonary complications may be more likely.

An updated international consensus definition of TRALI has recently been accepted for publication (Vlaar et al. 2019). This is intended to update the earlier Canadian Consensus definition and was produced using a Delphi consultation methodology between international experts, including a representative from SHOT. The new classification remains based on clinical features and takes account of updated criteria for acute respiratory distress syndrome (ARDS). It will become clearer how the new definition changes the understanding of pulmonary complications of transfusion and also how it interacts with updated definitions for TACO as the new classification becomes more widely used internationally. As a haemovigilance organisation, we consider that it remains important to distinguish antibody mediated cases in order to monitor preventative strategies. It is therefore proposed that from 2019 we will continue to classify cases according to the SHOT definition but provide a parallel classification using the new scheme for international comparison.

Reference

Vlaar APJ, Toy T, Fung M et al. (2019) A consensus redefinition of transfusion-related acute lung injury. *Transfusion* 2019 doi.org/10.1111/trf.15311.

17b Transfusion-Associated Circulatory Overload (TACO) n=110

Authors: Sharran Grey and Paula Bolton-Maggs

Key SHOT message

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

Update

The surveillance definition for TACO has been revised by a joint working group from the International Society of Blood Transfusion (ISBT) haemovigilance working party, the International Haemovigilance Network (IHN) and AABB with wide international consultation. SHOT has been a key contributor and collaborator in this work. Validation of the revised definition took place throughout 2017 and a workshop for the revision group with other leading interested parties and experts in the field was held in October 2018 as part of the AABB annual meeting.

The consensus of the workshop was agreement that the validated TACO definition criteria should now be published and with the objective of improving and standardising TACO surveillance. The transfusion-related acute lung injury (TRALI) definition has also been revised (Vlaar et al. 2019). There was recognition of the problematic nature of delineating the pulmonary complications of transfusion due to probable overlap and compounded by gaps in knowledge of the pathogenesis of these conditions. It is important this does not act as a barrier in reporting to SHOT and the transfusion-associated dyspnoea (TAD) category remains essential to ensure capture of all relevant pulmonary cases. There was considerable interest in the role of the inflammatory response in pulmonary complications of transfusion and new research is emerging in this area which will no doubt inform future revision of the definitions.

2017 saw the publication of the National Comparative Audit (NCA) of TACO and for the first time provided large-scale data on related clinical practice (Morton et al. 2017, NCA 2017). It was encouraging and useful confirmation to observe the high degree of concordance between the recommendations of the audit report and the recommendations and key messages from SHOT. This year's recommendation has been aligned to the TACO NCA recommendations with respect to patient age and body weight.

Recommendation

- A formal pre-transfusion risk assessment for transfusion-associated circulatory overload (TACO) should be undertaken whenever possible (especially if older than 50 years or weighing less than 50kg), as TACO is the most commonly reported cause of transfusion-related mortality and major morbidity

Action: All staff authorising transfusion

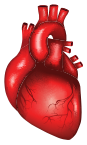
TACO Checklist	Red cell transfusion for non-bleeding patients	If 'yes' to any of these questions
	Does the patient have a diagnosis of 'heart failure' congestive cardiac failure (CCF), severe aortic stenosis, or moderate to severe left ventricular dysfunction? Is the patient on a regular diuretic? Does the patient have severe anaemia?	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 17b.1: Updated 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.

TACO=transfusion-associated circulatory overload

TACO developing with transfusion for severe anaemia is an emerging signal from the data, and is an under-recognised independent risk-factor. This was highlighted in last year's Annual SHOT Report (Bolton-Maggs et al. 2018, Case 18b.3) and continues to feature in this year's data. TACO can develop in patients with severe anaemia even in the absence of other risk factors for TACO (see Cases 17b.1 and 17b.3). For this reason, 'severe anaemia' has been added to the pre-transfusion risk assessment infographic (Figure 17b.1).

The data continues to show TACO in non-bleeding patients where the volume of red cells was in excess of that calculated for their body weight and target haemoglobin (see Case 17b.2). Weight-adjusted red cell dosing for non-bleeding patients remains a recommendation.

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, National Comparative Audit, 2017)

Action: All staff authorising transfusion

Deaths n=5

TACO resulted in death of the patient in 5 reported cases.

Major morbidity n=36

TACO remains the leading cause of transfusion-related mortality and major morbidity.

Demographic overview of cases

Table 17b.1: Demographics of TACO cases

Demographic	Number of reports
Deaths (imputability 3)	0
Deaths (imputability 2)	2
Deaths (imputability 1)	3
Major morbidity outcome (serious sequelae)	4
Major morbidity outcome (minor sequelae)	6
Major morbidity (signs and symptoms with risk to life with full resolution/unknown outcome)	26
Age	Range: 1 day - 97 years Median: 76 years
Top 3 medical specialties	Acute medicine (19/110) Haematology (18/110) Anaesthesia (10/110)
Bleeding patients (indication code R1 or 'massive bleeding' indicated)	21
Non-bleeding patients (other indication codes or not stated)	89

As seen in previous years, the demographics show 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, and this should be considered when delivering TACO mitigation and education plans.

Analysis by definition criteria

This year's data have been analysed using the reporting criteria developed by the joint working group described in the introduction (Wiersum-Osselton et al. 2019). The 2018 TACO case surveillance definition criteria are summarised below:

Patients classified with TACO (surveillance diagnosis) should exhibit at least one required criterion* with onset during or up to 12 hours after transfusion (SHOT continues to accept cases up to 24 hours), and a total of 3 or more criteria i.e. *A and/or B, and total of at least 3 (A to E)

*** Required criteria** (A and/or B)

A. Acute or worsening respiratory compromise and/or

B. Evidence of acute or worsening pulmonary oedema based on:

- clinical physical examination, and/or
- radiographic chest imaging and/or other non-invasive assessment of cardiac function

Additional criteria

C. Evidence for cardiovascular system changes not explained by the patient's underlying medical condition, including development of tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette and/or peripheral oedema

D. Evidence of fluid overload including any of the following: a positive fluid balance; clinical improvement following diuresis

E. Supportive result of a relevant biomarker, e.g. an increase of B-type natriuretic peptide levels (BNP) or N-terminal-pro brain natriuretic peptide) NT-pro BNP to greater than 1.5 times the pre-transfusion value

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 surveillance purposes and the criteria do not constitute clinical diagnosis for the purpose of real-time clinical interventions.

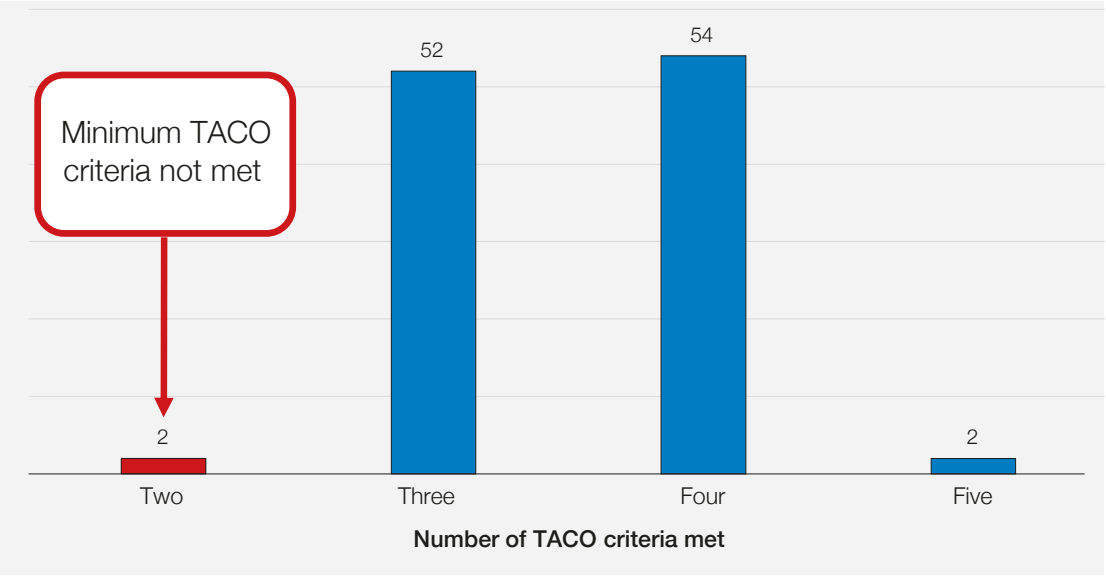


Figure 17b.2: Analysis of reports by the revised surveillance diagnosis criteria (number of criteria versus number of accepted cases)

TACO=transfusion-associated circulatory overload

There were 2 cases that scored only two criteria but were nevertheless accepted into the TACO category. This first case demonstrated respiratory distress during transfusion and radiological evidence of pulmonary oedema. The patient's condition worsened following diuretics but the patient had severe renal failure. No vital sign observations or fluid balance were available for assessment. The patient had additional comorbidities and risk factors predisposing to circulatory overload (aortic stenosis and hypoalbuminaemia). The second case had a similar respiratory and radiological picture with no response to diuretics. The fluid balance and vital sign observations were also unavailable. There was also a primary cardiac cause for pulmonary oedema (acute coronary syndrome) which complicated the assessment, and the patient had received a large volume of non-blood fluid. Taking the cases in their overall context, the evidence for TACO was clinically compelling and failure to meet the requisite number of criteria was due to lack of available data.

Demonstrating left atrial hypertension (LAH): an important aspect for categorisation of pulmonary complications of transfusion

Left atrial hypertension is an important discriminator when categorising the pulmonary complications of transfusion as radiological features in TACO and TRALI can be difficult to distinguish, and other clinical signs can be similar. This year 10/110 (9.1%) cases had echocardiography performed which was useful in demonstrating LAH. However, it is accepted that while useful for haemovigilance categorisation purposes the clinician assessing the patient may not require this investigation in order to clinically manage the patient. The 2018 TACO case surveillance definition criteria includes BNP/NT-pro BNP as an 'additional' criterion to support TACO. The role of BNP is to regulate blood pressure and blood volume. Only 3/110 (2.7%) cases reported to SHOT in 2018 provided BNP/NT-pro BNP test results. This information is especially useful when data for other criteria are not available, for example when a chest X-ray has not been performed, fluid balance not recorded or uncertain response to diuretics (especially when given in combination with allergy medications). NT-pro BNP is available on most biochemistry platforms (requiring a serum or ethylenediaminetetraacetic acid (EDTA) sample). Most laboratories will offer the test as part of primary care heart failure diagnostic service, or will be able to refer tests. It is valuable for professionals with haemovigilance responsibilities to enquire about their local services and the possibility of testing suspected TACO cases, which would only comprise a small number. The test is generally performed on an EDTA sample and therefore convenient to test the pre and post-transfusion samples without the need for separate samples to be taken. Non-cardiac comorbidities and pre-existing cardiac disease can raise NT-pro BNP. It is worth noting that NT-pro BNP is affected by a number of conditions not related to LAH. Further information can be accessed here: https://fpnotebook.com/cv/lab/BrnNtrtcPptd.htm. Scale change is important with a >1.5x increase from pre-transfusion value supporting TACO. A post-transfusion value in the normal range is not compatible with TACO and is therefore a good negative predictor.

Illustrative cases

Case 17b.1: Rapid correction of anaemia can precipitate TACO in the absence of other comorbidities and risk factors

A male in his 50s presented to the emergency department (ED) with a 3-4-week history of weakness and dizziness, and had felt unwell for the past 6 months. He was hypotensive (blood pressure (BP) 92/47) but did not show signs of acute haemorrhage though there was some altered blood on rectal examination. On admission his haemoglobin (Hb) was 34g/L, ferritin 26micrograms/L and the electrocardiogram (ECG) showed cardiac ischaemia. He was transfused two units of red cells with a plan for endoscopy and intravenous (IV) iron the following day. A third unit was planned if the post-transfusion Hb was <60g/L. The first unit was transfused over 31 minutes and the second over 65 minutes. After the second unit his oxygen saturations began to fall despite being on supplemental oxygen and his post-transfusion Hb was 51g/L. A third unit was transfused over 125 minutes and he developed worsening hypoxia, dyspnoea and crackles on chest auscultation. The chest X-ray showed an enlarged cardiac silhouette and pulmonary congestion. He was treated with diuretics and improved. Fortunately, the attending doctor cancelled the fourth unit which had been planned.

This patient certainly required transfusion to treat the symptoms of severe anaemia and cardiac ischaemia prior to IV iron replacement. The case is a good example of the risk of rapid correction of severe anaemia in the absence of haemorrhage. This patient had no other comorbidities or risk factors predisposing circulatory overload except severe anaemia. There was no indication for rapid transfusion. The development of increasing hypoxia after the second unit was a warning of TACO developing in this patient. In the absence of bleeding, the speed of correction should be commensurate with the pre-transfusion Hb level. This patient had iron deficiency anaemia, but it is worth noting that severe megaloblastic anaemia can cause cardiomyopathy, thereby increasing the risk of circulatory overload. Red cell transfusion should be avoided or minimised in these patients.

Case 17b.2: Excessive red cell volume given to an overloaded small patient where TACO was not initially suspected

A female in her 80s was admitted with a fractured neck of femur. She weighed 40kg and had a preoperative Hb of 109g/L. She received 2L of Hartmann's in theatre and returned to the ward with a positive fluid balance (+2425mL). Her postoperative Hb was 65g/L and she was haemodynamically stable. She was prescribed three units of red cells and her pre-transfusion vital sign observations were normal. Her vital sign observations after the first unit were normal but her fluid balance was then +3454mL. The second unit was given after which she became shaky and developed hypertension (175/82), pyrexia (38°C), tachycardia (102 beats per minute), tachypnoea (22 breaths per minute) and her oxygen saturation was 96% on 5L of oxygen. This was reported to the on-call orthopaedic doctor who requested further fluid to be administered stat (250mL Hartmann's) which resulted in a further deterioration of her respiratory status. The attending doctor suspected acute lung injury or sepsis (not circulatory overload). A chest X-ray was performed on the advice of the consultant haematologist whose opinion had been sought for a possible transfusion reaction. This was consistent with pulmonary oedema.

There were two striking aspects to this case. Firstly, was the choice of volume of red cells to correct the surgical anaemia. The calculation below is based on 4mL/kg raising the Hb by 10g/L (Norfolk, 2013), with a target Hb of 80g/L (cardiovascular risk factors have been assumed in a patient in her 80s).

Target Hb (g/L) – actual Hb (g/L) x [body weight (kg) x 0.4mL] = volume of red cells to transfuse to meet target Hb (mL)

80g/L – 65g/L x [40kg x 0.4mL red cells] = 240mL

This is equivalent to a single unit of red cells for a patient of this body weight. Three units are certainly excessive underlining the importance of weight-adjusted red cell dosing for non-bleeding patients. Although Norfolk states that 4mL/kg 'should only be applied as an approximation for a 70–80kg patient', Grey et al. (2018) have shown that the above calculation achieves the post-transfusion Hb target in around 90% of patients across a range of body weights.

The second aspect is failure to suspect circulatory overload in this patient. The patient already had a significantly positive fluid balance before transfusion and this had increased after the first unit of red cells. The development of deteriorating respiratory status, with hypertension, tachycardia, and pyrexia was interpreted as acute lung injury or sepsis and was treated with fluids which clearly exacerbated the circulatory overload. This illustrates the importance of measuring (and assessing) the fluid balance, and that the presence of pyrexia does not exclude TACO. Indeed, there is an increasing recognition that TACO may have an inflammatory component (see 2017 Annual SHOT Report (Bolton-Maggs et al. 2018)).

Case 17b.3: A complex presentation with difficult decision-making

A male in his 60s with history of factor XI deficiency and chronic obstructive pulmonary disease (COPD) had been referred to the colorectal team on a two-week pathway for investigation of anaemia (Hb 82g/L, platelets 92x10^9/L). He had felt increasingly unwell and presented to the ED. His Hb was 34g/L, platelets 27x10^9/L, neutrophils 0.58x10^9/L, he had renal failure (eGFR 36mL/min), hypoalbuminaemia, and prolonged clotting times (prothrombin time (PT) 23.1 seconds (s) and activated partial thromboplastin time (APTT) 90s). Per rectum examination showed melaena and endoscopy was planned for the following day. He had tachycardia and hypotension. The ED consultant suspected acute gastrointestinal bleeding and the patient was transfused a total of four units of red cells, three units of fresh frozen plasma (FFP), and one dose of platelets over 9 hours (total >2L in volume). He developed hypoxia (oxygen saturations <70%) and bradycardia (heart rate 35 beats per minute), and was pale and clammy. He was given oxygen therapy (15L) and diuretics which produced a good diuresis. He received cardiac monitoring and was transferred to the intensive therapy unit (ITU). The chest X-ray was consistent with pulmonary oedema and peripheral blood film was reported later and showed blast cells.

This was a complex presentation and although the local reviewer found rapid multi-component transfusion to be clinically justified at the time of admission, unfortunately the patient was later found not to have acute bleeding and developed TACO. The presence of blast cells in the peripheral blood was more suggestive of bone marrow failure as the cause of pancytopenia. The reviewer identified hypoalbuminaemia and renal failure as risk factors for TACO, but in common with Case 17b.2, severe anaemia is also a risk for TACO. However, if major bleeding was suspected, recognition of this may not have changed the course for this patient. The reviewer correctly stated that TACO may not be avoidable in major haemorrhage where a risk-balanced decision has to be taken for the consequences of major bleeding versus TACO. Local review identified the need for clinical reassessment after each unit which was not documented in this case, especially in the absence of signs of ongoing bleeding. It is easy to focus on the blood transfusion and clinical management aspects of TACO cases, but establishing a timely diagnosis can also have a critical role. An early blood film report has the potential to significantly change the management of a patient, and in this case may have led to more conservative blood component transfusion. This is not to say a patient with leukaemia could not also have acute gastrointestinal bleeding!

References

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

Morton S, Grant-Casey J, Bolton-Maggs P, et al. (2017) Skating on Thin Ice: National Audit of TACO Demonstrates Poor Recognition of Risk Factors. *Blood* 2017;**130(Suppl 1)**:2406. http://www.bloodjournal.org/content/130/Suppl_1/2406. [accessed 31 May 2019].

NCA (2017) National Comparative Audit of Blood Transfusion: Transfusion associated circulatory overload audit 2017 https://hospital.blood.co.uk/audits/national-comparative-audit/medical-audits/transfusion-associated-circulatory-overload-audit-2017/ [accessed 31 May 2019].

Norfolk D, (ed) (2013) Handbook of Transfusion Medicine (5th edn). The Stationery Office, London URL https://www.transfusionguidelines.org/transfusion-handbook [accessed 31 May 2019].

Vlaar APJ, Toy T, Fung M, et al. (2019) A consensus redefinition of transfusion-related acute lung injury. *Transfusion* 2019 doi.org/10.1111/trf.15311.

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

Transfusion-Associated Dyspnoea (TAD) n=8

17c

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).

There were 8 cases included as TAD for 2018, with only 2 of these initially reported as TAD. The other 6 cases were transferred from other reporting categories; 3 from TRALI and 3 from TACO.

Other cases reported initially as TAD were transferred to other categories, 1 case transferred to TRALI and 4 to febrile, allergic and hypotensive reactions (FAHR).

These transfers and the lack of data for many of the cases make it difficult to draw conclusions for the category of TAD. All cases are described in order to build up the series of cases over time. Cases related to death or major morbidity are included below, with the remaining 5 cases available on the SHOT website. This category is likely to be affected by the revised definitions of TRALI and TACO. (Vlaar et al. 2019; Wiersum-Osselton et al. 2019).

Deaths n=2

Case 17c.1: Death possibly related to the transfusion (transfer from TACO)

A woman in her 80s under investigation for pancytopenia developed bruising and a petechial rash. She was transfused with red cells (haemoglobin (Hb) 58g/L) and later with platelets but developed fever and was admitted. She became increasingly hypoxic with oxygen saturation falling to 76%. Chest X-ray showed widespread patchy shadowing. She had a cough with haemoptysis and chest pain. She also received intravenous immunoglobulin (IVIg) 1g/kg. Chest X-ray did not show evidence of fluid overload or consolidation. She declined further active intervention and died 2 days after admission. The TRALI review panel agreed that this case was more likely to be a combination of fluid overload and progressive lung infection on a background of pre-existing pulmonary fibrosis. The causes of death were recorded as 1a acute respiratory distress syndrome (ARDS), 1b pulmonary haemorrhage, TRALI and 1c immune thrombocytopenia.

Case 17c.2: An elderly man with haemorrhage who developed pulmonary and renal complications (transfer from TRALI; death possibly related to transfusion)

A man in his 80s was admitted to the intensive therapy unit from the emergency department with multiple organ failure following admission with hypovolaemic shock and a burst varicose vein. The major haemorrhage protocol was activated, and he rapidly received seven units of red cells (15-30 minutes per unit) in addition to four units of fresh frozen plasma and one of platelets. The pre-transfusion Hb was 110g/L. He was noted to have bilateral pulmonary infiltrates and crackles on auscultation. His troponin increased from 55 to 208ng/L and his pro-B-type natriuretic peptide (BNP) from 551 to 973pg/L and he required renal dialysis. He died within 24 hours of admission. This reads more like circulatory overload.

This case was considered for inclusion as a case of TACO but cardiovascular changes were not recorded and may have been modified by haemodynamic instability due to bleeding. There was also no record of fluid balance, no change in clinical condition with diuretic, and although there was some increase in BNP this was not >1.5 times the upper limit of normal. This patient probably had acute coronary syndrome which is consistent with the troponin results. The raised BNP may have been as a result of this event, worsening of pre-existing heart failure or failure to clear BNP because of renal failure. Although there is an increase it is difficult to interpret due to the other factors. Therefore, the case did not meet the ISBT criteria for TACO and was rejected by TRALI as the advisory team felt this was more likely to be circulatory overload.

It is inevitable that some cases with confounding factors or lack of clinical information provided will not strictly fit TACO or TRALI. Although these cases cannot be precisely classified it is important that they are acknowledged as this will help us understand the limitations and improvements needed in the other classifications.

Major morbidity n=1

Case 17c.3: Transfusion for menorrhagia results in respiratory failure (transfer from TRALI; major morbidity)

A woman in her 40s received a transfusion of six units of red cells for menorrhagia (continuous bleeding for 22 days). Her Hb was 45g/L (90g/L post transfusion). She had a history of chronic anaemia and previous transfusions. A pre-transfusion chest X-ray showed diffuse patchy infiltration/ consolidation. She developed shortness of breath within 2 hours of transfusion with saturation of 90%, no fever, heart rate 87 and normal blood pressure. Chest X-ray post transfusion showed asymmetrical pulmonary oedema. She required continuous positive airway pressure (CPAP) and then mechanical ventilation for 3 days. Her condition worsened despite steroids and diuretics. The donor of the triggering unit was an untransfused male so the local Blood Service decided this was not TRALI.

There was no improvement with diuretics which does not fit the criteria for TACO. However, this case is similar to TACO Case 17b.1, and is a warning to assess the need for transfusion of repeated units in patients with chronic anaemia who decompensate if transfused too much too rapidly.

Other cases

Further TAD cases can be found in the supplementary information on the SHOT website www.shotuk.org.

Commentary

Several cases with pulmonary features are moved between categories particularly when their descriptions do not meet the definition criteria. It is very helpful when reporters are able to provide as much detail as possible. There are cases both this year and in 2017 where further investigation for TRALI might have been warranted. It will be important to consider how the new international definition of TRALI impacts on these cases.

References

Vlaar APJ, Toy T, Fung M, et al. (2019) A consensus redefinition of transfusion-related acute lung injury. *Transfusion* 2019 doi.org/10.1111/trf.15311.

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