18 Pulmonary Complications

Pulmonary complications of transfusion are responsible for the majority of deaths and major morbidity from transfusion (61/115, 53.0%, deaths 2010 to 2016, Figure 3.2). During 2016 several discussions have taken place with international collaboration (haemovigilance working party of the International Society of Blood Transfusion (ISBT), the International Haemovigilance Network (IHN) and members of the American Association of Blood Banks (AABB)) about the criteria for diagnosis of transfusion-associated circulatory overload (TACO), and these are summarised in Chapter 18b that follows. Reviewing SHOT data for several years it is apparent that the number of confirmed cases of transfusion-related acute lung injury (TRALI) have reduced, and that further clarity was required about which cases to include. There are therefore changes in the TRALI definition summarised in Chapter 18a. Cases that are not assessed as at least possible TRALI have been moved to the category of transfusion-associated dyspnoea (TAD) (Chapter 18c), and the numbers in the cumulative summary graphs updated to reflect this.

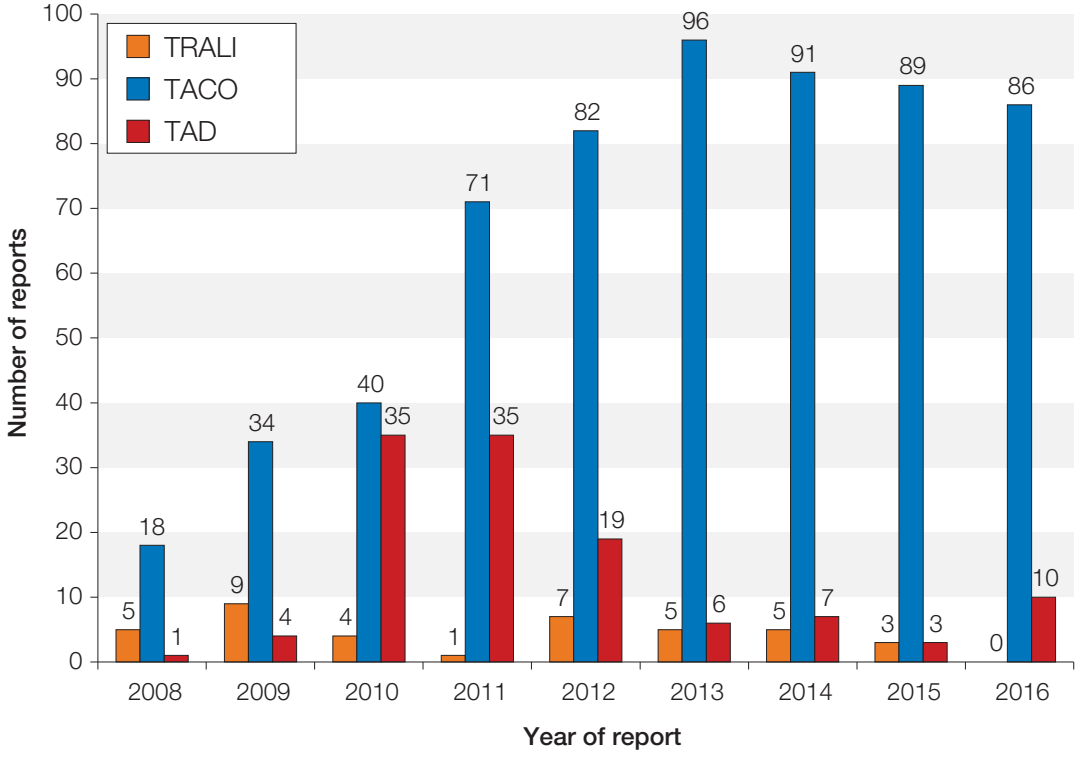


Figure 18.1: Reports of pulmonary complications by year 2008-2016 (revised to reflect updated TRALI definition)

18a Transfusion-Related Acute Lung Injury (TRALI) n=0

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 no confirmed cases of TRALI this year. Six cases were reported as suspected TRALI; 4/6 cases were transferred to transfusion-associated dyspnoea (TAD), 1/6 case to unclassifiable complications of transfusion (UCT) and one was withdrawn.

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

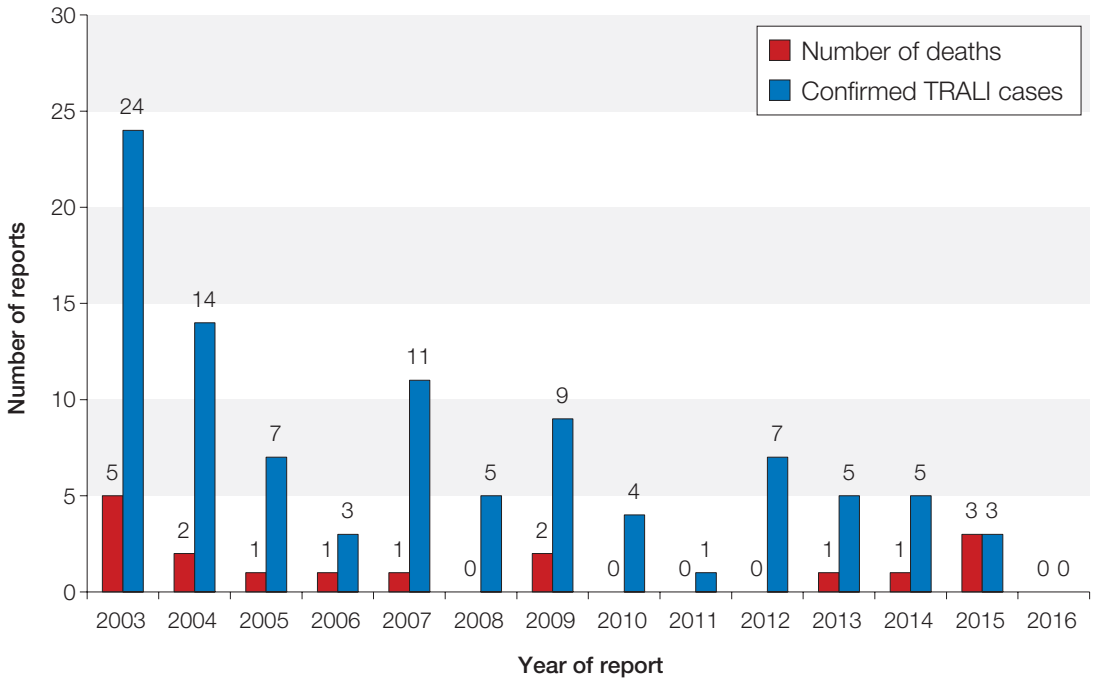


Figure 18a.1 shows TRALI cases from 2003-2016 reclassified using the new criteria. The use of male donors only for fresh frozen plasma (FFP) was implemented in 2003. Cases are recorded as deaths if death was at least 'possibly' related to transfusion (imputability 1 or greater).

Assessment of TRALI

In this year's report revised criteria for classifying TRALI are used. These give greater emphasis to the finding of leucocyte antibodies and use the presence of alternative explanations for respiratory compromise to determine imputability. The 'possible TRALI' (pTRALI) category is divided in to two categories, clarifying whether the uncertainty in diagnosis is due to the existence of alternative explanations or due to the absence of antibodies. Cases with negative serology and a dubious clinical history for TRALI have been transferred to the TAD category.

The revised criteria are outlined in Table 18a.1 below. Mapping showing how the revised criteria compare to the widely-used Canadian Consensus definitions (CCD) for TRALI is given in Table 18a.1 in order to help international comparison and Table 18a.3 shows how the 6 cases reported in 2016 would be classified by CCD.

Table 18a.4 compares the classification of historical and current cases between the two SHOT classification systems. This shows good concordance. The main difference relates to the handling of cases thought unlikely to be TRALI. It also shows that cases of 'antibody-negative TRALI' with a clear clinical history are rare.

Classification	Definition	Mapping to previous SHOT classification	Mapping to Canadian Consensus definition
Highly likely	Cases with a convincing clinical picture and positive serology	Highly likely	TRALI +positive serology
Probable	Cases with positive serology but other coexisting morbidity which could independently cause acute lung injury or fluid overload	Probable with positive serology	pTRALI +positive serology
Equivocal	Cases with positive serology in the clear presence of lung injury due to other causes or fluid overload	Possible with positive serology	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	Probable/possible with negative/absent serology	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	Unlikely	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	0
Equivocal	0
Antibody negative	0
Unlikely (transferred or withdrawn)	6

Table 18a.2: TRALI case probability (SHOT criteria) for cases reported in 2016

Canadian Consensus classification	Number of cases
TRALI	0
Possible TRALI	2
Not TRALI	4

Table 18a.3: Classification using Canadian Consensus definitions

Table 18a.4: Comparison of previous and revised classification: TRALI cases 2012-2016

Revised classification	Previous SHOT classification			
	Highly likely	Probable	Possible	Unlikely
Highly likely	3			
Probable		12		
Equivocal			2	
Antibody negative			3	
Unlikely				17

Illustrative case histories

In order to illustrate the revised classification, and compare assignment with the previous classification, some case histories from previous SHOT reports and this year's submissions are presented.

Case 18a.1: Highly likely (from the 2014 Annual SHOT Report)

A healthy 22-year-old woman had a 3L postpartum haemorrhage (PPH) after an elective caesarean section. She was transfused with four units of red blood cells in optimal additive solution (RBCOA), four FFP and two cryoprecipitate pools. Within 10 minutes of starting the cryoprecipitate transfusion she developed difficulty breathing and became cyanosed. Her oxygen saturation was 64%, respiratory rate 30 breaths per minute, pulse 125 beats per minute and her blood pressure (BP) increased. She was treated with 80mg furosemide and had a 2L diuresis but her condition worsened. Her chest X-ray showed patchy consolidation throughout both lungs. On the next day her respiratory function deteriorated further and she required intubation. She was ventilated for one day and then made a full recovery. Laboratory investigation identified multiple HLA antibody matches between donors and this patient: three female cryoprecipitate donors had concordant antibodies and one female RBCOA donor had concordant antibodies.

This case was classified as 'highly likely' and this remains unchanged - there is a classical history and multiple concordant antibodies.

Case 18a.2: Probable (from the 2015 Annual SHOT Report)

This patient was already on oxygen for pneumonia post autologous haemopoietic stem cell transplant (HSCT) but deteriorated rapidly 20 minutes after transfusion of two units of red cells and died of respiratory failure seven days later. Serology showed HLA class I antibodies cognate with the recipient.

This case was originally classified as probable TRALI. In the current classification this would also be classed as probable TRALI: there was severe deterioration with clear temporal relationship to transfusion and cognate antibodies, but it was not possible to rule out a coincidental worsening of the underlying pneumonia.

Case 18a.3: Equivocal - due to comorbidity (from the 2015 Annual SHOT Report)

This patient developed breathlessness 40 minutes following six units of red cells, four units of FFP and one pool of cryoprecipitate for a variceal bleed. There was pre-existing fluid overload before transfusion and a chest X-ray before transfusion suggested pneumonia. However antibodies cognate with the recipient were present in one red cell unit and two donors to the cryoprecipitate pool.

This case was originally classified as 'possible TRALI'. This case would be classed as 'equivocal TRALI' in the revised classification because there is large volume transfusion in the clear presence of pre-existing fluid overload and pneumonia, however the presence of antibodies cognate with the recipient cannot be ruled out as contributing to the respiratory deterioration.

Case 18a.4: Antibody-negative TRALI (from the 2012 Annual SHOT Report)

A 3-year-old boy undergoing vinblastine chemotherapy for astrocytoma became pyrexial, tachypnoeic and hypoxic 1 hour into transfusion after 140mL of a unit of RBCOA. Chest X-ray showed bilateral ground glass shadowing. He required admission for oxygen and made a full recovery after 2 days. The red cell donor was male with no antibodies on testing.

This case was originally classified as 'possible TRALI' in view of the clinical history and lack of other explanations but considering the absence of antibodies.

Case 18a.5: Unlikely - transfer to TAD (2016)

A 70-year-old woman with pre-existing evidence of infection on chest X-ray, and echocardiographic evidence of pulmonary hypertension and left atrial enlargement became hypoxic 5 hours after transfusion of a single pool of apheresis platelets. Bilateral interstitial disease was shown on computerised tomography (CT) scan of her lungs. She recovered with oxygen therapy and there was some improvement after diuretics. Serology was negative.

This case was transferred to TAD due to the negative serology and existence of multiple alternative explanations for her hypoxia, although the timing of the event would be compatible with TRALI.

Cumulative serological data

Since 1996, 204 of 324 (63.0%) reported cases have had full laboratory investigation for TRALI. Concordant antibodies were identified in 116/204 (56.9%) of these. The most frequently identified antibody specificities (either alone or in combination with other concordant antibodies) have been HLA-DR4 (22/116 cases, 19.0%), HLA-DR52 (17/116, 14.7%) and HLA-A2 (18/116, 15.5%). 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 (9/116 cases, 7.8%); HNA-2 (2/116, 1.7%); HNA-3a (2/116, 1.7%).

Analysis of reports of 184 complete TRALI investigations between 2001 and 2016 inclusive has shown that the specificities of concordant antibodies were as follows:

Table 18a.5: Concordant donor antibodies 2001 to 2016 inclusive

Concordant donor antibodies 2001 to 2016 inclusive				
HLA class I alone	HLA class II alone	Both HLA class I and HLA class II	Granulocyte-specific antibody (+/- HLA antibodies)	None identified
20/184 (10.9%)	36/184 (19.5%)	27/184 (14.7%)	18/184 (9.8%)	83/184 (45.1%)

Commentary

The definition of TRALI used by SHOT has been unchanged since 1995, and 12 years have passed since the Canadian Consensus definition was agreed (Kleinman et al. 2004). We consider that a revised definition is now appropriate in order to serve haemovigilance needs better, and to clarify the classification of pulmonary complications of transfusion. While the classical definition of 'hypoxia and chest X-ray abnormalities within 6 hours not due to other causes' is still valid, the difficulty from a classification point of view is that it is not possible to prove causation. The revised definition is a working definition which avoids the need to make a judgement on whether the event is caused by any morbidity present. Table 18a.4 shows that there is good consensus between current and previous classifications.

The association between leucocyte antibodies and TRALI is well established both in animal models and human studies, although there remain questions regarding pathogenetic mechanisms (Peters et al. 2015a). Most importantly, the success of TRALI prevention strategies, such as the use of male donor-only plasma, aimed at reducing the risk of transfusion of leucocyte antibodies supports a causative relationship (Müller et al. 2015). Antibody-mediated TRALI should therefore now be considered as a potentially preventable complication of transfusion. From a haemovigilance point of view, the practical need is to monitor antibody-associated cases in order to assess the effectiveness of prevention strategies. From this perspective, a purely clinical definition, where the presence of comorbidity excludes TRALI is unsatisfactory: there is no reason, for example, why fluid overload should offer protection from antibody-mediated damage.

In contrast, the nature of antibody-negative TRALI remains poorly understood (Peters et al. 2015b). While acute lung injury can be produced by manipulation of blood components in animal models, the relevance of these artificial models to lung injury in humans is unclear. Similarly, biological mediators

such as bioactive lipids which can cause lung injury in animal models have not, so far, been definitively demonstrated in human cases of TRALI. The practical need for these cases is for further research to identify possible mechanisms and preventive strategies. Given that there is no diagnostic test it is most helpful at this stage to restrict diagnosis of antibody-negative TRALI to cases which have a typical clinical history.

What is clear however, is that respiratory deterioration following transfusion is not uncommon. Many of the cases are multifactorial with several contributory factors coexisting; it is difficult in many cases to establish whether there was a causative relationship with transfusion at all. This is an important area for ongoing research but it is unhelpful for the monitoring of antibody-mediated TRALI to count cases thought unlikely to be TRALI in the TRALI statistics. Reassigning these 'unlikely TRALI' cases to the TAD classification will allow a broader approach to be taken to respiratory deterioration associated with transfusion.

There are certainly difficulties with defining TRALI based on antibody detection, and it is certainly not proposed that the demonstration of antibodies can yet be considered either a necessary or sufficient definition for TRALI. No serological test is completely sensitive and indeed assays such as Luminex bead assays are able to detect antibodies at lower levels than may have been possible in earlier reports. In addition, the difficulty of obtaining samples from both the recipient and all implicated donors means that some cases will not have complete serological investigation. It is certainly possible that some of the cases of 'antibody-negative TRALI' in fact relate to cases where antibodies are responsible but below limits of detection. Continuing to monitor the incidence of 'antibody-negative TRALI' may help to investigate this possibility, as the incidence would be expected to respond to preventive measures in parallel with the antibody-mediated cases.

Conversely, it is clear that the majority of donations with leucocyte antibodies do not cause TRALI. The risk of finding an antibody by chance increases with the number of donations received and thus the likelihood ratio of antibody testing for diagnosing TRALI decreases with the number of units transfused. In practice this will not affect the validity of classification, as patients with major haemorrhage are unwell almost by definition, thus having alternative explanations for respiratory deterioration and being assigned to lower imputability categories.

A final difficulty with revising the classification relates to international and historical comparison. As shown in the mapping above, it is fairly straightforward to translate between different classifications. The terminology 'equivocal TRALI' has thus been chosen for cases with positive antibodies but unclear history to avoid confusion with the 'possible TRALI' category in the Canadian Consensus classification.

In summary, we propose that the revised classification based on serology provides better separation between the haemovigilance need to monitor preventable antibody-associated cases and the investigative need to identify how to prevent pulmonary complications of transfusion. We also propose that the use of a pathologically-defined classification of TRALI gives a more objective basis for international comparison.

References

Kleinman S, Caulfield T et al. (2004) **Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel.** Transfusion 44, 1774-1789

Müller M, van Stein D et al. (2015) **Low-risk transfusion-related acute lung injury donor strategies and the impact on the onset of transfusion-related acute lung injury: a meta-analysis.** Transfusion 55(1), 164-175

Peters A, van Stein D, Vlaar AP (2015a) **Antibody-mediated transfusion-related acute lung injury; from discovery to prevention.** Br J Haematol 170, 597–614

Peters A, van Hezel M et al. (2015b) **Pathogenesis of non-antibody mediated transfusion-related acute lung injury from bench to bedside.** Blood Reviews 29, 51–61

Transfusion-Associated Circulatory Overload (TACO) n=86

18b

Authors: Sharran Grey and Paula Bolton-Maggs

Last year's analysis of SHOT data made a significant contribution to progress toward internationally agreed surveillance reporting criteria for TACO. The revision group representing the International Society of Blood Transfusion (ISBT) working party on haemovigilance in collaboration with the International Haemovigilance Network (IHN) produced new draft haemovigilance reporting criteria in 2016. The reports that have contributed to the 2016 data for this year's Annual SHOT Report played a key role in validating the new draft reporting criteria for TACO.

While there is still no single agreed reporting definition, SHOT continues to emphasise the importance of reporting all suspected cases of TACO.

Key SHOT message

- TACO must be suspected when there is respiratory distress with other signs, including pulmonary oedema, unanticipated cardiovascular system changes, and evidence of fluid overload (including improvement after diuretic, morphine or nitrate treatment), during or up to 24 hours after transfusion

Recommendation

- A formal pre-transfusion risk assessment for transfusion-associated circulatory overload (TACO) should be performed whenever possible as TACO is the most commonly reported cause of transfusion-related death and major morbidity. An example is shown in Figure 18b.1

Action: Trust/Health Board Chief Executive Officers and Medical Directors responsible for all clinical staff

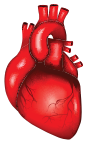
TACO Checklist	Red cell transfusion for non-bleeding patients	If 'yes' to any of these questions
	Does the patient have a diagnosis of 'heart failure' congestive cardiac failure (CCF), severe aortic stenosis, or moderate to severe left ventricular dysfunction? Is the patient on a regular diuretic?	1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

Draft ISBT reporting criteria 2016

1. Acute onset or worsening respiratory distress during or up to 12 hours after transfusion

2. Two or more of the following:

- **Evidence of acute or worsening pulmonary oedema (by physical examination or chest imaging)**
- **Evidence of unanticipated cardiovascular system changes (tachycardia, hypertension, jugular venous distension, peripheral oedema)**
- **Evidence of fluid overload (positive fluid balance, response to diuretic therapy with clinical improvement, change in the patient's weight in the peri-transfusion period)**
- **Elevation in natriuretic peptide (NP) levels (e.g. brain-natriuretic peptide (BNP), N-terminal (NT)-pro BNP) to greater than 1.5 times the pre-transfusion value**

In 2016, 86 cases were accepted as TACO which is similar to the previous year.

Deaths n=14

There were 14 deaths where the transfusion was considered to be contributory, 1 definitely related, 5 probably related and 8 possibly related.

Major morbidity n=18

There were 18 cases of major morbidity where transfusion was judged to be contributory. Ten cases of major morbidity (e.g. requirement for high level of care) resulted in major (e.g. invasive interventions to treat the TACO) or minor sequelae (non-invasive interventions) for the patient.

Demographic overview of cases

Table18b.1: Demographic overview of cases

Demographic	Number of reports	
Deaths (imputability 3)	1	
Deaths (imputability 2)	5	
Deaths (imputability 1)	8	
Major morbidity (serious sequelae)	5	
Major morbidity (minor sequelae)	5	
Major morbidity (signs and symptoms with risk to life with full resolution/unknown outcome)	8	
Age	0 days to 94 years Median 74 years	
Medical specialties (where data were provided)	Haematology Other medical specialties Surgical specialties/ anaesthetics Paediatrics/neonatal/other	29.1% (25/86) 44.2% (38/86) 16.3% (14/86) 5.8% (5/86)
Bleeding patients (indication code R1 or 'massive bleeding' indicated)	6	
Non-bleeding patients (other indication codes or not stated)	80	
Cases receiving red cells only (no other blood components)	90.7% (78/86)	
Red cells alone (without other intravenous (IV) fluids)	66.7% (52/78)	

Age analysis continues to show that TACO affects all age groups and is especially prevalent amongst the elderly because of the frequency of co-morbidities that predispose the patient to volume intolerance. This underlines the need to perform a pre-transfusion risk assessment on patients to identify those at risk, and take mitigating actions where appropriate. Haematology was the single medical specialty with the greatest number of patients developing TACO. This is because haematology patients are among the

most intensively transfused patients, many of whom are also elderly. The majority of cases occurred in non-bleeding patients requiring red cell transfusion indicating that there was probably opportunity to risk-assess the patient prior to transfusion and take mitigating actions. Concomitant IV fluids can complicate the assessment of the degree to which blood contributed to circulatory overload. The analysis shows that around a third of patients receiving red cell transfusion were also receiving non-blood fluids. If a patient develops signs of circulatory overload during or after transfusion and was also receiving fluids at the same time, or in the preceding 24 hours, it is important to report these cases to SHOT. This does not affect a diagnosis of TACO but may reduce the imputability assessment.

Surveillance diagnosis of TACO: towards internationally-agreed criteria

In order to support the advance of this collaborative work, the 2016 TACO data were analysed by three sets of criteria, two of which were used last year: clinical prioritisation of key features (CPKF); the draft ISBT 2014 criteria (DISBT 2014); and the additional new 2016 draft ISBT criteria (DISBT 2016). Multiple analyses were performed for cases reported in last year's report which highlighted several important issues that led to potential over or under-attribution of TACO. Those issues were used to revise the DISBT (2014) criteria. The purpose of this year's multiple analyses was to validate the revised DISBT (2016) criteria to ensure that valid cases were identified, providing confidence in an agreed set of reporting criteria for future use, or identifying further areas for revision.

CPKF reporting criteria

Cases accepted with symptoms and signs occurring within 24 hours of transfusion:

- Acute/worsening respiratory distress (in the absence of other specific causes)
- Acute/worsening of pulmonary oedema on imaging
- Evidence of a positive fluid balance
- Evidence of volume intolerance (response to treatment for circulatory overload or evidence of pulmonary oedema on clinical examination)

TACO was considered to be 'highly likely' with three or more features, or acute respiratory distress with pulmonary oedema on imaging; 'probable' with acute respiratory distress and clinical improvement with diuretic therapy (volume intolerance); and 'possible' with acute respiratory distress with evidence of a positive fluid balance.

DISBT (2014) reporting criteria

Acute or worsening respiratory distress within 6 hours of transfusion (some cases may occur up to 12 hours).

Primary features

- Evidence of acute or worsening pulmonary oedema with bilateral infiltrates
- Enlarged cardiac silhouette on imaging – enlarged heart contour should always be present if looked for
- Evidence of fluid overload – could be a positive fluid balance or a response to diuretic therapy combined with clinical improvement

Supporting features

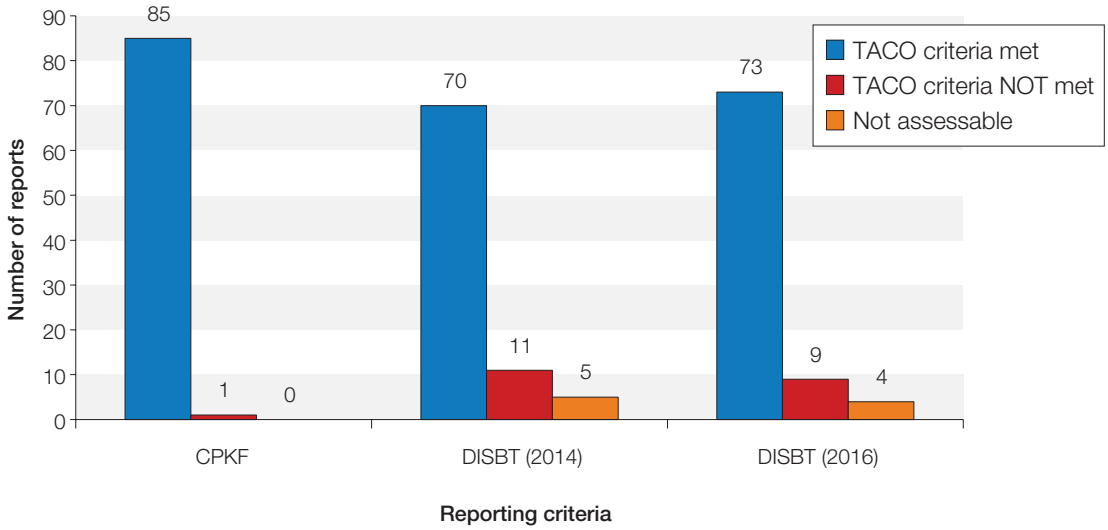
- Elevated BNP or NT-pro BNP to more than five times the pre-transfusion value (if available)
- Increased mean arterial pressure (MAP). MAP=DBP+1/3 (SBP-DBP) or, increased pulmonary wedge pressure. The MAP is typically raised, often with a widened pulse pressure. There may be hypotension in acute cardiac collapse. (DBP=diastolic blood pressure and SBP=systolic blood pressure)

'Definite' cases must have at least two primary features, or one primary and two supporting features. Cases with only one primary feature (e.g. without chest imaging) may be considered 'probable' or 'possible' depending on the presence of other supporting features.

Comparison of reporting criteria

This year 86 cases were analysed after withdrawals and transfer of some cases to other categories. Figure 18b.2 below compares each set of reporting criteria for cases which met the standards for TACO. CPKF and DISBT (2014) both employ a graded likelihood assessment (highly likely/definite, probable or possible), but the DISBT (2016) criteria only require the case to meet the minimum criteria without reference to likelihood. In order to standardise the comparison any cases with a positive degree of likelihood for CPKF or DISBT (2014) were considered to meet the criteria for TACO.

Figure 18b.2: TACO assessment by three sets of reporting criteria



There were 81.4% (70/86) of cases that met the criteria for TACO across all three reporting criteria. The 18.6% of cases (16/86) which did not agree provided useful data to further evaluate reasons for discrepancy, as detailed below.

TACO reporting criteria met for CPKF but not for DISBT (2014) and DISBT (2016) n=7

This related to timing of symptoms and signs occurring after 12 hours (n=2), and when there was only one other feature in addition to acute/worsening respiratory distress (n=5). Of the latter, this related to clinical improvement after diuretic only (n=3), and acute/worsening pulmonary oedema only (n=2). The significance of this could be argued two ways. Either the CPKF set of reporting criteria is over-sensitive, or that the DISBT (2014 and 2016) sets of reporting criteria may be too exclusive. This is compounded by BNP not being performed or available in the UK, meaning that there are fewer additional criteria usually available for assessment (only one case had a BNP performed in this reporting year). However five of the cases were assessed as 'probable' or 'possible' (i.e. lower likelihood descriptors) by the CPKF set of reporting criteria suggesting some lack of confidence in certainty. The remaining two cases were assessed as 'highly likely' but this was only based on acute/worsening respiratory distress and acute/worsening pulmonary oedema alone which may be insufficient for a confident surveillance diagnosis.

TACO reporting criteria met for CPKF and DISBT (2014) but not for DISBT (2016) n=1

This related to enlarged cardiac silhouette not being represented separately in the DISBT (2016) set of criteria and therefore not meeting the required minimum of two additional features. This was a neonate in whom there was pulmonary oedema but no other features. The baby had normal mean arterial pressure and heart rate for age. Enlarged cardiac silhouette is described in the pulmonary oedema criterion of the DISBT (2016) reporting criteria. If enlarged cardiac silhouette counted as a positive feature for unanticipated cardiovascular system changes, then this case would have met the DISBT 2016 set of criteria for TACO.

TACO reporting criteria met for CPKF and DISBT (2016) but not for DISBT (2014) n=4

Tachycardia was added to the DISBT (2016) set of criteria for unanticipated cardiovascular system changes. Cases where there was only one additional feature (pulmonary oedema or evidence of fluid overload) without changes to the blood pressure and where BNP was not performed, meant that the presence of tachycardia provided further positive evidence for TACO where previously the case would have been assessed as 'unlikely'.

TACO reporting criteria met for CPKF but not assessable by DISBT (2014) and DISBT (2016) n=4

Cases where there was only acute/worsening respiratory distress and acute/worsening pulmonary oedema are assessed as 'highly likely' by the CPKF set of reporting criteria, as no other diagnostic features are required. However, if the reporter has been unable to provide details of vital sign observations, response to diuretics, fluid balance etc., these cases are un-assessable by DISBT (2014) and DISBT (2016) sets of reporting criteria. Comprehensive case data provided by the reporter are important in ensuring robustness of the assessment.

Observations to inform further revision of the DISBT (2016) reporting criteria

- It may be useful to include cases where symptoms and signs occur up to 24 hours after transfusion. SHOT data show that there were 26 cases of TACO reported as occurring within 12-24 hours of transfusion 2010-2016 inclusive
- Enlarged cardiac silhouette should be included in the criteria for unanticipated cardiovascular system changes (not in the pulmonary oedema criteria regarding radiographic imaging)
- The introduction of tachycardia into the DISBT (2016) reporting criteria regarding unanticipated cardiovascular system changes has increased inclusivity of cases
- The CPKF reporting criteria may perhaps over-attribute TACO, especially where there is only pulmonary oedema as an additional feature and/or when there may be important data missing for a comprehensive and robust assessment

Validation of the TACO checklist

A TACO risk assessment in the form of a checklist was a recommendation in last year's report. This year's data were audited against the checklist and showed that 79.1% (68/86) of cases showed at least one positive feature on the checklist. Although this does not imply that TACO could have been prevented, it does endorse the sensitivity of the checklist for identifying risk factors and co-morbidities in patients who are at risk of TACO, allowing opportunity for intervention. Some transfusions will need to proceed despite risks for TACO being present but this should be conducted as a risk-balanced decision with mitigations put in place as far as possible, such as ensuring the appropriate dose of red cells to achieve the target haemoglobin level, prophylactic diuretics and close monitoring.

Case 18b.1: Urgent transfusion in the presence of risk factors for TACO

A patient with renal failure weighing 37kg with pre-existing fluid overload required red cell transfusion for severe symptomatic anaemia, haemoglobin (Hb) 50g/L). The patient had clinical signs of pulmonary oedema (raised jugular venous pressure, dyspnoea and frothy sputum). The patient also had a pericardial effusion and had required multiple resuscitations. One unit of red cells was prescribed and within an hour of starting the transfusion the patient began to complain of chest pain with increased work breathing, pyrexia, hypertension and tachycardia. The chest X-ray showed features of pulmonary oedema. The transfusion was stopped and the patient was given oxygen and underwent urgent haemodialysis with improvement in the symptoms.

Although the reporter did not explain why the transfusion could not be given at the same time as haemodialysis for optimum fluid management in this renal patient, it was clear that the patient required urgent transfusion. The patient had multiple risk factors for circulatory overload in addition to being overloaded prior to transfusion. Urgent transfusions are required even in the presence of risk factors for circulatory overload and this must be undertaken as a risk-balanced decision.

Mitigations and control measures are sometimes difficult to perform in time-limited situations, and especially challenging in renal failure where prophylactic diuretics may be contraindicated. There were many other examples in the reports where risks were present and where transfusion could have been deferred, treated or investigated prior to transfusion, highlighting cases of TACO that could potentially have been prevented.

Case 18b.2: Multiple positive features on the TACO checklist where TACO could probably have been prevented

An elderly patient weighing 51kg with pre-existing congestive cardiac failure (CCF) (ejection fraction 30%) and aortic stenosis received regular transfusions due to non-Hodgkin lymphoma. She was admitted with worsening dyspnoea and epigastric/chest pain. Two hours into the transfusion of a red cell unit she developed tachypnoea. The chest X-ray was suggestive of some infective consolidation but also pulmonary oedema/progressive heart failure compared to the previous image. She improved after diuretic treatment. The post-transfusion Hb was 98g/L.

Interestingly, this case was submitted as transfusion-associated dyspnoea (TAD) on the basis that there was no change in blood pressure or heart rate in this patient. The presence of pulmonary oedema and clinical response to diuretic treatment is good evidence of TACO by all reporting criteria discussed in this chapter. This patient had multiple risks as defined by the TACO checklist: CCF, aortic stenosis, and dyspnoea of undiagnosed cause (which may have been developing pulmonary oedema secondary to her pre-existing CCF). The reporter did not include the pre-transfusion Hb, but the post-transfusion Hb was 98g/L suggesting that the patient did not have severe anaemia requiring transfusion at the time of admission. She had low body weight so a dose-calculated partial unit may have been appropriate if she required transfusion at all.

The 20.9% (18/86) of cases that did not register positive features on the TACO checklist were evaluated for factors that could otherwise have potentially indicated that the patient was at risk of circulatory overload. These were grouped into those that could, or could not be prospectively identified.

Could not be prospectively identified n=12

- No obvious pre-disposing risk factors (but the patient's full past medical history was not available to SHOT to fully assess) (n=6)
- A condition that pre-disposed the patient to circulatory overload that was subsequently diagnosed as a result of the patient developing TACO (acute renal failure, cardiac dysfunction, cardiac compression) (n=3)
- Possible alternative cause for pulmonary oedema (acute coronary syndrome) but TACO equally likely with no other pre-disposing risk factors for circulatory overload (n=2)
- Pulmonary oedema possibly developing before transfusion but respiratory symptoms attributed to the patient's underlying condition (e.g. asthma) (n=1)

Potentially could be prospectively identified n=6

- Neonate with severe anaemia (n=1)
- Low serum albumin in the absence of other risk factors (n=1)
- Renal failure in the absence of other risk factors (n=4)

This provides further evidence for updating the TACO pre-transfusion checklist as shown in the revised infographic (Figure 18b.1), and SHOT makes this recommendation again for this reporting year.

Persistent poor practice in common clinical scenarios

Disappointingly, there were a number of cases where inappropriate transfusion led to TACO, and this has been repeated year-on-year. The inappropriate use of fresh frozen plasma (FFP) to reverse warfarin and overtransfusion of patients with haematinic deficiency is still occurring.

Case 18b.3: FFP used instead of prothrombin complex concentrate (PCC) due to incorrect anticoagulant management rationale

A 75-year-old patient was admitted with suspected lower limb ischaemia. He was already anticoagulated with warfarin for a metallic mitral heart valve. He had a 'poor chest' making him unsuitable for general anaesthetic and therefore required regional anaesthesia. The consultant haematologist was asked to give advice regarding his perioperative anticoagulant management. The consultant advised that the patient was not suitable for PCC because he/she believed there was greater risk of valve-related thrombosis and so suggested FFP and vitamin K instead. Two units of FFP were given on the ward and a further two were to be given in theatre. On arrival in theatre his respiratory status had deteriorated with tachypnoea, reduced oxygen saturation and increased oxygen requirement. Pulmonary oedema was diagnosed. He was treated with nitrates and diuretics and recovered.

Patients with mechanical heart valves require careful perioperative anticoagulant management to prevent valve thrombosis, and also to prevent bleeding caused by the surgical procedure itself. Warfarin should be fully reversed preoperatively with PCC and vitamin K. Anticoagulation is then alternatively managed with unfractionated heparin to allow maximum control by keeping the un-anticoagulated period during surgery to a minimum. Warfarin can be resumed postoperatively. There is no advantage to using FFP over PCC to minimise the risk of thrombosis. Both provide vitamin K dependent clotting factors but PCC has the advantage of having complete and rapid reversal due to the much greater concentration of factors and is both more reliable than FFP, and gives a smaller IV volume. This was critical in this case where the larger volume of FFP caused circulatory overload and pulmonary oedema in this patient who required emergency surgery.

Case 18b.4: Bleeding on direct oral anticoagulants

A 69-year-old patient with a history of CCF had persistent bleeding while anticoagulated with a direct oral anticoagulant (anti-Xa inhibitor) for atrial fibrillation. His prothrombin time (PT) and activated partial thromboplastin time (APTT) were slightly prolonged. He was given four units of FFP to treat the bleeding. He became hypertensive and developed tachypnoea and hypoxia. Pulmonary oedema was diagnosed. The patient was treated with diuretics and recovered.

The anti-Xa inhibitor the patient was taking is known to cause prolongation of the PT and APTT. These agents are not reversible with FFP. This patient was particularly vulnerable to circulatory overload posed by the relatively large volume of the FFP dose due to his pre-existing CCF. These drugs have a relatively short half-life and therefore omission of the drug is often sufficient to restore normal haemostasis if the patient does not have renal impairment. In the presence of major bleeding, specific reversal agents should be administered where licensed and available (e.g. for dabigatran, an anti-IIa agent, see literature review in Chapter 11d, Incidents Related to Prothrombin Complex Concentrates). Omission of the drug may have been appropriate for this patient and the presence of the drug can be evaluated by drug-calibrated anti-Xa assays (where available) if there is doubt about its clearance. There are few data for the use of PCC but it may be considered if the bleeding cannot be controlled with other measures such as tranexamic acid, and if the specific reversal agent is not available.

Case 18b.5: Red cell overtransfusion in chronic megaloblastic anaemia leading to TACO

A 90-year-old patient was admitted with severe megaloblastic anaemia (Hb 41g/L) and worsening peripheral oedema due to CCF. The consultant haematologist recommended six units of red cells but the ward staff decided to administer three. The patient developed dyspnoea, hypoxia and fever during the transfusion. The duty doctor diagnosed pneumonia and then eventually fluid overload. The chest X-ray showed worsening pulmonary oedema compared to the previous image performed on admission. The patient was treated with diuretics and recovered. The reporter stated that they felt that it was difficult to attribute fluid overload to transfusion because the X-ray suggested some patchy consolidation and the patient had peripheral oedema on admission.

This elderly patient was clearly overloaded prior to transfusion due to CCF and severe anaemia, putting her at greater risk of developing TACO. Three units of red cells are excessive in this situation given the chronicity of the anaemia and the risk factors for overload, and it is fortunate the original recommendation for six units was not actioned. Severe megaloblastic anaemia causes impaired cardiac muscle function thus red cell transfusion should be avoided wherever possible because of the risk of causing potentially fatal circulatory overload. The diagnosis of TACO was complicated by the presence of fever and possible pneumonia. It is of course possible that circulatory overload and a septic condition can co-exist which may confound the diagnosis of fluid overload. It is important to recognise that a patient who has pre-transfusion fluid overload (evidenced by worsening CCF and peripheral oedema in this case) may experience exacerbation of overload by transfusion. This was a clear case of TACO caused by excessive transfusion of red cells where there were obvious risk factors for circulatory overload. A single unit or weight-based dose of red cells with a prophylactic diuretic and close monitoring, preceded by vitamin B12 therapy would have been appropriate.

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Transfusion-Associated Dyspnoea (TAD) n=10

18c

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).

Key SHOT messages

- Most patients classified as TAD are very unwell with complicating pathology. Some of these had features suggestive of TACO but not enough reported detail to meet the SHOT criteria
- The pathophysiology of this group of complications requires further elucidation (Badami et al. 2015). There is some evidence that patients with sepsis are more at risk of respiratory complications following transfusion (Roubinian et al. 2015), a reminder that every transfusion, particularly of platelets, a rich source of biological response modifiers, (Garraud et al. 2013; Garraud et al. 2016), should be reviewed to ensure it is indicated

Ten cases are included, 2 reported as TAD, 3 transferred from TACO, 1 from acute transfusion reactions (ATR) and 4 from TRALI. Three cases were transferred from TAD to other categories, one to TACO and 2 to ATR.

Deaths n=0

There were no deaths related to transfusion in this category.

Major morbidity n=6

Six patients suffered major morbidity and are described in the case studies below.

Case details

Case 18c.1: A sick man reacts to a platelet transfusion

A 70-year-old man with acute myeloid leukaemia on chemotherapy with renal impairment became unwell at the end of a platelet transfusion (second pool) for epistaxis. He developed pyrexia and rigors and was considered to have possible sepsis. His respiratory rate (RR) increased from 17 to 36/min and he received oxygen (O_2) and bronchodilators with improvement in his clinical condition. He had a negative blood culture. His chest X-ray (CXR) was normal.

Case 18c.2: Respiratory distress with transfusion after surgery

A 66-year-old man developed acute respiratory distress, tachycardia and raised blood pressure (200/100mmHg) during red cell transfusion following elective surgery.

Around 01:30 he screamed for a nurse and was holding his abdomen. Analgesics were prescribed. At the same time he became wheezy and had chest pain. The RR was 40/min, blood pressure

202/100mm/Hg, pulse rate increased from 97 to 138 beats per minute, temperature was 37°C and oxygen saturation reduced to 90%. He was treated with oxygen and a bronchodilator and settled. A CXR showed signs of 'flash pulmonary oedema' thought to be associated with the transfusion of red cells.

Case 18c.3: A cardiac patient developed respiratory symptoms during transfusion

A 72-year-old man was transfused two units of red cells for a low haemoglobin (Hb) on the critical care unit (under care of cardiology). He had a history of ischaemic heart disease with three stents and a previous myocardial infarction, and was now generally unwell with diarrhoea. He had renal impairment and some evidence of heart failure. Changes to respiratory function and increased oxygen requirement were noted. A CXR showed early pulmonary oedema. Transfusion was completed at 19:00 and at 23:00 pO_2 dropped to 6.9. His oxygen requirement increased from 40% via facemask to 60% and then to 15L via facemask. He was given 40mg intravenous (IV) furosemide x 3 and passed 1580mL urine. TRALI was considered as a possible cause for the patient's ongoing symptoms following discharge from critical care. The TRALI expert panel concluded that the respiratory failure was more likely to be explained by the presence of heart failure, sepsis and TACO but there were not sufficient criteria for this latter diagnosis.

Case 18c.4: Influenza, septic shock and respiratory deterioration

A 30-year-old woman who was in intensive care with bilateral pneumonia related to H1N1 influenza and group A streptococcus septic shock developed respiratory distress during a second unit of red cells. She had some evidence of left ventricular and renal dysfunction related to her sepsis. Her CXR showed 'appearance compatible with overwhelming atypical pneumonia' and was the same after the reaction. Her pulse rate increased from 100 to 160bpm, her blood pressure increased and her respiratory rate increased from 19 to 50/min. She required oxygen and support with continuous positive airway pressure (CPAP). She had a diuresis of more than a litre after furosemide and was also treated with nitrates and diamorphine.

Case 18c.5: Unusual and unexplained respiratory deterioration after fresh frozen plasma (FFP) and cisplatin for malignancy

A 41-year-old woman was admitted with wheeze and cough and respiratory failure requiring admission to the intensive therapy unit (ITU) two days after treatment with two units of FFP and cisplatin. She initially had been treated for tumour-related (no detail given of primary) disseminated intravascular coagulation with raised d-dimers. The cause of the respiratory symptoms was unclear. A computerised tomography (CT) scan showed diffuse ground glass appearance. She responded to non-invasive treatment with a bronchodilator, oxygen and dexamethasone.

Case 18c.6: Respiratory complications with features of circulatory overload and infection

A 70-year-old woman with aplastic anaemia became unwell with shortness of breath following a platelet and a two-unit blood transfusion and required nebuliser and oxygen support 4.5 hours after completing the transfusion. Her oxygen saturation deteriorated from 95 to 84% with little change in respiratory rate, pulse, or blood pressure. She had mild fever of 37.4°C. She was treated with oxygen to 2L and her saturation improved to 94%. She was in positive fluid balance (1978mL) and had a diuresis of 4700mL following furosemide. Her respiratory rate remained between 18 and 20/minute and she continued on oxygen to maintain her saturations.

The donors of red cells and platelets were investigated and the results did not support antibody-mediated TRALI. The transfusion service also reported that the patient had strong human leucocyte antigen (HLA) antibodies and platelet autoantibodies. Pre-transfusion CXR three days prior to transfusion showed shadowing of right upper lobe 'query lung infection'. Post-transfusion CXR showed widespread pulmonary infiltrates and CT scan concluded that there was interstitial disease, possibly due to infection and other causes. HLA-matched blood was recommended for the patient due to poor platelet increment. However she died, unrelated to the transfusion events, eight days later.

Case 18c.7: A reaction to platelets probably associated with HLA antibodies

An elderly lady with myelodysplastic syndrome experienced breathlessness with reduced oxygen saturation 45 minutes after a platelet transfusion (pooled, in additive 70%). This necessitated admission to the ITU. There were no details of fluid balance; there was no improvement with furosemide. The donor was an untransfused male and the patient was found to have HLA antibodies which were thought to be responsible. Since this episode she has received HLA-matched platelets.

Case 18c.8: Respiratory deterioration after massive haemorrhage with some features of TACO

A 41-year-old woman developed signs of intraperitoneal haemorrhage three days following oocyte retrieval. This operation had been covered with IV heparin because she was known to have thrombophilia (factor V Leiden) and was on long term oral anticoagulation prior to surgery. The heparin was stopped on the day of haemorrhage. She experienced major haemorrhage and during resuscitation received four units of red cells, eight of FFP, a unit of platelets and 766mL of salvaged blood. In addition she received 1900mL of other fluids. She developed reduced oxygen saturation and tachypnoea within six hours and required CPAP, was transferred to the high dependency unit for seven days. CXR showed 'pneumonia in both midzones and fluid on the left indicating possible transfusion-related acute mediastinal lung injury'. TRALI investigations were negative. She was febrile without tachycardia. She improved with the IV fluids and did not receive diuretics. She improved slowly and was on CPAP for four days.

Case 18c.9: Respiratory deterioration after transfusion of red cells

A 71-year-old man (who had a hemihepatectomy for metastatic carcinoma) developed a reaction 25 minutes after starting a transfusion of red cells. At the first assessment there were no objective abnormal signs, but after restarting the transfusion further symptoms resulted in cessation of the unit. His oxygen saturation fell for several hours. A CXR showed some increased shadowing. He deteriorated despite treatment with bronchodilators and oxygen and required transfer to the ITU for two days. No further details were given.

Case 18c.10: Probable fluid overload in a man with severe liver disease

A 48-year-old man with serious alcoholic liver disease was awaiting transplant. He had refractory ascites and hydrothorax which was drained every week. Following difficulty with ascitic drainage he developed abdominal pain and was admitted the next day to the intensive care unit. He was thought to have internal bleeding. Siting of a chest drain was followed by massive haemorrhage (requiring transfusion of 12 units of red cells, 10 of FFP, three platelet doses, eight units of cryoprecipitate and additional albumin solution). The day following this fluid balance (excluding blood components) was +2.5L. Later in the day he was noted to have a low platelet count of 55x10^9/L and international normalised ratio (INR) of 2, so one unit of FFP and one of cryoprecipitate were administered using pressure bags. He then developed respiratory compromise. His oxygen saturation fell from 93 to 80% (on 35% FiO_2), respiratory rate increased from 16 to 30 breaths per minute and his pulse rate was 130 beats per minute. A CXR afterwards showed left-sided pulmonary oedema. He had 1.5L drained via a surgical chest drain 2.5 hours before the reaction. He was put on CPAP and continuous veno-venous haemofiltration to remove fluid as he had inadequate renal function. He improved with this treatment but died 10 days later from his underlying disease. This may have been transfusion-associated circulatory overload but there was not sufficient information to classify as this at the time of reporting.

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