19 Pulmonary Complications

This chapter includes data for cases reported as transfusion-associated circulatory overload (TACO) and transfusion-associated dyspnoea (TAD).

It does not include cases of acute transfusion reaction in which there was a respiratory component to their reactions e.g. allergy with bronchospasm, wheeze, stridor, angioedema or anaphylaxis. These are found in Chapter 14 Acute Transfusion Reactions (ATR). The data for Transfusion-Related Acute Lung Injury (TRALI) (Chapter 27) can be found on the SHOT website, www.shotuk.org under SHOT Annual Reports and Summaries. TRALI has decreased with the move to males as the source for all fresh frozen plasma (FFP). It is less common than TACO.

Note that for the purposes of the European Union (EU) legislation, serious adverse reactions (SAR) are defined as any reactions in patients that are 'life-threatening, disabling or incapacitating, or which result in or prolong hospitalisation or morbidity'. These must be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) (a legal requirement).

Transfusion-Associated Circulatory Overload (TACO) n=91

Authors: Harriet Lucero and Paula Bolton-Maggs

The current definitions of TACO are unsatisfactory. Tachycardia is a non-specific sign, and the blood pressure may decrease or increase. The International Society of Blood Transfusion (ISBT) working party on definitions is currently making a revision. The SHOT data collected in 2014 have been analysed against four different available definitions.

Key SHOT messages

- Current definitions for TACO are under revision – use of different definitions results in different numbers of cases

- TACO may occur at any age

- Cases should be reported to SHOT if there is evidence of respiratory distress that has improved with treatment for circulatory overload such as diuretics, nitrates or morphine

Current ISBT definition (revision in progress)

Any 4 of the following within 6 hours of transfusion

- Acute respiratory distress

- Tachycardia

- Increased blood pressure

- Acute or worsening pulmonary oedema

- Evidence of positive fluid balance

Overall 91 cases were analysed compared to 96 in 2013.

- Death was recorded for 13 patients, and in 6 of these TACO was contributory: imputability 3 (definite) in one case, imputability 2 (likely contribution) in 3 cases and imputability 1 (possibly related) in 2 cases

- Major morbidity (admission to intensive care or high dependency with ventilation) was recorded in 36 cases. Most cases occurred on the wards and were routine transfusions (Table 19.1)

Location of transfusion	
ED	2
HDU/ITU/CCU	12 (13.2%)
Theatres	3
Wards	60 (65.9%)
Day unit	6
Outpatients	4
Community hospital	2
Delivery ward	2

Emergency or routine transfusions	
Emergency or urgent	32 (35.2%)
Routine	59 (64.8%)

Table 19.1: Location and urgency of transfusion

ED=Emergency department, HDU=high dependency unit, ITU=intensive therapy unit, CCU=coronary care unit

The age range was from 1 to 98 years, median 69.5 years. The age distribution by decade is shown in Figure 19.1. It is important to note that although TACO most commonly occurs in the elderly it can occur at any age. Younger patients may be vulnerable because of associated medical conditions. It is notable that two cases occurred after transfusion at community hospitals resulting in change in practice in one. It is unfortunate that the case in which the relationship between transfusion and death was certain was transfusion of an elderly man with anaemia due to folate deficiency whose clinical history had not been fully documented and whose care was described as 'unacceptable'.

Case 1: A young person with serious comorbidity died following transfusion

A 22 year old woman with decompensated alcoholic liver disease was in intensive care, intubated and ventilated. Her coagulation tests were deranged and the decision was made to transfuse 3 units of fresh frozen plasma (FFP), 2 of cryoprecipitate and 1 unit of red cells. After the unit of red cells, which was the last component to be given, she suffered cardiac arrest, and required 10 minutes of cardiopulmonary resuscitation before return to spontaneous circulation. The chest X-ray after this event was markedly worse than before. The patient died the following day and the clinical team considered that the transfusion had contributed to her death.

Case 2: TACO follows transfusion in a community hospital

An elderly man with disseminated malignancy including pulmonary metastases was admitted to his community hospital for transfusion of 2 units of red cells. He suffered from pre-existing congestive cardiac failure and renal impairment, and was short of breath. The staff were concerned but encouraged by the oncology team at the hospital to proceed. Later the same day (between 6 and 12 hours later) the man was admitted to hospital with fluid overload, and with treatment produced a diuresis of more than 4L but later died. The transfusion was considered contributory to his death. Following review it was agreed that patients with pre-existing cardiac and other co-morbidities would not be accepted for transfusion in the community hospital.
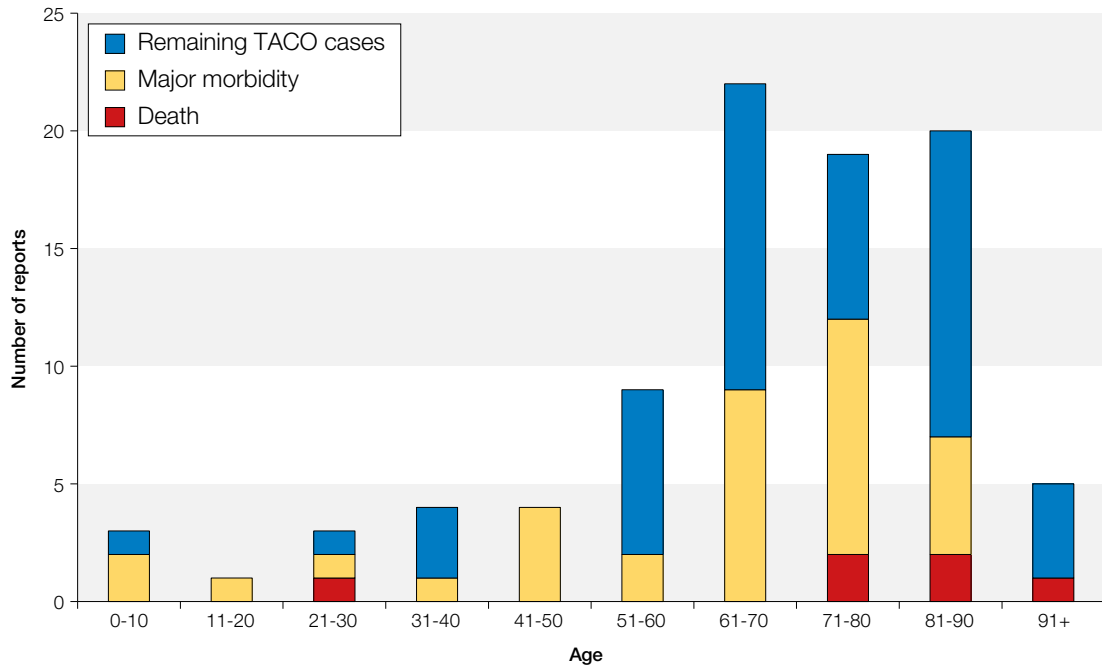
Diagnosis of TACO

Cases this year were assessed for the probability of TACO against 4 different definitions. The current ISBT definition is not satisfactory for a number of reasons. Hypo or hypertension may occur; tachycardia is a very non-specific sign. TACO is probably underreported. All cases of suspected TACO should be reported even if they do not meet the current ISBT definition. All cases of dyspnoea associated with improvement following treatment of circulatory overload should be reported.

The four definitions compared are as follows:

1. Current ISBT definition

Any 4 of the following within 6 hours of transfusion

- Acute respiratory distress

- Tachycardia

- Increased blood pressure

- Acute or worsening pulmonary oedema

- Evidence of positive fluid balance

It has been appreciated for some time now that this definition does not capture all cases of TACO. Potential reasons for this include the probability being reduced by the reporter not providing the information such as blood pressure (BP) or heart rate. Also it is now known that TACO can occur with hypotension and cases can occur after 6 hours as demonstrated by SHOT. This was reviewed in more detail in last year's Annual SHOT Report when the' key features' definition was developed by Hannah Cohen.

2. 'Key features' definition from 2013 Annual SHOT Report (KF)

- Acute respiratory distress (in the absence of other specific causes)

- Acute or worsening pulmonary oedema

- Evidence of a positive fluid balance

- Evidence of volume intolerance

The author (Hannah Cohen) reviewed all of the information available in the reports to determine the probability of TACO. The decision was mainly based on the key features listed above but also included other information such as the patient's weight and findings on clinical examination to reach a conclusion. This demonstrated that more cases could be considered as 'highly likely' TACO in comparison to the ISBT definition, however this assessment was not based on a reproducible scoring system and therefore is not easy to replicate.

3. Draft revised ISBT definition (DRISBT) (January 2015)

Cases of TACO are characterised by acute or worsening respiratory distress within 6 hours of transfusion (some cases may occur up to 12 hours), with the following features:

Primary features

- Evidence of acute or worsening pulmonary oedema with bilateral infiltrates

- An enlarged cardiac silhouette on chest imaging - enlarged heart contour should always be present if looked for

- Evidence of fluid overload - evidence of fluid overload could be a positive fluid balance or a response to diuretic therapy combined with clinical improvement

Features to support the diagnosis are:

- Elevated B-type natriuretic peptide (BNP) or N-terminal (NT)-pro BNP to more than 1.5 times the pre-transfusion value (if available)

- Increased mean arterial pressure or increased pulmonary wedge pressure. Typically the mean arterial pressure (MAP) is raised, often with widened pulse pressure; however hypotension may occur (in cases of acute cardiac collapse)

Confirmed cases (definite imputability - 3) should show at least two primary features or one in combination with two supportive features. Cases with only one primary feature (e.g. without chest imaging) may be reported as possible (imputability 1) or probable (imputability 2) TACO depending on supporting features.

In patients in intensive care who may be receiving positive pressure ventilation with varying degrees of positive end expiratory pressure (PEEP), pulmonary oedema may be difficult to diagnose at higher levels of PEEP or indeed become apparent if PEEP is reduced or removed.

There are potential concerns regarding the use of this definition within the United Kingdom where BNP and NT-pro BNP are not routinely available. It is also not routine practice to measure the pulmonary wedge pressure or mean arterial pressure. The MAP can be derived from the systolic (SBP) and diastolic (DBP) blood pressure. MAP=DBP + 1/3 (SBP-DBP).

4. Clinical prioritisation of key features (CPKY)

CPKY is based upon the 'key features' used in the 2013 Annual SHOT Report (Bolton-Maggs et al. 2014) but provides a defined weighting to each of the features to improve reproducibility as described below. Cases can also be classified as 'highly likely' if there is other hard evidence not included in the key feature categories such as post mortem data.

- Acute respiratory distress (in the absence of other specific causes)

- Acute or worsening 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)

For the purpose of this report TACO was considered 'highly likely' with ≥ 3 features, or acute respiratory distress with pulmonary oedema on chest X-ray; 'probable' with respiratory distress and response to treatment for circulatory overload (volume intolerance) and 'possible' with respiratory distress and positive fluid balance.

This definition allows TACO to be considered 'probable' if there is dyspnoea not attributable to another cause that responds to treatment for circulatory overload without the need for imaging. This would fit with hospital practice within the UK to treat the symptoms before imaging is obtained and also allows for the fact that imaging when done is often delayed in the non-emergency setting. Chest X-ray imaging is often reviewed by the treating clinicians in the first instance when a patient is in hospital and therefore there may not be detailed comments recorded such as the cardiac silhouette.

Comparison of results

This year 91 cases were submitted for analysis as TACO. Table 19.2 and Figure 19.2 below shows a breakdown of the probability of TACO in each of the cases.

Table 19.2:
Probability of
TACO by 4 different
definitions

	Original ISBT	DRISBT	KF	CPKY
Highly likely	17	39	67	51
Probable	30	9	11	26
Possible	21	21	8	2
Unlikely	23	22	5	12
Total	**91**	**91**	**91**	**91**

The data in Table 19.2 are shown in Figure 19.2 where 'highly likely' and 'probable' cases of TACO have been combined. More cases are considered to be TACO by the definitions using additional clinical features than by the proposed and previous ISBT definitions.

Figure 19.2:
Probability of
TACO by 4 different
definitions
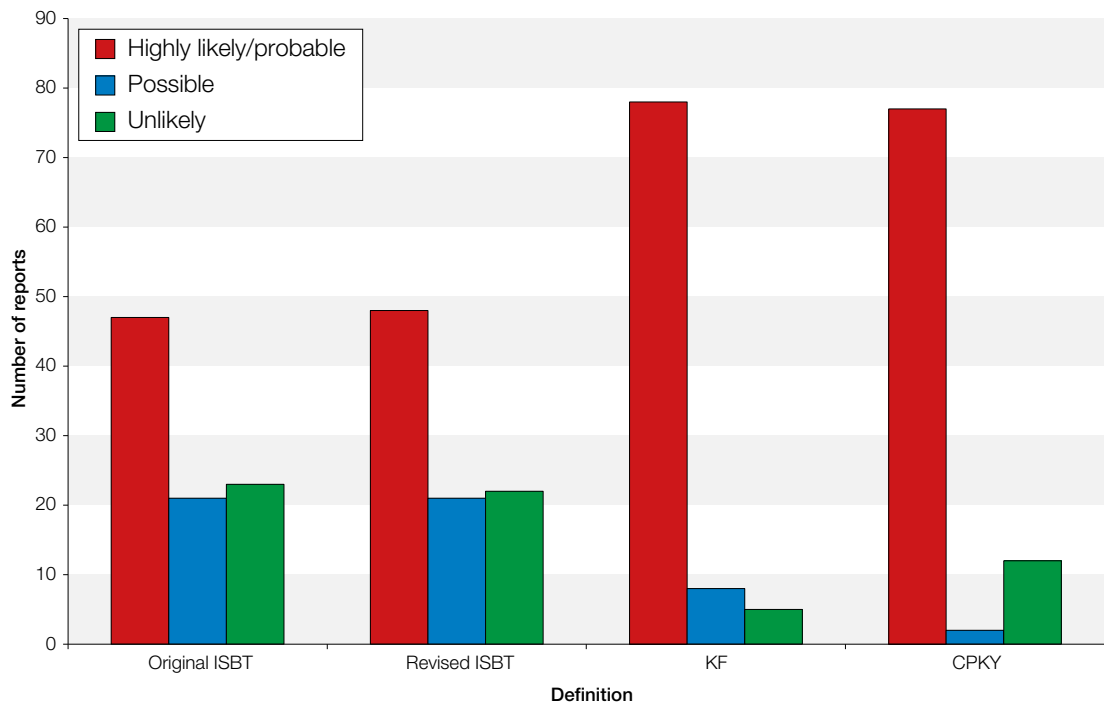
In cases reported to SHOT there remains a high incidence of death and major morbidity which were reported in 42/91 cases (46.2%). It is possible that TACO itself is not always associated with such a high level of morbidity but that the reporting of TACO is much more likely if there was a significant level of morbidity associated with the incident.

TACO cases reported to SHOT include 8 that presented after 6 hours, and 7 after 12 hours.

SHOT reporting demonstrates that approximately half of cases of TACO are seen in association with other intravenous (IV) fluid infusions (42/91, 46.2%) and the majority have pre-existing co morbidities such as pre-existing congestive cardiac failure (59/91, 64.8%).

This year 8 patients received their transfusion in community hospitals or day case units and of these 4 had delayed presentation as the patient was initially discharged, so would be excluded by any definition with a cut-off of 6 hours.

Pre-existing clinical features as risk factors for TACO in small volume transfusions

A total of 15/91 patients (16.5%) received just a single unit of red cells with no other components, 14/15 were considered to be 'probable' or 'highly likely' TACO using the CPKY definition. The median age in this group of 15 patients was 83 ranging from 65-98 years, and 3 patients weighed less than 55kg.

	Single unit transfusion (14 patients)	Overall data (89 patients)*
Fluid overload	8 (57%)	42 (47%)
Cardiac failure	4 (29%)	25 (28%)
Renal impairment	4 (29%)	35 (39%)
Liver impairment	2 (14%)	10 (11%)
Low albumin	1 (7%)	20 (22%)

Table 19.3: Pre-existing risk factors in patients receiving single units of red cells

No data in 2 cases

Case scenarios

Below are four cases which highlight different aspects and risk factors for TACO.

Case 3: Communication error

A female patient aged 92 years was on the intensive therapy unit (ITU) and following consultant review a decision was made to transfuse 2 units of blood over 2 days. The blood was then prescribed as 2 units over 2 hours each. A second consultant reviewed the patient and decided to over-rule the initial decision and deemed transfusion unnecessary. However the patient was transferred to a ward with the original prescription (2 units of blood to be transfused over 2 hours). The blood transfusion took place a day later after a review by a third consultant. It is not clear what the third consultant concluded from what has been reported to SHOT but the prescription chart remained unaltered.

The patient developed hypertension and breathlessness 2 hours after completing the second unit of blood. Pulmonary oedema was confirmed on the chest X-ray.

This case highlights the common observation of errors resulting from failures to communicate information. There was an initial communication error and then subsequent decisions were documented but not fully acted upon. The error was not noticed as the patient was transferred to another ward where the patient received the transfusion despite a third review.

The reporter noted that the patient improved following administration of furosemide but with possible prolongation of her hospital stay. This case also highlights the importance of the general advice regarding transfusions not to give 2 without review in patients at risk of TACO. If the patient had been reviewed following the initial unit of blood, perhaps the second unit might not have been given or diuretics could have been prescribed to prevent the resulting pulmonary oedema.

Case 4: Underreporting of TACO, a case identified after the notes were reviewed for other reasons

This 93 year old male was unwell with disseminated intravascular coagulation (cause not reported), congestive cardiac failure (CCF) and a lower respiratory tract infection at the time of the transfusion. The patient was being transfused with FFP during which he developed shortness of breath which improved after treatment with furosemide.

This case was only identified after a review of the notes which was undertaken for other reasons. No chest imaging was requested. This case supports the suspicion that TACO is under-recognised and under-reported.

Cases 5 and 6: Variability in probability of TACO with different decision aids

Case 5: TACO with no imaging

A 94 year old male, known to have underlying pulmonary hypertension, chronic anaemia and a haemoglobin of 91g/L was transfused red cells. Approximately 50 minutes into the transfusion the patient became hypertensive (although the mean arterial pressure was not raised), developed tachycardia and the oxygen saturation dropped. No imaging results were provided; the clinical examination was reported to reveal bibasal crepitations. The patient responded to diuretics and improved following a 700mL diuresis.

This case highlights some of the practical problems of identifying TACO using the different definitions listed above. According to the original ISBT criteria the case is 'probably' TACO (3/5) and the proposed revised ISBT criteria the case is 'possibly' TACO. This case supports the theory that TACO should be considered 'probable' in the context of the clinical situation (dyspnoea with no other likely cause), and a response to treatment for fluid overload. In this case the diagnosis was also supported by the clinical findings submitted to SHOT. This case also highlights the potential for developing TACO in a patient with underlying co-morbidities after a small volume transfusion.

Case 6: Delayed presentation

A 67 year old female patient was transfused with 3 units of red cells as an outpatient and was then readmitted more than 24 hours later with breathlessness, tachycardia, hypotension, fever and rigors. The patient was initially treated with IV fluid and antibiotics with a working diagnosis of infection and a chest X-ray was performed. Once the patient was reviewed by a haematologist on the admission unit the diagnosis was changed to TACO. By this time the chest X-ray had been formally reported and demonstrated pulmonary oedema, the patient had been treated with diuretics. On a repeat chest X-ray the oedema had resolved and the symptoms had improved.

Due to the timings and the treatment in this case it is difficult to give a clear answer whether this was a case of TACO. Both the new and revised ISBT criteria would dismiss the possibility of TACO as the patient presented after more than 12 hours.

The difficulty when applying the 'key features with clinical judgement' criteria (definition 4) is that the patient was initially treated with IV fluids and antibiotics and it is not clear when the first X-ray was taken in relation to this treatment. The X-ray did demonstrate conclusive pulmonary oedema which resolved following treatment with diuretics but the acute respiratory distress could have another cause i.e. infection. It was therefore classified as 'possible' TACO for this report.

Case 7: Difficult diagnosis: TACO or transfusion-related acute lung injury (TRALI)?

A 77 year old lady with a past medical history of hypertension, laparoscopic anterior resection for sigmoid colon cancer was admitted with lethargy, shortness of breath on exertion and poor appetite. On examination she was very pale although haemodynamically stable and clinical examination was essentially normal. She had evidence of significant iron deficiency anaemia with no signs of gastrointestinal (GI) bleeding, Hb 54g/L. Her electrocardiogram (ECG) demonstrated some ST depression in the lateral leads. A diagnosis of severe iron deficiency anaemia secondary to likely recurrence of colorectal cancer was made. The treatment plan was to transfuse 2-3 units of plasma-reduced red cells slowly over a couple of days with other radiological and GI investigations in due course.

Following transfer to a ward, she was transfused the 1st unit of red cells at 18:40 which finished at 23:00 with no major problems. She was independently mobile to the toilet following the transfusion. However, 2 hours later (01:00) she was found to have elevated early warning score (tachycardia, respiratory rate 26 breaths per minute, oxygen saturation 88%, and sounding 'very chesty') and medical help was sought.

She was in severe respiratory distress with rapid deterioration and minimal response to high dose diuretics with severe type 2 respiratory failure. ECG showed no change from earlier, and the chest X-ray was in keeping with possible acute respiratory distress syndrome (ARDS)/severe pulmonary

oedema. She eventually lost cardiac output at 04:40 despite on-going efforts to resuscitate her and died at 05:00. Bloods during the peri-arrest showed acute kidney injury (urea 9.6mmol/L, creatinine 146micromol/L) elevated troponin and Hb 79g/L.

This case highlights some of the difficulties facing clinicians. The patient had significant anaemia and although haemodynamically stable there were subtle ECG changes to suggest possible ischaemia. She was transfused 1 unit of red cells slowly and seemed to be stable immediately after the transfusion. However, she subsequently deteriorated with gross changes on the chest X-ray and continued to deteriorate despite high doses of diuretics. This case was initially submitted as possible TRALI but on review by the expert panel was transferred to TACO. Given the elevated troponin it appears a cardiac event occurred. It is impossible to say when the cardiac event occurred. This is therefore a case of pulmonary oedema which may be due to the transfusion or an alternative cause (cardiac event). However given the timing of the reaction and the timing of the transfusion it appears that the transfusion contributed to the death.

COMMENTARY

From the discussion about the definition of TACO and the cases listed above it remains clear that a formal definition of TACO is hard to achieve. For definite imputability (3) the revised ISBT definition provides the strongest level of evidence but limitations remain regarding its practical application in the UK.

The American National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol (U.S. Centers for Disease Control and Prevention 2014) uses a two-fold method in the diagnosis of TACO. Firstly the probability of circulatory overload is assessed and considered likely if any 3 of the following are present; acute respiratory distress, elevated BNP, elevated central venous pressure (CVP), evidence of left heart failure, evidence of positive fluid balance or radiographic evidence of pulmonary oedema. Then the imputability of the circulatory overload being related to the blood component is considered. 'Definite' (imputability 3) is considered when no other explanations for circulatory overload are possible. 'Probable' (imputability 2) is when transfusion is a likely contributor and either the patient received other fluids or the patient has a history of cardiac insufficiency that could explain the circulatory overload but transfusion is just as likely to have caused the circulatory overload.

Concerns with the above definition are again the use of BNP and CVP which are not routinely available in the UK and the definition of evidence of left heart failure is not clear. This could mean evidence provided by clinical examination such as bibasal crepitations or peripheral oedema, or it could be based on echocardiogram, all of which are valid clinically. There is also an omission of the response to potential treatment, we have previously found this information to be important in the diagnosis of TACO. This American approach however could provide reassurance to the clinical community that they should report all cases of circulatory overload to SHOT even if they do not think the blood component was the primary cause.

For the purpose of SHOT and other local audits a more pragmatic approach may be of benefit. This would allow cases to be considered as TACO if there was dyspnoea associated with a clinical response to treatment for circulatory overload as in definition 4 (CPKY).

The true extent of TACO remains unclear and further audit or research should be considered. A poster at the 2014 British Blood Transfusion Society Scientific Meeting demonstrated a significant number of TACO cases identified by a case note review which had not been reported to SHOT (Bartholomew and Watson 2014).

References

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