

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

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Definition:

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

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

Key SHOT messages

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

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

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

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

Deaths n=5

Case 18c.1: Acute severe reaction to transfusion

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

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

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

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

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

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

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

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

A man in his 40s with a known history of alcohol abuse and liver cirrhosis was admitted to the intensive therapy unit with a variceal bleed. His Hb was 71g/L and platelet count was $43 \times 10^9/L$ with coagulopathy. He received several blood components (three units of red cells, two units of platelets, four units of fresh frozen plasma (FFP)) prior to two units of cryoprecipitate (cryo). Before he received the cryo he was self-ventilating on room air, respiratory rate was 25/min and oxygen saturation was >94%. After starting the cryo there was an abrupt deterioration in his gas exchange resulting in emergency intubation and ventilation. His post-intubation CXR showed marked (new) bilateral interstitial infiltrates. Prior to the transfusion of cryo the central venous pressure (CVP) was 13mmHg and his fluid balance was 3L positive over 36 hours. He had received a total of 1.4L of crystalloid in the 24 hours prior to his intubation. The remainder of his positive fluid balance represented blood component support. An echocardiogram performed later in his admission showed a normal left ventricle with an estimated ejection fraction of 60% and normal right ventricular function. He received a total of 300mg of furosemide in bolus doses over the 24 hours after intubation. This had

no appreciable effect on his gas exchange and he continued to require very high levels of ventilatory support with FiO₂ consistently greater than 60% with mean airway pressures around 20cm of water.

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

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

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

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

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

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

Major morbidity n=4

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

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

There was not enough information to classify this as TACO.

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

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

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

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

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

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

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

Commentary

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

Reference

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