19 Uncommon Complications of Transfusion (UCT) n=31

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Definition:

Occurrence of an adverse effect or reaction temporally related to transfusion, which cannot be classified according to an already defined transfusion event and with no other risk factor other than the transfusion, and no other explanation.

Serious reactions in this category are reportable to the European Union (EU) as 'uncategorised unintended responses'.

Abbreviations used in this chapter

BP	Blood pressure
BSH	British Standards for Haematology
CCP	COVID-19 convalescent plasma
CLL	Chronic lymphocytic leukaemia
CPR	Cardiopulmonary resuscitation
CT	Computed tomography
CVA	Cerebrovascular accident
ECG	Electrocardiogram
ED	Emergency department
Hb	Haemoglobin
ICU	Intensive care unit
IV	Intravenous
LIMS	Laboratory information management system
NEWS	National early warning score
RCI	Red cell immunohaematology
REMAP-CAP	Randomised, embedded, multi-factorial, adaptive platform trial for community-acquired pneumonia
TA-GvHD	Transfusion-associated graft-versus-host disease
TANEC	Transfusion-associated necrotising enterocolitis
UCT	Uncommon complications of transfusion

Key SHOT messages

- Reporting uncommon and unusual complications post transfusion helps to gain a better understanding of these complications, identify risk factors, and develop risk-reduction strategies
- Some complications can be avoided by making appropriate transfusion decisions including volume of the component to be transfused, rate of transfusion, specific transfusion requirements and patient monitoring
- All appropriate investigations should be carried out in case of any suspected transfusion reactions according to BSH guidelines (BSH Tinegate et al. 2012)
- Reporters must submit all relevant information including results from any investigations done when reporting the incident to SHOT to help categorise and assign imputability to reported cases
- Transfusion reactions in acutely unwell COVID-19 patients with multisystem complications continue to be a challenge and it is difficult to ascertain causality

Recommendation

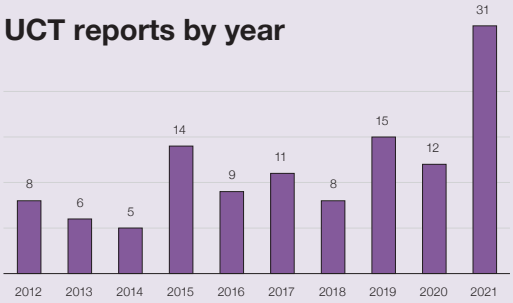
- Reporters are encouraged to continue to report cases with unusual reactions to transfusion and provide all details including clinical features and results of completed investigations when submitting the report

Action: All staff involved in transfusion

Headline data 2021

Number of reports n=31
Deaths n=7
Major morbidity n=2

UCT reports by year



Demographic data

Male n=14 | Female n=17 | Adults n=29 | Paediatric n=2

Blood component data

Red cells n=20
Platelets n=5
Plasma n=6
Multiple components n=0
Other n=0

Introduction

Cases with reactions reported in patients with temporal relation to transfusions that cannot be classified into other categories are included in this chapter. These could be due to several non-transfusion related contributory factors such as underlying diagnosis, medications, and co-morbidities. Learning from these events will improve our understanding of transfusion complications and help identify appropriate risk reduction measures. Occasionally, error reports that do not fit under other categories are included here to ensure learning is captured and shared.

The total number of incidents reported and included in this category has increased in 2021 but this may not truly reflect an increased risk from transfusions. A few cases included here may fall into other categories with some overlapping features.

Deaths related to transfusion n=7

There were 7 deaths reported in this category, all with imputability recorded as 'possible', imputability 1.

The cases are detailed below:

Stroke in acute COVID-19 patients who also received CCP n=3

Case 19.1: Stroke while sedated and on ventilation

A patient in his late 40s was admitted to the ICU with COVID-19 pneumonia. He was recruited to the REMAP-CAP trial and received one unit of CCP. He was subsequently diagnosed with a stroke approximately 3 weeks later. As the patient had been sedated for ventilation, the exact onset of the stroke could not be determined. A head CT scan confirmed a massive infarction. The patient died soon after.

Case 19.2: Stroke 3 days after receiving one unit of CCP

A patient in his 70s with hypertension, asthma (on inhalers), pre-diabetes, chronic kidney disease, bilateral total hip replacement, thalassaemia trait, thrombocytopaenia and previous cerebrovascular accident (on clopidogrel) was admitted to the ICU with a diagnosis of COVID-19. He was recruited to the REMAP-CAP trial and received one unit of CCP. He was diagnosed with a CVA 3 days later and deteriorated despite ongoing support. The main cause of death was attributed to be COVID-19 infection and stroke.

Case 19.3: Stroke diagnosed the day after receiving CCP

A patient in his 70s with high blood pressure, asthma, gastro-oesophageal reflux, and ischaemic heart disease was receiving care in ICU following a diagnosis of COVID-19. The patient had been recruited to the REMAP-CAP trial and received one unit of CCP but was diagnosed with a CVA the following day. The patient continued to deteriorate despite supportive measures and died 2 days later. The patient had been confused before intubation hence the exact onset of the stroke cannot be determined.

Commentary: Neurologic complications in patients with COVID-19 are common in hospitalised patients. More than 80% of hospitalised patients may have neurologic symptoms at some point during their disease course (Liotta et al. 2020). Stroke has been associated with COVID-19 in approximately 1 to 3% of hospitalised patients, with higher rates in those with more severe COVID-19. Several stroke subtypes may occur, including ischemic stroke, intracranial haemorrhage, and cerebral venous sinus thrombosis. In addition to traditional stroke mechanisms, potential mechanisms of ischemic stroke related to COVID-19 include hypercoagulability, inflammation, renin-angiotensin-aldosterone system dysfunction, and cardiac dysfunction (Elkind et al. 2020). Given the frequent association of stroke in COVID-19 with typical vascular risk factors and traditional stroke mechanisms, it is difficult to ascertain the degree to which the transfusion of CCP which has both anticoagulant and procoagulant plasma proteins contributed to the complication. In view of this, the imputability is recorded as 'possible' in these cases.

Other deaths reported in this category n=4

In 1 case, a premature baby died with transfusion-associated necrotising enterocolitis. This case has been described in Chapter 22, Paediatric Cases (Case 22.2).

Case 19.4: Patient death during transfusion and lack of regular observations

A patient in his 70s with type 2 diabetes mellitus, leg ulcers and hypertension was admitted to the hospital with signs of intestinal obstruction and a Hb of 73g/L. A red cell unit was requested and transfused overnight. Observations recorded for the patient an hour and 20 minutes after commencement of the transfusion had a NEWS of 3 with O2 saturations of 94%; BP 106/47 (which was drop from patient's baseline); no further observations were carried out until after 75 minutes when a cardiac arrest call was put out and CPR commenced but the patient could not be revived.

Whilst it is unclear if the death was directly related to the transfusion, the case has been included due to a temporal correlation and to highlight the importance of adequate monitoring during transfusion support and follow up investigations in case a transfusion reaction is suspected as in this case.

Case 19.5: Patient with cold agglutinins not given red cells through a warmer

A patient in his 70s was admitted to the urology ward with haematuria and received two units of red cells. The transfusion laboratory was not aware of any acute adverse reactions to the transfused units at the time as no contact had been made by the ward. The laboratory was notified by the haematology consultant 3 days later that the patient had died and queried if the blood transfusion may have been a contributory cause of death. The patient had a strong cold autoantibody and hence, samples were sent to the RCI laboratory for crossmatching red cells. The two units had been issued by RCI as 'suitable' with accompanying comments that blood should be transfused through a blood warmer. The ward was also contacted and directly relayed the same message regarding use of a blood warmer. It subsequently transpired that the first unit of red cells was not administered

via a blood warmer, and the patient became unwell. The second unit that was prescribed was administered through a warmer. Staff assessing the patient attributed the respiratory distress to COVID-19.

There were no further investigations, and it cannot be ascertained if the transfusion contributed to the patient's outcome.

Case 19.6: Acute deterioration and multiorgan dysfunction in a patient with chronic lymphocytic leukaemia

Limited details were available regarding the patient's clinical status and investigations results. A patient in his mid-80s who had chronic lymphocytic leukaemia received leucodepleted red cell transfusions as an outpatient. In view of previous treatment with purine analogue the patient needed irradiated blood components, but this was missed by the requesting medic and whilst the LIMS had a note that the patient needed irradiated components, this did not create an alert flag nor prevent issue of non-irradiated blood components. Two units of non-irradiated red cells were transfused uneventfully. The patient started feeling unwell the next day, felt tired and was pyrexial. He continued to deteriorate and developed tachypnoea with low oxygen saturations over the next 24 hours. The patient was then taken to the ED the following day (day 3 post transfusion) and was admitted with a diagnosis of suspected infection. There was a mention of multiple bilateral pulmonary emboli, acute kidney injury with worsening renal impairment and fluid overload. The patient was initially stable but deteriorated and had deranged liver functions and diarrhoea. The patient continued to deteriorate, and the decision was made after discussions with family that the patient was for end of life care. The patient needed further transfusions and two red cell units were given which were again non-irradiated. On this occasion, although it was recognised that the patient needed irradiated blood components, due to the urgency of transfusion in a deteriorating patient and potential delay in procuring irradiated components, the patient received standard blood components. The patient deteriorated and died approximately 10 days following the initial transfusion.

The initial error of elective transfusion of non-irradiated blood components was only identified during incident review after the patient's death. TA-GvHD was considered but very unlikely. No autopsy or biopsies were done.

The cause of death from the coroner was listed as 'Sepsis of unknown origin, high grade transformation of CLL, subdural haematoma, ischaemic heart disease, cerebrovascular disease and chronic kidney disease'.

Commentary: While the patient did not receive irradiated blood components following previous use of bendamustine, it is unlikely that the clinical picture of the patient was related to TA-GvHD. The clinical course was too quick for TA-GvHD as the patient was unwell from day 1 post transfusion and had other significant issues such as multiple pulmonary emboli, acute kidney injury and worsening sepsis which can explain the multiple organ dysfunction in this patient. TA-GvHD is a rare, usually fatal, complication of transfusion of cellular blood components containing lymphocytes. This is usually characterised by fever, rash, diarrhoea, hepatitis, and pancytopenia 2-30 days after transfusion. Diagnosis is confirmed by detecting persistent donor lymphocytes from a transfused component in affected tissue biopsy or peripheral blood of recipients. Diagnosis can be challenging due to competing differentials and lack of leucocytes.

The red cells received by the patient were leucodepleted and more than 14 days old which also makes TA-GvHD less likely. Components implicated in TA-GvHD have been typically whole blood and red cells and, in most cases in published literature, the implicated component was either described as fresh or as ≤10 days old. There have been no cases implicating components stored for >2 weeks (Kopolovic et al. 2015; Jawa et al. 2015 and Uchida et al. 2013). Features of TA-GvHD noted in the Kopolovic et al. review include rash (80.2%), fever (67.5%), elevated liver enzymes (66.4%), pancytopenia (65.2%), diarrhoea (43.1%), bone marrow aplasia (22.7%) or hypocellularity (17.2%) and hepatomegaly (13.5%). Relevant abnormalities occur 1-6 weeks after transfusion, with the median time from transfusion to first symptom being 11 days. Most reported cases (61.6%) occurred in men. Overall survival rate is reported to be 8.4% (Ostro et al. 2014). Irradiation remains the most effective means to reduce the risk of TA-

GvHD. Whilst leucodepletion can be protective, there is insufficient evidence to recommend leucocyte depletion alone to prevent TA-GvHD in susceptible patients (Foukaneli et al. 2020).

No investigations were undertaken in this case to help rule out TA-GvHD. The case has been included here in view of the deterioration of the patient post transfusion and there are valuable lessons to be learnt from gaps in the processes identified during the incident investigations which include: lack of staff awareness of the indications and rationale for irradiation, lack of robust processes to capture specific transfusion requirements, suboptimal LIMS which failed to create a flag despite a note indicating the need for irradiated components and allowed release of non-irradiated components.

Analysis of reports from SHOT (2010-2019), where patients failed to receive irradiated components when indicated according to BSH guidelines (BSH Tinegate et al. 2012) was carried out. There were 956 incidents of failure to receive irradiated components all due to errors. One hundred and seventy-two incidents were excluded from analysis, 125 of 172 (72.7%) because of missing essential information. No cases of TA-GvHD were reported in this cohort. The 784 patients received 2809 components (number unknown for 67 incidents). Most failures occurred in patients treated with purine analogues (365) (Elliot et al. 2021).

Major morbidity n=2

Case 19.7: Ischaemic cardiovascular event in a patient with myeloma following platelet transfusion

A woman in her 60s with refractory IgA lambda myeloma became acutely unwell 30 minutes after receiving a platelet transfusion. She reported chest tightness, developed acute respiratory distress syndrome, became hypertensive and had bilateral chest wheeze with crepitations. She continued to deteriorate despite being given chlorphenamine and IV hydrocortisone. A peri-arrest call was put out and adrenaline administered. She was assessed by the crash team, furosemide was administered, chest X-ray indicated pulmonary oedema, blood gases showed pH 7.1, PO2 10, PCO2 8, Lactate 5.3 and a decision was made to transfer to ICU for further management where the patient was intubated and ventilated. An ECG showed T wave inversion and ST depression in lateral leads. The patient improved with supportive measures in the ICU and recovered completely.

It is unclear whether the ischaemic event was coincidental, or the platelet transfusion was contributory.

Details of the 2nd case can be found in Chapter 23, Haemoglobin Disorders (Case 23.9).

Other cases n=22

Several other cases were reported in this category and have been detailed in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/).

Conclusion

Blood components should be transfused based on guidelines and clinical assessment. Unnecessary transfusions should be avoided. While transfusions are largely safe, complications do still occur and the nature of the reaction may not be immediately apparent especially as transfusion recipients often have complex underlying clinical conditions, the symptoms of which may mimic a transfusion reaction. All team members involved in the transfusion chain play an integral role in preventing errors and in early identification of transfusion complications. Appropriate training and regular education of interdisciplinary teams consisting of transfusion laboratory staff, medical and nursing staff involved in the transfusion process is paramount to achieve safe transfusion.

SHOT
Serious Hazards of Transfusion

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