Avoidable, Delayed or Under/ Overtransfusion (ADU) and Incidents Related to Prothrombin Complex Concentrate (PCC) n=347

11

Authors: Paula Bolton-Maggs, Simon Carter-Graham, Catherine Booth and Josephine McCullagh

Abbreviations used in this chapter

AAA	Abdominal aortic aneurysm
ADU	Avoidable, delayed or under/overtransfusion
AF	Atrial fibrillation
AML	Acute myeloid leukaemia
APML	Acute promyelocytic leukaemia
ATD	Adult therapeutic dose
BMS	Biomedical scientist
BP	Blood pressure
BSH	British Society for Haematology
CAS	Central alerting system
CT	Computed tomography
CVST	Cerebral venous sinus thrombosis
DIC	Disseminated intravascular coagulation
DOAC	Direct acting oral anticoagulant
EHP	Expert haematology panel
ERCP	Endoscopic retrograde cholangiopancreatography
ED	Emergency department
EVD	External ventricular drain
FBC	Full blood count
FFP	Fresh frozen plasma
GI	Gastrointestinal
GP	General practitioner
Hb	Haemoglobin
HSE	Handling and storage errors
ICH	Intracranial haemorrhage
ICU	Intensive care unit
ID	Identification
INR	International normalised ratio
IT	Information technology
ITP	Immune thrombocytopenia
IUT	Intrauterine transfusion
IV	Intravenous
LIMS	Laboratory information management system
MH	Major haemorrhage
MHP	Major haemorrhage protocol
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National comparative audit
NHS	National Health Service
PCC	Prothrombin complex concentrate
SOP	Standard operating procedure
TACO	Transfusion-associated circulatory overload
UK	United Kingdom
VITT	Vaccine induced thrombotic thrombocytopenia
VKA	Vitamin K antagonist

Key SHOT messages

- Delays in blood component transfusion and PCC administration are often multifactorial, including staffing issues, and impact on patient safety
- Avoidable transfusions could be reduced by improved management of haematinic deficiency
- Many men and women >50 years of age could receive emergency group O D-positive units rather than group O D-negative
- Avoidable errors continue to be made in paediatric prescribing and administration

Recommendations

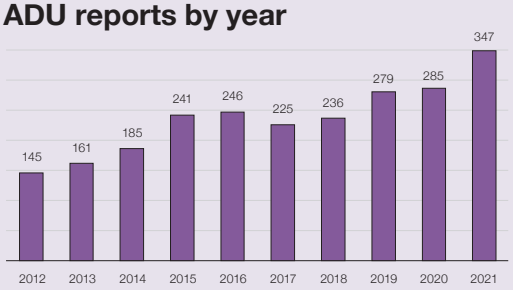
- Safe staffing levels must be ensured in hospitals both in clinical areas and transfusion laboratories and capacity plans must be reviewed regularly

Action: Hospital chief executive officers, medical directors, nursing directors, transfusion laboratory managers, pathology leads, hospital transfusion committees

Headline data 2021

Number of reports n=347
Deaths n=9
Major morbidity n=12

ADU reports by year



Demographic data

Male n=166
Female n=173
Unknown n=8

Adults n=296
Paediatric n=33
Unknown n=18

Blood component data

Red cells n=250
Platelets n=37
Plasma n=14
Multiple components n=22
PCC n=18
Granulocytes n=1
Cryoprecipitate n=1
Unknown n=4

Overview of ADU Cases

- Delayed transfusions n=179
- Avoidable transfusions n=116
- Under or overtransfusion n=34
- Incidents related to PCC n=18

Deaths related to transfusion n=9

There were 9 transfusion-related deaths, all due to delays. The imputability for all the deaths was 1: 'possibly related'. The cases are described in Chapter 11a, Delayed Transfusions.

Major morbidity n=12

There were 12 cases with major morbidity.

- Delays n=7
- Under transfusion n=2
- Over transfusion n=1
- PCC n=2

Near miss cases n=12

- Delayed transfusion n=1
- Avoidable transfusion n=4
- Under or overtransfusion n=6
- PCC n=1

Problems with MHP activations n=51

There were 51 cases with reported activation of the MHP (25 of these occurred out-of-hours)

- 28 delays (2 deaths possibly related)
- 17 avoidable use of O D-negative red cells
- 2 undertransfusion
- 4 overtransfusion

Human factors questions - impact of staffing issues

Human factors questions for reporters were modified for 2021. In answer to the question 'To what extent was there a mismatch between workload and staff provision around the time of the incident?' 91 reports noted this was 'fully', 'a lot' or 'some', and the majority, 56/91 (61.5%) impacted delayed transfusion, including 1 possibly related death (Table 11.1).

	Delays	Avoidable	Under or over	PCC
Fully n=9	7	0	1	1
A lot n=36	26	7	2	1
Some n=46	23	17	6	0
Total n=91	**56**	**24**	**9**	**2**

Table 11.1: To what extent was there a mismatch between workload and staff provision around the time of the incident?

Recommended resources

Avoidable, Delay and Under or Overtransfusion (ADU) Cumulative Data:
https://www.shotuk.org/resources/current-resources/data-drawers/avoidable-delay-and-under-or-overtransfusion-adu-cumulative-data/

UKTLC: Capacity planning guidance May 2021
https://www.shotuk.org/resources/current-resources/uktlc/

11a Delayed Transfusions n=179

Authors: Paula Bolton-Maggs, Josephine McCullagh and Simon Carter-Graham

Definition:

Where a transfusion of a blood or blood component was clinically indicated but was not undertaken or was significantly delayed or non-availability of blood components led to a delay with impact on patient care (not restricted to emergency transfusion).

Key SHOT messages

- Errors have been reported at all steps in the transfusion pathway and delays in provision of transfusion support to patients are incremental along the patient journey including transfers between wards or hospitals
- Communication issues continue to contribute to delays at all points of the transfusion pathway
- Reports where major haemorrhage protocols were not activated or not followed appropriately continue to be reported
- Staffing issues with poor patient to staff ratios in the clinical areas contribute to delays in administration of blood components. Staffing challenges in the transfusion laboratories are also contributory
- Paediatric major haemorrhage is rare and staff are often unfamiliar with the necessary procedures

Recommendations

- All actions recommended in the SHOT CAS alert 2022 must be completed to address preventable transfusion delays and ensure patient safety
- MHP are activated following rapid identification of actual, or suspected, major haemorrhage, with or without traumatic coagulopathy. These must be acted upon promptly like any other resuscitation calls to ensure effective treatment is delivered without any delays to bleeding patients
- Equipment (bleeps, pagers, printers) must be checked on a regular basis to prevent them contributing to delays in emergencies
- Hospitals who care for children should have a paediatric major haemorrhage protocol and ensure the relevant paediatric clinical and laboratory staff receive appropriate education and training

Action: Hospital transfusion committees, all transfusion staff

Introduction

Delayed transfusions continue to cause concern and the number of reports increase year on year (Figure 11a.1). These concerns resulted in publication of a CAS national alert, 'Preventing transfusion delays in bleeding and critically anaemic patients', with actions for hospitals including review of their policies and procedures (SHOT 2022). These actions should result in a reduction in delayed transfusion. Although there was a shortage of blood sample tubes in 2021 no cases of delay were reported in relation to this

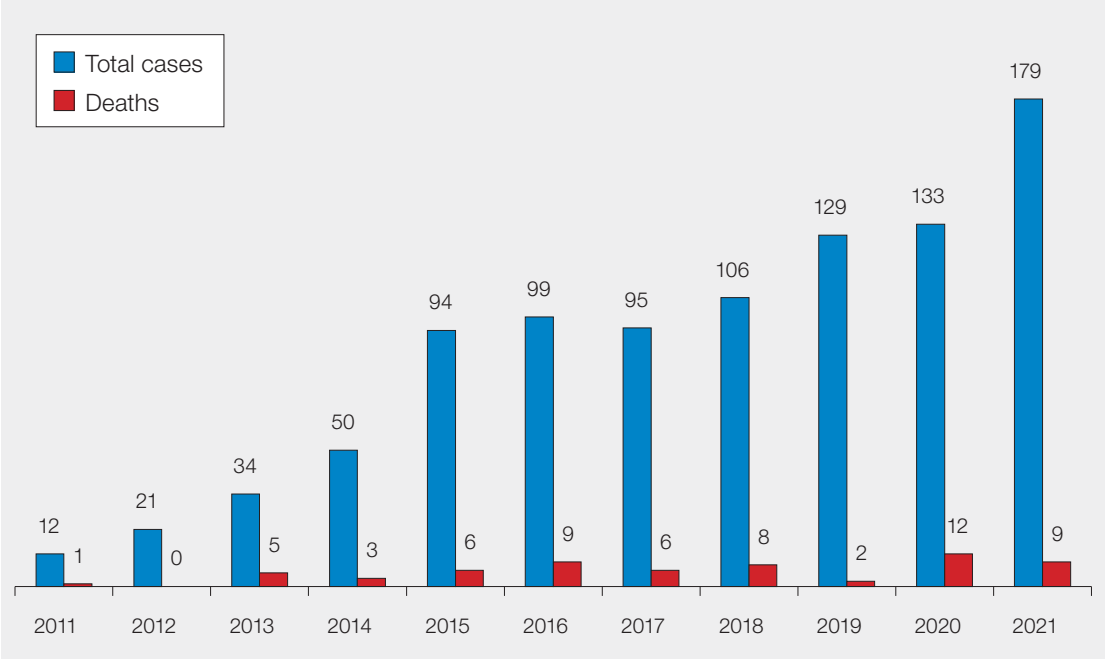


Figure 11a.1: Delayed transfusion reports and deaths by year 2011 to 2021 (n=952, deaths n=61)

Deaths related to transfusion n=9

Nine deaths were reported where the delay played a part, including 1 death in a premature infant with severe anaemia (Case 22.1 in Chapter 22, Paediatric Cases). Imputability in all these cases was 'possible'. There were 12 deaths reported in 2020.

Case 11a.1: Urgent need for blood during surgery - pager failure

Theatre staff needed blood during repair of an AAA for a man in his 80s but could not contact the BMS due to pager failure. The delay was 30 minutes and was thought to have contributed to the patient's death.

Major haemorrhage drills should include testing of communication channels and equipment. Clinical staff must be able to reach transfusion laboratory staff in case of emergencies.

Case 11a.2: Delayed transfusion contributes to death due to myocardial ischaemia

A man in his 80s with myocardial ischaemia and anaemia, Hb 63g/L, received a first unit of red cells but the second was delayed for 12 hours contributing to his death. There were several issues:

- *The request form had incorrect details so was rejected*
- *The revised request form could not be found when the porter came to collect the unit. The porter did not inform the clinical area of this*
- *A further collection form had to be sent*
- *All these factors and poor communication contributed to the delay. It is important that transfusion requests are completed accurately to avoid delays – 'Get it right first time every time'*

Case 11a.3: An unexpected death from sickle cell disease

A young man with sickle cell disease had a routine ERCP with removal of a biliary stent and went home. The next day he was admitted with fever and treated for biliary sepsis (Klebsiella was grown from the blood culture). His bilirubin remained high over the next 3 days and on day 5 he developed a sickle cell crisis with an acute chest syndrome. He rapidly deteriorated and was admitted to the intensive care unit. He developed multiple organ dysfunction and died. The review noted failure to act on the deteriorating condition in a timely manner (failure to escalate the deteriorating early warning scores) and failure to initiate prompt transfusion after recognition of deterioration. The patient was admitted to a general medical ward where staff were not familiar with sickle cell disease, and was

not managed by the haematology team directly. The coroners report suggested earlier transfusion should have been considered.

The above resulted in a recommendation from the All-Party Parliamentary Group on sickle cell and thalassaemia report (Sickle Cell Society 2021) 'No one's listening' that all NHS organisations must ensure that haematology teams are informed whenever a sickle cell patient accesses or is admitted to the hospital to ensure the patient's clinical history is known and advice can be passed on regarding their care. Staff managing the patient in this case were unfamiliar with sickle cell disease and failed to seek input from the haematology team regarding his management in a timely manner. There was no delay in the provision of blood once the haematology team were notified and a decision was made to proceed with an emergency automated red cell exchange. The APPG report includes several key recommendations that are critical to ensure safe and timely provision of care for sickle cell patients. One of the main recommendations is to ensure all healthcare professionals in the UK are trained and are familiar with management of patients with sickle cell disorder. Training should cover diagnosis, presentations, management, acute complications (such as pain, acute chest syndrome, stroke) and ongoing care and featuring direct contributions from sickle cell patients.

Learning point

- Care of patients with sickle cell disease is complex and specialised. Urgent referral to haematology locally and liaison with a specialist centre is recommended to optimise care (Sickle Cell Society 2018; BSH 2016; Trompeter et al. 2020; Sickle Cell Society 2021)

Case 11a.4: Confusion between two patients needing transfusion in the ED

Emergency red cell units were given to the wrong patient resulting in delay of blood to the intended patient and inappropriate use of emergency blood to the transfused patient. ED staff had not been able to talk to the BMS who was on the telephone about another transfusion issue. The intended recipient, Patient 1, a male in his 90s, had a Hb of 47g/L and died 15 hours after the initial request with the delayed transfusion cited as contributory. Two units of emergency blood were issued 10 minutes after the doctor requested them but were transfused to Patient 2, a woman in her 70s needing urgent surgery who had the major haemorrhage protocol activated in theatre later. Patient 1 received two units about 4.5 hours later, and two more 4 hours later. There were additional issues with unlabelled samples, wrong paperwork and training of porters.

Learning points

- Communication issues frequently contribute to delayed transfusions. It is important to be concise, clear, and provide all necessary patient identification information to the transfusion laboratory including urgency of transfusion
- Failure to label samples correctly, errors in safety checks pre transfusion, wrong paperwork, and poor training all contribute to delays. It is vital to get it right first time to avoid such delays

Additional case studies for deaths possibly related to transfusion can be found in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/).

Major morbidity n=7

Seven patients suffered major morbidity related to the transfusion delays, 4 patients died due to other causes and 3 patients recovered (these were all associated with MHP activation and communication failures).

Case 11a.5: Delayed transfusion resulted from looking at the wrong result

A man in his 50s was admitted with difficulty breathing and had a Hb of 58g/L falling to 48g/L 2 days later. The MHP was activated, and he was transfused and required admission to the ICU which might have been avoided if he had been transfused in a timely way. The doctor had looked at the wrong Hb result on the computer (101g/L from a different date).

Case 11a.6: Slow provision of components due to lack of clear communication

A man in his 50s was admitted with upper GI bleeding. MHP was initiated but red cells did not arrive in the expected time frame from the laboratory (within 15 minutes). Emergency red cell units from a satellite refrigerator were transfused and a second MHP call was initiated in view of ongoing bleed and patient deterioration. It was identified that a lack of clarity about the urgency of the MHP call resulted in a delay in provision of the blood components.

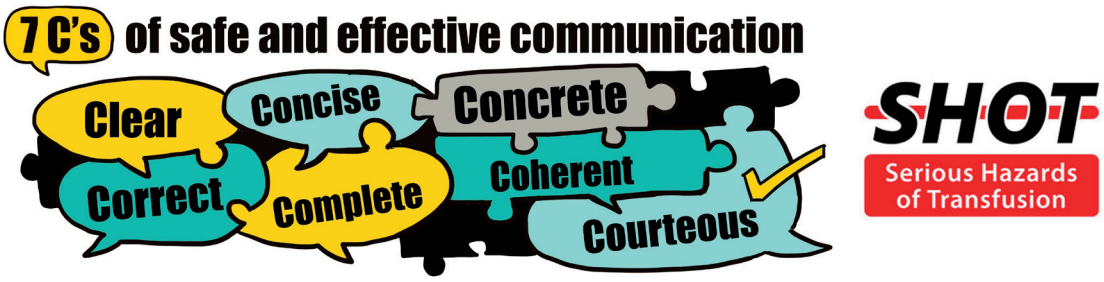
Case 11a.7: Patient struggled with breathing overnight due to delayed transfusion

A man in his 60s with cirrhosis suffered a peritoneal bleed with a Hb of 49g/L. Delay was caused by three factors: the first sample was unlabelled; a new antibody was present in the second sample (2 hours later) so was sent to the Blood Service out-of-hours for crossmatch. Although the blood was ready for transfusion by 02:00 it could not be transfused until 06:45 due to lack of ward staff. The patient struggled to breathe overnight.

Learning points

- Clinical staff at the site of a major haemorrhage alert should only have to telephone a single emergency number and have a standard script covering all essential information. Then the call can be cascaded from switchboard to other essential services. This will avoid staff dealing with the emergency being delayed by unnecessary calls
- Labelling errors must be avoided especially in emergency situations to avoid transfusion delays

A further case where the patient suffered major morbidity is discussed in Chapter 14, Laboratory Errors (Case 14.2).



Staffing and logistic issues resulting in delay

Case 11a.8: Delayed transfusion due to staff shortage (1)

A postnatal woman was seen by a doctor on a Sunday and was noted to have a Hb of 64g/L. She was symptomatic so a transfusion was requested. Blood was issued in the afternoon and confirmed by the transfusion laboratory. On review the following day the team were told that the blood was not given because the ward staff were too busy, and this was not escalated. Her Hb was now 55g/L and so further blood was requested and transfused.

Case 11a.9: Delayed transfusion due to staff shortage (2)

A woman being given palliative care had a Hb of 68g/L and a unit of red cells was requested. There was a delay of 5 days due to having staff shortages and avoiding transfusion overnight. The transfusion was eventually given with help from a neighbouring ward.

Learning point

- Staffing and workload issues have been reported as contributory factors to transfusion delays. Safe staffing levels appropriate to the workload must be in place so that necessary transfusions are not delayed. Contingency plans must be in place so that staff competent in providing transfusion support are available especially in case of emergencies

Case 11a.10: Delay in urgent transfusion caused by lack of labels in the remote refrigerator printer

A man with gastrointestinal bleeding came to theatre, shocked with hypotension and tachycardia and a Hb of 70g/L. He was eligible for electronic issue, but staff were unable to release blood from the electronically controlled refrigerator as there was no paper in the printer for the compatibility tags. Staff had to wait for the transfusion laboratory staff to come to theatre to put the labels in. During the first telephone call requesting help the staff were told the transfusion laboratory staff were in the middle of handover. The second telephone call was made by the anaesthetic consultant who said they needed someone to 'come now'. The label printer did not generate a local nor remote alert when empty and was designed to count a specified number of printed labels. It was supposed to send a remote alert when it reached a low threshold. Access to the printer was open to anyone, and is easily knocked, resulting in misalignment of the feed.

Case 11a.11: Incomplete testing results in delayed intrauterine transfusion

A severely anaemic fetus required intrauterine transfusion. A unit was requested on the basis of previous maternal antibodies (anti-c and anti-E) but the current sample displayed an additional antibody (anti-Jk^{a}) meaning the selected unit was incompatible. The hospital BMS had not completed the maternal antibody identification panels. A further unit had to be sourced from elsewhere in the country and there was a delay of 24 hours.

Case review identified that the hospital BMS required complete retraining in the manual section, was having difficulty understanding written English, and that there were staff shortages that were being addressed. The BMS has been successfully retrained and competency demonstrated. At the time of this incident the transfusion laboratory was on the hospital's risk register due to lack of staff in general and experienced staff in particular. They have continued to recruit and retain staff and are constantly reviewing and updating their training packages.

Lone working out-of-hours was identified in 4 reports as contributing to laboratory delays. One of these was a patient with sickle cell disease needing exchange transfusion for whom the wrong group had been ordered. They had to be admitted overnight.

Learning points

- Laboratory staff working in transfusion should be adequately trained and competency-assessed
- All lone workers should be adequately supported through their training and competency-assessment to ensure they are equipped with adequate skills and knowledge. Laboratory management have a responsibility to ensure all staff members are competent before exposing them to lone working

Delays associated with the Blood Services

Unavoidable delays

The presence of irregular antibodies may require samples to be sent to the Blood Service for investigation and crossmatch. Delays in provision of suitable blood components was noted for 14 cases. Patients with autoimmune haemolysis may have severe anaemia and require urgent transfusion, such as 1 case where the Hb was 34g/L so concessionary release was agreed for one red cell unit and two more became available from the Blood Service 5 hours later. Patients should not die from anaemia or bleeding.

Learning points

- Laboratory staff should liaise with clinicians and consider the urgency. The laboratory should have a policy for concessionary release of best matched red cells
- There should be clear communication between the hospital transfusion laboratory and the Blood Service about the urgency of request and any expected delays in provision to allow concessionary release

Avoidable delays

In 5 cases errors occurred at the Blood Service.

Case 11a.12: Red cells sent to the wrong hospital

An elderly man required transfusion to treat anaemia due to chemotherapy. The Blood Service used a taxi to send crossmatched and stock red cells but to the wrong hospital. A new crossmatch was arranged as the units would have been out of temperature control with another taxi transfer. The transfusion was delayed until the next day.

Case 11a.13: Miscommunication results in cancelled crossmatch and overnight admission of the patient

An elderly woman was found to have irregular antibodies. The sample was sent to the Blood Service laboratory for investigation on a morning transport run. Later the Blood Service laboratory was contacted both by telephone and email from the hospital to note that the patient required transfusion the following morning. Overnight the request was cancelled following discussion between the hospital BMS (who had not received a handover about this) and the Blood Service staff. This was a miscommunication. The patient had to be rebled and was admitted overnight. The email was found in the 'deleted' folder.

There were errors at both the hospital (handover not done and order not completed on the computer system) and the Blood Service laboratory (information poorly displayed or not accessible).

Case 11a.14: Hospital staff unable to contact the on call BMS at the Blood Service

The Blood Service laboratory could not be contacted on multiple occasions in the middle of the night when platelets were required urgently for an elderly patient with thrombocytopenia and haemoptysis. There was a 4-hour delay.

Investigation at the Blood Service identified that the hospital services telephone was diverted to the on-call colleague's work telephone which was out of order at the time. This was incorrect procedure as this was already known and the BMS had requested calls be diverted to their personal telephone, but the latest rota had not been updated with this information. This highlights the importance of having robust contingency plans for communication between clinical and laboratory staff in case of emergencies. Communication methods must be reliable with clear processes in place for escalation.

Additional case studies can be found in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/)

Learning points

- Errors anywhere along the transfusion pathway including Blood Service errors can contribute to delays in transfusion
- Human factors also impact staff working in the Blood Services. Training in this should be provided and human factors/ergonomics should be used in system design to reduce the risk of errors

Delays associated with major haemorrhage n=28

See the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/) for details.

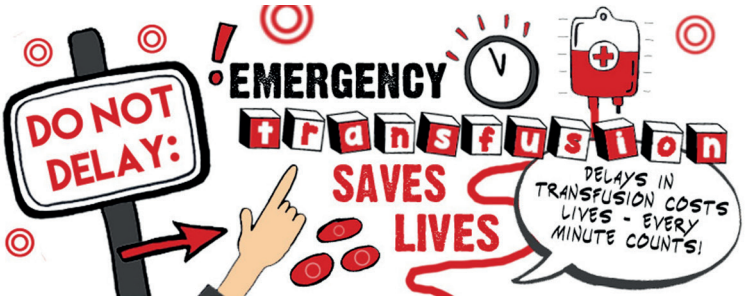
Near miss cases n=1

Case 11a.15: MHP activated for the wrong patient

Activation of the MHP for Patient 1 from the delivery suite was the incorrect patient. This should have been for Patient 2, so there was potential for delay in issuing the correct blood group for the patient in an emergency situation. However, this was recognised very quickly by clinical staff so did not result in significant delay.

Conclusion

The urgent provision of blood components and/or blood products is vital for life threatening bleeding and severe anaemia. Delays in provision and transfusion of blood components puts patients at risk and may contribute to death. Transfusion delays continue to be reported and multiple factors are usually contributory. Communication failures were identified in 48.0% of reports as a continuing problem leading to or compounding delay. Failures in team function contributed to some extent in 50.3%, and workload issues are also identified in a third of reports. Individual patient factors were much less likely to contribute. Staffing shortages are a widespread problem across the NHS and have been identified as a contributory factor in many cases of delayed transfusion reported in 2021. Urgent actions are needed to ensure safe staffing in clinical areas and laboratories and staff should escalate these issues to their managers and review their capacity plans. The recommended actions as per the SHOT CAS alert will help address preventable transfusion delays and improve patient safety. Patients should not die or suffer harm from avoidable delays in transfusion.



SHOT
Serious Hazards of Transfusion

Recommended resources

SHOT Bite No. 8: Massive Haemorrhage Delays
https://www.shotuk.org/resources/current-resources/shot-bites/

SHOT Video: Delayed Transfusion in Major Haemorrhage
https://www.shotuk.org/resources/current-resources/videos/

SHOT Webinar: Every Minute Counts
https://www.shotuk.org/resources/current-resources/webinars/

UK Transfusion Guidance in Response to the Shortage of Blood Collection Tubes
https://www.shotuk.org/resources/current-resources/

References

BSH Davis B, Allard S, Qureshi A, et al. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. *British Journal of Haematology* 2016;**176(2)**:179-191.

BSH Davis B, Allard S, Qureshi A, et al. Guidelines on red cell transfusion in sickle cell disease. Part II: indications for transfusion. *British Journal of Haematology* 2016;**176(2)**:192-209.

Sickle Cell Society. No One's Listening – A Report (2021). https://www.sicklecellsociety.org/no-ones-listening/ [accessed 05 May 2022].

Sickle Cell Society. Standards for the clinical care of adults with sickle cell disease in the UK. 2nd Edition:2018. https://www.sicklecellsociety.org/sicklecellstandards/ [accessed 05 May 2022].

SHOT. Preventing transfusion delays in bleeding and critically anaemic patients SHOT/2022/001 (2022) https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103190 [accessed 05 May 2022].

Trompeter S, Bolton-Maggs P, Ryan K, et al. National comparative audit of blood transfusion: 2014 audit of transfusion services and practice in children and adults with sickle cell disease. *Transfus Med.* 2020;**30(3)**:186-195.

Trompeter S, Estcourt L, Mora A, et al. The haemoglobinopathy survey: The reality of transfusion practice in sickle cell disease and thalassaemia in England. *Transfus Med* 2020;**30(6)**:456-466.

11b Avoidable Transfusions n=116

Authors: Paula Bolton-Maggs, Catherine Booth and Simon Carter-Graham

Definition:

Where the intended transfusion is carried out, and the blood component itself is suitable for transfusion and compatible with the patient, but where the decision leading to the transfusion is flawed.

Key SHOT messages

- For a patient with anaemia, unless there is haemodynamic instability, pause and investigate before transfusing. The definitive treatment will be correcting the underlying cause
- If a patient's results are unexpected or outwith expected trends, consider whether they fit the clinical picture. If not an emergency, repeat before acting on them
- Unless the patient is critically unstable due to bleeding, speak to the transfusion laboratory before accessing emergency group O red cells (or at least before removing multiple emergency units)
- Caution must be exercised when acting on Hb results from point-of-care machines. Ideally the result must be confirmed with a venous sample if time allows

Recommendations

- Avoidable transfusion in patients with haematinic deficiency puts them at risk of TACO. Clinical staff should be familiar with full blood count results that suggest deficiencies of iron (microcytosis), or B12 or folate (macrocytosis)
- Local transfusion training should include the indications for group O emergency red cells and how to check if group-specific or crossmatched units are available
- Laboratories should have a mechanism for alerting other pathology departments to erroneous results – a diluted sample withdrawn by biochemistry should trigger review of haematology samples taken at the same time

Action: Hospital transfusion teams, UK medical schools, transfusion laboratory managers

Introduction

There were 116 reports of avoidable transfusion compared to 110 in 2020.

Deaths related to transfusion n=0

There were no deaths reported related to avoidable transfusions.

Major morbidity n=0

There were no cases of major morbidity related to the transfusion.

Haematinic deficiency n=6

Six people were transfused for haematinic deficiency: 1 had B12 deficiency, the others had iron deficiency (4 female, 2 male). Two were found to be iron deficient preoperatively and this was not corrected resulting in the need for perioperative transfusion.

Case 11b.1: Avoidable transfusion for B12 deficiency

Two units of red cells were given to a patient with B12 and folate deficiency. His Hb was 39g/L with macrocytosis. He was referred by his GP with pancytopenia. He had symptomatic anaemia and a single unit transfusion would have been reasonable, but the administration of the second unit could have been avoided.

Pancytopenia is a characteristic feature of B12 or folate deficiency.

Case 11b.2: Avoidable transfusion for iron deficiency

A woman with symptomatic iron deficiency had a Hb of 27g/L. She was transfused three red cell units, and her post-transfusion Hb was 56g/L. She was stable with no overt bleeding or cardiovascular compromise, but she went on to receive two more red cell units. Iron replacement was not considered. The locum haematology consultant did not review the patient's latest Hb or iron results before authorising the extra two units.

Case 11b.3: Avoidable transfusion of group O D-negative emergency blood in an iron deficient patient

A man admitted to the ED with gastrointestinal bleeding was found to have a Hb of 49g/L, with a ferritin of 2micrograms/L. Four units of red cells were requested with no clinical details and urgency was also not indicated. The laboratory staff liaised with the haematology registrar who approved issue of one unit of red cells following discussions with the gastroenterologist. It was agreed that transfusion was appropriate to stabilise prior to endoscopy. In the meantime, the treating team had transfused emergency O D-negative red cells, but the laboratory staff were not updated. After two units the Hb was 68g/L. The first unit of group O blood was justifiable, but as a male, he could have received O D-positive red cells.

Learning points

- Haematinic deficiencies can be detected before severe anaemia develops and transfusions are indicated only in patients with haemodynamic instability
- All relevant clinical information must be provided to the transfusion laboratory to enable issue of appropriate blood components. The urgency of the transfusion must be stated clearly
- Hospitals need to review policies for use of emergency group O D-positive rather than D-negative for appropriate patients

The recently published NCA on medical use of blood found that 20% of patients receiving transfusion were found to have iron deficiency once investigation was complete (NCA 2022). This indicates that cases with avoidable transfusions for haematinic deficiency are significantly under-reported to SHOT contrary to published guidance (NICE 2015, Royal College of Pathologists 2019).

Errors due to verbal handover n=13

Four unnecessary transfusions were given as a result of incorrect verbal handover of treatment plans and in 3 of these there was no prescription for the transfused components. In another 5 patients a decision to transfuse was made based on incorrect results given verbally. Four patients were transfused based on handover of previous treatment plans, when subsequent medical reviews had identified that transfusion was no longer necessary.

Handover is a safety critical point in the working day. It is essential that accurate and timely information is communicated between members of staff to ensure continuity of care. This information should be documented in a standardised format where possible to ensure clarity and limit any interpretation errors. Structured, standardised communication methods overcome barriers and foster a safety culture. Change in shifts is a particularly risky time for such errors if staff taking over do not independently check the plan or relevant results.

Avoidable transfusion of group O D-negative units in patients with major haemorrhage n=17

Sixteen were due to clinical errors and 1 to laboratory error. In 15 cases the MHP was activated but in 2 it was not.

Crossmatched units were available for 8, and group-specific red cells could have been provided for another 2.

Communication issues were reported for 5/17 cases and in another none of the traceability paperwork was completed for any of the emergency blood including the prescription.

Case 11b.4: Confusion caused by duplicate hospital numbers

A woman in her 30s was admitted for elective surgery. The surgical team requested that blood be available but when they needed it, it was not ready because the BMS expected a second group sample (which was not necessary as she had a group record with another hospital number). The woman was bleeding heavily so the MHP was called and emergency group O D-negative was used. She was transfused three units of blood, four units of FFP and two pools of cryoprecipitate.

The reporting organisation had three sites; two sites use the same hospital number. This caused confusion for this patient who had more than one hospital number which was not noticed by the BMS.

The outcome from this case was to change the LIMS so that it linked patients by NHS number in the background so patients with two hospital numbers could be easily identified and blood issued.

Case 11b.5: Errors in procedure

An elderly man with neutropenic sepsis (myelodysplasia) was transferred from a ward to the coronary care unit. He developed hypotension and an initial Hb check done was 58g/L. The MHP was activated and although a repeat Hb was 73g/L he received two units of group O D-negative red cells based on the erroneous Hb result. O D-negative red cells were used despite the fact that crossmatched red cells were available. There were several errors noted in this case such as prescription errors, incomplete information on the traceability records with no patient ID information and acting on erroneous Hb results. The first Hb result may have been from a diluted sample.

Use of O D-positive units would have been appropriate n=13

Eight of these were male and 5 were females over 50 years of age who could have received group O D-positive units.

Avoidable transfusion of platelets n=17

These included 6 cases where the platelet count was above the threshold for platelet transfusion, 2 cases with spurious low counts due to clumping, another with a clot in the sample and 3 patients with immune thrombocytopenia. Others included platelets ordered for the wrong patient, platelets given the night before an invasive procedure by mistake, wrong blood in tube and cancelled surgery after platelets were transfused.

Learning points

- Thrombocytopenia is infrequently associated with bleeding and platelets should only be transfused according to guidelines (BSH Estcourt et al. 2017)
- Platelet transfusions are not indicated for ITP except in serious bleeding
- Clinical staff should be aware of platelet thresholds above which transfusion of platelets is not appropriate
- Unexpected low platelet counts should be repeated, and a blood film reviewed

Case 11b.6: Did the platelet transfusion contribute to thrombosis?

A patient with COVID-19 VITT and post thrombolysis intracranial haemorrhage with mass effect required an EVD. Platelet count originally was 16x10^9/L and increased to 46 after 2 ATD of platelets. Haematology advice to the ICU consultant and neurosurgeon was to proceed with EVD because

- *Platelet count of >80x10^9/L was not achievable*
- *The patient was unlikely to bleed given that he had VITT and was prothrombotic (i.e., thrombocytopenia would not translate into a higher risk of bleeding)*
- *There was a reasonable possibility that a platelet transfusion might cause thrombosis*

The neurosurgical registrar insisted on an additional ATD of platelets before surgery but was unwilling to wait for a check of the platelet count prior to theatre. The FBC was checked at 18:15 immediately after return to ICU from theatre. The platelet count was 33x10^9/L, with no increment following the third unit. The patient did not bleed. Subsequent postoperative head CT/CT venogram at 22:40 showed no worsening of bleed but there was a new CVST (not present on 01:34 scan), that subsequently progressed despite adequate anticoagulation. The patient recovered slowly and was discharged to another hospital.

The reporter wrote 'given the mechanism of VITT, there is a high probability that the platelet transfusion(s) directly contributed to the new CVST'.

Later review noted that:

- This is a new disease process and correct treatment remains unclear
- Current guidelines suggest platelet count >100x10^9/L is needed for neurosurgery (although this is contentious)
- It cannot be said with certainty that the additional platelet transfusion was the sole cause for sinus thrombosis in this patient

As a result, the incident has been downgraded from moderate harm. In addition, the ICU consultant noted that the right sided venous thrombosis is on the same side as the infarct and hydrocephalus with mass effect had occurred. It is reasonable to suggest that raised pressure probably affected venous flow and increased the risk of thrombosis from mechanical means (and prior to platelet transfusion) (i.e., thrombosis is multifactorial).

The patient was discharged to another hospital 3 weeks later and continued to suffer extensive and progressive arterial and venous thrombosis despite therapeutic anticoagulation with argatroban.

Commentary: VITT was first reported in 2021 (Greinacher et al. 2021, Pavord et al. 2021, Perry et al. 2021, Schultz et al. 2021). This case occurred in May 2021. This is a new condition and the guidance for management is evolving over time. Intravenous immunoglobulin and non-heparin anticoagulants are recommended (Scully et al. 2021). An expert haematology panel (EHP) was convened on 22 March 2021 meeting several times a week (Chevassut et al. 2021), collecting information from reported cases (Pavord et al. 2021) and giving advice on management. The EHP has a 'live' guidance document found here https://b-s-h.org.uk/media/20499/guidance-version-22-20210903.pdf. This notes that it is not

clear whether platelet transfusions should be given or not, and that they may be indicated to cover neurosurgery. There is also guidance from the intensive care society found here: https://www.ics.ac.uk/Society/COVID-19/PDFs/Management_VITT_Guidance.

This guidance is also unclear about platelet transfusion but states this: 'Platelets only for surgery or major bleed'. They suggest caution: 'There are theoretical reasons to try and avoid platelet transfusions in case they could exacerbate the pathological disease process, analogous to thrombotic thrombocytopenic purpura, however there is no evidence that giving platelets does actually cause any harm at this stage.' This is their conclusion: 'Note: It is unclear whether platelet transfusions will exacerbate the condition, the risk/benefit in supporting platelets <50x10^9/L on anticoagulation who a secondary cerebral bleed and not requiring procedure is unknown and therefore clear advice cannot be offered at the time of writing'.

All cases of suspected VITT should continue to be reported centrally so that more can be learned from study of as many cases as possible.

Case 11b.7: Inappropriate transfusion for immune thrombocytopenia

An elderly man with ITP on a background of chronic lymphocytic leukaemia received 50mL of platelets before transfusion was stopped as his platelet count was 1258x10^9/L. His previous count 2 weeks before was 13x10^9/L but he had been treated with eltrombopag. The plan was to review the count before proceeding with platelet transfusion but that was overruled by a doctor.

ITP is not treated with platelet transfusions unless there is serious bleeding (which is rare). Treatment guidelines recommend immune suppression and use of thrombopoietic mimetic agents such as eltrombopag (Thachil et al. 2018, Provan et al. 2019). This patient showed a very good response.

In 1 case, the patient received a platelet transfusion in error following a wrong blood in tube incident. This was investigated thoroughly and appropriate corrective and preventative actions were taken. This case has been described in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/) as well as in Chapter 5, Acknowledging Continuing Excellence in Transfusion (ACE) acknowledging the thorough and effective incident investigation.

Learning points

- When a patient has thrombocytopenia, it is important to find out the cause before requesting a platelet transfusion, particularly to exclude a spurious result
- Some causes of thrombocytopenia are associated with thrombosis rather than bleeding, including VITT and thrombotic thrombocytopenic purpura (similar mechanisms)

Avoidable transfusion of plasma components n=8

In 4 cases, patients received plasma components although coagulation tests were normal with no bleeding. Two cases related to errors involving COVID-19 convalescent plasma (1 patient received CCP instead of FFP, and the other received CCP after recovery from COVID-19. This patient had initially been randomised to receive CCP which was delayed due to sample errors but was given CCP prior to discharge which was deemed unnecessary). One patient received cryoprecipitate after an erroneous low fibrinogen was recorded due to interference in the test by dabigatran (Kanda et al. 2021). In the final case the respiratory team wanted INR <1.5 to perform a pleural tap. The FFP was transfused after the procedure had taken place.

As with transfusions in iron deficiency, these cases will most likely represent the tip of the iceberg in relation to unnecessary plasma transfusions. In the recently published NCA of use of FFP in neonates and children, more than 75% of FFP transfusions given to neonates were to correct abnormal coagulation results, in the absence of bleeding or surgery (NCA 2021). This is contrary to BSH guidelines (BSH New et al. 2016).

Learning points

- Use of FFP in non-bleeding patients with normal coagulation tests must be avoided
- There is no evidence to support prophylactic use of FFP in non-bleeding patients with pre-procedural abnormal standard coagulation tests (BSH Green et al. 2018)

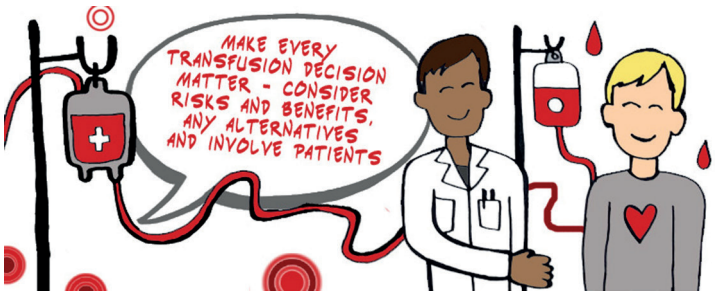
Near miss cases n=4

The 4 near miss cases are detailed in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/).

Conclusion

Unnecessary or excessive transfusion continues to be reported in patients with haematinic deficiencies, suggesting a reactive response in transfusing to correct anaemia rather than investigating and treating the cause (BSH Fletcher et al. 2022). Errors continue to occur due to decisions based on inaccurate results from clotted or diluted samples, platelet clumping, wrong blood in tube or point-of-care machines. Unexpected results should be confirmed on a repeat sample unless the patient is unstable due to bleeding. Shift changeover is a particularly dangerous time for communication errors. Transfusions should not be prescribed or administered based on verbal handover alone without confirmation in the patient's notes and after review of any relevant results. Staffing pressures, working in unfamiliar areas or on call and multiple competing priorities contribute to this.

Group O units can be lifesaving in an emergency, but O D-negative should be preserved for women of childbearing potential and robust systems are needed to ensure a switch to group specific or crossmatched units as soon as these are available.



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Recommended resources

New e-learning resources:

Anaemia
Includes modules 'Anaemia - the only introduction you need', 'Anaemia in primary care patients' and 'Anaemia in hospital patients'
https://hospital.blood.co.uk/training/clinical-courses/

Blood component use in major haemorrhage
https://www.e-lfh.org.uk/programmes/blood-component-use-in-major-haemorrhage/

The NHSBT O D-negative toolkit
https://hospital.blood.co.uk/patient-services/patient-blood-management/o-d-negative-red-cell-toolkit/

Royal College of Pathologists - Choosing Wisely
https://www.rcpath.org/profession/patient-safety-and-quality-improvement/patient-safety-resources/choosing-wisely/recommendations-for-transfusion-medicine.html

References

BSH Estcourt LJ, Birchall J, Allard S, et al. on behalf of the British Committee for Standards in Haematology. Guidelines for the use of platelet transfusions. *Br J Haematol.* 2017;**176**(3):365-394.

BSH Fletcher A, Forbes A, Svenson N, et al. Guideline for the laboratory diagnosis of iron deficiency in adults (excluding pregnancy) and children. *Br J Haematol.* 2022;**196(3)**:523-529. https://doi.org/10.1111/bjh.17900 [accessed 05 May 2022].

BSH Green L, Bolton-Maggs P, Beattie C, et al. British Society for Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding. *Br J Haematol.* 2018;**181(1)**:54-67.

BSH New HV, Berryman J, Bolton-Maggs PHB, et al. Guidelines on transfusion for fetuses, neonates and older children. *Br J Haematol.* 2016;**175(5)**:784-828.

Chevassut T, Hunt BJ and Pavord S. VITT, COVID-19 and the Expert Haematology Panel: The story of how the UK responded to emerging cases of vaccine-induced immune thrombocytopenia and thrombosis during the vaccination programme. *Clinical Medicine (Lond).* 2021;**21(6)**:e600-e602.

Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med*. 2021;**384(22)**:2092-2101. DOI: 10.1056/NEJMoa2104840.

Kanda GS, Ho WK, Rodrigues C, et al. Pitfalls in the assessment of disseminated intravascular coagulation in patients on dabigatran. *Pathology* 2021;**53(5)**:623-627.

NCA. 2018 Audit of the use of Fresh Frozen Plasma, Cryoprecipitate, and Transfusions for Bleeding in Neonates and older Children (2021). https://hospital.blood.co.uk/audits/national-comparative-audit/ [accessed 06 May 2022].

NCA. 2019 Re-audit of the Medical Use of Red Cells (2022). https://hospital.blood.co.uk/audits/national-comparative-audit/national-comparative-audit-reports/ [accessed 20 June 2022].

Pavord S, Scully M, Hunt BJ et al. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. *N Engl J Med*. 2021;**385(18)**:1680-1689.

NICE (NG24). Blood transfusion (2015). https://www.nice.org.uk/guidance/ng24 [accessed 05 May 2022].

Perry RJ, Tamborska A, Singh B, et al. Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study. *Lancet* 2021;**398**(10306):1147-1156.

Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Advances* 2019;**3(22)**:3780-3817.

Royal College of Pathologists. Recommendations for transfusion medicine (2019). https://www.rcpath.org/profession/patient-safety-and-quality-improvement/patient-safety-resources/choosing-wisely/recommendations-for-transfusion-medicine.html [accessed 05 May 2022].

Schultz H, Sorvoll IH, Michelsen AE, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. *N Engl J Med*. 2021;**384(22)**:2124-2130.

Scully M, Singh D, Lown R, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. *N Engl J Med*. 2021;**384(23)**: 2202-2211.

Thachil J, Bagot C, Bradbury C, et al. A United Kingdom Immune Thrombocytopenia (ITP) Forum review of practice: thrombopoietin receptor agonists. *Br J Haematol.* 2018;**180(4)**:591-594.

Under or Overtransfusion n=34

11c

Authors: Paula Bolton-Maggs, Catherine Booth, Simon Carter-Graham

Definition:

A dose/rate inappropriate for the patient's needs, excluding those cases which result in transfusion-associated circulatory overload (TACO). Infusion pump errors leading to under or over transfusion (if it did not lead to under/over transfusion then it is reportable under handling and storage errors (HSE).

Key SHOT messages

- Volume calculation for transfusions in paediatric patients continues to be a concern. Clinical staff involved in prescribing/authorising blood components for children must be familiar with calculating and prescribing correct doses
- Hb increment following transfusions should be checked and used to guide further transfusion support

Recommendations

- Hospitals should ensure their paediatric transfusion guidelines are updated to include calculations in g/L and not g/dL
- Staff who authorise paediatric transfusion should be trained so that they know how to calculate the correct dose of all components

Action: Hospital transfusion teams, Royal College of Paediatrics and Child Health

- Transfusion essentials must be included in the paediatric curriculum and staff should have access to regular and relevant updates. A close liaison with the hospital transfusion committee is vital to ensure that learning is optimised from reported events and trends

Action: Royal College of Paediatrics and Child Health, hospital paediatric clinical leads

Introduction

In this category with a total of 34 reports, 6 were under and 28 were overtransfusions. This is an increase compared with 2020 when 25 cases were reported. Errors in paediatric prescribing or administration resulted in 12 cases of overtransfusion in children.

The following themes emerged:

- Incorrect volume calculation in paediatrics
  - 2 cases where calculations using g/dL were used with Hb result in g/L, so volume was out by a factor of 10
  - Absence of appropriate checks: failure to notice when calculated volume exceeded adult therapeutic dose, and a 15kg child's weight mis-transcribed as 46kg

- Correct volume prescribed for paediatric patients, but complete unit administered
- Overtransfusion in sick/bleeding patients who are hypotensive where other causes for low BP were not considered and no interim Hb checks made

Deaths related to transfusion n=0

There were no deaths reported relating to under or overtransfusion in 2021.

Major morbidity n=3

Case 11c.1: Overtransfusion for GI bleeding

A woman in her 60s, weight 46kg, died following a GI bleed from a duodenal ulcer. Four units of red cells were requested because of a falling Hb (113 to 88g/L over 5 hours). After three units had been transfused over a 3-hour period her Hb was 203g/L. The overtransfusion did not contribute to the patient death.

Staff were not expecting this degree of Hb increment from three units of red cells with a baseline Hb of 88g/L but perhaps the low body weight had not been taken into consideration.

Case 11c.2: Unexpected bleeding during elective surgery

The patient suffered a major haemorrhage due to bleeding from an unidentified source during an elective laparoscopic inguinal hernia repair. The MHP was called 7 hours after the start of surgery. After about 11 hours in theatre the wound was packed, and the patient was transferred to the ICU. The bleeding could not be stopped and the patient died. This was a complex case where slow, insidious bleeding gradually worsened into a state of cardiovascular collapse due to major haemorrhage and DIC.

This was reported as undertransfusion because it was thought that this patient with active bleeding and worsening clinical status received fewer units of FFP (four units) and platelets (one ATD) than indicated for major bleeding (total 17 units of red cells) with evidence of DIC. This relative undertransfusion did not contribute to death.

Case 11c.3: Concealed blood loss after caesarean section

A woman underwent caesarean section and lost 1.3L of blood during the surgery which appeared to have been successfully managed with surgical techniques and two units of red cells. However, 8-9 hours after the delivery, she became very unwell and was taken back to theatre with suspected internal bleeding. A large amount of blood was found in her abdomen, and it was difficult to stop the bleeding and repair its source. She required a hysterectomy. The MHP was activated, and several components transfused. The patient lost 7.3L of blood in total and was transferred to the ICU for ongoing monitoring.

Undertransfusion in this case was due to delay in staff not recognising the extent of the internal bleeding following surgery. The patient had also improved partially following the initial top up transfusion which falsely reassured the treating team.

Paediatric cases

As in previous years errors in prescribing were notable and recorded in 9/12 overtransfusions. In the other 3 cases administration errors resulted in transfusion of more than had been prescribed.

Two children with malignant disease died but this was not related to the transfusion errors.

In 2 cases the wrong formula was used resulting in 10-fold error (calculated in g/dL rather than g/L). Hb has been measured in g/L rather than g/dL for several years. Calculations are available in the paediatric transfusion guidelines (BSH New et al. 2016).

All were transfusions of red cells except 1 infant who received an excess of platelets.

Learning point

- Prescribing errors for blood components in children are common. Hospitals should review their paediatric transfusion guidelines and ensure they contain updated units and calculations

Additional paediatric cases of overtransfusion have been covered in detail in Chapter 22, Paediatric Cases, as well as in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/).

Under or overtransfusion in relation to major haemorrhage n=6

There were 6 cases, 4 of overtransfusion including 2 cases of haemorrhage during surgery for abdominal aortic aneurysm. An obstetric case is discussed above.

In another case with intra-abdominal bleeding following percutaneous coronary intervention there was extreme haemodynamic instability with multiple peri-arrest episodes intraoperatively which necessitated massive transfusion. Multiple (14) red cell units were transfused but relatively fewer plasma and platelet components (four FFP, two platelets). On reflection of the MH incident and in retrospect it seems that a different combination of volume resuscitation may have been more appropriate therefore limiting the number of red cell units given. The patient made a full recovery and was discharged 3 days later. Undertransfusion was reported in the surgical case described above (Case 11c.2).

In a further case the MHP was activated in the absence of any bleeding. The woman in her 60s had known history of anaemia and on admission to the ED was unwell with a reduced level of consciousness and had very low Hb (26g/L). However, eight units of emergency O D-negative red cells were prescribed by a consultant and transfused within an hour, and she received four units of FFP. CT confirmed no active bleeding. The post-transfusion Hb was 139g/L. This was also avoidable use of group O D-negative units. With such a low Hb in an unwell patient, a more controlled red cell transfusion was appropriate with one or two units sufficient to bring Hb to acceptable levels.

Learning points

- Blood loss may be difficult to estimate during major haemorrhage especially in covert bleeding
- It is helpful to obtain regular measurements of Hb to guide transfusion support to help avoid under and overtransfusion
- Blood gas analysers may be used for this if they are quality assured for this purpose and the sample is handled correctly

Near miss cases n=6

Case 11c.4: Misreading the blood count results

A prescriber erroneously interpreted a patient's platelet count as his Hb (the last three results were 89, 68 and 66) so booked him into for a two-unit red cell transfusion the same day. Blood was taken for a repeat blood count, film and a crossmatch sample was also taken. An IV cannula was inserted, and he waited for his transfusion. The blood was placed in the blood refrigerator on the ward. A nurse asked why the patient was having a blood transfusion when his Hb was 141g/L which was when the prescriber realised their error. The patient did not receive any blood.

Five other cases are described in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/).

Conclusion

Paediatric cases continue to be overrepresented in this category with calculation or administration errors resulting in overtransfusion. Measures are needed to improve transfusion safety in children and neonates. This is a role for paediatricians as well as the hospital transfusion team.

Blood loss in major haemorrhage in adults can be difficult to assess. Regular monitoring of blood parameters is recommended and should be performed. Blood gas analysers may be used for this as long as they are quality assured for this purpose and the sample is handled correctly.

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Recommended resources

SHOT Bite No. 4: Paediatrics
https://www.shotuk.org/resources/current-resources/shot-bites/

Key information from the BSH paediatric guidelines
https://www.shotuk.org/resources/current-resources/paediatric/

Reference

BSH New HV, Berryman J, Bolton-Maggs PHB, et al. Guidelines on transfusion for fetuses, neonates and older children. *Br J Haematol.* 2016;**175(5)**:784-828.

Incidents Related to Prothrombin Complex Concentrate (PCC) n=18

11d

Authors: Paula Bolton-Maggs, Josephine McCullagh and Simon Carter-Graham

Definition:

Hospitals are asked to report incidents related to PCC infusion where there was delay or inappropriate transfusion. (Allergic reactions should be reported to the MHRA)

Key SHOT messages

- PCC administration is an emergency treatment used for reversal of oral anticoagulants (warfarin and DOAC) and should be started within an hour of the decision being made before the patient is transferred to other wards or departments
- PCC does not affect heparin treatment and should not be used for its reversal. Use protamine sulphate for heparins with advice from a haematologist
- The ED should ensure they have clear instructions for PCC administration and have 24-hour access to it
- The use of fixed dose PCC simplifies management and can reduce the time to treatment
- Medical and nursing staff working in the ED should be trained in the prescription, reconstitution, and administration of PCC

Recommendation

- All ED must have a protocol for use of PCC with clear instructions for dose, reconstitution, and administration. Staff should be appropriately trained in using PCC
- Use of PCC should be regularly audited for timeliness and appropriateness

Action: Medical directors of acute Trusts/Health Boards

- The haemostasis task force of the BSH should consider guidance on the use of a fixed dose of PCC for emergency treatment

Action: Haemostasis task force of the BSH

Introduction

PCC incidents mainly occurred in an elderly population aged 70 years or more, median age 82 years. There were 3 younger patients, 1 a teenager. There were 11 reports of delayed infusion, and 1 inappropriate treatment for a patient receiving heparin. Other issues were inappropriate infusion rates and confusion over the dose.

All patients (except 1) were taking anticoagulants, either warfarin or apixaban/edoxaban; 1 patient was on low molecular weight heparin and was prescribed PCC when the instruction from the haematologist was to give protamine sulphate. This patient in his 80s had COVID-19 pneumonitis and severe epistaxis. Six patients had intracranial haemorrhage and 1 was admitted with head injury.

The SHOT CAS alert released in 2022 also addresses preventable PCC delays. One of the recommended actions was for all healthcare organisations to ensure their transfusion policies and procedures include agreed criteria where rapid release of PCC is acceptable without the initial approval of a haematologist.

Deaths related to transfusion n=0

There were no deaths reported that were related to the PCC incidents.

Major morbidity n=2

Case 11d.1: PCC delay because of need to weigh the patient

A woman in her 80s on apixaban for AF, with upper GI bleeding was in the ED and received red cells. Confusion was caused by the requirement for her weight, and she was not well enough to get off the trolley. This hospital had a fixed dose policy but shared on call haematology staff with another NHS organisation who use a weight-based dose. It was not clear if she received the dose but was put on an end-of-life pathway and died unrelated to the PCC issues.

She was described as having major morbidity and was very unwell.

Case 11d.2: Difficulties in accessing PCC resulting in delayed administration and extension of ICH

An elderly patient on apixaban presented to the ED following trauma with a head injury at 17:31. The report of a head CT at 22:25 showed ICH. PCC was requested. On this site the transfusion laboratory was shut after midnight, so PCC was kept in the emergency drugs cupboard with access restricted to the site manager and pharmacists. The PCC could not be found in the emergency drugs cupboard. The on-call pharmacist was contacted who recommended discussion with the transfusion laboratory at the main site. The main site BMS offered to transport the PCC but to prevent further delay the clinician chose to transfer the patient to the main site where PCC was issued (06:42). A repeat CT scan the next day showed extension of ICH.

This demonstrates the potential impact of delay in administration of PCC in ICH and the importance of replenishing emergency stock to ensure 24/7 availability of these emergency products.

Delays n=11

Delays were caused by poor communication, transfer of patients between departments or setting inappropriately long infusion times. Patients with intracranial bleeding experienced delays of 4, 6 and 8 hours.

Case 11d.3: **Off licence use of PCC**

A teenager was very unwell and admitted to the intensive care unit with an initial diagnosis of APML. The patient had coagulation disturbances and was prescribed PCC 3000IU but received 1000IU. FFP, platelets and cryoprecipitate were also given which were appropriate for AML with coagulopathy, however there is no literature to suggest PCC is indicated or appropriate in this setting.

The two commercial preparations of PCC available are currently only licensed for reversal of vitamin K antagonists. There is published evidence for benefit in haemorrhage in patients on DOAC (Hitchcock et al. 2021, Milioglou et al. 2021, Milling et al. 2021, Nederpelt et al. 2021), however there are specific reversal agents for DOAC (Cuker et al. 2019, Gomez-Outes et al. 2021) demonstrated to be of benefit in ICH (Vestal et al. 2022). PCC carry a risk of thrombosis and are relatively contraindicated in the setting of disseminated intravascular coagulation.

PCC (two different products available) have been used off label in a variety of other settings (Tanaka et al. 2021), particularly cardiac surgery (Katz et al. 2022, Santana and Brovman 2022).

Case 11d.4: Long delay in treatment for ICH with staffing and communication issues

A patient on warfarin presented with frontal ICH. CT confirmed this diagnosis 21 hours after admission. After rapid discussion with the haematologist at 17:00, PCC was requested and issued at 17:40. This plan was not communicated to the ward staff until 21:00. The ward was very busy and short-staffed with many sick patients. The need for additional staff was escalated without success. The patient was difficult to cannulate, and the PCC was given at 01:50 the next morning (about 8 hours from the decision) and with a slow rate as 1500IU took over 1 hour and 50 minutes to administer.

Additional factors included unfamiliarity of staff with PCC prescription and administration.

Learning points

- Medical and nursing staff working in emergency departments and medical/surgical admissions units should be trained in the use of PCC so that it can be administered without delay for specific anticoagulant reversal in the face of major haemorrhage
- The staff should be aware of the indications and also have clear information about how to administer it
- PCC should be rapidly accessible, and consideration given to keeping a stock in the ED (note that this blood product must be fully traceable)
- Immediate reversal of anticoagulant should take place (and certainly within an hour) especially in cases of suspected ICH

Commentary

Fixed dose PCC

Continued confusion about dose and rate of infusion suggest that a fixed dose regimen might be safer. The literature demonstrates good correction of the INR in most (Bizzell et al. 2021) including patients with ICH with a fixed dose of 2000IU (Dietrich et al. 2021). More recently haemostatic efficiency was shown. In an open-label, multicentre, randomised clinical trial, patients with non-intracranial bleeds requiring VKA reversal with 4F-PCC were allocated to either a 1000IU fixed dose of 4F-PCC or a variable dose based on weight and INR. Effective haemostasis was achieved in 87.3% (n=69 of 79) in fixed and 89.9% (n=71 of 79) in the variable dosing cohort. Median door-to-needle times were reduced to 109 minutes (range 16 to 796) in fixed compared with 142 (17 to 1076) for the variable dose (P=.027). An INR < 2.0 at 60 minutes after 4F-PCC infusion was reached in 91.2% versus 91.7% (P=1.0) (Abdoellakhan et al. 2022). Another meta-analysis of fixed dose versus variable dose of PCC reviewed data from 10 studies including 988 patients.

Fixed dose PCC was associated with reduced mortality and a shorter order-to-needle time. These authors advocated further studies focusing on clinical outcomes (Mohammadi et al. 2021). It is not clear what the optimal fixed dose should be. Whether a fixed dose or weight-based regimen is used, follow up of the INR for patients on warfarin (who should also receive vitamin K) is essential to ensure the dose was adequate and to determine if further PCC is required.

Use of PCC for DOAC reversal

PCC may also be used for DOAC (Sweidan et al. 2020). Canadian authors recommend the specific antidote idarucizumab 5g for a patient on dabigatran. For a patient on a Xa inhibitor (apixaban, rivaroxaban), PCC 2000IU is recommended; if significant bleeding persists after 1 hour, a second dose of 2000IU of PCC should be considered. While not approved in Canada, a specific antidote to Xa inhibitors, andexanet alfa, has also been used in these situations as a continuous infusion (Callum et al. 2021).

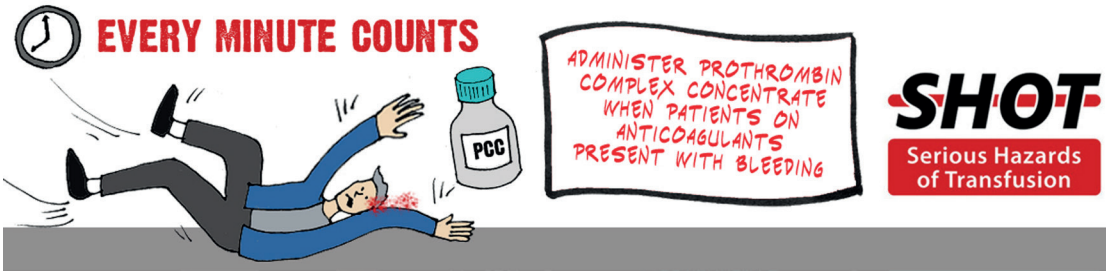
Reversal of oral anticoagulation in patients with ICH has been reviewed noting the importance of rapid treatment (Kuramatsu et al. 2019). A meta-analysis of reversal agents (PCC, idarucizumab and andexanet) for bleeding related to DOAC evaluated 60 studies with 4735 patients. Mortality of those with ICH was 20%; effective haemostasis was achieved in 75-81% and was similar for all agents and a particularly high thromboembolism rate was noted for andexanet (Gomez-Outes et al. 2021). New agents are in development including ciraparentag, a small molecule that works against several anticoagulant agents (Ansell et al. 2022).

Near miss cases n=1

An elderly woman had her weight incorrectly recorded resulting in an inappropriately high dose of PCC. Fortunately, this was recognised, and the prescription revised down to the correct dose.

Conclusion

PCC is an important treatment for immediate reversal of vitamin K antagonists and other oral anticoagulants and should be given immediately once a decision is made to reverse anticoagulant effect. All clinical staff involved in the acute care of patients with suspected serious haemorrhage, particularly ICH, who are eligible for reversal should ensure that they know how to obtain, reconstitute, and administer PCC. Delays can contribute to patient death.



References

Ansell J, Bakhru S, Laulicht BE, et al. Ciraparantag reverses the anticoagulant activity of apixaban and rivaroxaban in healthy elderly subjects. *Eur Heart J.* 2022;**43(10)**:985-992. doi: 10.1093/eurheartj/ehab637.

Abdoellakhan RA, Khorsand N, Ter Avest E, et al. Fixed Versus Variable Dosing of Prothrombin Complex Concentrate for Bleeding Complications of Vitamin K Antagonists-The PROPER3 Randomized Clinical Trial. *Ann Emerg Med.* 2022;**79(1)**:20-30.

Bizzell AC, Mousavi MK and Yin E. Fixed- versus variable-dose prothrombin complex concentrate protocol for vitamin K antagonist reversal. *Int J Hematol.* 2021;**114(3)**:334-341.

Callum J, Petrosoniak A and Haas B. The 7 Ts of Massive Hemorrhage Protocols (2021). https://emergencymedicinecases.com/7-ts-massive-hemorrhage-protocols/?start=true [accessed 05 May 2022].

Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. *Am J Hematol.* 2019;**94(6)**:697-709.

Dietrich SK, Mixon MA and Rech MA. Fixed-dose prothrombin complex concentrate for emergent warfarin reversal among patients with intracranial hemorrhage. *Am J Emerg Med.* 2021;**49**:326-330.

Gomez-Outes A, Alcubilla P, Calvo-Rojas G, et al. Meta-Analysis of Reversal Agents for Severe Bleeding Associated With Direct Oral Anticoagulants. *J Am Coll Cardiol*. 2021;**77(24)**:2987-3001.

Hitchcock Z, Smith SD, Le LT, et al. A Retrospective Review of Four-Factor Prothrombin Complex Concentrate for Factor Xa Inhibitor-Related Bleedings. *J Pharm Pract*. 2021;8971900211026839.

Katz A, Ahuja T, Arnouk S, et al. A Comparison of Prothrombin Complex Concentrate and Recombinant Activated Factor VII for the Management of Bleeding With Cardiac Surgery. *J Intensive Care Med*. 2022;**37(2)**:231-239.

Kuramatsu JB, Sembill JA and Huttner HB. Reversal of oral anticoagulation in patients with acute intracerebral hemorrhage. *Crit Care.* 2019;**23(1)**:206-214.

Milioglou I, Farmakis I, Neudeker M, et al. Prothrombin complex concentrate in major bleeding associated with DOACs; an updated systematic review and meta-analysis. *J Thromb Thrombolysis* 2021;**52(4)**:1137-1150.

Milling TJ, Refaai MA and Sengupta N. Anticoagulant Reversal in Gastrointestinal Bleeding: Review of Treatment Guidelines. *Dig Dis Sci.* 2021;**66(11)**:3698-3714.

Mohammadi K, Yaribash S, Sani MA, et al.. Efficacy and Safety of the Fixed-Dose Versus Variable-Dose of 4-PCC for Vitamin K Antagonist Reversal: A Comprehensive Systematic Review and Meta-Analysis *Cardiovasc Drugs Ther*. 2021. doi: 10.1007/s10557-021-07192-0.

Nederpelt CJ, Naar L, Krijnen P, et al. Andexanet Alfa or Prothrombin Complex Concentrate for Factor Xa Inhibitor Reversal in Acute Major Bleeding: A Systematic Review and Meta-Analysis. *Crit Care Med.* 2021;**49(10)**:e1025-e1036. doi: 10.1097/CCM.0000000000005059.

Santana JM and Brovman EY. Prothrombin complex concentrates in cardiac surgery: where are we? *Curr Opin Anaesthesiol.* 2022;**35(1)**:36-41.

SHOT. Preventing transfusion delays in bleeding and critically anaemic patients SHOT/2022/001 (2022) https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103190 [accessed 05 May 2022].

Sweidan AJ, Singh NK, Conovaloff JL, et al. Coagulopathy reversal in intracerebral haemorrhage. *Stroke Vasc Neurol*. 2020;**5(1)**:29-33.

Tanaka KA, Shettar S, Vandyck K, et al. Roles of Four-Factor Prothrombin Complex Concentrate in the Management of Critical Bleeding. *Transfus Med Rev.* 2021;**35(4)**:96-103.

Vestal ML, Hodulik KJ, Mando-Vandrick ML, et al. Andexanet alfa and four-factor prothrombin complex concentrate for reversal of apixaban and rivaroxaban in patients diagnosed with intracranial hemorrhage. *J Thromb Thrombolysis.* 2022;**53(1)**:167-175.