6 Acute Transfusion Reactions

Definition

Acute transfusion reactions are defined in this report as those occurring at any time up to 24 hours following a transfusion of blood or components, excluding cases of acute reactions due to incorrect component being transfused as these are covered in Chapter 4

This category accounted for 9.3% of non-infectious hazards reported and 9.1% of all hazards.

There were 6 outstanding reports from the previous reporting year for which 5 questionnaires were eventually received although on review one of these was, in fact, an incorrect blood component transfused and is now transferred to that section. The remaining 4 are included in the analysis. Forty-four valid initial reports were received and 39 completed questionnaires (including 4 from the previous year). The 9 outstanding questionnaires will be included in next year's analysis. An additional 12 reports did not fit the definition of ATR and have been withdrawn by the analyst.

This chapter highlights the main findings from 39 completed questionnaires.

There were 5 deaths in this group; 1 probably related to the transfusion, 1 possibly related to the transfusion and 3 unrelated to the transfusion. There were 2 instances of major morbidity and renal failure as a result of haemolytic transfusion reactions.

Gender (37 reports)

Male 21

Female 16

Age (38 reports)

Age range	3 months to 84 years
Median	66 years

Components implicated (39 reports)

Red cell - allogeneic	8
Red cell – post-operative salvage	1
Platelets	13 (8 apheresis units and 5 from pooled buffy coats)
Fresh frozen plasma	17 (all not viral inactivated)

Reactions in which red cells were implicated

There were 8 cases, with one death possibly related to the transfusion, and two cases of major morbidity. Six reactions occurred during the transfusion, 1 within 7 hours of completing the transfusion and 1 unknown. The following reactions were seen:

Table 6
Reactions in which red cells were implicated

Reaction type	Number of cases
Haemolytic or incompatibility reaction	4
Anaphylactic/anaphylactoid[+]	1
Allergic[++]	1
Unknown/unclassifiable	2

[+] anaphylactic/anaphylactoid (hypotension with 1 or more of: rash, dyspnoea, angioedema)

[++] allergic (1 or more of: rash, dyspnoea or angioedema **without** hypotension)

Haemolytic or Incompatibility Reactions

In 4 cases, there were features of haemolysis

Case 1

A 75 year old male with no previous transfusion history had a coronary artery bypass graft (CABG) performed, during which he bled excessively and was transfused with 14 units of red cells, 13 units of FFP and one unit of platelets. Within 7 hours of the procedure, the patient developed a fever, rigors, and chest pain. He became hypotensive, was noted to pass dark urine and was found to have a strongly positive DAT(IgG), hyperbilirubinaemia, spherocytes, haemoglobinuria, disseminated intravascular coagulation and deteriorating renal function that required dialysis.

The patient had two antibody screens pre-operatively. The first performed at the pre-assessment clinic was weakly positive and a provisional specificity of an anti-E was given on the basis of a positive reaction with one R_2R_2 cell. The patient's Rh phenotype was R_2r, the DAT was negative and an auto-E was questioned. The second antibody screen performed on admission was negative but he was crossmatched with E negative units. Post-operatively the patient's plasma contained a strong anti-E ,reacting 5+ in IAT and anti-E was eluted from the red cells. These post-operative findings were confirmed by the reference laboratory and an auto-anti-E was again suggested to be responsible.

There are very few cases of an autoantibody being stimulated by transfusion, and the rapid response over a few hours is surprising. However, the finding that anti-E could be eluted from the E negative units transfused would support the hypothesis that this was an autoantibody.

Case 2

A 30 year old female was transfused 2 units of red cells on account of a post-partum haemorrhage and required 2 further units a few days later. During the second transfusion episode, she became febrile, dyspnoeic and was noted to be passing dark urine. She was subsequently found to have a positive DAT (IgG only), haemoglobinuria and deteriorating renal function and required dialysis and admission to ICU. Her pre and post-transfusion antibody screens were repeatedly negative using an automated DiaMed technique. These samples were referred to the Reference Laboratory who detected an anti-Jk^b and an anti-K in the pre-transfusion sample by papain IAT only, and confirmed that the implicated unit was Jk^b positive.

The reporting hospital has since amended its protocol for investigating red cell transfusion reactions to include additional techniques.

Case 3

An example of a patient with an anti-Do^a who as a result of two consecutive transfusions, experienced a delayed haemolytic transfusion reaction followed by an acute haemolytic transfusion reaction. The vignette is included in Chapter 7 (Delayed Transfusion Reactions).

Case 4

A 50 year old female with myelofibrosis required regular transfusion support. The patient had experienced a febrile reaction during a transfusion of 3 units of red cells approximately 3 weeks earlier but a decision was taken to continue the transfusion with chlorpheniramine cover. On the following occasion, the red cell transfusion was stopped after 50ml on account of rigors and a tachycardia and following the transfusion the patient was noted to have a raised bilirubin. She had a negative IAT antibody screen pre and post transfusion and the DAT was negative throughout. However when samples were referred to the local Reference Centre, the patient was found to have an anti-c+E together with a non-specific papain autoantibody in the pre-transfusion sample.

It is not known why these antibodies were missed and the reporting hospital has since amended its protocol for investigating red cell transfusion reactions to include the use of enzymes and low ionic-strength saline (LISS) tube techniques.

Anaphylactic/anaphylactoid reactions

One patient who was IgA deficient developed an anaphylactic reaction due to anti-IgA.

Case 5

A 70 year old male had an anaemia of chronic disease and was undergoing debridement of an infected foot. On the first occasion, after 86ml of red cells had been transfused, the patient developed dyspnoea with tachycardia and profound hypotension. He was successfully resuscitated and repeat testing of the pre and post transfusion sample revealed no red cell incompatibility and bacterial cultures were negative. Two weeks later, a further red cell transfusion was given with hydrocortisone and chlorpheniramine pre-medication. After one hour the patient developed severe rigors and the blood pressure rose from 134/80 to 206/120.

The transfusion was again aborted and the patient resuscitated with hydrocortisone and chlorpheniramine. At this stage the patient was tested for IgA deficiency and found to be IgA deficient with an anti-IgA antibody. Subsequent transfusions of washed red cells have been tolerated.

A severe allergic reaction should have been suspected after the first transfusion.

Reactions of unknown aetiology

Case 6

An 80 year old female, with a non-Hodgkin's lymphoma and previously untransfused, had a positive DAT(IgG only) but a negative red cell antibody screen (Ortho BioVue IAT). The patient was also reported to have an autoimmune haemolytic anaemia although no clinical details are available. Three units of red cells were issued electronically. During the third unit, the patient developed a fever, breathlessness, hypotension and a reduced level of consciousness. The transfusion was stopped and antibiotics were prescribed. The patient died two hours later. The patient had a negative antibody screen post transfusion and the units were compatible when retrospectively crossmatched.

No bacterial cultures were taken, a chest X-ray (CXR) was not performed and it is not clear whether any of the symptoms were related to the transfusion rather than underlying sepsis.

The reporting hospital now perform a serological crossmatch on patients with a positive DAT.

Case 7

A 20 year old male, who had undergone an orthotopic liver transplant 15 years earlier and who was known to have a warm autoimmune haemolytic anaemia had not required red cell support for several years. On the reported occasion, after an unspecified volume of red cells, the patient developed a fever, rigors, hypotension, nausea and vomiting. Pre-transfusion testing revealed a positive DAT (IgG only),and an autoantibody reactive in the IAT with no apparent specificity. No testing was undertaken to exclude underlying alloantibodies and no serological crossmatch was performed. The post transfusion sample again showed a strong autoantibody.

Subsequent red cell transfusions, given slowly, have been well tolerated.

Reaction to a unit of autologous salvaged blood

Case 8

An 84 year old male who had undergone a total knee replacement was transfused with unwashed red cells salvaged post-operatively. After 550ml had been given, the patient developed a fever, rigors and dyspnoea requiring bronchodilators and high dependency unit (HDU) admission. Bacterial cultures of both the unit and the patient were negative.

Filtered salvaged blood contains cytokines that may have been responsible for the reaction

Reactions in which FFP was implicated

There were 17 reports in this group, of which 15 occurred during the transfusion, and 2 within 2 hours. The following reactions were seen:

Table 7

Reactions in which FFP was implicated

Reaction Type	Number
Anaphylactic/anaphylactoid	8
Allergic	8
Unknown/unclassifiable	1

Anaphylactic/anaphylactoid

There were 8 patients in this category, all of whom recovered from the reaction. Seven occurred during the transfusion, and where information is available, started after 50-200 mL FFP had been given. The eighth case was noted within 30 minutes of completing the infusion.

Five cases had dyspnoea, of which one had a CXR performed (result unknown) and one had blood gases taken confirming hypoxia.

Four patients required adrenaline in addition to hydrocortisone and chlorpheniramine, of which 2 were also given bronchodilators. A fifth patient was given hydrocortisone and chlorpheniramine and a sixth oxygen alone. It is not clear what medication was prescribed for the remaining 2 patients.

Five of the 8 patients were investigated for IgA deficiency, with negative findings.

Four out of 8 FFP transfusions can be justified, (included in table 8 below).

Case 9

A 68 year old man on warfarin was scheduled for a colonoscopy and biopsy and had been asked to discontinue his anticoagulants three days before admission. On admission, the day before the intended procedure, his INR was 1.65 and he was prescribed FFP.

Within 10 minutes of starting the transfusion, the patient had developed an urticarial rash. He was seen within a few minutes by which time he had become hypotensive, BP 58/33, wheezy, developed rigors and lost consciousness. He required two IM injections of adrenaline, in addition to 200mg hydrocortisone, 20mg chlorpheniramine and crystalloids/colloids over 30 minutes to become haemodynamically stable. He was also given nebulised salbutamol and oxygen. He had a normal IgA level.

Allergic reactions (not anaphylaxis)

There were 8 patients in this group, all of whom were also dyspnoeic. 6 had a rash which was accompanied by angioedema in 2 cases. The remaining 2 had rigors in addition to dyspnoea.

No CXRs were performed. 4 were investigated for IgA deficiency with negative findings and there were no investigations performed in the remaining 4 who had all been previously transfused.

3 out of the 8 FFP transfusions can be justified (included in table 8).

Case 10

A 43 year old male with Crohn's disease, also on warfarin for a previous pulmonary embolus, was noted to have an infected Hickman line. He was scheduled for surgery 3 days later but was not informed to discontinue his warfarin. He was admitted 2 days before surgery and was found to have an INR of 2.9 and was prescribed FFP.

At the end of the first unit, the patient developed a rash, a swollen tongue, and became dyspnoeic with an oxygen saturation of 88%. He responded to hydrocortisone, chlorpheniramine and nebulised salbutamol. His IgA level was normal.

Unclassifiable

Case 11

An 80 year old patient (gender not reported) was admitted with sepsis and disseminated intravascular coagulation. He/she was transfused with one pool of platelets followed by FFP. During the second unit of FFP the patient became breathless but had no other features of an allergic reaction. The unit was discontinued, the patient received hydrocortisone and chlorpheniramine and further FFP was transfused later at a slower rate without problems. Although a reaction to FFP could have accounted for the breathlessness, alternative explanations include fluid overload and the underlying sepsis.

Inappropriate use of FFP

Coagulation results are not available for some reports and these have been designated as possibly indicated. However, it is apparent that at least 5 of the 17 FFP transfusions were not indicated.

Table 8

Indications for FFP transfusion

Category	Number patients	Indication given
Clinically indicated	7	TTP – 1 Massive transfusion – 2 Liver disease with haemorrhage – 2 DIC with haemorrhage – 1 Warfarin reversal - 1* (*INR >10, haematemesis, jaundice, abdominal pain ? for surgery)
Possibly indicated	5	Warfarin reversal, bleeding – 1 Perioperative bleed in the absence of massive transfusion – 4
Not indicated	5	Non-urgent warfarin reversal in absence of bleeding – 3 Liver disease in the absence of haemorrhage or intervention – 1 Enoxaparin (Clexane) reversal on account of bleeding at site of injections - 1

Reactions in which platelets were implicated

There were 13 reactions in this group, of which 11 occurred during the transfusion, 2 within 2 hours and 2 were recognised up to 8 hours following the transfusion. One patient died as a result of an anaphylactoid reaction and there were 3 other deaths unrelated to the transfusion.

Table 9

Reactions in which platelets were implicated

Reaction Type	Number of cases
Haemolytic	2
Anaphylactoid (see text above)	1
Allergic	9
Unknown	1

Haemolytic reactions

Case 12

A 31 year old male with acute lymphoblastic leukaemia had undergone an unrelated donor stem cell transplant. Both the donor and the patient were genotyped as group A_1. On day +8, the patient received platelets from a group O apheresis donor who had tested negative for high titre anti-A/B on ten occasions. Although the patient was asymptomatic at the time of the transfusion, within 24 hours there were features of haemolysis with a positive DAT, hyperbilirubinaemia, spherocytosis, a falling haemoglobin and deteriorating renal function. Dialysis was not required but the patient had delayed engraftment (>21 days) with neutropenia dependent upon granulocyte-colony stimulating factor. He went on to become polymerase chain reaction (PCR) positive for CMV on day +25 and died of CMV pneumonitis on day+40.

Retrospective manual testing of the apheresis donor demonstrated an IgM anti-A titre of >1:1024 (saline agglutination) and an IgG anti-A titre of >1:8192 (LISS tube IAT). Although the patient died from CMV pneumonitis, he received CMV seronegative blood components. The haemolytic episode however could have contributed to the delayed engraftment.

Case 13

A 3 month old female infant, group A Rh D negative, was born with a ventricular septal defect (VSD) and cardiac atresia and was being supported on extra-corporeal membrane oxygenation (ECMO). She had received large quantities of blood components over the previous 7 days and in the 24 hours leading up to the report had been given 7 aliquots of group O Rh D negative neonatal platelets due to a shortage of A Rh D negative neonatal platelets at the Blood Service. Within 24 hours haemolysis was noted with a free plasma haemoglobin of 316g/L. The DAT was positive and anti-A was eluted from the red cells. The baby subsequently died though not as a direct result of the haemolysis.

Anaphylactic/anaphylactoid reactions

Case 14

A 72 year old male with aplastic anaemia, known to have cardiac impairment, had been treated with antilymphocyte globulin (ALG) but was still red cell and platelet dependent, requiring 2 pools of the latter on a weekly basis. After receiving 250mL of an apheresis platelet concentrate he developed a rash which initially settled with hydrocortisone but he went on to become hypotensive and dyspnoeic. The patient was resuscitated with antihistamine, hydrocortisone and adrenaline but suffered cardiac arrest, developed irreversible ventricular fibrillation and died.

He had a normal level of IgA and culture of the platelet unit was negative.

Allergic reactions (not anaphylactic)

Nine cases of allergic reactions were reported in patients who had all been previously transfused. All patients made a full recovery following treatment with antihistamines and in some cases, hydrocortisone.

Seven of the 9 reactions were accompanied by fever and in 4 of these, the units were sent for bacterial culture with negative findings.

Six were accompanied by transient dyspnoea and no chest X-rays were performed.

Two patients had no investigations performed.

Five patients were tested for HLA and/or human platelet antigen (HPA) antibodies and of these 2 were found to have HLA antibodies and 1 to have HPA antibodies. There is no information as to whether these patients were found to be refractory to random platelets or whether the reaction occurred prior to the development of refractoriness.

Two patients were tested for IgA deficiency with negative findings and 1 patient was additionally tested for mast cell tryptase and Am and Gm antibodies.

Unclassifiable

Case 15

A 72 year old male with end-stage chronic lymphocytic leukaemia required red cell and platelet support. Towards the end of a transfusion of a unit of buffy coat derived platelets he developed a fever, chills, rigors and dyspnoea. A CXR was performed which showed upper lobe blood diversion and pulmonary oedema. He was treated with a diuretic, nebulised bronchodilators, oxygen and broad spectrum antibiotics. The platelet pool was not sent for culture but the red cells from the 4 donors were cultured with negative results. The patient's discharge was postponed but he later recovered.

The CXR findings were more in favour of left ventricular failure than TRALI but this does not provide an explanation for the fever and rigors. Bacterial contamination of the platelet preparation has not been satisfactorily excluded.

Response times

The majority of patients were seen as soon as possible by a doctor but a haematologist was not always consulted in the management of a reaction and a minority of incidents involving platelets were brought to a haematologist's attention.

Table 10

Time taken for patient to be reviewed by a doctor

Response Times	Red cells (8)	FFP (17)	Platelets (13)
Stat	3	9	8
< 30 minutes	2	3	3
< 60 minutes		1	1
> 60 minutes			
Not available	3	4	1
Late reaction			
Total	8	17	13
Involvement of Haematologist	**4**	**9**	**5**

Changes made to procedures

Two laboratories that failed to detect red cell alloantibodies using their routine IAT technique now employ additional techniques for investigating haemolytic transfusion reactions.

The laboratory that employed electronic issue for a patient thought to have an autoimmune haemolytic anaemia has now reverted to serologically crossmatching blood for these patients.

Reporting of acute transfusion reactions

Table 11

Reporting of reactions to the Hospital Transfusion Committee, Hospital Laboratory and the local Transfusion Centre

Reported to	Red cells (8)	FFP (17)	Platelets (13)
Hospital Transfusion Committee	7	14	13
Hospital laboratory	7	17	10
Transfusion centre	5	8	11

COMMENTARY

- The majority of ATRs (30/39) were due to FFP and platelets, as in previous years. 93% (26/28) allergic or anaphylactic/anaphylactoid reactions were due to these 2 components.
- It is apparent that FFP has a notable risk of causing an acute reaction and yet is often inappropriately prescribed, particularly when there is a non-urgent need for warfarin reversal.
- Two group A infants developed haemolytic transfusion reactions after receiving group O neonatal platelets, tested for high titre anti-A/B.
- Only 5/8 patients experiencing an anaphylactic reaction to FFP were investigated for IgA deficiency.
- Two patients with serious reactions to platelets had no investigations whatsoever. Although platelet concentrates pose the highest risk of bacterial contamination, cultures were only performed in 4/9 cases when the reaction was accompanied by a fever.
- Haematologists are not frequently involved in the management or investigations of suspected acute transfusion reactions which can lead to inappropriate diagnosis and treatment.
- Whilst there is no requirement to perform a DAT as part of routine pre-transfusion testing, samples from patients who are found to have an autoimmune haemolytic anaemia should be referred to a reference laboratory to exclude underlying alloantibodies.

RECOMMENDATIONS

- The BCSH guideline dealing with the investigation and management of acute transfusion reactions is awaited and emphasis should be placed upon the need for identifying underlying causes that will impact upon the choice of future component therapy.

  Action: BCSH

- There is continued evidence of inappropriate clinical use of FFP, despite the availability of recently published BCSH guidelines[12] on appropriate use and existing recommendations for the management of warfarin reversal[13]. Further local audits and educational programmes should be encouraged through the Transfusion Committee network.

  Action: Regional and hospital transfusion committees

- The recent BCSH transfusion guideline for neonates and older children[9] states that group A recipients should receive group A platelets, but accepts that group O can be transfused as a second alternative provided that these components are lacking high titre anti-A or anti-B. However Transfusion Service testing for high titre anti-A/B cannot confidently exclude all dangerous donations and the Services should be encouraged to ensure that sufficient group A platelets are always available for these patients.

  Action: UK Transfusion Services