13. 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 11

This category accounted for 11.9% of non-infectious hazards reported and 11.7% of all hazards.
Thirty seven initial reports (all new) were received. In addition a further 7 reports were received which were felt not to fit the definition of ATR or which were subsequently withdrawn by the reporter.
This chapter highlights the main findings from 31 completed questionnaires.

Overall there were 6 deaths in this group, of which one was thought to be definitely due to the transfusion, 3 were felt to be unrelated to, and 2 possibly related to, the transfusion. The remaining patients survived without long-term sequelae other than one patient with ongoing malaise.

Gender (31 reports)

Males	10
Females	21

Age (31 reports)

Age range	1 month - 86 years
Median	65 years

Components implicated (31 reports)

Red Cells	13
Red Cells and Platelets	1 (apheresis platelets)
Fresh frozen plasma	7
Platelets	10 (of which 2 were apheresis units and 8 were pools)

Leucocyte-depleted components were transfused in all patients.

1. Reactions in which red cells were implicated

There were 13 cases and 11 survived, one with persistent debility. Eleven reactions occurred during the transfusion, one occurred within 2 hours of completing the transfusion and one at 8-12 hours. Two patients died, in one case due entirely to the underlying disease and in the second, who had pulmonary complications, the death was probably unrelated to the transfusion. The following reactions were seen:

Table 26

Reaction type	Number of cases
Haemolytic or incompatibility reaction	6
Anaphylactic[+]	2
Allergic[++]	2
Pulmonary oedema	1
Hypoxia + acidosis (neonate)	1
Hypertension	1

[+]anaphylactic/anaphylactoid (hypotension with one or more of: rash, dyspnoea, angioedema)
[++]allergic (one or more of: rash, dyspnoea or angioedema **without** hypotension)

Haemolytic or Incompatibility Reactions

In 6 cases the reaction was felt to be acute haemolysis or a febrile reaction due to red cell incompatibility (antibody demonstrated).

Case 1
This 20 year-old female had undergone an unrelated bone marrow transplant for acute myeloid leukaemia (AML) 6 months prior to the incident. The donor was Group O and the patient group A. Post-transplant she had received A RhD positive red cells, apparently without incident. Ten days after her most recent Group A transfusion she presented with a Hb of 55 g/L, platelet count of 3 x 10^9/L and a bilirubin of 38μmol/L. Three A positive units were cross-matched at the local Transfusion Centre and she received an apheresis pool of platelets (group and timing not stated). During the third unit she developed dark urine but was otherwise asymptomatic. Subsequently she was shown to have weak anti-A1, strong complement coating and a cold autoantibody. The blood was not given through a blood warmer (ward unaware of cold-autoantibody). The transfused units were apparently shown to have been Group A2 and the ABO mismatch was therefore thought not to be the cause of the haemolysis. Subsequent transfusions through a blood warmer, in a warm environment were effective but the patient died due to a pulmonary embolism $2^1/_2$ weeks later. The reaction has been ascribed to "exacerbation of cold-antibody mediated AIHA". It is not clear if haemolysis due to an incompatible platelet transfusion has been excluded.
There are a number of uncertainties over this case. In view of the time since transplant it would be anticipated that Group A red cells would be incompatible in this patient due to presence of donor anti-A. Indeed she was shown to have anti-A1 which would be consistent with her becoming group O. It is not clear if her "cold autoantibody" may, in fact, have been anti-A of donor origin. It would be surprising if all three red cell units were Group A2 – the frequency of A2 is about 20% and there is therefore a 1 in 125 chance of randomly selecting 3 A2 units. As the group of the platelet unit is not given it is not clear if there may have been a contribution to haemolysis from this – for example if a Group O, high-tire haemolysin unit was given.

Case 2
This 75 year-old female with CML who had required several recent transfusions, received 3 units of red cells and developed fever, rigors, restlessness, vomiting and diarrhoea during the third unit. Initial investigation revealed a raised bilirubin and haemoglobinuria but the patient was allowed home after overnight observation. 5 days later she was readmitted with renal insufficiency, requiring dialysis and remains more frail and less able to manage than previously. Serological investigation revealed no evident cause. The patient was DAT positive (IgG) pre- and post-transfusion. Investigation of pre- and post-transfusion serum (including autoabsorption) revealed only a non-specific autoantibody with no underlying alloantibody. It is presumed that this patient experienced exacerbation of auto-immune haemolysis although it is not clear to what degree haemolysis was apparent before the transfusion.

Case 3
This 25 year-old female with sickle cell anaemia was generally unwell with a Hb of 70 g/L. Two units of red cells were transfused, followed by a further 2 units 9 days later (Hb 40 g/L). Two days later an automated red cell exchange was performed. This raised the Hb to 110g/L but within 5 days her Hb had again fallen to 30g/L. A diagnosis of hyperhaemolytic transfusion reaction was made and a further 2 units were given with steroid and intravenous immunoglobulin (IVIgG) cover. The patient stabilised with this approach. Throughout this period the antibody screen was negative and the DAT remained negative apart from immediately post IVIgG. Fourteen units of donor red cells had been destroyed over a period of 17 days. Acute haemolytic episodes are seen occasionally in sickle cell anaemia patients and may not, in fact, be due to the transfusion per se.

Three patients had haemolytic or febrile reactions which may have been due to red cell incompatibility.

Case 4
This patient developed fever, rigors, dyspnoea and restlessness during transfusion but had no evidence of haemolysis. A positive DAT and anti-Wra was detected in the post-transfusion sample. This antibody is rarely a cause of haemolysis but no other cause was found in this case.

Case 5
This patient experienced a febrile transfusion reaction and was found to have become DAT positive but without evidence of haemolysis. Anti-E had been detected in the pre-transfusion sample but a post-transfusion sample was shown to contain anti-Jk^b in addition. The patient had been recently transfused (2 weeks previously) and the subsequent pre-transfusion sample was drawn less than 48 hrs before the transfusion. The pre- and post-transfusion antibody screen and identification were carried out using the same column technology. The Jk^b status of the units was not stated. Unfortunately the timing of the post-transfusion sample was not given and so it is not clear how rapidly this second antibody appeared.

Case 6
This elderly patient with myelofibrosis and hypersplenism had anti-E and anti-Kp^b detected in the pretransfusion sample and was therefore being transfused with recovered frozen red cells. She was DAT positive but had no recent transfusions. During the transfusion of a second unit of washed, deglycerolised red cells she developed nausea, vomiting and jaundice. The pre-transfusion bilirubin level was not stated and it is not clear how quickly the bilirubin rose to the stated value of 150µmol/L. She presumably had a degree of underlying haemolysis and/or sequestration due to her splenomegaly. A post-transfusion sample, investigated at the RTC, was shown to contain only a weak auto-anti-D in addition to the alloantibodies. The cause of this reaction is, therefore, unclear.

Anaphylaxis

Two patients developed a severe anaphylactic reaction during a red cell transfusion. In one of these cases a transfusion of platelets on the previous day had also caused anaphylaxis (reported to SHOT) but the true nature of this was only recognised when the second event occurred. Investigation revealed only anti-Gm (no additional details supplied by reporter). It is not clear if anti-Gm alone can cause anaphylaxis although this antibody was considered causative by the reporter. Washed red cells and platelets in Platelet Storage Medium have been given on many occasions since without adverse reaction.

Allergic reactions

There were 2 apparent allergic reactions in this group

Pulmonary Oedema

Case 7
This 75 year-old man received 2 units of red cells for bleeding from a gastrointestinal tumour. During the transfusion he developed fever, rigors, back pain and dyspnoea. A chest X-ray revealed pulmonary shadowing (?oedema, ? adult respiratory distress syndrome). He deteriorated and died soon afterwards. Cultures from the pack grew coagulase negative staphylococci, as did post-mortem cultures from the patient but these were felt to be of doubtful significance. The cause of death was given as cardiac failure due to ischaemic heart disease. There were no antibodies detected in the red cell donors although the patient had "a white cell antibody reaction in the serum". The reporter felt that the absence of donor antibodies excluded TRALI although this is not necessarily the case. It was felt, on balance, that this reaction was secondary to a cardiac ischaemic event, resulting in cardiac failure.

Hypoxia and Acidosis in a Neonate

Case 8
This four week old preterm infant (weight and gestation not stated) was transfused with 10-15 mL from the third aliquot from a 3 week-old paedipack. The infant became hypoxic (O_2 saturation 40%) and acidotic, and was managed with an infusion of sodium bicarbonate. No investigations seem to have been performed on the neonate or on the pack, other than a pack pH, which was 6.7. This is not exceptionally low for a unit of stored red cells and would not be expected to lead to acidosis, particularly in the setting of a slow top-up transfusion. In view of the inadequacy of the investigations performed, a transient acute lung injury or bacteraemia cannot be excluded.

Hypertension

Case 9
A 34 year-old female with a gastric tumour became hypertensive during a red cell transfusion in a hospice. The second unit was commenced without managing the hypertension and had to be discontinued after 100mL. The cause of the hypertension was not elucidated.

2. Reactions in which FFP was implicated

There were 7 reports in this group, four reactions occurring during transfusion and 3 within 2 hours of completion.

Table 27

Reaction type	Number of cases
Anaphylactic	3
Allergic	2
Hypotension	1
Cardiac Failure	1

Anaphylactic/anaphylactoid reactions

There were 3 patients in this category. One received FFP prior to undergoing endoscopic retrograde cholangio-pancreatography (no coagulation details given), one received FFP before surgery for haematuria (again no coagulation status given) and a third patient had just completed 2 units of FFP for management of post-cardiac surgery bleeding. The first 2 patients recovered from anaphylaxis with no ill effects but the third patient died 48 hours later from ongoing haemodynamic problems, having been resuscitated with multiple episodes of defibrillation.

Allergic reactions (not anaphylaxis)

Two patients suffered apparent allergic reactions, one with pruritic rash and restlessness and the second with rash, dyspnoea and angioedema. Both patients received FFP for excessive warfarinisation without bleeding (see below).

Hypotension

Case 10
This 56 year-old female patient who was not on angiotensin converting enzyme inhibitors and with no other recognised predisposing cause developed hypotension during plasma exchange for Guillain-Barré Syndrome. The plasma exchange was carried out using hetastarch and FFP as the replacement fluids (in equal volumes). Patients with Guillain-Barré syndrome may have autonomic instability which may be exacerbated during plasma exchange and it is therefore unclear to what extent the FFP administration contributed to the reaction. In addition, it is not clear that FFP was indicated in this case (see below).

Cardiac Failure

A 68 year-old female patient with haematuria due to excessive warfarinisation developed cardiac failure within 2 hours of completing an infusion of 2 units of FFP, presumably due to fluid overload. She recovered without ill effects.

Inappropriate use of FFP

Three patients received FFP for warfarin overdosage (with bleeding in one). One experienced an allergic reaction with angioedema, a second developed a pruritic rash and the third developed cardiac failure. The guidelines on management of anticoagulation[8] suggest the use of prothrombin complex concentrate may be more appropriate in over-warfarinised patients who have life-threatening bleeding but this may not be immediately available in some smaller or more remote hospitals. Currently, only HT-DEFIX (SNBTS) is licensed for this purpose in the UK. In addition, in the absence of life-threatening bleeding, administration of a blood product should not be necessary as these patients can be managed with withdrawal of warfarin and administration of vitamin K, unless there is co-existing liver disease. One patient was receiving FFP (case 10) during plasma exchange for Guillain-Barré Syndrome and became hypotensive. She recovered without sequelae. FFP is not recommended as replacement fluid during plasmapheresis other than in the management of thrombotic thrombocytopenic purpura (TTP). Hypotension can develop during plasmapheresis, even in the absence of FFP use.

3. Reactions in which platelets were implicated

There were 10 cases in this group of which 6 reactions occurred during the transfusion, 3 within 2 hours and 1 haemolytic reaction which is likely to have occurred immediately but which was not recognised for 3 days. Three patients who had reacted to platelets died. However, this was felt not to be due to the transfusion reaction. All other patients in this group recovered without sequelae.

Table 28

Reaction type	Number of cases
Anaphylactic	6
Allergic	1
Haemolytic	3

Cases 11, 12, 13
In each of these three cases a unit of Group O platelets was administered to a Group A recipient and led to a haemolytic transfusion reaction or subsequent cross-matching problems. Two were platelet pools which had not been tested for haemolysin titres and the third was an apheresis unit which had been tested but not designated high-titre anti-A, B. This patient developed renal failure, requiring dialysis and subsequently died from causes that were thought probably unrelated to the adverse event. In each of these cases a Group A unit of platelets was not readily available.

4. Reaction in which a combination of red cells and platelets was implicated

Case 14
A 16 year-old with acute leukaemia, who had received a transfusion of apheresis platelets, closely followed by a transfusion of red cells, developed an extensive itchy rash following 100mL of his first unit of red cells. It was not possible to ascribe this definitely to either of these products.

Response times

In 2 cases no details about the response times (notification of doctor and patient being seen by doctor) were given. In all other cases a doctor was notified within 15 minutes of the reaction occurring or was present at the time. A haematologist was notified or was aware in 25 cases and was not notified in 4 cases (no record in 1). In general, appropriate involvement of medical staff occurred at an early point in the event.

Patient Monitoring

There was a wide range of frequency of nursing observations prior to the onset of the reaction.[4] In 11 cases no details about the frequency of patient monitoring is given. It is not at all clear if this is because no monitoring was performed. One patient seems to have been on only routine 4-hourly observations while the remainder were on continuous monitoring or had observations performed at intervals of 10-60 minutes.
Of the patients who developed anaphylaxis, there is no record of monitoring in 3 cases, one was on only 4-hourly observations while the remainder were on continuous monitoring or 10-60 minute observations.

Investigations

Only 9 patients out of 18 who experienced allergic, anaphylactic or respiratory problems underwent investigation for the presence of white cell antibodies or other alloantibodies. In most cases these investigations seemed to be incomplete ("normal IgA, no platelet antibodies"). Of the 4 patients who had positive results on immunological testing, one had HLA antibodies, one was reported to have IgA deficiency (?tested for anti-IgA) and anti-neutrophil antibodies were demonstrated in a donor of FFP transfused to a recipient who developed angio-oedema. The patient who died as a result of anaphylaxis was initially considered to have suffered from TRALI and investigations of the donors of his FFP showed that one, a female donor, had anti-HLA antibodies only, which did not show specificity for the patient's HLA type. Review of the case by the SHOT Writing Group suggested that this case appeared to be an anaphylactic reaction rather than TRALI.

Reporting to Blood Centres and Hospital Transfusion Committees

The HTC was made aware in 80% of cases which is increased in comparison with previous years, reflecting wider availability of these committees and better awareness of their remit. The transfusion laboratory was notified in all but one case.

Table 29
Reporting of reactions to the local Transfusion Centre, the HTC and the Hospital Laboratory (31 cases)

Reported to	Number
HTC	25
Hospital Laboratory	29
Transfusion Centre	25

In 7 cases the reporter stated that practice had been changed as a result of the incident. In 2 cases this relates to the screening of platelet donations for high-titre haemolysins (threshold changed or testing introduced for pooled platelets). The other changes relate mainly to the transfusion protocols for the individual patients rather than a general change in practice.

COMMENTARY

- In 17/31 cases the reaction was ascribed to platelets or FFP. Platelets may also have been implicated in a patient who also received red cells. As 11 times as many red cells units are issued compared to platelet units and 7 times as many red cell units as FFP units it is apparent that the risk of an acute reaction is significantly higher with the administration of platelets or FFP.

- It is recommended that FFP and platelets should be transfused rapidly and yet it is difficult to justify this on the basis of deterioration of the pack contents. Coagulation factor decline in thawed FFP, for example, affects FVIII and FV levels in the main, yet these are generally not a significant contributor to any observed coagulopathy. Platelets will not deteriorate during a period of a few hours, unagitated, at room temperature. It is accepted, however, that in some circumstances clinical expediency may dictate that a rapid infusion is necessary - for example in the presence of acute bleeding.

- Again, as noted previously, patients have received FFP inappropriately in some cases, particularly for warfarin reversal in the absence of bleeding, and are experiencing life-threatening reactions.

- ABO-incompatible platelet pools and apheresis units are a recognised cause of haemolytic transfusion reactions. Pooled platelets prepared from buffy-coats are suspended in the plasma of one donor. They are, then, just as likely to contain high-titre anti-A or B as an apheresis unit but routine screening for high-titre haemolysins has been introduced only recently in some areas of the UK, in response to the noted haemolytic episodes.

- Under-investigation of acute and delayed adverse events is common and leads to difficulty in ascribing a precise cause.

- The frequency of patient monitoring during transfusion, particularly of platelets and FFP, was very variable and perhaps not carried out in many cases. This is of concern, particularly as these two components are generally infused rapidly and have a relatively high frequency of adverse events as noted above.

RECOMMENDATIONS

- **Patients receiving any blood component must be monitored or observed in such a way that an acute reaction can be detected early. In addition to baseline observations before commencing each transfusion, each patient should be checked after 15 minutes infusion of each new unit or pool.[4]**

- **National guidelines on anticoagulation[8] which include clear guidelines on managing excessive warfarinisation should be circulated more widely, in a form which is accessible to surgeons and clinicians of all grades. It is rarely appropriate to give FFP for this purpose and it is generally sufficient to stop the warfarin and give vitamin K where necessary. Appendix 11 contains a summary of the guidelines on reversal of anticoagulation prior to surgery and in over-warfarinised patients.**

- **Platelet units contributing to pools prepared by the "dry buffy-coat method" should undergo testing of the "plasma donor" for the presence of high-titre haemolysins, similar to that performed for apheresis units. Ideally, however, Group O donors with high-titre haemolysins should not be used as plasma donors in platelet pools. Clinicians should avoid giving Group O platelets to Group A or B recipients unless this will result in a clinically significant delay. A recent entry in "Blood Matters" deals specifically with this topic and is included at Appendix 12.**

- **The feasibility of using only male donors as donors of clinical FFP and plasma for platelet pools should be explored as these will be less likely to have allo-antibodies to any cellular antigens.**

- **More detailed investigation of patients experiencing immune reactions to components would clarify the nature of these reactions and should be considered particularly in cases with anaphylaxis or pulmonary manifestations. However, it is not clear that detailed investigation of other allergic reactions would be cost-effective, unless these are recurrent and causing problems in managing the patient effectively.**

- **The BCSH Transfusion Task Force is drafting a guidelines for the investigation and management of ATR. This will be presented at the next British Society of Haematology meeting in 2002.**

- **The recommendations for appropriate administration rates for FFP and platelets should be revisited in order that clinicians can feel able to infuse these more slowly if the clinical condition permits. This will allow more monitoring of the patient and perhaps early detection of an acute event at an earlier point in the transfusion.**