12. 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 10

This category accounted for 10.3% of non-infectious hazards reported and 10.1% of all hazards.
There were 6 outstanding reports from the previous reporting year for which 5 questionnaires were eventually received and are included in the analysis. 1 outstanding report was written off after the 6 month deadline had passed. For an explanation of the system of maintaining deadlines please see chapter 4 "Overall organisation and reporting system."
From 54 new initial reports there were 48 completed questionnaires. The 6 outstanding questionnaires will be included in next year's analysis. Additionally 5 reports did not fit the definition of ATR and have been withdrawn, 4 by the analyst and 1 by the reporter.
This chapter highlights the main findings from 48 completed questionnaires.

There were 7 deaths in this group; 1 probably related to the transfusion, 1 possibly related to the transfusion and 5 unrelated to the transfusion.

Gender (48 reports)

Males	27
Females	21(one female recipient was involved in 2 reports)

Age (48 reports)

Age range	2 days to 93 years
Median	67 years

Components implicated (48 reports)

Red cells	17	
Platelets and cryoprecipitate	1	
Platelets	10	(4 from apheresis and 6 from pooled buffy coats)
Platelets and fresh frozen plasma	1	(pooled buffy coat platelets)
Fresh frozen plasma	18	(1 solvent detergent treated)
Cryodepleted fresh frozen plasma	1	

Reactions in which red cells were implicated

There were 17 cases, with one death probably related to the transfusion, one possibly related to the transfusion and 2 deaths due to the underlying disease. 13 reactions occurred during the transfusion, 3 within 2 hours of completing the transfusion and 1 within 7 hours of completing the transfusion. The following reactions were seen:

Table 28
Reactions in which red cells were implicated

Reaction type	Number of cases
Haemolytic or incompatibility reaction	8
Anaphylactic[+]	2
Allergic[++]	5
Neutropenia	1
Hypoxia and acidosis (neonate)	1

[+] anaphylactic/anaphylactoid (defined clinically as 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 6 cases, red cell alloantibodies or autoantibodies were thought to have contributed to the reaction.

Case 1
A 74 year old female with high grade B-NHL and a previous transfusion history, was found on pre-transfusion testing to have a positive DAT (C3d) and a weak antibody in her serum showing no specificity. A presumptive diagnosis of autoimmune haemolysis was made. These findings were confirmed by the reference laboratory who provided 2 units of red cells that were weakly incompatible by IAT crossmatch. The patient became febrile with a tachycardia and hypertension during the transfusion, which was stopped after 60mL. Post-transfusion, her haemoglobin fell and she had circulating spherocytes. The post-transfusion serum reacted more strongly with panel cells than with the patient's own cells and was referred to the International Blood Group Reference Laboratory (IBGRL), who found anti-Vel. The patient received further units, unselected for Vel, prior to the receipt of the IBGRL findings and suffered no further reactions. However she was receiving steroids for a presumptive diagnosis of autoimmune haemolysis in association with her B-NHL. It is not known whether the anti-Vel was an autoantibody or alloantibody, although IBGRL favoured the latter explanation. The patient died 3 weeks later from her underlying disease.

Case 2
A 69 year old female with acute myelofibrosis/acute myeloid leukaemia was transfused 2 units of red cells for her anaemia. She had received 8 units of red cells within the preceding 4 weeks and the pre-transfusion sample, taken within 48 hours of the reported transfusion, showed a positive DAT (IgG) but a negative serum antibody screen. 3-4 hours after the completion of the transfusion, she collapsed at home with chest pain and dyspnoea. She was taken to another hospital, where she was admitted to ICU with haemoglobinuria, other biochemical evidence of haemolysis and deteriorating renal function and subsequently died.
Retrospectively, her pre-transfusion serum contained an anti-C, detectable only using papain-treated red cells in the IAT and the eluate contained an anti-C-like antibody and an anti-e-like antibody. She had been transfused with R_1r and R_2r units and post-transfusion there was no detectable antibody in her serum and the eluate again contained an anti-C-like antibody and an anti-e-like antibody. Her Rh genotype was suggested to be R_1R_2 on the basis of polymerase chain reaction. Bacterial cultures of the 2 units and the patient were negative.
The patient was found to have mitral stenosis at post-mortem but was thought to have died as a result of haemolysis. The most likely explanation is an exacerbation of autoimmune haemolysis as a result of the transfusion. Autoimmune haemolysis could also have contributed to her excessive red cell transfusion requirements over the 4 weeks prior to her demise.

Case 3
A 10 year old girl had undergone an unrelated (cord) stem cell transplant for acute myeloid leukaemia 2 months earlier at another centre and post-transplant had been diagnosed to have an autoimmune haemolytic anaemia. The reporting hospital had not been provided with any details of her previous transfusion record including the donor's and recipient's original ABO groups. On this occasion she was grouped as O, with a positive DAT (IgG and C) and positive antibody screen. All further testing was performed by the reference laboratory but no details are available. During the reported transfusion, she developed back pain and dark urine and was confirmed to have haemoglobinuria and hyperbilirubinaemia. She was immediately transferred back to the transplant centre.
It was assumed that the patient had suffered an exacerbation of the underlying autoimmune haemolysis but further information has not been available.

Case 4
A 76 year old female with probable myelodysplasia and a weakly positive DAT (IgG) was found to have an antibody in her serum, reacting with all panel cells but not her own cells. These reactions were not observed using plasma and units were issued on the basis of their compatibility using plasma for crossmatching. The patient became febrile and hypotensive during the transfusion which was stopped after 100mL. Investigations confirmed haemolysis but no deterioration of renal function. Subsequent testing at the reference laboratory confirmed the presence of an anti-Vel, reactive only in serum.
The laboratory now recommend that all transfusion reactions are investigated using both serum and plasma.

Case 5
A 66 year old female with acute myeloid leukaemia and sepsis, transfused uneventfully 12 days earlier, had a positive DAT (IgG and C3d) and antibody screen on pre-transfusion testing. The sample was referred and an anti-E was identified in the serum following alloabsorption with Rh identical and Jk^a negative cells. The patient was transfused, 2 days after the sample was taken, with E negative units and became febrile and hypotensive during the first unit, which was stopped. The post-transfusion sample contained anti-E+Jk^a and the unit transfused was Jk^a positive. The anti-Jk^a was not detected on retrospective retesting of the pre-transfusion sample.

Case 6
A 93 year old male, known to have anti-k and to have recently undergone an abdominal aortic aneurysm repair, was readmitted as an emergency with bleeding from an infected surgical site. He was transfused as an emergency in casualty with 1 unit of "emergency O neg" (group O, rr, K negative) red cells during the time the laboratory was being provided with a sample and accessing the historical records. The clinicians in casualty were made aware of the need for k negative blood but the patient required resuscitation with 3 further units of k incompatible blood before compatible units could be provided. The patient complained of loin pain during the initial transfusion and died 48 hours after admission. It is not clear to what extent the haemolysis contributed to his death.

In the following 2 cases, although anti-Jk^a was demonstrated following the transfusions, it is not clear whether the antibody had contributed to the reaction.

Case 7
A 43 year old male with a mixed connective tissue disorder, had bled following a renal biopsy and had received 11 units of red cells in the 6 days prior to the reported transfusion. There was no other known transfusion history although the patient had been found to have a positive DAT in 1995. The pre-transfusion sample taken less than 48 hours before the reported transfusion showed a negative DAT and antibody screen. The patient developed fever and rigors during the transfusion and the post-transfusion sample showed a positive DAT (IgG) and the serum contained anti-Jk^a. There was a modest rise in bilirubin from 8 to 18umol/L but the haemoglobin remained stable. No bacterial culture was performed on the 4 units of red cells given, but coagulase negative staphylococci were cultured from the tip of the arterial line and some of the blood cultures. The patient had developed 2 other febrile episodes in the 48 hours preceding the reported transfusion and the "transfusion reaction" may have been due to the infected arterial catheter, rather than the anti-Jk^a.
No eluate was performed on the post-transfusion sample and the units given were not typed for Jk^a, to confirm that a Jk^a incompatible unit had been transfused. Although no previous transfusion history had been elicited, it is extremely unlikely that the detected anti-Jk^a represented a primary response to transfusions given within a 6 day period.

Case 8
A 68 year old male with myelofibrosis and no previous transfusion history developed dark urine during a 3 unit red cell transfusion and was confirmed to have haemoglobinuria. His haemoglobin initially rose from 80g/L to 112g/L but had fallen to 88g/L 48 hours later. His bilirubin rose from 41µmol/L to 138µmol/L over the same period. His pre- and post-transfusion samples had negative antibody screens and negative DATs, but a sample taken 18 days after the reaction contained an anti-Jk^a, reactive only with homozygous cells. 2 of the 3 units transfused were Jk^a positive. The patient was transfused 4 months later when his antibody screen was negative. He received 2 units matched for K, Jk^a, Fy^a and S but again developed haemoglobinuria with no apparent serological cause.
No explanation was found for the haemolysis, except for a degree of hypersplenism.

Transfusion Related Alloimmune Neutropenia

Case 9
A 2.2kg male infant born at term was diagnosed as having transposition of the great vessels. He underwent a switch procedure at 4 weeks and the operation proceeded without complication. On the 2nd post operative day, 80mL of plasma reduced blood containing approximately 12.5mL/kg of plasma was transfused over 4 hours. Preoperative and postoperative white cell counts (WCC) were normal. 2 hours before the transfusion the WCC was 7.4 x 10^9/L with a normal differential. 2 hours post-transfusion the WCC had fallen to 0.7 x 10^9/L

(neutrophils 0.06, monocytes 0.08, lymphocytes 0.48 and eosinophils 0.01 x 10^9/L). The count was repeated twice with the same results. The neutropenia persisted and 48 hours post-transfusion a bone marrow was performed. This showed active myelopoiesis to the stage of metamyelocytes but no band or segmented forms. Treatment was started with daily Granulocyte Colony Stimulating Factor (G-CSF) 3 ug/kg sc and the neutrophil count returned to normal at 5 days post-transfusion. The chest X-ray showed no infiltrates and there was no evidence of respiratory distress syndrome to suggest Transfusion Related Acute Lung Injury.
Plasma from the donor unit was tested for HLA and neutrophil antibodies. A strongly reacting antibody to human neutrophil antigen 1b (HNA-1b) was detected with chemiluminescence, immunofluorescence and monoclonal antibody capture assays. The patient had a genotype of HNA-1a1b.
The donor was an untransfused multiparous female aged 48 years. Her last pregnancy was 19 years before the current donation and there was no history suggestive of alloimmune thrombocytopenia. Her genotype was HNA-1a1a and her husband's genotype was HNA-1b1b.

This case has been fully documented in the Lancet[17] and is reported here with the permission of Dr JP Wallis.

Anaphylactic/anaphylactoid reactions

Two patients developed anaphylactic/anaphylactoid reactions during red cell transfusions, and both survived with no ill effects. One was tested for IgA deficiency, with negative results and has subsequently been uneventfully transfused with washed red cells.

Allergic

There were 4 apparent allergic reactions in this group.

Hypoxia and Acidosis in a Neonate

There was one case reported of a 5 month old girl with pneumonia, who became increasingly tachypnoeic and acidotic after receiving 15mL/kg red cells with a pH of 6.9. This pH is within the expected range for red cells and would not have contributed to the acidosis.

Reactions in which FFP was implicated

There were 19 reports in this group, (including the report implicating cryodepleted FFP) of which 16 occurred during the transfusion, 2 within 2 hours and 1 between 2 and 7 hours of completing the transfusion. The following reactions were seen:

Table 29
Reactions in which FFP was implicated

Reaction Type	Number
Anaphylactic	7
Allergic	9
Febrile	1
Hypotension	1
Cardiac failure	1

Anaphylactic/anaphylactoid

There were 7 patients in this category, all of whom recovered from the reaction, but one of whom later died unrelated to the transfusion. All but one patient received a combination of hydrocortisone and adrenaline. One patient developed oliguria and required additional inotropic support and a second with bronchospasm required additional bronchodilators and oxygen.
Two patients were investigated for IgA deficiency, with negative findings; in 1, the nature of the reaction was confirmed with an elevated plasma tryptase level and the second patient had Gm1 antibodies. Four patients had respiratory symptoms, of whom 2 had a chest X-ray performed, the results of which are unfortunately not available. Another patient, although reported to be asymptomatic was found to have a reduced O_2 saturation.
In 1 patient, there was no clear indication for prescribing FFP.

Case 10
A 52 year old female was undergoing plasmapheresis with cryodepleted FFP for thrombotic thrombocytopenic purpura when, towards the end of the procedure, she developed a rash and became hypoxic and hypotensive. She was resuscitated with adrenaline and hydrocortisone and has since been receiving SD-FFP (pooled) as replacement plasma. The patient had a normal IgA level but anti-Gm1 antibodies were found in her plasma.

Case 11
A 2 day old term female who had had a traumatic delivery, received blood components for a coagulopathy and subaponeurotic haemorrhage. The patient had no untoward effects from the first 3 aliquots of a dedicated FFP paedipack, and had also received red cells, platelets and cryoprecipitate. At the end of receiving the last aliquot of 32mL plasma, she developed a rash, dyspnoea, bradycardia and hypotension. A chest X-ray showed no infiltrates and she recovered following hydrocortisone. Further transfusions were given uneventfully with hydrocortisone cover.

Allergic reactions (mild)

There were 9 patients in this group, 3 with a rash and 6 with dyspnoea and a fever. Two of the latter had chest X-rays performed; 1 not reported and the second with negative findings.

Hypotension

Case 12
A 73 year old male with chronic renal failure received 1 unit of FFP whilst having his vascular line changed (no coagulation results given). He became hypotensive after receiving 100mL FFP and was treated with antihistamines and a diuretic. It is not known whether he was being treated with angiotensin converting enzyme (ACE) inhibitors.

Cardiac failure/ myocardial infarct

Case 13
A 73 year old male, with metastatic rectal carcinoma and on warfarin, was given 3 units of FFP prior to an emergency Hickman line removal. Two hours later he became dyspnoeic, was diagnosed to have left ventricular failure and later found to have a raised troponin level, consistent with a myocardial infarct.

Inappropriate use of FFP

In 12 of the 19 reports, sufficient information was provided to suggest that the use of FFP was justified.

The use of FFP could not be justified in 2 patients; 1 was overdosed with warfarin, but was not bleeding nor was there an imminent procedure and the second received FFP post-operatively, when there was no active bleeding and no prothrombin time (PT) had been performed. Five patients, with no medical reason for a bleeding tendency, received FFP during elective procedures when less than 6 units of red cells were transfused. No coagulation findings were reported.

Reactions in which a combination of components was implicated

There was 1 case of fluid overload and 1 allergic reaction.

Case 14
A 39 year old female with acute myeloid leukaemia (M3) had received 4 units red cells, 19 units cryoprecipitate, 8 units of FFP and 1 pool of buffy coat derived platelets. Six hours later she developed dyspnoea, hypoxia (O_2 sats. 92%) and tachypnoea and the chest X-ray was consistent with pulmonary oedema. She made a full recovery with oxygen, diuretics, bronchodilators and hydrocortisone but developed a similar episode following another transfusion of multiple units of plasma containing components.
The reporter was uncertain as to whether this reaction represented fluid overload or TRALI. However since investigations for TRALI were negative and the patient had received several litres blood components on each occasion and made a rapid recovery, this case has been classified as fluid overload by the SHOT team.

Case 15
A 77 year old female received 1 pool of buffy coat platelets and 4 units of FFP at the time of coronary artery bypass grafting. No details of coagulation studies are provided. Two hours later she developed a rash, angioedema, dyspnoea and hypoxia. She was treated with hydrocortisone and nebulised bronchodilators. Investigations revealed reduced complement levels and a raised plasma tryptase level in keeping with an allergic reaction.

Reactions in which platelets were implicated

There were 10 reactions in this group, of which 7 occurred during the transfusion, 2 within 2 hours and 1 between 2 and 7 hours following the transfusion. One of these patients patient died from haemorrhage, despite platelet transfusion support and was subsequently found to be alloimmunised to anti-HPA5b and a second patient died unrelated to the transfusion. All other patients recovered from their reactions without sequelae.

Table 30
Reactions in which platelets were implicated

Reaction Type	Number of cases
Anaphylactic	3
Allergic	7

Nine of the 10 patients had received previous transfusion support.

No further immunological investigations were performed on the 3 patients with anaphylactic/anaphylactoid reactions, despite the fact that 2 of the 3 had not previously received plasma or platelets and could have been IgA deficient. 1 patient became hypoxic with an O_2 saturation of 92%

Five patients with allergic reactions had further immunological investigations.
Two patients with allergic reactions were found to have anti-HPA antibodies and had no further reactions on receipt of HPA matched platelet donations. It is not known whether these patients were refractory to random platelet concentrates or to what extent the transfusion of HPA matched platelets improved the post transfusion increments. One patient with rash and dyspnoea was found to have Gm antibodies but the subsequent tolerance of platelet transfusion is unknown. In 1 case the donor plasma was found to contain multispecific HLA Class II antibodies. Finally, 1 recipient was found to have anti-Chido.

One patient with repeated allergic reactions consisting of rash, dyspnoea and tachycardia was documented to have no further problems when receiving platelets in suspension medium rather than plasma.

Six of the 10 reactions were accompanied by dyspnoea, including the case in which the donor plasma contained HLA Class II antibodies. All required treatment with hydrocortisone and 2 also received nebulised bronchodilators and oxygen. One chest X-ray was performed in this group with negative findings.

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 FFP were brought to a haematologist's attention.

Table 31
Time taken for patient to be reviewed by a doctor from being called

Response Times	Red cells (17)	FFP (21)*	Platelets (10)
Stat	5	12	5
< 30 minutes	5	5	4
< 60 minutes	2		
> 60 minutes	1		
Data not available	2	3	
Late reaction	1		1
Not seen	1	1	
Total	17	21	10
Involvement of Haematologist	**14**	**7**	**9**

* includes cases in which other components were transfused

Patient Monitoring

In 18/48 cases, the reporter could not access records of nursing observations taken during the transfusions. Records of observations made during platelet transfusions outside an intensive care setting were notably absent. The frequency of patient observations met the standards given in the BCSH guideline[6] in only 6/11 red cell and 7/15 FFP transfusions.

Table 32
Frequency of patient monitoring during transfusion

Frequency monitoring	Red Cells (17)	FFP (21)*	Platelets (10)
Constant (ICU)	**1**	**2**	**2**
Pre / 15 min post	**5**	**5**	**0**
30 minute intervals	**4**	**5**	**0**
Hourly	**1**	**0**	**0**
> hourly/none	**0**	**3**	**2**
Not available	**6**	**6**	**6**
Total	**17**	**21**	**10**

* includes cases in which other components were transfused

Investigations

3/12 anaphylactic reactions were investigated. 1/2 investigations involving red cells were negative as were the 2/7 investigated reactions involving FFP. No investigations were performed on recipients of platelets who suffered this type of reaction.

Of the allergic reactions, 1/3 involving red cells was investigated with a negative outcome. Investigations of 5/10 allergic reactions to FFP (in 2 cases given in conjunction with other components) revealed positive findings in 2/5 transfusions. In 1 case HLA antibodies were found in the patient and at least 1 of the donors and 1 patient had Gm antibodies. 5/7 patients with allergic reactions to platelets were investigated with positive findings as indicated above.

Changes made to procedures

The laboratory reporting case 4, an acute haemolytic reaction attributed to an anti-Vel reactive only in serum, has changed its protocol for investigating transfusion reactions to include the requirement for both serum and plasma samples.
Three other laboratories took action as a result of reporting acute transfusion reactions to FFP. Two hospitals where the reaction occurred when FFP was inappropriately prescribed have reaudited the usage of this component as part of an educational programme. A third hospital in which a patient suffered an anaphylactic reaction to FFP now requires that a haematologist is contacted to advise upon the management of reactions to all blood components.

Reporting of acute transfusion reactions

All but 1 acute transfusion reactions were reported to the hospital laboratory. 82% of reactions involving red cells were reported to the Hospital Transfusion Committee and 76% and 70% of those involving FFP and platelets. Reactions were reported to the local Transfusion Centre when samples were sent for further investigation.

Table 33
Reporting of reactions to the Hospital Transfusion Committee, Hospital Laboratory and the local Transfusion Centre

Reported to	Red cells (17)	FFP* (21)	Platelets (10)
Hospital Transfusion Committee	14	16	7
Hospital laboratory	16	20	10
Transfusion centre	12	10	8

* includes cases in which both FFP and platelets were transfused

COMMENTARY

- The majority of acute transfusion reactions (31/48) were due to FFP and platelets, as in previous years, with 79% (27/34) allergic or anaphylactic reactions due to these 2 components.
- It is apparent that FFP has the highest risk of causing an acute reaction and yet is often inappropriately prescribed[10].
- Haematologists were frequently not involved in the management or investigations of acute reactions involving FFP.
- A minority of transfusions, particularly those involving platelets, were monitored in accordance with BCSH recommendations[6].
- In 4/12 cases where a haemolytic transfusion reaction was either suspected or confirmed, the DAT was positive with the cells being coated with IgG, and no eluate or additional investigations were performed.
- There were 5 cases of anaphylactic/anaphylactoid reactions in patients who had not been previously exposed to plasma containing components and who were not investigated for IgA deficiency.
- Investigations of allergic transfusion reactions were performed in the majority of recipients of plasma containing components. In 3/5 platelet recipients, investigations revealing HPA and/or HLA antibodies influenced the future transfusion support of the patient.
- Alloimmune neutropenia, in the absence of clinical features of transfusion-related acute transfusion injury, has been reported as an additional complication of transfusing plasma containing antibodies against human neutrophil antigens

RECOMMENDATIONS

- **Patients receiving any blood component must be monitored to detect an acute reaction. Patients must be checked prior to the transfusion of each component and 15 minutes after its commencement.**

- **Patients who have had a severe allergic reaction (anaphylactic/anaphylactoid) should be investigated for IgA deficiency.**

- **Where plasma samples are routinely used for pre-transfusion testing, it is recommended that serum samples are also used in the investigation of suspected transfusion reactions.**

- **Particular care should be taken when providing blood for patients with a positive DAT, who are known to have an autoimmune haemolytic anaemia or have been recently transfused. Referral to a reference centre, if time allows, should be considered.**

- **There is a need for a guideline dealing with the investigation of all acute transfusion reactions.**

- **There is continued evidence of inappropriate use of clinical FFP[10], and further local audits and educational programmes should be encouraged. A revised BCSH guideline is expected during 2003; in the meantime, existing BCSH guidelines[8, 9] should be followed.**

- **The options for using untransfused males as donors of clinical FFP and for suspending platelets in plasma-free media should be pursued by the UK blood services.**

- **When the care of patients with haematological disorders requiring transfusion support is shared, there is a risk that not all pertinent transfusion history will be available to both sites. In the absence of networked pathology information systems, it is essential that local procedures are devised for adequate communication between laboratory as well as clinical teams.**