7 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 Section 4

Eighty-nine completed questionnaires were analysed. Twenty-one were withdrawn by the analyst; 15 of these were reports of non-haemolytic febrile reactions, one of which occurred following the re-infusion of red cells salvaged post-operatively, in 5 the symptoms were due to the underlying pathology and the final report withdrawn was of an unavoidable incompatible transfusion that did not lead to a reaction.

This chapter highlights the main findings from 68 completed questionnaires.

Gender (68 reports)

Males 35 Females 33

Age (68 reports)

Age range	6 months to 84 years
Median	56 years

Components implicated (68 reports)

Red cells	23
Platelets	20 (8 apheresis units and 12 from pooled buffy coats)
Granulocytes	1
Fresh frozen plasma (FFP)	22
FFP - solvent-detergent	1
Red cells and FFP	1

Deaths and major morbidity

There was 1 death in this group, likely to be related to transfusion (imputability level 2) and 7 reports of major morbidity; 6 likely to be related (imputability level 2) and 1 possibly related (imputability level 1) to transfusion.

Table 17

Deaths and major morbidity

Outcome	Imputability level	Case number	Component	Reaction type	Comment
Death	2	10	FFP	Anaphylactic/ anaphylactoid	Obstructive jaundice. Vit K not given
Major morbidity	2	6	Red cells	Anaphylactic/ anaphylactoid	Cardiac arrest, severely atopic recipient
	2	8	Red cells	Unclassifiable	Hypoxia requiring ventilation
	2	11	FFP	Anaphylactic/ anaphylactoid	Cardiac arrest
	2	12	FFP	Anaphylactic/ anaphylactoid	Myocardial infarct
	2	13	Platelets	Unclassifiable	Respiratory arrest
	2	14	Granulocytes from family member	Anaphylactic/ anaphylactoid	Ventricular tachycardia
	1	9	Red cells	ALI	Multiple factors

Reactions in which red cells were implicated

There were 23 cases, with 3 instances of major morbidity; 2 likely to be due to the transfusion and 1 possibly due to the transfusion. 17 reactions occurred during the transfusion, 3 within 2 hours, 1 within 7 hours and 1 within 24 hours of completing the transfusion. In the final case the precise timing was unclear.

The following reactions were seen:

Table 18

Reactions in which red cells were implicated

Reaction type	Number of cases
Haemolytic	5
Anaphylactic+	5
Allergic++	8
Unclassifiable	2
Febrile	3 (of 14 initially reported)

+ anaphylactic/anaphylactoid (hypotension with 1 or more of: rash, dyspnoea, angioedema)
++ allergic (1 or more of: rash, dyspnoea or angioedema **without** hypotension)

Haemolytic Reactions

In 3 of the 5 cases, a reference laboratory was involved in either providing antigen matched units or the subsequent investigation of the reaction.

Case 1

A case of a 69 year old lady with a transfusion-dependent myeloproliferative disorder and multiple red cell alloantibodies (anti-K+Kp^a+S+C+Fy^a+Kn^a/McC^a) who had experienced a delayed transfusion reaction to a previous transfusion (see case 13 in the Delayed Transfusion Reaction Chapter). She developed an anti-M over this period but the red cells causing the acute reaction were M-negative.

Case 2

A 65 year old male with gastrointestinal (GI) bleeding had been transfused with red cells within the previous 14 days. A sample less than 48 hours old was used to crossmatch 2 further units. The patient developed a fever and back pain at some stage within the 24 hours following the transfusion. This was not documented contemporaneously, and the nursing staff were unaware of a reaction having occurred. There was however no post-transfusion increment in haemoglobin and brown plasma was noted in the sample sent to the laboratory 36 hours later. The pre-transfusion antibody screen was negative using plasma (DiaMed). Post-transfusion, anti-Jk^a was found in the plasma and eluted from the red cells. Retrospective testing of a pre-transfusion serum sample showed weak reactions with no demonstrable specificity.

Case 3

A 33 year old female, with unexplained red cell aplasia, required monthly red cell transfusions and she had been previously noted to pass dark red urine in the 24 hours following transfusion. On this occasion a poor haemoglobin increment and hyperbilirubinaemia were also noted. The DAT was positive (C3d only), her antibody screen was consistently negative using DiaMed ID and there was no evidence of paroxysmal nocturnal haemoglobinuria (PNH). The reference laboratory found an auto anti-c reacting by DiaMed enzyme IAT.

Subsequent transfusions of R_1R_1 cells have been given with no adverse effects.

Case 4

A 72 year old lady with disseminated carcinoma of the ovary and a previous carcinoma of the breast was transfused in a community hospital with 2 units of red cells. Within 2 hours of completing the second unit, she became febrile and passed dark urine. She was known to have been transfused in 1999 but there was no record of subsequent transfusions. Her pre-transfusion antibody screen using Immucor Capture-R was negative, as were 4 previous antibody screens dating back to 1999. The units had been issued electronically.

The laboratory was only informed of the reaction 10 days later and the post-transfusion sample revealed an anti-K reacting weakly in DiaMed IAT. Further investigation confirmed that the first unit given was K positive.

Case 5

A 45 year old male with HIV, anaemia and a positive DAT (IgG and C3d), being treated with antiretroviral therapy was transfused with 2 units of red cells. The patient was not known to have autoimmune haemolysis (rare in this condition although a positive DAT is common). After receiving 100mL of the second unit, he developed rigors, back pain, restlessness and hypotension. He was noted to pass dark urine and his bilirubin subsequently rose to 51µmol/l. The unit was confirmed to be ABO identical and the antibody screen was negative pre- and post-transfusion. Further retesting of the pre-transfusion sample including a repeat crossmatch confirmed the negative findings, but samples were not referred to a reference laboratory. He has not received further red cells in this hospital and there is no further follow-up.

Anaphylactic/anaphylactoid reactions

Five anaphylactic/anaphylactoid reactions were reported. There was one case of major morbidity (case 6) and a second patient already on the intensive therapy unit (ITU), required further inotropic support following initial resuscitation.

Case 6

A 37 year old female was known to have severe atopic eczema, asthma and to be allergic to peanuts. As a toddler, she developed urticaria following ingestion of peanut butter but by the age of 16 years had obstructive laryngeal oedema on inhaling peanut powder. She was not allergic to latex and had no previous transfusion history.

Following a caesarean section for haemolysis, elevated liver enzymes, and a low platelet count (HELPP) syndrome and a post-partum haemorrhage, she was transfused with 2 units of red cells when she returned to the ward. The first unit was transfused uneventfully. The second unit was commenced after an interval of 2 hours and within the first 5 minutes she had difficulty breathing, collapsed and had a cardiac arrest from which she was successfully resuscitated.

Serial mast cell tryptases showed an elevation to 60.1ug/l 2 hours after the arrest with a fall to normal levels 24 hours later, in keeping with mast cell degranulation. Subsequent investigation of the patient revealed a normal IgA level, a total serum IgE level >5000u (NR 5-120) and strongly positive IgE radioallergosorbent test (RAST) to nuts, eggs and wheat.

Given the temporal relationship of her reaction to the second unit of red cells, the question was raised as to whether this donor had eaten any of the allergens to which she was known to be allergic. However both donors' sera were tested for peanut protein with negative findings. An alternative explanation of the patient having inadvertently ingested a known allergen was thought less likely given her immediate post-operative state.

Of the 4 remaining cases, 3 were not investigated and the fourth was not IgA deficient.

Allergic Reactions

There were 8 allergic reactions reported with features as noted below:

Table 19

Clinical features of allergic reactions to red cells

Case No.	Fever	Rigors	Hypertension	Rash	Dyspnoea	Hypoxia	Angioedema
15	x	x	x		x	x	
16	x				x		x
17	x			x			
7	x	x	x		x		
18				x	x	nk	x
19	x				x	x	
20		x			x	nk	
21	x		x		x	x	

(nk = not known)

In 4 of the cases, fever and dyspnoea (without recorded wheeziness) were the only manifestations, with reduced oxygen saturation, when measured. HLA antibodies were recorded in 2 but not tested for in the remaining 2.

In 5 out of the 8 cases IgA levels were measured, with one IgA deficiency but no anti-IgA.

Case 7

A 22 year old male climber had a combined tibia/fibula fracture and required a post-operative transfusion. After 50mL, he became febrile with rigors, wheezy, hypertensive and vomited. His white cell count was normal at 7.2 x 10^9/l before the transfusion, but fell to 1.6 x 10^9/l immediately following with only 0.02 x 10^9/l neutrophils. He responded promptly to hydrocortisone, antihistamine and a bronchodilator. The neutrophil count returned to normal within 5 hours. Cultures of the patient and the red cells were negative, a mast cell tryptase was not performed.

The patient's serum did not contain granulocyte specific antibodies and the transient nature of the neutropenia suggests that margination could have occurred. The chest x-ray (CXR) showed no abnormality.

Febrile reactions

Of the 17 febrile reactions reported this year, 3 are included in the report. Two were the result of red cell alloantibodies not detectable in the patients' pre-transfusion antibody screen, and the electronic issue and transfusion of incompatible units. An anti-Wr^a caused fever and chills following the transfusion of 140mL red cells, and an anti-Bg^a caused fever towards the end of the transfusion. In neither case were features of haemolysis mentioned.

A third febrile reaction in a 74 year old male resulted in an overnight admission for observations since the reaction provoked chest pain and restlessness.

Of these 17 febrile reactions, sufficiently severe to stop the transfusion, there are only 9 reports of the units being cultured.

Unclassifiable reactions

Case 8

An 83 year old male with a lymphoplasmacytoid lymphoma and an IgM paraprotein had already received 4 units of red cells within the last 48 hours. During transfusion of the fifth unit he became febrile, hypertensive and dyspnoeic. The transfusion was stopped for immediate investigation of red cell incompatibility and then recommenced. The symptoms returned, worse than previously and, since his dyspnoea and wheeziness did not immediately respond to piriton, hydrocortisone and salbutamol,(oxygen saturation 82% on 100% O_2) he required intubation. He recovered within 3 hours. Investigations for TRALI were negative and although the features could be in keeping with a severe allergic reaction, a component of hyperviscosity/fluid overload cannot be excluded.

Case 9

A 32 year old male with sickle cell disease was admitted with an evolving acute chest syndrome and over the following 48 hours he was transfused with 3 units of red cells followed by an exchange transfusion of 6 units. His chest symptoms improved. On the third day he was given a further 2 units of red cells without incident. The transfusion finished at 2340 hours and his observations remained stable until 0600 hours when he had a grand mal fit. He was subsequently noted to be hypoxic and tachypnoeic and required intubation. He then had a cardiac arrest from which he was successfully resuscitated. The CXR showed bilateral pulmonary infiltrates consistent with acute lung injury (ALI).

TRALI was suspected by the intensivists but the last 2 units and the patient's serum tested negative for HLA and granulocyte antibodies. Volume overload was considered in view of his known renal impairment. However in addition to the red cells, other factors including his recent chest syndrome and likely hypoxia during a grand mal fit, could have contributed to the development of ALI.

Reactions in which FFP was implicated

There were 24 reports in this group (one in conjunction with red cells), with one death likely to be due to the transfusion and 2 instances of major morbidity also likely to be due to the transfusion. Eighteen occurred during the transfusion and 6 within 2 hours of the transfusion.

The following reactions were seen:

Table 20

Reactions in which FFP was implicated

Reaction type	Number
Anaphylactic/anaphylactoid	14
Allergic	9
Hypotension	1

Anaphylactic/anaphylactoid

Of the 14 patients in this group, one received solvent detergent treated FFP during plasma exchange and the remainder, standard FFP.

It is questionable whether the FFP was indicated for the cases resulting in mortality and morbidity.

Case 10

A 17 year old male with Burkitt's lymphoma had obstructive jaundice and a coagulopathy, secondary to lymphadenopathy in the porta hepatis. He required intrathecal chemotherapy and FFP was given prior to lumbar puncture, to correct his abnormal coagulation screen.

After receiving 100mL FFP he started to wheeze, and rapidly became hypotensive and had a cardiac arrest. He received adrenaline, antihistamines and bronchodilators prior to the arrival of the cardiac team. Resuscitation was unsuccessful.

The patient had not been given vitamin K which should have corrected the prolonged coagulation screen.

Case 11

A 64 year old male was recovering from an abdominal aortic aneurysm repair. There was minimal fresh blood loss from the wound or drains and a coagulation screen showed a prolonged activated partial thromboplastin time (APTT) of 50 seconds, which the reporters felt to be spurious and possibly due to heparin in the line. However, he was prescribed FFP and within 40 minutes developed an irritant skin rash. Five minutes later he was wheezing and within the following 5 minutes his systolic blood pressure had fallen to 50mm Hg and he had a cardiac arrest. He was ventilated for 24 hours.

Case 12

An 83 year old female on Warfarin had not discontinued this drug prior to an elective femoro-popliteal bypass graft. Consequently she was prescribed FFP pre-operatively. She developed pruritus, angioedema and became hypotensive shortly after commencing the second unit. As a consequence, she sustained a myocardial infarct and was admitted to the coronary care unit (CCU).

Ten of the 14 cases were investigated. None were found to have IgA deficiency. Six investigations included mast cell tryptase, of which one was positive.

Three of the 14 had chest X-rays performed, 2 of which showed bilateral pulmonary oedema.

Allergic reactions (not anaphylaxis)

There were 9 patients in this group.

Four out of the 9 had more than one feature of an allergic reaction (rash, dyspnoea and angioedema).

Four had further investigations but none were IgA deficient. In two, investigations included mast cell tryptase, which were raised in one.

Hypotension

One patient undergoing plasma exchange for thrombotic thrombocytopenic purpura (TTP) experienced hypotension, nausea and hypothermia to 33^{0}C, attributed to the administration of a rapid large volume of cold FFP.

Inappropriate use of FFP

Coagulation results are not available for all cases satisfying the definition of massive transfusion, but these have been included as clinically indicated.

Category	No. of patients	Indication given
Clinically indicated	14	TTP - 2 DIC with haemorrhage - 1 Massive transfusion - 4 Liver disease with intervention - 2 Pre-operative correction coagulopathy - 1 Post-operative bleed with raised INR - 4
Possibly indicated	2	In obstructive jaundice, without trial of Vitamin K prior to lumbar puncture - 1 Postoperative aneurysm repair, prolonged APTT, ? spurious - 1
Not indicated	8	Liver disease with no bleeding - 1 Postoperative, no bleeding - 3 Carcinoma colon, no bleeding - 1 Warfarin reversal prior to elective surgery or for minor haemorrhage - 3

Reactions in which platelets were implicated

There were 20 reactions to platelets, of which 17 occurred during the transfusion, 2 within 2 hours and one within 7 hours following the transfusion. One patient suffered major morbidity, likely to be as a result of the transfusion.

Table 21

Reactions in which platelets were implicated

Reaction type	Number of cases
Anaphylactic/anaphylactoid	5
Allergic	11
Hypotension	3
Unclassifiable	1

Anaphylactic/anaphylactoid reactions

Five patients suffered anaphylactic/anaphylactoid reactions, 3 following the transfusion of pooled buffy coat derived platelets and 2 following apheresis platelets.

One patient initially developed a skin rash and mild dyspnoea. The transfusion was temporarily stopped whilst an antihistamine and hydrocortisone were given. On restarting the transfusion the patient rapidly developed an anaphylactoid reaction.

Three of the 5 who were receiving platelets in a day ward setting required admission.

All were multi-transfused recipients. Three were investigated for HLA and human platelet antigen (HPA) antibodies with negative findings. Three of the 5 are still platelet dependent and receiving platelets in platelet suspension medium (PSM) with no adverse reactions.

Allergic reactions

Eleven patients suffered allergic reactions.

Seven out of the 11 had more than one feature of an allergic reaction (rash, dyspnoea and angioedema).

Five were investigated, 2 for IgA deficiency and 2 for HLA antibodies, with negative findings. Two of the 5 were also tested for mast cell tryptase, one of which was increased.

Hypotensive reactions

Three patients, who were not receiving angiotensin-converting enzyme (ACE) inhibitors, had hypotension alone.

Unclassifiable

Case 13

A 24 year old female with high grade Non Hodgkins Lymphoma (NHL), was platelet and red cell dependent post allograft. Within 5 minutes of the transfusion of apheresis platelets, she started to sweat profusely, complained of 'tightness' in her chest, developed a tachycardia and her BP rose to 170/110. On examination she had reduced air entry with crackles and an oxygen saturation of 75% and subsequently had a respiratory arrest.
The patient was an out-patient who had received no other parenteral fluids that day, making volume overload very unlikely. Cultures of the patient and the platelet concentrate were negative.
A CXR performed following the arrest showed 'ground glass' changes, rather than bilateral pulmonary oedema. She recovered on ITU but was subsequently found to have a large intracerebral bleed, which may have been precipitated by the reaction.

Reaction in which granulocytes were implicated

There was one case of an anaphylactic/anaphylactoid reaction with major morbidity.

Case 14

A 32 year old male with aplastic anaemia received granulocytes from a family member. During the transfusion, his blood pressure dropped to unrecordable levels and he lost consciousness. He was successfully resuscitated with hydrocortisone, piriton and adrenaline and subsequently required amiodarone for adrenaline induced ventricular tachycardia.
He was admitted to HDU.

Response times

The majority of patients were seen as soon as possible by a doctor, and a Consultant Haematologist was also consulted for reactions involving red cells or platelets.

Table 22

Time taken for patient to be reviewed by a doctor

Response times	Red Cells (23)	FFP (24) *	Platelets (21)≠
< 15 minutes	12	20	15
< 30 minutes	3	1	3
< 60 minutes	2		1
> 60 minutes	2		
Unknown	4	3	2
Total	23	24	21
Involvement of Haematologist	**19**	**10**	**15**

* includes case in which both FFP and red cells were transfused
≠includes case involving granulocyte concentrate

Changes made to procedures

Two hospitals have reinforced the need to avoid elective transfusions during night shifts as a result of reactions being inadequately managed at this time.

Reporting of acute transfusion reactions

All but 1 acute transfusion reactions were reported to the hospital laboratory and the majority were also reviewed at the Hospital Transfusion Committee. Three of the 5 haemolytic reactions involved the Transfusion Centre and other reactions were reported to them when samples were referred for investigation.

Table 23

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

Reported to	Red Cells (23)	FFP (24) *	Platelets (21) ≠
Hospital Transfusion Committee	20	16	16
Hospital laboratory	23	24	20
Transfusion centre	18	7	12

* includes case in which both FFP and red cells were transfused
≠includes case involving granulocyte concentrate

COMMENTARY

- Case 1 illustrates the difficulties posed by patients with complex antibodies requiring repeat transfusions.
- There is still significant inappropriate prescription of FFP.
- There has been an increase in the number of allergic or anaphylactic/anaphylactoid reactions reported due to red cells.
- In only 9/17 patients reported to have significant febrile reactions to red cells were bacterial cultures performed.
- The reactions cause by red cell alloantibodies (anti-Wr^a and anti-Bg^a), not detectable using screening cells meeting BCSH recommendations, did not result in haemolysis.
- Transfusion reactions occurring at night or in a community setting may not be managed as promptly.

RECOMMENDATIONS

- Pre-transfusion testing on patients who have been recently transfused and require further transfusion should be carried out in accordance with BCSH Guidelines[21] relating to the timing of pre-transfusion samples.

  Action: Hospital transfusion laboratories.

- BCSH Guidelines[22] on the management of anticoagulation in the peri-operative period and on the management of excessive anticoagulation should be followed. Excessive anticoagulation with minor haemorrhage should be treated by stopping the drug and if necessary with intravenous vitamin K.
- BCSH guidelines[9] for the use of FFP should be followed. Its use for the correction of abnormal coagulation results in the absence of bleeding is not justified.

  Action: Consultant haematologists with responsibility for transfusion should ensure that BCSH guidelines are incorporated into local protocols.

- All serious transfusion reactions must be fully investigated. Bacterial cultures must be taken in a febrile reaction, when the rise in temperature exceeds 1.5^{0}C or the reaction is otherwise sufficiently severe to merit discontinuing transfusion. An update of BCSH guidelines is in progress.

  Action: Consultant haematologists with responsibility for transfusion should implement current best practice.[12,13]

- Blood should not be transfused outside of core hours unless clinically essential.

  Action: Hospital CEOs, consultant haematologists with responsibility for transfusion together with HTCs and HTTs.

- Against the background of a trend towards provision of care closer to the patient, there is a need for a standard of practice to be developed for transfusion in the community setting, including provision for appropriate management and reporting of adverse reactions and events.

  Action: UK National Blood Transfusion Committees to facilitate and co-ordinate.