7. Acute Transfusion Reaction (ATR)

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, haemolytic reactions, TRALI or those due to bacterial contamination of the component.

DATA SUMMARY

Total number of cases	**114**	*Implicated components*		*Mortality / morbidity*	
		Red cells	**51**	Deaths due to transfusion	**0**
		FFP	**20**	Deaths in which reaction was contributory	**1**
		Platelets	**40**	Major morbidity	**5**
		Other (salvaged red cells)	**2**		
		(cryoprecipitate)	**1**		

Gender		*Age*		*Emergency vs. routine Core hours vs. out of core hours*		*Where transfusion took place*	
Male	**62**	<16 years	**7**	Emergency	**21**	A & E	
Female	**52**	<1 year	**2**	Routine	**87**	Theatre	
		<4 weeks	**0**	Not known	**6**	ITU/HDU/recovery	
						Wards	
				In core hours	**86**	Community	
				Out of core hours	**26**	Other	
				Not known	**2**	Not known	**114**

Information technology and appropriateness of transfusion (in the opinion of the SHOT reviewer)		
In how many cases was failure or absence of IT a factor?	**N/A**	
In how many cases was a transfusion possibly unnecessary or inappropriate?	**6**	**(FFP)**

Current category definitions

- **Isolated febrile**
  - rise in temperature >1^{0}C with or without minor rigors and chills
- **Minor allergic**
  - skin irritation with or without rash
- **Anaphylactic/anaphylactoid/severe allergic reaction**

  Anaphylactic/anaphylactoid reaction:
  - Hypotension with 1 or more of: rash, dyspnoea, stridor, wheezing, angioedema, pruritus, urticaria, during or within 24 hrs of transfusion

  Severe allergic reaction:
  - A severe allergic reaction with immediate risk to life occurring during or within 24 hours of transfusion, characterised by bronchospasm causing hypoxia, or angioedema causing respiratory distress
- **Hypotension**
  - a drop in systolic and/or diastolic pressure of >30mm Hg occurring during or within 1 hour of completing transfusion, when all other categories of adverse reactions have been excluded together with underlying conditions that could explain hypotension
- **Febrile with other symptoms/signs**
  - rise in temperature >1^{0}C, with no features of an allergic reaction, but with 1 or more of myalgia, nausea, change in blood pressure or hypoxia

Analysis

Of the 124 questionnaires received, 10 were withdrawn because symptoms were due to underlying disease or other cause, leaving 114 cases. The number of reports continues to rise. This may be due to improved haemovigilance. However, if the increase is sustained in the future, possible factors contributing to this will need to be examined. It is worth noting that the reporting rate is very variable, with many large hospitals reporting no reactions, yet some small hospitals report several. There is no geographic pattern to this.

The median age of patients is 59 (range 35 days to 88), which is considerably younger than last year (72). There were 62 male and 54 female patients.

Figure 6
ATR cases 1996 to 2007
[Totals include cases of Acute Haemolytic Transfusion Reaction (AHTR) to 2006]

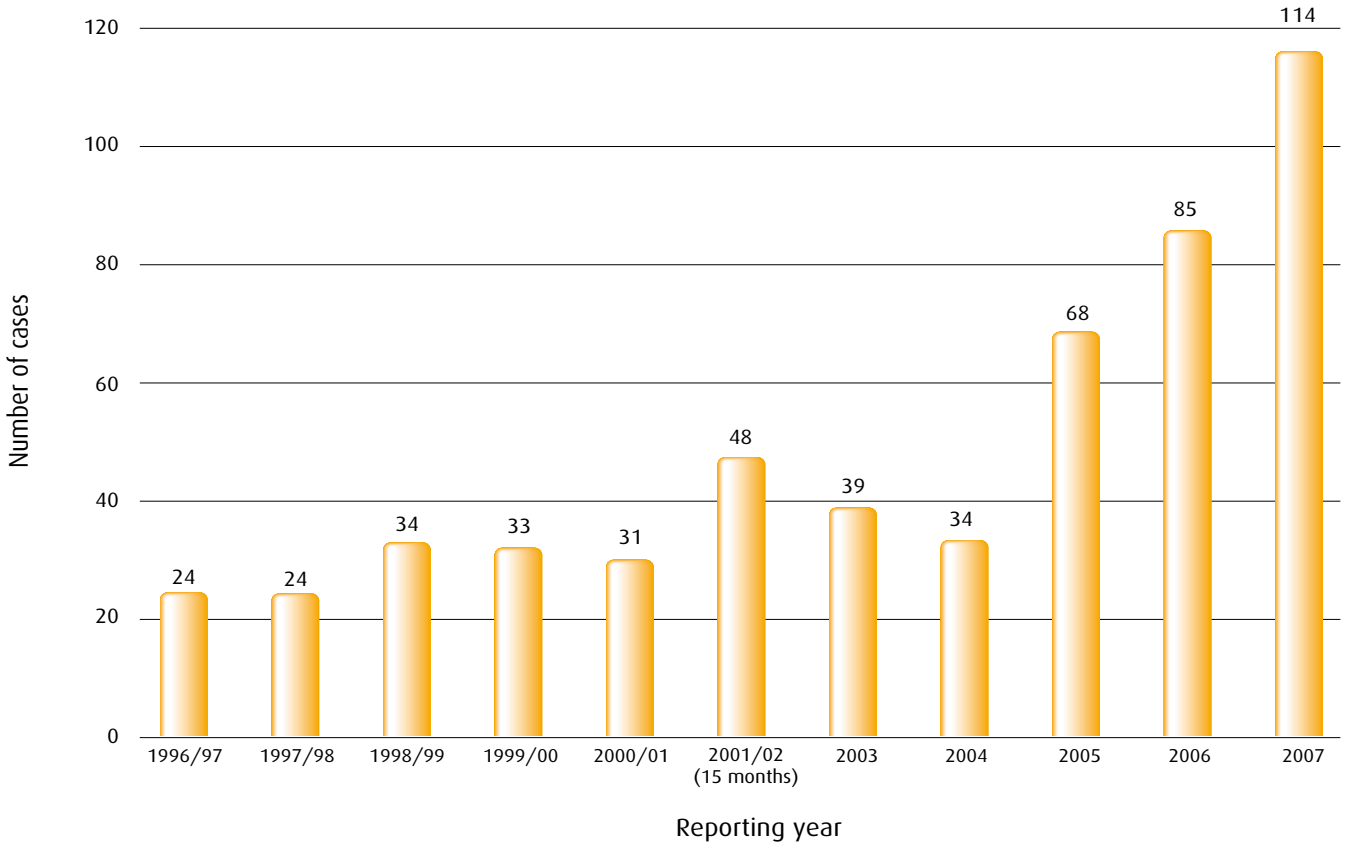

Table 21
Components implicated

Reaction	RBC n = 51	Salvaged RBC n = 2	Platelets apheresis n = 19	Platelets buffy coats n = 21	FFP * n = 20	Cryo ** n = 1	Total n = 114
Isolated febrile	12	1	3				**16**
Minor allergic	14		4	12	7		**37**
Severe allergic	2		4	1	5		**12**
Anaphylactoid	6		6	7	7	1	**27**
Hypotension	1	1					**2**
Febrile with other symptoms / signs	16		2	1	1		**20**
Total	**51**	**2**	**19**	**21**	**20**	**1**	**114**

* All FFP cases related to standard FFP

** Two pools of cryoprecipitate were transfused

Mortality

Two patients in this series died, and their details are given below.

Case AA1 apheresis platelets

An 8-month-old female infant was already very ill with cardiac problems and sepsis, and was prescribed apheresis platelets because of a postoperative platelet count of 11. She received the first unit of 61 mL over 20 minutes without problems. Ten minutes after starting the second unit, having received 14 mL, she became flushed and developed profound hypotension and reduced oxygen saturation, and later died. The clinical team decided that the anaphylactic/anaphylactoid reaction had accelerated what was likely to be inevitable clinical deterioration.

Case AA2 FFP

A 38-year-old male patient with peritonitis received 4 units of FFP to correct deranged clotting prior to emergency surgery. At the end of the fourth unit, he developed symptoms suggestive of an anaphylactic/anaphylactoid reaction, notably angioedema, dyspnoea with oxygen saturation of 90% and a fall in diastolic blood pressure of 20 mm Hg. The patient required ventilation and later died. Later, E. Coli was isolated from the patient's blood cultures. The referring team state that the death was not due to a transfusion reaction, and it cannot be stated that these symptoms were in any way related to the transfusion.

Major morbidity

There were 2 cases of major morbidity with imputability 2, with 1 of them due to an anaphylactic/anaphylactoid reaction and 1 due to a severe allergic reaction. These are described later in the text (Cases AA6 and SA1).

There were also 3 cases of major morbidity with imputability 1.

Anaphylactic/anaphylactoid reactions (AA)

There were 27 cases, including 2 deaths, described above, and 3 cases of major morbidity.

Case AA3 apheresis platelets

A 24-year-old male had ALL with sepsis and platelets of 3 x 10^9/L. He collapsed with profound hypotension 10 minutes after a transfusion of irradiated CMV negative platelets, and was given respiratory support on ITU for 10 days, after which he made a complete recovery. TRALI was excluded after full investigations. Mast cell tryptase was normal. Serum IgA was low but no IgA antibodies were detected. HLA antibodies were negative. Washed platelets were subsequently given with no problems.

Case AA4 RBC

A 65-year-old female received the first unit of red cell transfusion for chemotherapy-associated anaemia. Seventy minutes after the start of transfusion, having received 150 mL, her blood pressure dropped from a baseline of 121/54 to 70/40. She developed supraventricular tachycardia which required cardioversion and treatment with adenosine, with successful outcome.

Case AA5 RBC

A 5-week-old female infant was being investigated for possible tracheomalacia. She had had a previous transfusion, and had received 9.6 mL of the implicated unit when she became pale, sweaty, bradycardic, hypotensive and tachypnoeic. In view of the deterioration, she was transferred to a specialist unit. The clinical picture was very complex, but an anaphylactic/anaphylactoid reaction cannot be excluded.

Case AA6 cryoprecipitate

A 65-year-old female patient received 2 pools of cryoprecipitate at the end of surgery to investigate a pelvic mass. Within 30 minutes she developed a rash and nausea, and her blood pressure became unrecordable. She was reintubated and taken to ITU. Investigations proved negative.

Table 22
Clinical features of remaining 22 cases of anaphylactic/anaphylactoid reactions

Case No.	Component type	Rash	Angioedema	Dyspnoea O_2 sats (%) where recorded	BP	Impaired consciousness or collapse	Interval from starting transfusion in minutes
AA7	Buffy coat platelets	√	√	√	>30 mm Hg drop		15
AA8	Buffy boat platelets	√			'profound'		<5
AA9	Buffy coat platelets	√		√	?		5
AA10	RBC			√	30 mm Hg drop		5
AA11	FFP			√	80/55 (40 mm Hg drop in systolic)		?
AA12	FFP	√		√ sats normal	68/30 (40 mm Hg drop)		5
AA13	FFP		√	√	dropped		20
AA14	RBC			√ sats 80	70/42 (50 mm Hg drop)		5
AA15	RBC			√ sats 95 as ventilation adjusted	?	ventilated	15
AA16	Buffy coat platelets	√		√ sats 85	slight		60
AA17	Buffy coat platelets	√			60 mm Hg drop systolic		60
AA18	Buffy coat platelets	√		ventilated	65/40		15
AA19	Apheresis platelets	√		√ sats 42	Profound drop		10
AA20	Buffy coat platelets			√ 79%	>30 mm Hg drop		10
AA21	Apheresis platelets	√			>30 mm Hg drop		25
AA22	Apheresis platelets	√			> 30 mm Hg drop		?
AA23	RBC			√ 90%	28 mm Hg drop systolic		40
AA24	FFP	√		√ 82%			2
AA25	FFP	√	√		40 mm Hg drop in diastolic		15
AA26	FFP	√	√		> 30 mm Hg drop		30
AA27	Apheresis platelets	√		ventilated	70 mm Hg drop		90

Severe allergic reactions (SA)

Twelve severe allergic reactions were reported, with 1 case of major morbidity.

Case SA1 buffy coat platelets

A 69-year-old female patient with myelodysplasia received 1 pool of buffy coat derived platelets prior to total knee replacement. Fifteen minutes later she developed angioedema with a fall in her oxygen saturation to 86% on oxygen. She was treated with continuous positive airway pressure (CPAP) for 3 days, with slow resolution of her symptoms.

One case involving a major reaction is discussed in the section on reactions with coincidental red cell antibodies (Case AB4).

Table 23
Clinical features of the remaining 10 cases with severe allergic reactions

Case no.	Component type	Rash	Fever/ Rigors	Dyspnoea	Hypoxia, sats	Angioedema	Time from starting transfusion (minutes)
SA2	Apheresis platelets	√		√	√ sats 'dropping'	√	35
SA3	Apheresis platelets	√		√	√ 95%	√	5
SA4	FFP			√	√ 86%		25
SA5	FFP	√	√	√	√-not stated		60
SA6	FFP	√		√	√ 84%		?
SA7	Apheresis platelets			√	√ 92%		5
SA8	RBC		√	√	√ 81%		90
SA9	Apheresis platelets			√	?		
SA10	FFP	√		√	√ 90%		45
SA11	FFP		√	√	√ 80%		20

Hypotension

There were 2 reports of hypotension in the absence of other features suggestive of anaphylactic/anaphylactoid reactions.

Case H1 RBC

A 63-year-old male patient was planned to have 2 units of red cells for cancer-related anaemia. Within 15 minutes of starting the first unit, he complained of chills, nausea and feeling faint. His blood pressure fell from 120/71 to 88/58. He recovered without any treatment.

Case H2 autologous

An 82-year-old male patient underwent vascular surgery with intraoperative cell salvage. His systolic blood pressure dropped by 40 mm Hg, and vasoconstrictors were administered. The transfusion team decided that the reaction was related to incomplete cell washing. Further details are given in the autologous section below.

Febrile reactions with other symptoms or signs

There were 20 reports, 16 with donated red cells, 2 with apheresis platelets, and 1 each with FFP and buffy coat platelets. Five of these cases became hypertensive. Oxygen desaturation was described in only 1 case.

Isolated febrile and minor allergic reactions

There were 37 reports of minor reactions, and 16 of isolated febrile reactions.

Autologous red cells

There were 2 reports of reactions to salvaged red cells. These are discussed on page 110.

Case AR1

See Case H2 above.

Case AR2

A 64-year-old male patient, who had previously been transfused on two occasions, had 600 mL of blood collected via a Bellovac drain after knee replacement. The report states that the blood was reinfused over 4 hours and 30 minutes. The patient then developed an isolated febrile reaction. No investigations were performed.

Paediatric cases

There were 7 cases in patients under the age of 16. Two of these occurred in infants under the age of 1. One was an anaphylactic/anaphylactoid reaction to apheresis platelets in a 35-day-old female infant with multiple cardiac problems. This reaction was considered to have possibly contributed to her death (Case AA1). The other was an anaphylactic/anaphylactoid reaction to red cells in an 8-month-old female infant who had significant co-morbidity (Case AA2). These cases are described in the earlier section dealing with anaphylactic/anaphylactoid reactions. The other 6 reactions were in children aged between 1 and 12, with 5 of the cases being minor allergic reactions, and 1 being a severe allergic reaction, described below (Case P1). Five of the cases were due to platelets (2 to apheresis platelets, and 3 to buffy coat platelets).

Case P1 apheresis platelets

A 7-year-old boy with T-cell ALL received two paedi-packs of apheresis platelets. The first was transfused without problems, but towards the end of the second unit he developed angioedema, rash and tachycardia, and became hypertensive and hypoxic. He was treated with oxygen, hydrocortisone and piriton, and his symptoms resolved. Culture of the unit was negative. HLA antibodies were not demonstrated.

Acute transfusion reactions in which post-transfusion antibodies were demonstrated (AB)

There were 4 cases in which patients had symptoms consistent with acute transfusion reactions, but who were also shown to have low titres of alloantibodies in the post-transfusion sample. The first 2 of these cases were first reported as ATRs, but the other 2 were initially reported as haemolytic transfusion reactions. None of these cases had clinical or laboratory evidence of acute or delayed haemolysis, and it was felt that the alloantibodies were not the cause of the acute reactions, hence their inclusion here.

Case AB1

A 64-year-old male patient, with no past history of transfusion, received 1 unit of red cells because of postoperative bleeding. Within 2 hours of stopping the transfusion, he developed a temperature rise of more than 1.5°C and rigors. Serological investigation of pre- and post-transfusion samples using 5 different panels gave varying but inconclusive results. The samples were referred to a reference centre, and a high-titre, low-avidity anti-Rodgers antibody was demonstrated.

Case AB2

A 66-year-old man developed pyrexia (temperature rise >1.5°C) and rigors during the second unit of a transfusion. Blood had been electronically crossmatched according to BCSH guidelines. Serological investigation of the post-transfusion sample showed he had developed a positive direct antiglobulin test, and a positive serological crossmatch with the second unit. Further referral to a reference centre revealed that the patient had developed anti-Wr^a. There was no rise in bilirubin, and no laboratory evidence of haemolysis.

Case AB3

A 74-year-old female patient with pancytopenia, who had not previously been transfused, received the first of a planned 3 red cell units. After receiving 80 mL she developed back pain, dyspnoea, pyrexia, rigors, vomiting and raised blood pressure. The symptoms responded promptly to steroids and antihistamine. Pre- and post-transfusion samples showed a strong positive direct antiglobulin test with IgG and C3d. She was shown to have an auto-anti-Fy^a in the pre- and post-transfusion samples, and an allo-anti-S in the post-transfusion sample. There was no significant rise in bilirubin or other evidence of haemolysis.

Case AB4

A 37-year-old female who was known to have detectable HLA antibodies, and who was receiving pre-transplant conditioning for a bone marrow transplant, received 2 units of group A red cells without problems. Two weeks later she received another transfusion and developed a severe allergic reaction within 5 minutes of starting the first unit. Serological investigations showed that she was group A2 and had probably developed a weak anti-A1 after the previous transfusion. There was no increase in bilirubin and serum haptoglobin remained stable. The reference laboratory advised that the weak anti-A1 was a coincidental finding.

Investigations

- **Bacteriological investigation of patient's blood and transfused component**
  This was performed in 60 cases, with either negative findings or growth of a species unlikely to be of clinical significance. The majority of reports in which bacteriology was not performed were related to minor allergic reactions, but it was also not performed in 7 isolated febrile reactions, and 7 febrile reactions with other symptoms and signs.
- **HLA/HPA investigations**
  These were performed in 14 cases, 6 of which were severe allergic reactions or anaphylactic/anaphylactoid reactions. Positive results were obtained in 7 cases.
- **Serum IgA and IgA antibodies**
  These were performed in 22 cases. Two patients had low serum IgA, and 1 patient was found to have positive IgA antibodies.
- **Mast cell tryptase (MCT) assays**
  These were only performed in 4 cases, and no abnormal results were found.
- **Red cell serological investigations**
  Eight patients had red cell serological investigations, including two patients who were initially referred as having haemolytic transfusion reactions. Post-transfusion antibodies were identified in four cases, described above.

DISCUSSION

Use of FFP

Twenty of the case reports were associated with infusion of FFP, in all cases the standard product provided by UK blood services. There were 6 reports associated with inappropriate use of FFP. In all 6 of these cases, FFP was given for warfarin reversal. SHOT draws attention to BCSH guidelines which indicate that prothrombin complex concentrate (PCC), rather than FFP, is the product of choice for the reversal of oral anticoagulation (warfarin) in patients with major bleeding[4]. In the absence of major bleeding, PCC (or FFP if PCC is not available) could be used if warfarin reversal is required for emergency surgery.

Management of acute transfusion reactions

The majority of cases received some form of treatment for their transfusion reaction. Forty-five patients received both hydrocortisone and an antihistamine, 19 cases were reported as receiving an antihistamine, and 12 as receiving hydrocortisone alone. Other drugs that were used include paracetamol (21 cases), adrenaline (12 cases, all of which were anaphylactic/anaphylactoid or severe allergic reactions) and salbutamol (8 cases – 6 of which were anaphylactic/anaphylactoid or severe allergic reactions). It is of interest that there were 3 reports of patients receiving pethidine for management of rigors. This is a treatment that appears to be being used more frequently. There is a specific indication for the use of pethidine to manage transfusion reactions in patients who are receiving intravenous amphotericin[14], but, outside this specific recommendation, the evidence base for this treatment is unclear.

COMMENTARY

- Acute transfusion reactions continue to be an important and largely unpredictable hazard of transfusion.
- The number of reports has risen yet again, with a total of 114 reports, compared to 85 in 2006.
- This chapter is based on case reports from 55 hospitals. Notably 9 transfusion teams, including some from small hospitals, reported 54 (46%) of the above cases. This suggests that the number of reports received does not accurately reflect the prevalence of this type of reaction.
- Classification of acute transfusion reactions remains problematic, with many reports not fitting into currently accepted categories. Current categories for classification can be found in the SHOT toolkit[15]. Standard definitions for surveillance of non-infectious adverse transfusion reactions will be published by the International Society for Blood Transfusion (ISBT). BCSH guidelines on the management of acute transfusion reactions are being produced.

- There are four cases (AB1-4) who had evidence of a post-transfusion antibody, yet who had features of acute transfusion reactions and no evidence of haemolysis. Meticulous investigations of transfusion reactions may reveal more such cases in the future.
- There is variability in the investigation and management of acute transfusion reactions.
- Eighty-one of the reactions developed more than 15 minutes into the transfusion (68%), and 39 (34%) occurred more than 30 minutes after the start. The 2005 National Comparative Audit[7] of bedside transfusion practice suggests that the majority of patients do not have observations recorded after 15 minutes. This highlights the need for transfusions to be administered at times, and in locations, permitting careful observations of the patient, and strengthens the advice that out-of-hours transfusions should be avoided if at all possible.
- Twenty of the case reports were associated with infusion of FFP, in all cases the standard product provided by UK blood services. There were 6 reports associated with inappropriate use of FFP. In all 6 of these cases, FFP was given for warfarin reversal.

RECOMMENDATIONS

New recommendations from this report

- Hospitals should have a policy that ensures that serious adverse reactions to transfusions are recognised and reported. This is a legal requirement under the BSQR.

  Action: Trust CEOs, HTCs, HTTs

- Prothrombin complex concentrate (PCC), rather than FFP, is the product of choice for the reversal of oral anticoagulation (warfarin) in patients with major bleeding. In the absence of major bleeding, PCC (or FFP if PCC is not available) could be used for warfarin reversal for emergency surgery.

  Action: HTCs, HTTs, Consultant haematologists with responsibility for transfusion

Recommendations still active from previous years

Year first made	Recommendation	Target	Progress
2006	Serious transfusion reactions can occur at any stage during the transfusion, emphasising the need to keep all patients visible and accessible to nursing staff. Out of hours transfusions should be avoided unless essential and where there is adequate monitoring	**HTTs**	The national comparative audit of overnight transfusion has added to the evidence that overnight transfusions need to be monitored as closely as those carried out during the daytime
2005	All serious transfusion reactions must be fully investigated. Bacterial cultures must be taken in a transfusion reaction, when the rise in temperature exceeds 1.5ºC or the reaction is otherwise sufficiently severe to merit discontinuing transfusion	**Consultant haematologists with responsibility for transfusion**	BCSH guidelines on the investigation and management of transfusion reactions are being developed