11. Acute Transfusion Reactions (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, transfusion-related acute lung injury (TRALI), TACO, or those due to bacterial contamination of the component.

DATA SUMMARY

Total number of cases	**400**	*Implicated components*		*Mortality/morbidity*	
		Red cells	**264**	Deaths due to transfusion	**0**
		FFP (including 1 MB and 2 SD)	**44**	Deaths in which reaction was implicated	**1**
		Platelets (57 apheresis, including 3 HLA matched components, 23 pooled, 7 unknown type, including 1 platelet component in PAS)	**86**	Deaths in which reaction was not implicated	**1**
		Multiple components transfused	**6**	Major morbidity	**27**

Gender		*Age*		*Emergency vs. routine and core hours vs. out of core hours*		*Where transfusion took place*	
Male	**184**	18 years+	**363**	Emergency		A & E	
Female	**215**	16 years+ to 18 years	**4**	Routine		Theatre	
Unknown	**1**	1 year+ to 16 years	**28**	Not known		ITU/HDU/Recovery	**2**
		28 days+ to 1 year	**3**	In core hours		Wards	
		Birth to 28 days	**2**	Out of core hours		Community	
				Not known/applicable		Other	
		Total	**400**			Not known	

In total 440 questionnaires were received; 28 were withdrawn, 6 were transferred to the autologous chapter, 10 to the TACO chapter, and 2 to the TAD chapter. A further 6 cases were transferred in from other sections: 1 each from HSE, TRALI and TTI, and 3 from HTR. A total of 400 cases have been reviewed for this chapter.

There were 193 febrile and 114 allergic reactions, and 30 whose features were indicative of anaphylaxis. There were also 28 reactions with mixed febrile and allergic features, 6 hypotensive reactions, and 29 which could not be classified further.

Mortality

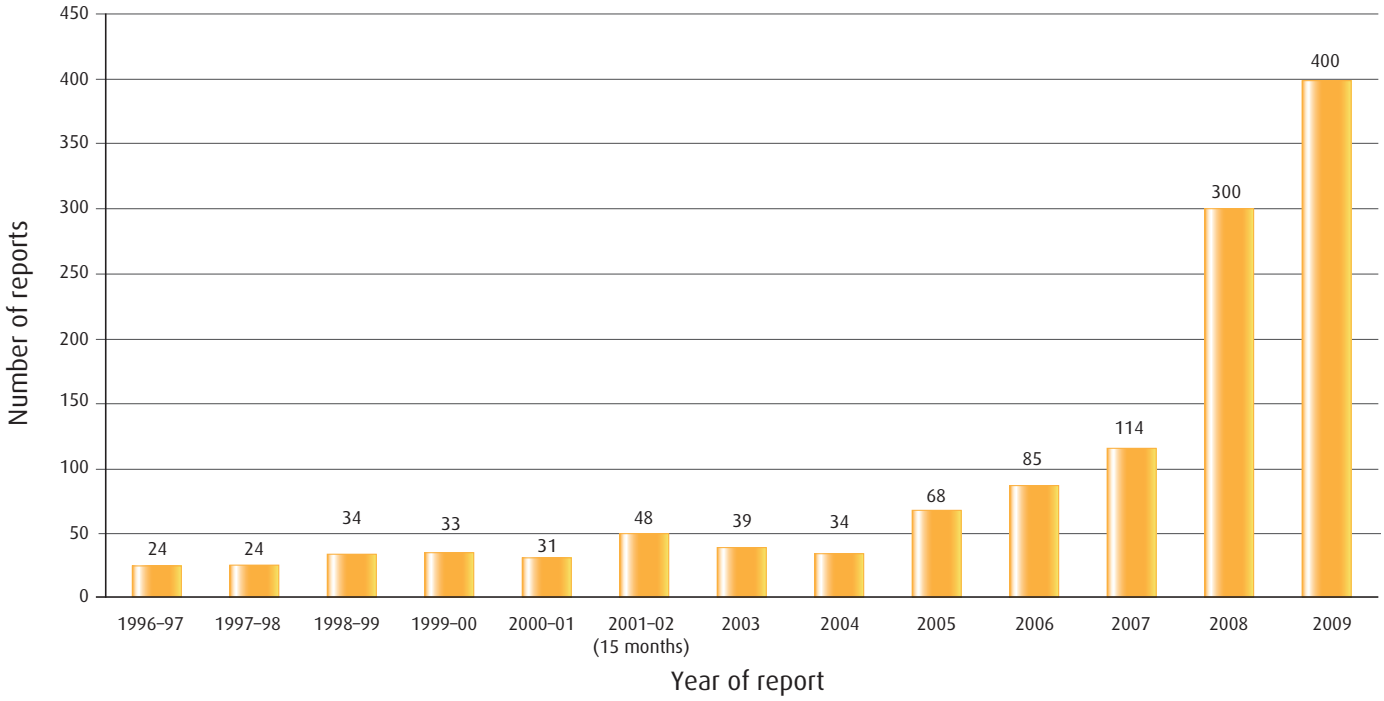
In 1 case, the patient's symptoms may have been attributable to a transfusion reaction and the possibility that the reaction could have contributed to the patient's death could not be completely excluded.

Case 1

Possible fatal reaction

A male patient with alcoholic liver disease was transfused with standard FFP. He became dyspnoeic and died during transfusion of the second unit. NHSBT was contacted and associated units from the donation were withdrawn. TRALI was ruled out as both plasma donors were male. Microbiological tests of the unit were negative. IgA investigations of the recipient were requested but not performed. The postmortem investigation demonstrated pneumonia and cirrhosis. It is not possible to state whether the dyspnoea was caused by a transfusion reaction of some type, and, if so, whether this contributed to the patient's death, as case notes are no longer accessible.

Figure 11
ATR cases 1996–2009



Classification of non-fatal acute transfusion reactions

The classification of acute transfusion reactions can be difficult, as reactions are frequently seen in patients with intercurrent illness who may have other causes for their symptoms. Classification does not necessarily have any bearing on the management of the acute reaction or of future transfusions.

Major morbidity

Applying the SHOT criterion of 'Life-threatening acute reaction requiring immediate medical intervention', there were 27 cases of major morbidity from ATR where the immediate symptoms or signs were sufficiently severe for a delay in treatment to be life-threatening, even though recovery was usually rapid.

There were 17 anaphylactic reactions, 1 of which complicated a severe postpartum haemorrhage and resulted in the patient temporarily requiring intubation (Case 3, below), and 5 of which led to the crash team being called; in all these cases the patient recovered without cardio-respiratory support. There were 7 severe febrile reactions: the case below; 2 patients described as having reversible shut-down of their peripheral circulation; and 4 patients requiring acute management of hypotension (2 with adrenaline and 2 with volume replacement). Life-threatening reactions were also experienced by 2 patients with severe mixed febrile and allergic reactions, and 1 with a severe allergic reaction. One patient suffered a severe febrile reaction to a red cell transfusion and experienced worsening of pre-existing renal failure (Case 2, below).

Case 2

Did the transfusion reaction contribute to renal failure?

A female patient with acute renal failure and peripheral ischaemia was given a red cell transfusion. After 20 minutes, she developed a severe febrile reaction, with chest pain and dyspnoea. Her low urine output dropped further. She was given paracetamol. No investigations were performed. The reporting team stated that they could not exclude acute transfusion reaction as a cause for the deterioration in renal function.

In addition to the SHOT classification of acute transfusion reactions by death or major morbidity, the International Society for Blood Transfusion (ISBT) has developed standard definitions for non-infectious adverse transfusion reactions. These will help haemovigilance organisations generate data that will be comparable at an international level. Meanwhile, the following definitions have been put forward by the writing group of the forthcoming BCSH guideline on the investigation and management of acute transfusion reactions. Therefore, ATRs according to this classification are also shown.

Table 34
BCSH classification of Acute Transfusion Reactions

Category	1 = Mild	2 = Moderate	3 = Severe
Febrile type reaction	A rise in temperature up to 2°C with no other symptoms/signs	A rise in temperature of 2°C or more, and/or rigors, chills, other inflammatory symptoms/signs which precipitate stopping the transfusion	A rise in temperature of 2°C or more and/or rigors, chills or other inflammatory symptoms/signs which necessitate stopping the transfusion, medical review and/or hospital admission or prolongation of stay
Allergic type reaction	Transient flushing, urticaria or rash	Wheeze or angioedema with or without flushing/urticaria/ rash but without respiratory compromise or hypotension	Bronchospasm, stridor, angioedema or circulatory problems which require urgent medical intervention and/or, directly result in or prolong hospital stay, or anaphylaxis (severe, life-threatening, generalised or systemic hypersensitivity reaction with rapidly developing airway and/or breathing and/or circulation problems, usually associated with skin and mucosal changes)[29]
Reaction with both allergic and febrile features	Features of mild febrile *and* mild allergic reactions	Features of both allergic and febrile reactions, at least one of which is in the moderate category	Features of both allergic and febrile reactions, at least one of which is in the severe category
Hypotensive reaction		Isolate fall in systolic or diastolic pressure of 30 mm or more in the absence of allergic or anaphylactic symptoms; no/ minor intervention required[30]	Hypotension leading to shock (e.g. acidaemia, impairment of vital organ function) without allergic or inflammatory symptoms; urgent medical intervention required

Severity of reactions

Of the reactions that could be classified, 45 were severe, 197 moderate, and 132 were mild. (Cases of moderate and mild reactions are included on the website.)

Severe reactions

Although acute transfusion reactions are rarely associated with death or morbidity, they may present with severe symptoms in the acute situation. Of the 45 severe reactions (which includes the 27 life-threatening reactions in the section on major morbidity), 19 were anaphylactic, 5 were consistent with severe allergy, 14 were febrile, 6 showed mixed febrile and allergic features, and 1 was hypotensive. Reactions can present in any patient irrespective of whether they have experienced reactions previously. This highlights the need for transfusion to take place where there are

adequate resources both for monitoring the patient and for managing acute reactions, particularly anaphylaxis. This also applies to transfusions carried out in community hospitals or at home. (Additional cases of severe reactions are available on the SHOT website.)

Case 3

Anaphylactic reaction complicating massive transfusion

A young woman suffered a large (3 litre) PPH and was given 6 red cell units, 4 units of FFP and 2 pools of platelets. At the time of giving either the platelets or the plasma, she developed urticaria, angioedema, dyspnoea and tachycardia. Her O_2 saturation dropped from 98% to 80%, and her BP, having previously been normal, was unrecordable. She was intubated as an emergency and the cardiac arrest team were called. She was managed with intramuscular adrenaline, hydrocortisone and antihistamine, and settled within 48 hours. Investigations showed that HLA antibodies were present. Blood cultures of the patient were negative. MCT levels remained normal throughout.

Learning point

- Anaphylaxis should be managed according to the guidelines set out by the UK resuscitation council.[29] Patients should be transfused only where there is a member of staff present who is trained in the management of anaphylaxis and has access to appropriate treatment, particularly intramuscular adrenaline.

Other reactions reported as severe

Many incidents reported as acute transfusion reactions have some features which led them to be categorised as severe febrile or hypotensive reactions. However, the symptoms may have been due to other causes.

Case 4

Possible anaphylactic reaction

An elderly woman who was being transfused in a community setting developed itching a few minutes into a transfusion of apheresis platelets. Intravenous chlorphenamine 10 mg was administered. The patient rapidly became hypotensive (lowest BP 76/60) and unresponsive, but slowly recovered after administration of hydrocortisone 200 mg, adrenaline 0.5 mg, and O_2. She was admitted to hospital and discharged 3 days later. This may have been anaphylaxis, but hypotension is a recognised side effect of chlorphenamine.

Reactions which were not possible to classify further

There are 29 cases included in this chapter in which the hospital transfusion teams, using the information present at the time, decided that a diagnosis of acute transfusion reaction was most likely. Further attempts to classify these reactions were not pursued, as management of the patient, and exclusion of other potentially serious causes of the symptoms, should be the main priority of the clinical team, and are not dependent on classification of the reaction type. The following case illustrates some of the diagnostic difficulties that can be encountered.

Case 5

Possible febrile transfusion reaction

An elderly woman who had suffered a fractured neck of femur, dehydration and pressure sores was transfused with 3 red cell units over several days. During the transfusion her temperature rose by 1.9°C, and her blood pressure fell to 64/40. Blood cultures were positive for several species including Pseudomonas, but the unit of blood had been discarded. The transfusion team decided that, despite the patient's complex history, an ATR could not be excluded. The blood service was contacted and a recall of other related components was carried out.

Timing of reaction after start of implicated unit

Where recorded, and excluding 34 cases in which the reaction was reported after the transfusion was completed, the median time of onset of symptoms was 45 minutes. The time of onset differs for different types of reactions as seen in Table 35. It is worth noting that, for all types of reactions except anaphylaxis, which tends to have a more rapid onset, the mean time of onset is greater than 15 minutes, at which time observations are usually first recorded.[19] This emphasises the need for close observation of patients throughout the duration of the transfusion.

Table 35
Median time of onset of reaction by reaction type

Type of reaction	Number of cases where time given	Median time of onset, mins (range)
Febrile	177	60 (1–540)
Allergic	107	40 (1–420)
Anaphylactic	28	15 (1–110)
Mixed febrile and allergic	25	35 (1–195)
Hypotensive	6	20 (15–60)
Unclassifiable	23	60 (5–660)
Total	**366**	**45 (1–660)**

Learning point

- Acute transfusion reactions can occur at any time during the transfusion. Patients require careful observation throughout the transfusion process.

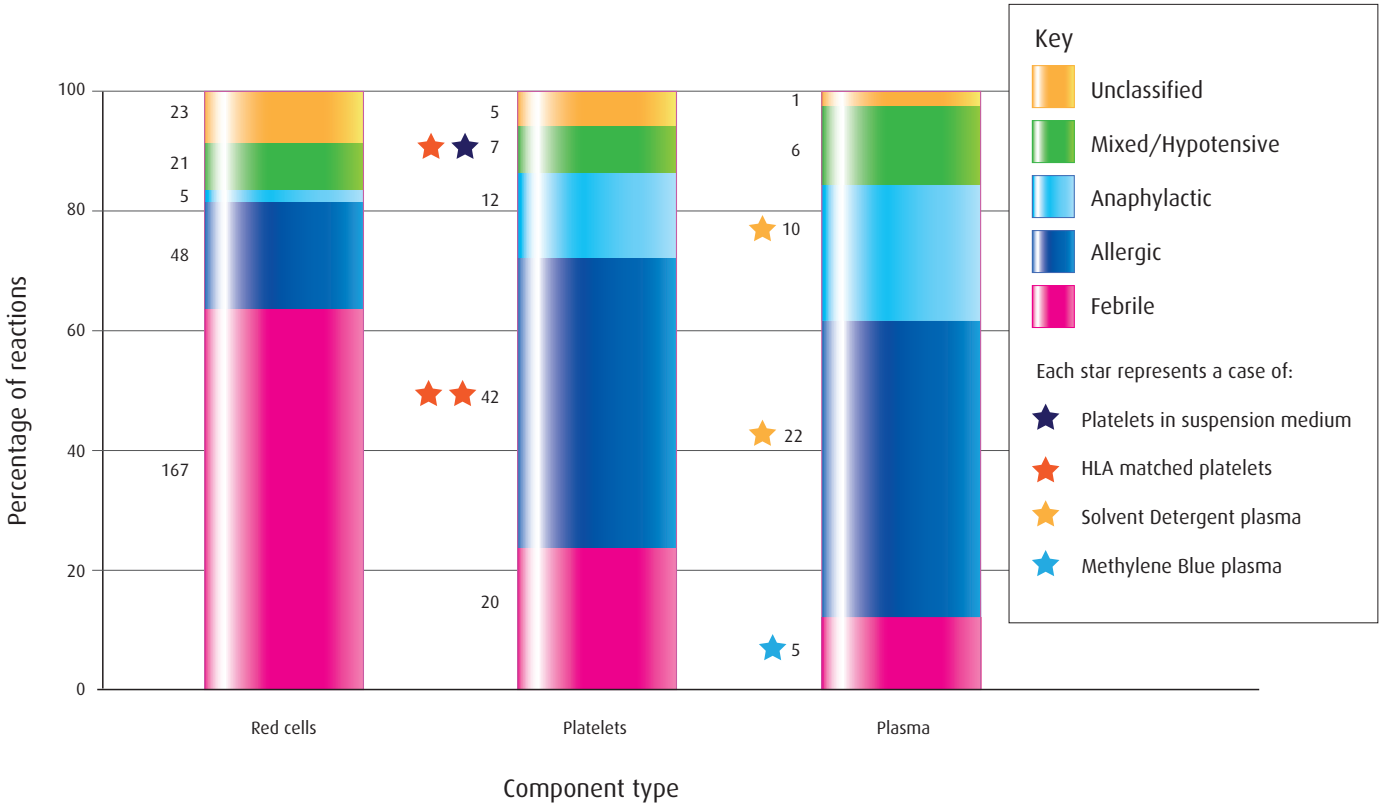
Reactions by component type

The incidence of febrile and allergic/anaphylactic type reactions by component is summarised in Table 36 below. The data in Figure 12 (also below) suggest that febrile reactions are less common with plasma than with red cell or platelet transfusions; allergic or anaphylactic reactions are much more frequent with plasma-rich components, especially platelets.

Table 36
Incidence of reactions by component type

Component	Febrile reactions, incidence per 100,000 units	Allergic or anaphylactic reactions, incidence per 100,000 units
Red cells	7.6	2.4
Platelets	7.5	20.3
Plasma	1.6	10.4

Figure 12
Reaction by component type (excluding 6 reactions which could not be attributed to a particular component)



Management of transfusion reactions

Stopping or slowing the transfusion

Drug treatment of transfusion reactions was covered in the 2008 SHOT Annual Report (page 96). Analysis of 2009 data shows no change in pattern. A breakdown of management of the transfusion (where information was available) is indicated in the table below.

Table 37
Management of the transfusion during ATRs

Action	Number of reports
Continue	6
Stop transfusion	264
Stop temporarily *(not known if restarted)*	21
Transfuse more slowly	7
Transfusion slowed, then stopped	3
Already completed	64
No information	35
Total	**400**

Management of subsequent transfusions

The following comments were received regarding subsequent transfusion management of individual patients:

- Washed components in future 9 reports
- Prophylaxis with antihistamine and/or hydrocortisone 8
- HLA matched components 7
- Blood to be given through warmer 1
- Diuretics to be used 1

Investigations

The value of investigations in ATR was discussed in the 2008 SHOT report. The most commonly performed investigations in 2009 are shown in Table 38 below.

In 101 patients, no investigations were performed: in the majority of these cases the reactions were mild, but 44 moderate and 6 severe reactions were not investigated. In all but the mildest cases, the possibility of other severe causes of adverse reactions such as TRALI, TACO, red cell incompatibility, or transfusion-transmitted infection, should be kept in mind. Core investigations, as set down in the recommendations, should be performed.

Table 38
Commonly performed investigations

Investigation	Number of reports	Number of positive or abnormal results
Bacterial culture of patient and /or unit	96	Patient blood cultures were positive in 13 cases, none of which were associated with positive blood component cultures. Nine of these were isolated febrile reactions reported with red cells. The fever was related to sepsis rather than transfusion, and highlights the difficulties in ascribing imputability. Cultures of the blood component were positive on 7 occasions, in all cases thought to be due to contaminants (4/7 components were red cells).
Red cell serology	35	Nil significant.
Mast cell tryptase assay	24	In 6 cases MCT rose then returned to baseline. A typical abnormal result is seen in Case 6 below.
Serum IgA levels with or without antibodies	96	Nil.
HLA antibody screen	46	Class I antibodies found in 2 cases.

Case 6

Role of mast cell tryptase (MCT)

An adult male patient who required a chest drain and had platelets of 60 x 10^9/L was given a pool of buffy coat platelets. Twenty minutes after the start of transfusion, he developed a rash, hypotension and dyspnoea. His O_2 sats fell to 50%. The transfusion was stopped, and he was treated with nebulised salbutamol. He improved within 4 hours. MCT was measured – initially 86.2 µg/L, 128 at 4 hours, and 12.1 after 24 hours (normal level < 13 µg/L). Serum IgA was normal and blood and platelet cultures were normal. The pattern of rise and fall of the MCT level is consistent with anaphylaxis,[31] and the history would suggest that this was related to the transfusion.

Bacterial culture of patient and unit

The possibility of transfusion-transmitted bacterial infection should be considered when assessing a patient who is reacting adversely to transfusion, especially when platelets are being transfused. The blood component should be inspected for signs of contamination. If bacterial contamination is considered to be a possibility, the implicated unit should also be cultured and the relevant blood centre informed, so that components from the same donor(s) can be withdrawn as necessary. A revised protocol for hospital sampling is being developed by NHSBT, with advice on the circumstances in which components should be sent to the reference transfusion microbiology laboratory.

Pyrexia and rigors may indicate moderate or severe transfusion reactions, or, more rarely, bacterial transfusion-transmitted infection. This year a number of cases that were referred from hospitals in England and North Wales to the National Bacteriology Laboratory did not meet the criteria for TTI as there was no evidence of the same transmissible infection in patient and donor. The majority of these were not reported to SHOT by the referring hospital. It is recommended that such adverse reactions should be reported because, if a patient has fever or rigors, it is appropriate to record this as an ATR.

A reaction in which the donor was implicated

In this case there was no evidence base to guide investigations on the donor. However, there may be occasions when a transfusion reaction is sufficiently severe, or is accompanied by unusual features such as new cytopenia, when investigation of the donor may be appropriate. Guidance on donor investigations is being prepared by NHSBT.

Case 7

Reactions in multiple recipients

One incident involved 3 infants in the same hospital who received paedipaks from 1 red cell donor, and who all developed rashes which resolved quickly. No investigations of the recipients were performed. The donor was contacted by a blood service consultant, who reported that there was no history of illness or allergy.

Learning points on investigations

- The recommendation that patient HLA, HNA and HPA studies should only be performed in selected cases, after discussion with a blood service consultant, still stands (see below).[32]
- It is striking that, despite concern among clinicians over the risks of transfusing patients who are IgA deficient, there have been no ATR reports related to this in 2009, and only 1 case in the last 5 years. Many aspects of IgA deficiency are in need of further study.[33] In order to determine the true significance of deficiency, and hence produce appropriate guidelines, it is recommended that IgA is measured in all cases of severe allergy or anaphylaxis.
- MCT is the recommended laboratory test to aid in the diagnosis of anaphylaxis, although it does not contribute to management in the acute phase. Patients who have been diagnosed with anaphylaxis should be considered for referral to an allergy clinic for advice on managing future reactions.[29]

Appropriateness of transfusions

From the data available, it can be difficult to assess the appropriateness of the transfusion. However, there were 3 cases of inappropriate transfusion with FFP for warfarin reversal in patients with no, or minor, bleeding. In 4 cases red cell transfusion, in relatively young patients with iron deficiency without evidence of bleeding, appeared inappropriate.

Reporting of ATRs

Forty-nine cases were reported to SHOT only, and not to the MHRA. In 4 cases patients appeared to have experienced minor morbidity as their hospital stay had been prolonged, and these reactions should have been reported to MHRA.[34]

The majority of cases (292) were discussed at the HTC, and this resulted in new local recommendations in 17 instances. Recommendations included: improvement to adverse incident reporting, management plans for a particular patient, and plans to improve training, monitoring, patient assessment or investigation. In 1 case, reinforcement of the hospital's warfarin reversal policy was advised.

COMMENTARY

- The number of acute transfusion reactions reported has increased further this year. This is mainly accounted for by increased numbers of febrile or allergic reactions, as anaphylactic and hypotensive reactions have not increased, and this is likely to be due to better reporting practice.

- Haemovigilance plays an important role in collating information on acute transfusion reactions for which the causes are not well understood, e.g. isolated hypotension. Continued reporting of such cases is valuable so that patterns and causations may be identified.

RECOMMENDATIONS

New recommendations

- All moderate and severe transfusion reactions should have investigations performed. Core investigations should include full blood count, U&E, LFT, repeat group and screen, and urinalysis. Additional investigations should be performed as dictated by the patient's symptoms. Bacterial culture of the patient and unit should be performed if TTI is thought to be a possibility. In such cases, a blood service consultant should be contacted for consideration of recall of associated components from the implicated donation.

  Action: HTCs, HTTs

- IgA should be measured in all patients who experience severe allergic or anaphylactic reactions. Measurement of IgA will help assess the relevance of IgA deficiency, and has clinical relevance for the patient, as it may indicate part of the spectrum of common variable immunodeficiency.[33]

  Action: HTCs, HTTs

Previous recommendations that are still current

Year first made	Recommendation	Target	Progress
2008	It cannot be assumed that all adverse reactions to blood or products are due to an ATR as currently defined in this chapter. Unless the diagnosis is clear, patients whose reactions are moderate or severe* should be fully investigated, with a view to identifying other potentially serious causes of the symptoms such as TRALI, bacterial contamination, TACO or haemolysis. In addition, it should be borne in mind that symptoms may be due to the patient's underlying condition or other intercurrent illness. Hospitals should have a policy for the investigation and management of ATRs, based on current best practice. An update of BCSH guidelines is in progress. * *Previously this recommendation read: '... reactions severe enough to warrant stopping'. However, a review of reports indicates that in nearly all such cases transfusions are discontinued.*	**HTCs, HTTs**	BCSH guidelines in preparation will stress the importance of recognising and managing symptoms.
2008	As the mechanism of ATR is still not clear, the role of unselected testing for HLA, HPA or HNA antibodies appears very limited.[32] Patients who experience anaphylactic or severe allergic reactions after platelets should have an increment measured between 1 and 24 hours after transfusion. A severe reaction could indicate platelet refractoriness, in which case HLA testing is indicated. Otherwise, for severe allergic reactions without refractoriness, the next step should be a trial of PAS-suspended platelets, or washed components, before embarking on HLA testing.	**HTCs, HTTs**	This will be stressed in the forthcoming BCSH guideline.
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.	**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.