13.

Acute Transfusion Reactions (ATR)

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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), transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD) or those due to bacterial contamination of the component.

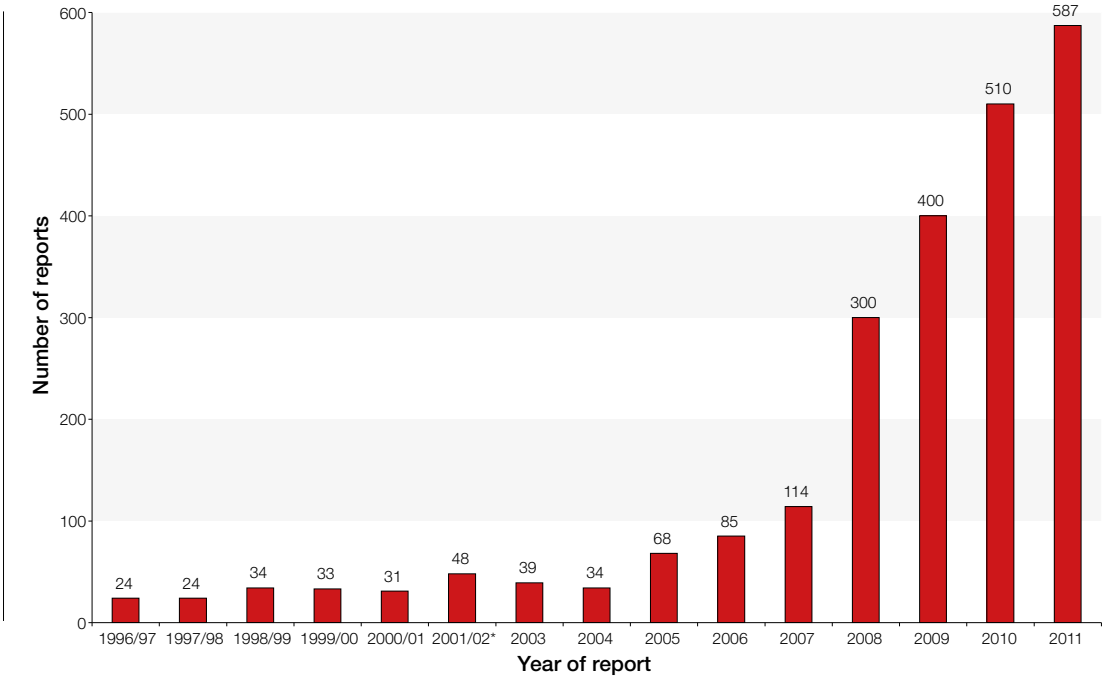
DATA SUMMARY
Total number of cases: 587

Implicated components		Mortality/morbidity	
Red cells	388	Deaths *probably/likely* due to transfusion	0
FFP	46	Deaths *possibly* due to transfusion	2
Platelets	145	Major morbidity	53
Other (cryo)	1		
Multiple components	7		
Unknown	0		

Gender		Age		Emergency vs. routine and core hours vs. out of core hours		Where transfusion took place	
Male	300	≥ 18 years	536	Emergency	59	A&E	6
Female	282	16 years to <18 years	6	Urgent	86	Theatre	23
Not known	5	1 year to <16 years	37	Routine	413	ITU/NNU/HDU/Recovery	58
		>28 days to <1 year	2	Not known	29	Delivery/Postnatal	16
		Birth to ≤28 days	3			Wards	396
		Not known	3	In core hours	426	Community	6
				Out of core hours	157	Outpatient/day unit	74
				Not known	4	Not known	8

587 cases have been included in the analysis. This includes 4 cases transferred from haemolytic transfusion reaction (HTR), 4 from previously uncategorised complication of transfusion (PUCT) and 1 from right blood right patient (RBRP). A further 20 cases with predominantly respiratory features were transferred to TAD and 12 to TACO. 5 cases were withdrawn as the reporters subsequently attributed the clinical features to other causes.

Figure 13.1
Cases of ATR since 1996



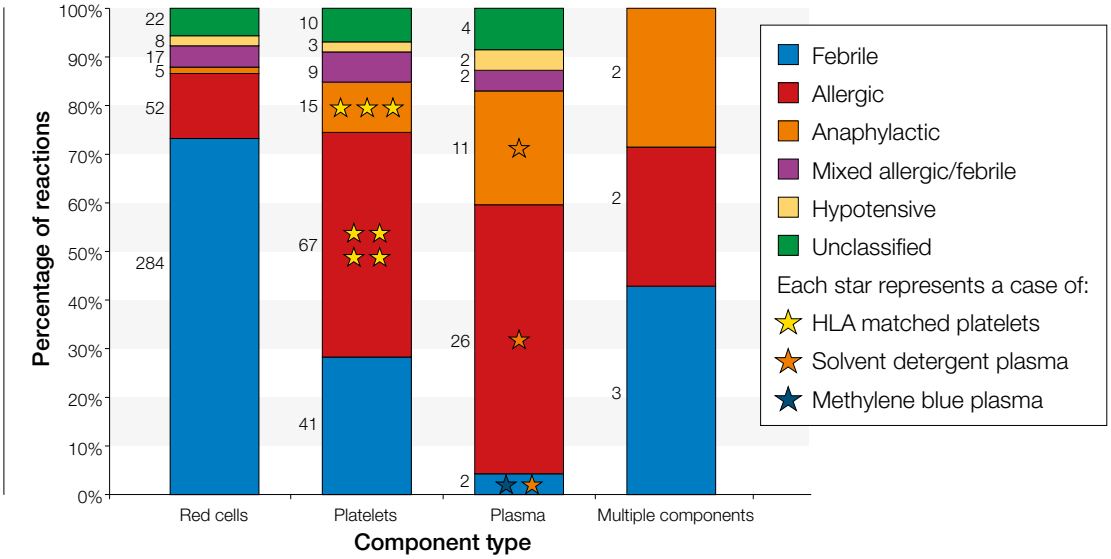
Introduction

Although the total number of reports has increased from 510 in 2010 to 587 this year, the pattern of reactions remains similar (see Figure 13.2, reactions by component type) and figures for anaphylaxis and major morbidity are similar. Where possible, reactions have been classified according to the International Haemovigilance Network/International Society of Blood Transfusion (IHN/ISBT) draft definitions which have recently been published[15], (see Table 13.1, IHN/ISBT classification of ATRs) but, as in previous years, many reactions are difficult to classify. In many cases, symptoms and signs may be due to either the patient's underlying condition or to transfusion.

Table 13.1
Current IHN/SHOT/BCSH classification of acute transfusion reactions

	1 = Mild	2 = Moderate	3 = Severe
Febrile type reaction	A temperature ≥ 38°C and a rise between 1and 2°C from pre-transfusion values, but no other symptoms/signs	A rise in temperature of 2°C or more, or fever 39°C or over and/or rigors, chills, other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion	A rise in temperature of 2°C or more, and/or rigors, chills, or fever 39°C or over, or other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion, prompt medical review AND/OR directly results in, or prolongs hospital 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)
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		Isolated fall in systolic blood pressure of 30 mm or more occurring during or within one hour of completing transfusion **and** a systolic blood pressure 80mm or less in the absence of allergic or anaphylactic symptoms. No/minor intervention required	Hypotension, as previously defined, leading to shock (e.g. acidaemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required

Figure 13.2
Reaction by component type



Types of reactions

As far as possible, reactions have been classified and the following figures obtained:

- 330 febrile (115 mild, 201 moderate, 14 severe)
- 180 allergic (83 mild, 64 moderate and 33 anaphylactic or severe allergic)
- 28 mixed allergic/febrile
- 13 hypotensive
- 36 blank or unclassifiable

Imputability

- 22 were stated by reporters to be certain (imputability 3)
- 162 were likely/probable (imputability 2) including 4 in which a possible alternative cause was identified
- 293 possible (imputability 1)
- 71 were excluded by reporters, usually because an alternative cause was considered more likely, but these have been kept in this chapter as it is often difficult to determine the cause of adverse symptoms/signs associated with transfusions
- 5 not assessable
- 34 blank

Deaths n=2

There were two deaths in which a transfusion was possibly implicated (imputability 1), and 13 which were considered to be unrelated to any transfusion reaction.

Case 1

Possible fatal transfusion reaction in a patient with multiple problems

An elderly male patient with multiple co-morbidities including pneumonia and a pulmonary embolus was transfused with fresh frozen plasma (FFP) prior to endoscopy. 15 minutes into transfusion of the first unit, he developed dyspnoea and suffered a fatal cardiac arrest. During attempted resuscitation he was noted to be developing a florid coalescing rash. Post mortem examination was inconclusive. Serum IgA was normal. A pre-transfusion mast cell tryptase was normal but a post transfusion sample was unsuitable for analysis as it was grossly haemolysed.

It was concluded that the clinical picture may represent an anaphylactic reaction to plasma, although other potential causes such as DIC or sepsis could not be ruled out, and the rash was not suggestive of urticaria. The patient's frail condition may have contributed to the severity of any reaction.

Case 2

Febrile reaction may have contributed to death

An adult male with metastatic gastric cancer and thrombocytopenia had haematemesis and septicaemia. One hour after the start of a red cell transfusion, his temperature rose 2.5°C to 39.5°C. He developed anxiety, tachycardia and respiratory distress. His oxygen saturation dropped to 80% but responded to oxygen therapy. His blood pressure remained satisfactory but he died four hours later.

Major morbidity n=53

Although only 7 cases were reported as being associated with major morbidity, a further 33 were reported as experiencing severe or life-threatening reactions. Thirteen of these cases had a clinical picture suggestive of anaphylaxis, 2 had features of moderate allergic reactions, 2 had severe febrile reactions and 7 had moderate febrile reactions.

In addition, a further 13 cases, not reported as having a severe or life-threatening reaction, had features leading to a classification of anaphylaxis, and 10 were classified as having severe febrile reactions either because of hypoxia, hypotension, or admission of a day case to a ward or high dependency unit.

Ascribing major morbidity can be difficult in acute transfusion reactions, as, although signs and symptoms can be severe, they are often transient. The IHN describes reactions as life-threatening if major intervention such as use of vasopressors or admission to intensive care is required to prevent death, or severe if the reaction requires, or prolongs, hospitalisation[15].

Specific types of reactions

Anaphylactic reactions n=33

Anaphylaxis is defined by the UK Resuscitation Council (UKRC)[49] and National Institute for Health and Clinical Excellence (NICE)[50] as: "…a severe, life-threatening, generalised or systemic hypersensitivity reaction… characterised by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes."

33 reactions were consistent with anaphylaxis or severe allergy. Seven of these were in paediatric patients, including one neonate. Six reactions occurred in either a hospice or outpatient setting. Twelve reactions occurred in haematology patients. Only 18 patients were recorded as being given adrenaline (or noradrenaline), the former stated as being the first line drug in anaphylaxis by the UKRC[49].

Case 3

Reaction to cryoprecipitate

A young female patient undergoing spinal surgery was given a pool of standard cryoprecipitate as part of a massive transfusion. Within half an hour she developed urticaria and a sudden drop in cardiac output. She was treated with adrenaline, antihistamine and hydrocortisone. No investigations were reported.

Hypotensive reactions n=13

Thirteen reactions were classified as being hypotensive. 7/13 (54%) reports originated from cardiothoracic surgery, a specialty which accounted for 20/586 (3.4%) of reports in total. Three of the 7 patients were in ITU, 2 in theatre, 1 in recovery, and 1 had no information about location. The diagnosis of a hypotensive reaction can be difficult, especially in a patient in whom haemorrhage is suspected. However, in these cases, there was no evidence of continuing bleeding. Hypotensive reactions are stated to be more common in patients on ACE-inhibitors and in patients with abnormal bradykinin metabolism. These reactions merit further study.

Severe febrile reactions n=14

Fourteen febrile reactions were classifiable as severe: 9/14 cases were associated with red cell transfusion. Five patients had temperatures of 39°C or higher (in one case 41.3°C) The additional factors which led to a severe classification were hypotension (6 cases), hypoxia (3 cases), shock (1 case) and transient loss of consciousness in 1 case. In addition to managing hypotension and/or hypoxia, recognition of these severe reactions is important as the presentation may suggest possible bacterial transfusion-transmitted infection.

Case 4

Severe febrile reaction following post partum haemorrhage (PPH)

A young female experienced a 2L PPH. During the second unit of red cells transfused her temperature rose 2.3°C, and she had rigors, tachycardia, hypertension, tachypnoea and vomiting. She also had cold cyanosed peripheries. The red cell unit was investigated for possible bacterial contamination but cultures were negative. The patient made a good recovery.

Speed of onset

The time of symptoms from the start of transfusion was recorded in 252 cases. The median time was 30 minutes (range 1-240 minutes).

Management of transfusion reactions

Stopping the transfusion

It is important to temporarily stop the transfusion and confirm the identity of the component and the patient, and check for obvious contamination. In severe reactions, the component should be taken down and retained for further investigation if necessary, and venous access maintained by physiological saline. (However, clinical judgement is required in the case of hypotension in a bleeding patient, where continuation of the transfusion may be life-saving). There is no published evidence which will guide clinicians as to whether continuation of transfusions in milder reactions would be of harm. In 2011, the following actions were recorded:

- 391 reports mentioned stopping the transfusion, including 122 mild reactions
- 8 transfusions were continued then stopped as symptoms recurred or worsened
- 4 continued at same rate
- 8 continued at slower rate
- 61 reports stated that the transfusion had been completed already
- 115 did not mention the fate of transfusion

Treatment

69 reports stated that no medication was given to treat the reaction, 340 stated that medication was given and 178 reports were left blank.

Many of the 340 cases were treated with several drugs.

- 33 received antihistamine alone
- 7 received steroid alone
- 111 paracetamol alone
- 4 salbutamol alone
- 1 adrenaline alone
- 184 received combinations, mostly involving the above four drugs. Of these, 82 received antihistamine and hydrocortisone

Adrenaline was mentioned as being given, in combination with other drugs, in 34 reports, and noradrenaline in nine.

Fifteen patients were given oxygen, and three reports mention that patients who were on already on oxygen therapy at the time of the reaction, had their flow increased.

The forthcoming BCSH guidelines on acute transfusion reactions[13] will cover treatment. Paracetamol may provide symptomatic relief in moderate or severe febrile reactions, and antihistamine, either topical or systemic, may have a role in allergic reactions. The role of steroids is unclear. Adrenaline is the first line drug in anaphylaxis, and antihistamine and hydrocortisone may have a role in shortening the anaphylactic reaction and preventing recurrence[49].

Investigations

The purpose of investigations should be to contribute to patient management, for example, by excluding other causes for the patient's symptoms/signs, or by guiding management of further transfusions by identifying a likely cause for the present reaction. There are only two examples in the 2011 data of an investigation identifying a likely cause: two case of anaphylaxis associated with IgA deficiency (IgAD), discussed below.

Respiratory investigations

77 patients were reported as having oxygen saturations measured: 28 provided results, only 1 case was mentioned as having falling saturation.

19 cases were reported as having a chest X-ray: none reported changes. 2 patients had evidence of chest infection, 1 case was consistent with pulmonary embolus and 1 case had cardiac enlargement.

Investigations for IgA deficiency

IgA deficiency, defined as serum IgA level < 0.07 g/L with normal levels of other immunoglobulins, forms part of the spectrum of common variable immunodeficiency[51]. It was historically considered an important cause of severe transfusion reactions, although results from cumulative haemovigilance data show that such cases are very rare. IgA was reported as having been measured in 67 patients but only 15 cases which had anaphylaxis or severe allergy. The two vignettes below (the second one occurring in 2010 and describing an atypical reaction), indicate that occasional cases do arise. In both these cases, there was a high titre of IgA antibodies, a feature which is reported to be a predictor of severe reactions. A low IgA in the setting of generalised hypogammaglobulinaemia is not considered a risk factor for severe reactions (see Case 7, below).

Case 5

Severe reaction associated with IgA deficiency

An adult female with an undetermined bleeding disorder was given plasma prior to a dental procedure. Shortly after the start of the transfusion, she complained of an itch in her arm, followed by flushing, chest tightness, a strange sensation in her neck and pain in her head and back. She transiently lost consciousness. Serum IgA was measured at < 0.06 g/L, and her IgA antibodies were very high at 1 in 8,198. The reporting clinical team were seeking a management plan for further transfusions.

Case 6

Atypical reaction associated with IgA deficiency

A male patient experienced two similar moderate to severe febrile reactions two days apart. On each occasion he complained of back pain and rigors within a few minutes of starting the transfusion. On investigation, his IgA level was undetectable and he had anti IgA titre of 512. The advice was given that, although febrile reactions are not typical of IgA deficiency, the findings should not be ignored. A careful management plan should be developed and subsequent components should be IgA deficient if possible. The team were also advised to refer the patient to an immunologist for assessment of his immunodeficiency.

Case 7

Generalised hypogammaglobulinaemia

An elderly male patient with chronic lymphocytic leukaemia experienced a severe febrile reaction to red cells. Investigations included immunoglobulins. IgA was on the low side at 0.09 g/L, but IgG was also low.

Learning point

- A patient who has experienced a severe reaction and shown to have IgA deficiency should have a management plan for future transfusions. In addition, discussion with an immunologist, regarding management of common variable immunodeficiency, is important.

Mast cell tryptase

Mast cell tryptase (MCT) is a measure of mast cell degranulation. A typical "rise and fall" pattern, with the peak 1-3 hours post-reaction, is characteristic of anaphylaxis, but as the first vignette below shows, may also occur in less serious cases. Persistently raised MCT is seen in a range of haematological disorders (see second case below), as well as systemic mastocytosis, renal failure, and indeed any condition causing chronic pruritus[52]. The test does not identify the cause of anaphylaxis.

MCT was measured on 14 occasions. In two episodes, a "rise and fall" was seen, in the first vignette below and in a second case.

Case 8

"Typical" mast cell tryptase pattern in a moderate to severe allergic reaction.

A young male received standard plasma during plasma exchange. Within 15 minutes he developed urticaria, dyspnoea and angioedema, but hypotension was not described. He was treated with adrenaline, hydrocortisone and an antihistamine. A mast cell tryptase was raised at over 30 microg/L shortly after the reaction, but fell to 6.8 microg/L 24 hours later (normal level <13 microg/L).

Case 9

A raised MCT is not always due to anaphylaxis

An adult male with newly-diagnosed acute myeloid leukaemia experienced what appeared to be a minor febrile reaction shortly after transfusion of plasma and platelets. A single mast cell tryptase was very high at 100 microg/L.

A repeat sample should be performed: a return to baseline would suggest anaphylaxis, which would be unlikely in this case. Persistently raised MCT could be compatible with this underlying diagnosis.

Investigations to exclude bacterial contamination

Bacterial contamination is part of the differential diagnosis to consider when a patient presents with marked rise in temperature or severe rigors, especially when there is evidence of hypoxia, hypotension or shock. It is extremely unlikely in mild or moderate febrile reactions. 234 cases were reported as having blood cultures performed, including 159 febrile reactions, 48 allergic, 10 mixed allergic/febrile, 3 hypotensive and 14 unclassifiable reactions. The blood components involved were red cells (170 reports) platelets (46) plasma (15) and multiple components (3). 27 positive patient blood cultures were reported, but, in many cases, the positive finding appeared to be due to intercurrent septicaemia. In severe febrile reactions, the most important action is to contact a blood service consultant, for consideration of recall of any associated components from this donation, and discussion of further investigations of the implicated component. (Ten reports specifically mention that the implicated units were referred to blood service bacteriology laboratories for culture.) The vignette below describes contact with the Blood Service. The reaction may not have been sufficiently severe to necessitate an immediate recall, but concern was raised as the patient had a positive blood culture.

Case 10

ATR mimics bacterial infection, but transfusion-transmitted infection is excluded

An adult female with cancer was receiving a red cell transfusion as an outpatient. Near the end of the first unit, she developed a temperature rise of 1.5°C with rigors and a rise in blood pressure (a common feature in febrile reactions). She later vomited. The transfusion was discontinued and the unit was quarantined. Hospital blood culture showed a coagulase-positive staphylococcus. A Blood Service consultant was then contacted, and a recall was performed. The unit was sent for culture which was negative, and bacterial transfusion-transmitted infection was excluded.

Learning point

- If there is reason to suspect bacterial contamination, it is important to contact the Blood Service, even if the hospital is performing their own cultures of the unit, in order that the need for a recall of associated components can be considered promptly.

Human leucocyte antigen (HLA), human platelet antigen (HPA) and human neutrophil antigen (HNA) investigations

These were recorded as being performed in 27 cases, 8 with abnormal results. From the clinical information provided, this did not appear to be an appropriate investigation in any of the cases as none mentioned platelet refractoriness or new cytopenia[53].

Appropriateness of transfusion

This is difficult to assess. However, 18 reporters stated that transfusion had not been clinically indicated according to current BCSH guidelines. These reports included 9 red cell transfusions, 6 platelet and 3 plasma transfusions. No details are available except for one case of inappropriate use of plasma for warfarin reversal, which has led to a change in hospital policy on FFP use.

Reactions to methylene blue (MB-FFP) or solvent detergent treated plasma (SD-FFP)

This year, there have been three reactions in which *solvent detergent plasma* was implicated: severe reaction in an infant, described in detail (Case 5) in the paediatric chapter (Chapter 22), a mild allergic reaction, and one undefined reaction of low imputability. *Methylene Blue (MB)* treated plasma was initially implicated in the severe reaction, but has since been transfused to this individual without problems. MB plasma was also implicated in a mild febrile reaction of low imputability in a neonate.

Another European Union (EU) country has reported a higher rate of anaphylaxis with MB versus standard plasma, and there are case reports of patients whose allergy skin testing for methylene blue and related compounds was positive[54]. In 2011 only 1 reaction, a mild febrile reaction, was related to MB-FFP and from 2007-2011 there has been a total of 8 MB-FFP ATR reports (1 including multiple components), of which 5 were severe reactions (3 anaphylactic and 2 hypotensive).

COMMENTARY

Since 2007, the number of SHOT ATR cases has shown a steady increase. However, the number of cases of anaphylaxis has stayed relatively constant, ranging from 27 cases in 2007 to 33 in 2011. This suggests that more serious reactions have been reported in the past, but the increase in numbers probably reflects more comprehensive reporting of less serious events. The chart of reactions by component (Figure 13.2) shows a similar pattern to the charts of 2009 and 2010.

Now that the ATR reports could be considered to be in a “steady state”, it is timely to consider their value. Through comprehensive reporting, SHOT is able to monitor any change in reactions associated with new components or processes, and to compare our data with other countries’ haemovigilance schemes. The data on methylene-blue plasma is an example of this. The investigation of ATRs is a very interesting area: some investigations can help in the immediate management of the patient (e.g. oxygen saturation, full blood count and chest X-ray where appropriate), but one of the main purposes of investigations should be to exclude other serious adverse reactions e.g. transfusion-transmitted infection (TTI), TRALI and HTR where the clinical picture is not clear cut. However, performing all tests indiscriminately, in all cases, is not appropriate. Occasionally, investigations can guide selection of components for future transfusions, for example identification of IgA deficiency associated with severe allergic reactions.

Recommendations

- If a transfusion reaction is considered sufficiently severe that bacterial contamination is considered as a possible diagnosis, clinicians must contact the Blood Service to discuss whether a recall of associated components from the donation is necessary. This applies even when the hospital performs its own bacterial testing of the component.

  Action: Hospital Transfusion Teams (HTTs)

- Any reactions to fresh frozen plasma (FFP) (all types) should be reported to SHOT and investigated in detail.

  Action: Hospital Transfusion Committees (HTCs)

- Patients who have experienced an anaphylactic transfusion reaction should be discussed with an immunologist regarding further investigation and management.

  Action: Haematologists

For active recommendations from previous years and an update on their progress, please refer to the SHOT website