15 Acute Transfusion Reactions (Allergic, Hypotensive and Severe Febrile) (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. However, the possibility that a reaction could belong to one of these serious categories must be kept in mind during recognition, initial assessment and treatment.

DATA SUMMARY
Total number of cases: n=320

Implicated components		Mortality/morbidity	
Red cells	182	Deaths definitely due to transfusion	0
Fresh frozen plasma (FFP)	31*	Deaths probably/likely due to transfusion	0
Platelets	96	Deaths possibly due to transfusion	0
Cryoprecipitate	0	Major morbidity	76
Granulocytes	0	Potential for major morbidity (Anti-D or K only)	0
Anti-D Ig	0		
Multiple components	11		
Unknown	0		

Gender		Age		Emergency vs. routine and core hours vs. out of core hours		Where transfusion took place	
Male	121	≥18 years	298	Emergency	34	Emergency Department	13
Female	192	16 years to <18 years	4	Urgent	49	Theatre	14
Not known	7	1 year to <16 years	15	Routine	213	ITU/NNU/HDU/Recovery	39
		>28 days to <1 year	2	Not known	24	Wards	174
		Birth to ≤28 days	1			Delivery Ward	17
		Not known	0	In core hours	168	Postnatal	0
				Out of core hours	70	Medical Assessment Unit	0
				Not known/Not applicable	82	Community	3
						Outpatient/day unit	57
						Hospice	0
						Antenatal Clinic	0
						Other	3
						Unknown	0

(ITU=Intensive therapy unit; NNU=Neonatal unit; HDU=High dependency unit)

**Including 2 reactions to methylene blue-treated FFP (MB-FFP) and 2 reactions to solvent-detergent treated FFP (SD-FFP)*

This analysis includes 320 cases including 4 transferred from haemolytic transfusion reactions (HTR) and 3 from unclassifiable complications of transfusion (UCT). A further 3 cases with predominantly respiratory features were transferred to TAD and 8 to TACO. Other cases were withdrawn as the reporters subsequently attributed the clinical features to other causes, and others were classified as mild and these have now not been included in the main analysis, according to recent SHOT guidance.

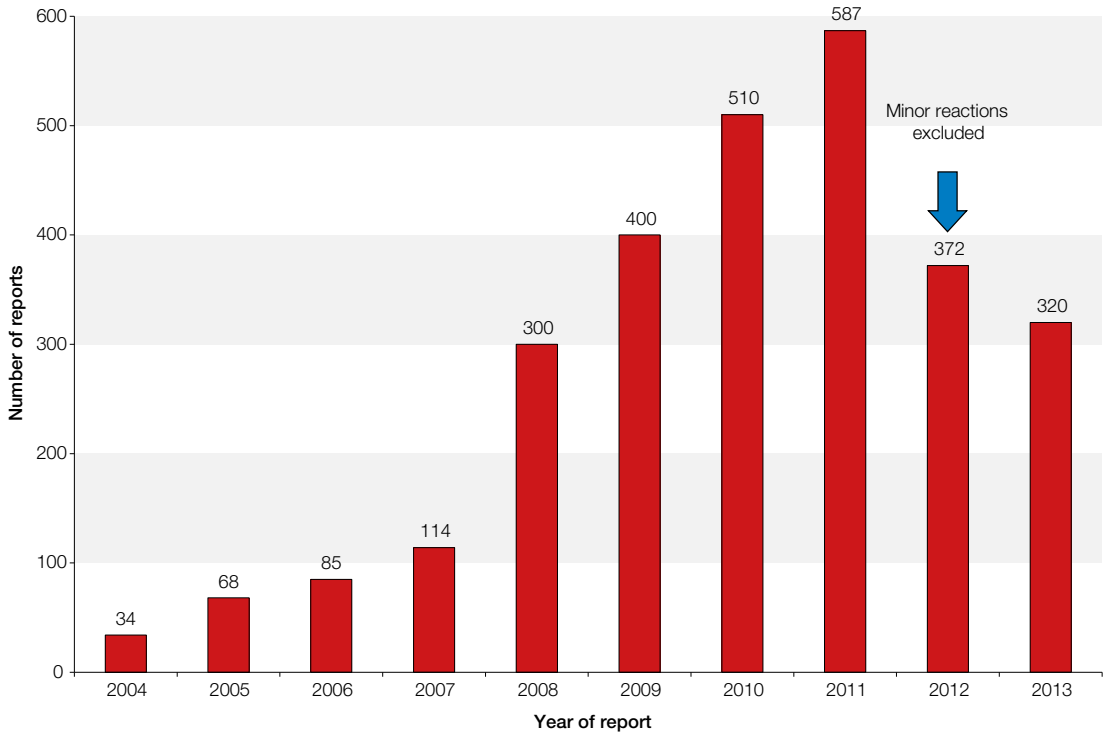


Figure 15.1: Numbers of cases of acute transfusion reactions 2004-2013

Introduction

The total number of ATR cases reported has fallen slightly since last year, from 372 to 320. Where possible, reactions have been classified according to the latest International Haemovigilance Network/ International Society for Blood Transfusion (IHN/ISBT) draft definitions which are available online [49]. These have been adopted by the British Committee for Standards in Haematology (BCSH) [50].

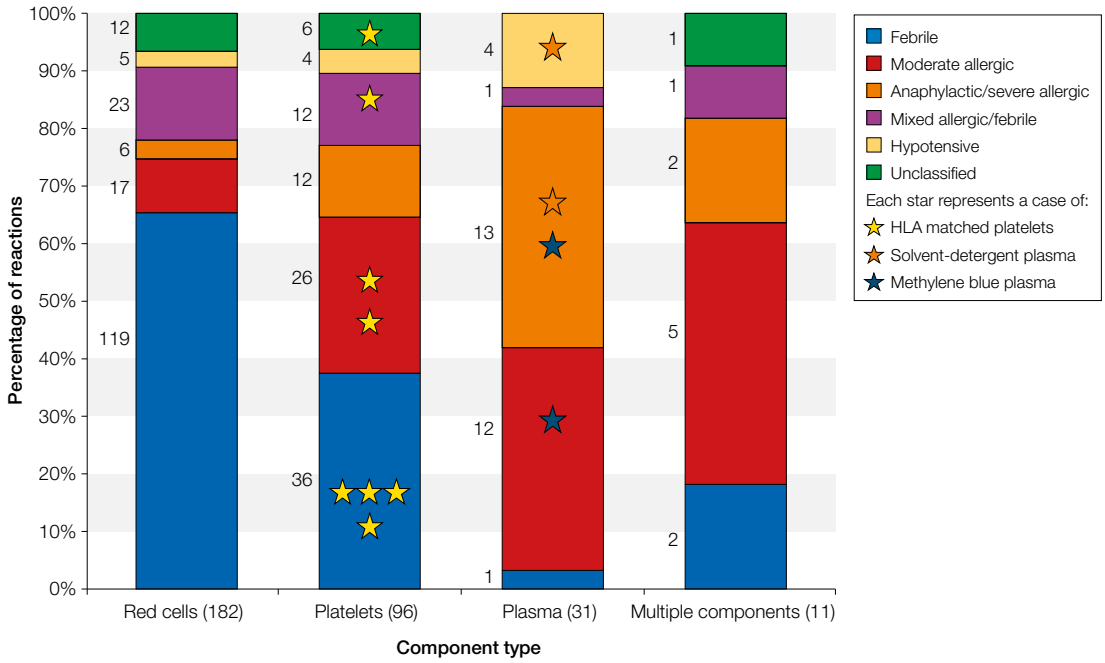
The pattern of reactions remains similar (see Figure 15.2, reaction by component type). The figures for anaphylaxis and severe reactions are similar. As in previous years, many reactions are difficult to classify. In some of these cases, symptoms and signs could be due to the patient's underlying condition rather than transfusion. This is more likely to be true for reactions where multiple components were given and where patients have complex clinical problems. This year, many reports lacked important details about blood pressure changes, which has led to 19 cases being unclassifiable.

Types of reactions

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

- 158 febrile (136 moderate, 22 severe)
- 93 allergic (33 anaphylactic or severe allergic, 60 moderate)
- 37 mixed allergic/febrile (5 severe, 30 moderate and 2 whose severity could not be determined as insufficient information was provided)
- 13 hypotensive (6 severe, 6 moderate and 1 whose severity could not be determined as insufficient information was provided)
- 19 reactions were unclassifiable as the reaction was significant but not typical of an acute transfusion reaction. These included reactions where pain was a significant feature, or where the patient felt faint or lost consciousness. The imputability of many of these reactions is difficult to determine

Figure 15.2: Reaction by component type



The pattern is similar to previous years, in that febrile reactions are rarely seen with plasma and much reduced with platelets compared to red cells. There is a larger number of mixed allergic/febrile reactions: whether this is due to more detailed reporting is unclear.

Reactions in children

There were 22 reactions in children aged less than 18 years. These are further discussed in Chapter 25 Paediatric Cases.

Deaths n=0

Although there were 14 deaths reported in patients having ATRs, none was thought to be related to the transfusion.

Severe reactions n=76

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 [49].

There were 66 cases which the analysts classified as severe, consisting of 33 cases of anaphylaxis or severe allergic reaction, 22 severe febrile reactions, 5 severe hypotensive reactions and 6 severe mixed febrile and allergic reactions.

In addition to these 66 cases, a further 10 cases have been included as they were described by reporters as experiencing severe reactions although the reported symptoms and signs suggested moderate reactions. There were no patients reported to have long-term morbidity.

These cases indicate that transfusion reactions, although rarely associated with prolonged morbidity, may nevertheless have a significant impact on the patient and on hospital resources.

Specific types of reactions

Anaphylactic or severe allergic reactions n=33

Anaphylaxis is defined by the UK Resuscitation Council (UKRC) [51] and National Institute for Health & Care Excellence (NICE) [52] 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’. Case 1 (below) provides a characteristic

example of an anaphylactic reaction in an obstetric setting.

Thirty three reactions were consistent with anaphylaxis or severe allergy, one in a 1 year old child who died. Death was stated to be unrelated to the reaction. Seven occurred on day units. Only one case cited the possibility of another agent potentially being the cause of the reaction (oral morphine).

Fifteen patients documented to have anaphylactic reactions were recorded as being given adrenaline which is stated to be the first line treatment by the UKRC. In 10 cases this was given with other medication, most commonly antihistamine and hydrocortisone. In two cases it was given as the sole medication. Noradrenaline was given in two cases.

The number of cases of anaphylaxis reported to SHOT in recent years has remained very stable, as can be seen in Figure 15.3.

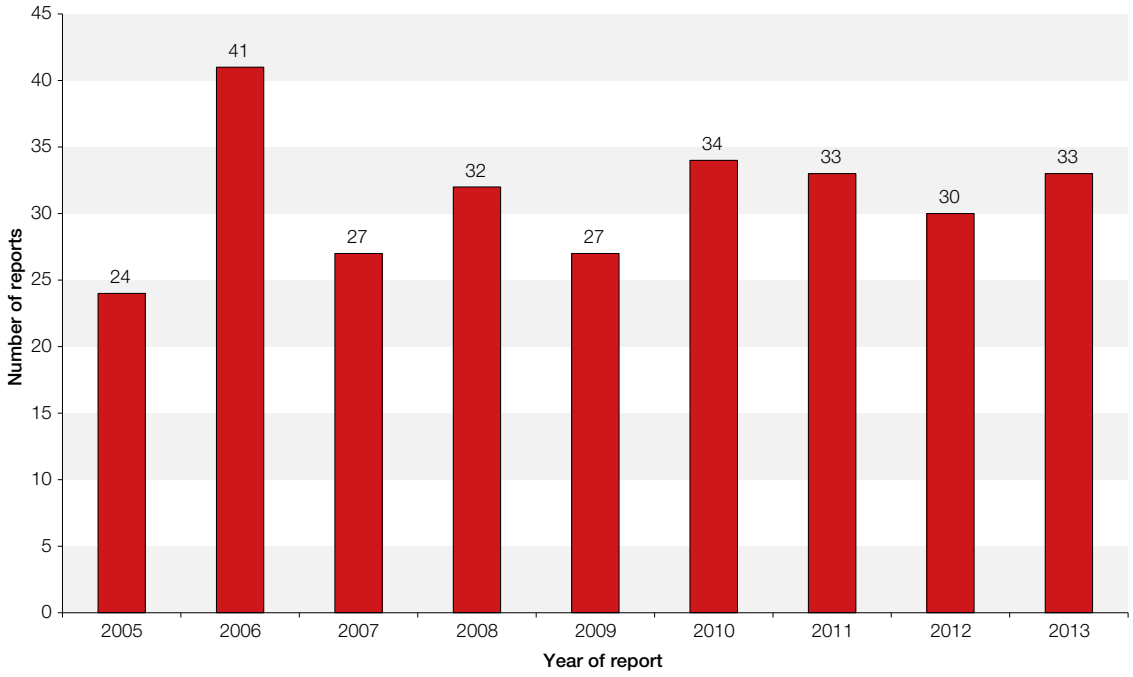


Figure 15.3: Cases of anaphylaxis 2005-2013

Case 1: Anaphylaxis triggered by FFP

A patient with a postpartum haemorrhage (PPH) received 2 units of red cells and 1 unit of fresh frozen plasma (FFP) with no ill effect. She had a further unit of red cells and a second unit of FFP. Eight minutes into this transfusion, the nurse noticed the patient was coughing, and had swollen eyes, lips and throat. There was evidence of bronchospasm and O2 saturations dropped. Blood pressure was unrecordable and the patient briefly lost consciousness. She was treated with adrenaline, intravenous (IV) hydrocortisone, chlorphenamine, salbutamol nebuliser and a multiple electrolyte replacement fluid, as well as syntocinon for management of the PPH.

Moderate allergic reactions n=60

These include reactions with respiratory components, not severe enough to be termed anaphylaxis. This includes 19 patients with angioedema.

Hypotensive reactions n=13

Six reactions were assessed as being severe. However, key data on blood pressure prior to, and during, the reaction were often not available.

Previous SHOT reports have suggested that hypotensive reactions tended to occur during or shortly after cardiac bypass procedures. However, there was only one severe hypotensive reaction reported in a cardiac surgery patient in 2013.

Severe febrile reactions n=22

Twenty-two febrile reactions were classified as severe. Five reports involved patients with underlying sepsis or line infection (two reports from the same patient).

The differential diagnosis of a severe febrile reaction includes bacterial transfusion-transmitted infection (TTI), an acute haemolytic transfusion reaction, and underlying inflammation or infection. If bacterial TTI is considered a possibility, the Blood Service should be contacted regarding recall of associated components from the donation, and the unit should be cultured by a department that has the capability of sampling the unit by aseptic technique as well as culture.

Case 2: A severe febrile reaction

One hour and 20 minutes into a transfusion of red blood cells the patient developed 2.2°C rise in temperature, severe rigors, tachycardia, vomiting, chest pain and a decrease in oxygen saturation. Rigors prevented measurement of the blood pressure. The urine was positive for haemoglobin, but the patient was known to have haematuria. Cold antibodies were detected which were felt not to have been responsible for the reaction. The implicated unit was negative on culture.

Mixed febrile/allergic reactions n=37

Reactions were classified as mixed as there was a combination of febrile features and a rash. Five cases were severe.

How transfusion reactions present

Whilst 114 reactions were first noticed by patients and a further seven by relatives, 148 reactions were first detected by routine observations. Although 117 of these were moderate reactions, 24 were severe/life-threatening (7 could not be classified). Out of the 24, 11 were severe allergic/anaphylactic reactions, and 1 was a severe hypotensive reaction. The median time of onset (where data were provided) was 30 minutes. This highlights the value of routine observations in the early detection of significant adverse events.

Speed of onset

The time of onset of symptoms from the start of transfusion of the implicated component was recorded in 128 cases. The median time to onset was 30 minutes (range 1 minute to 7.5 hours).

Management of the transfusion

Stopping the transfusion

In the case of a suspected transfusion reaction it is important to stop the transfusion at least temporarily, confirm the identity of the patient and that documented on the component, and check for obvious contamination. In severe reactions, the component should be taken down and retained for further investigation as necessary and venous access maintained by physiological saline. (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 to guide clinicians as to whether continuation of transfusion in moderate or mild reactions would be of harm.

Reports on the fate of transfusion were received as follows:

- 224 reports stated the transfusion was discontinued
- 2 transfusions were continued then stopped as symptoms recurred or worsened
- 2 cases continued at the same rate
- 5 cases continued at a slower rate
- 12 were stopped temporarily for observation: it was not clear what the subsequent management was
- 64 reports stated that the transfusion had already been completed
- 11 provided no details of further management

Transfusion reactions occurring at home

There were 57 reactions in day case patients, including 15 cases with features of severe reactions. Three patients experienced reactions when they had returned home.

Outpatient departments and day case units should ensure patients have information about what to do if they undergo a transfusion reaction.

Investigations

The purpose of investigation is to contribute to continued patient management, for example, by excluding other causes for the patient's symptoms/signs, and to guide management of further transfusion. Data for 2013 were encouraging as, in many cases, investigation was directed towards the patient's presenting symptoms and signs. However, there is still evidence that inappropriate testing for human leucocyte antigen (HLA), human platelet antigen (HPA) and granulocyte antibodies is being performed.

Respiratory investigations

A chest X-ray was reported to have been performed in 30 cases, and oxygen saturation in 70 cases.

Investigations for Immunoglobulin A (IgA) deficiency

IgA levels were measured in 53 patients: 14 with features of anaphylaxis, 16 other allergic reactions, 12 febrile reactions, 6 mixed allergic/febrile reactions, 3 hypotensive reactions and 2 unclassifiable reactions. There were two reports of very low levels, both in patients who had experienced anaphylaxis. Immunologists define IgA deficiency as an IgA level <0.07g/L, in the presence of normal levels of other immunoglobulins, in patients aged 4 years or more. It may form part of the spectrum of common variable immunodeficiency. However, the Blood Service experience is that the few patients who have been shown to be IgA deficient with severe allergic transfusion reactions have had very low IgA levels, <0.0016g/L, often in the presence of anti-IgA antibodies. In practice, about one in 500 of the UK population have a level as low as this, and 25% of people with very low IgA levels also have anti-IgA antibodies. IgA levels are now frequently measured as part of the investigation of coeliac disease and other auto-immune diseases. Given the rarity of severe reactions and comparative frequency of IgA deficiency, in the absence of a history of transfusion reaction, these patients should receive standard blood components [53].

Mast cell tryptase

There were only two reports showing a slight sequential 'rise and fall' in mast cell tryptase (MCT). One was a report of a patient with anaphylaxis and one related to a patient with a moderate allergic reaction. Several reports contained only one MCT result which was elevated, which on its own is of little diagnostic value. In one case three serial results were all moderately high. This is not typical of anaphylaxis. MCT testing is not routinely required, but if needed because the clinical diagnosis of anaphylaxis is in doubt, then serial MCT levels should be performed. Few cases seem to have had serial MCTs performed and it appears this test is rarely used in UK transfusion practice. Although MCT testing is often quoted as being important in the investigation of anaphylactic reactions to transfused blood and components, there are very few published studies of its role in transfusion reactions. In practice, adequately-timed samples are rarely obtained. The diagnosis of anaphylaxis should therefore primarily be made on clinical grounds.

HLA/HPA/granulocyte antibodies

HLA testing of the patient was performed in 16 cases, and HPA testing in two cases. Only one of the patients was reported to be refractory to platelets. For the 13 cases where diagnosis was known, 8 were haematology patients. Positive results were found in 10 cases, and in 5 instances the clinical team decided to use HLA-matched platelets in the future. These instances included one severe and two moderate febrile reactions, a moderate allergic, and a moderate mixed allergic/febrile reaction.

Comment

Patients who experience transfusion reactions should not be HLA- or HPA-antibody tested unless they experience repeated severe reactions that are not reduced by using washed red cells or platelets in suspension medium or there is evidence of platelet refractoriness [54]. This year, SHOT received 8 reports of moderate/severe reactions to HLA-matched platelets with a similar incidence per 100,000 units issued to that seen with standard platelets.

Investigations to exclude bacterial contamination

Patient blood cultures were performed in 149 cases, the majority having febrile reactions (n=99). Cultures were positive in 17 cases, but none of these were associated with severe febrile reactions, and were very unlikely to have been caused by bacterial contamination during transfusion.

In 115 reports the unit was cultured. Implicated components were: red cells, 71 instances, platelets, 38, plasma, 5, platelets and plasma in one. Cases included 12 severe febrile reactions where the investigation was highly appropriate, 12 cases of anaphylaxis and one severe hypotensive reaction (in these cases it may have been appropriate if the cause of collapse was not clear). In 62 moderate febrile reactions, 10 mixed allergic/febrile reactions, 2 moderate hypotensive reactions and 11 cases of moderate allergic reactions, cultures were performed and were likely to have been inappropriate. In five additional cases the reaction could not be easily classified. In 66 cases the culture was performed by the hospital laboratory and in 44 cases by the Blood Service, both laboratories in three cases and not stated in two cases. There were three reports of positive growth from hospital cultures which were later found to be negative by Blood Service laboratories. None of the units investigated by Blood Service laboratories had positive cultures. The initial positive growth was usually of mixed organisms and likely to be due to contamination at the point of sampling.

Very few of the 66 reports involving culture of the unit by hospital laboratories mention contacting the appropriate Blood Service to discuss recalling other components from the implicated donation (although undoubtedly this will have been done in many of the cases). This is an essential and potentially life-saving action when bacterial contamination of blood components is suspected.

Comment

Despite the fact that there have been no cases of bacterial transfusion-transmitted infection of blood components reported by the UK Blood Services in the last four years (including 2013), bacterial contamination should remain part of the differential diagnosis when a patient presents with a marked rise in temperature or rigors, especially when there is evidence of hypoxia, hypotension or shock.

Seven of the 40 cases of bacterial TTI reported to SHOT since 1996 (last cases in 2009) were associated with red cells. Febrile reactions are most common with red cells, and in 2013, 119 of the 182 reports implicating red cells were of febrile reactions, 13 of which were severe. In fact the unit was cultured in only 5 of these instances.

Bacterial infection has not been described with plasma transfusion, and reactions to plasma do not require unit cultures to be carried out.

When bacterial contamination is suspected, the clinical team should contact a Blood Service consultant to discuss the need for a recall of associated components from the donation.

Reactions to methylene blue-treated plasma components (MB-FFP or cryoprecipitate) or solvent-detergent treated plasma (SD-FFP) n=4 patients in total

Methylene blue-treated components

There were two reactions: a teenage boy who was being treated for haemorrhage developed what appeared to be a severe allergic (but not anaphylactic) reaction and a 7 year old with angioedema, a moderate allergic reaction.

Solvent-detergent treated plasma

There were two reactions, both in adult patients undergoing plasma exchange. One patient who experienced severe hypotension was later exchanged using standard plasma with no problems. Imputability was stated to be certain. A second patient experienced anaphylaxis.

Transfusion reactions are considered to be less frequent, and usually less severe, with solvent-detergent treated plasma (SD-FFP) than with standard plasma, possibly due to dilution of donor allergens in a large pool, or denaturation of allergens via the solvent detergent process. Analysis of allergic reactions to plasma reported to SHOT 2010-2012 showed the incidence was 2 per 100,000 with SD-FFP compared to 11.5/100,000 with standard plasma ($p<0.001$). Although 'standard' SD-FFP is still available, all new stock ordered by hospitals will have been treated to eliminate prions.

Recommendations

New recommendations

- Reporters should report cases fully, including clinical data such as temperature and blood pressure prior to, and during, a reaction, especially if fever or hypotension is reported

Action: Hospital Transfusion Teams (HTT)

- Patients who have experienced transfusion reactions should only be tested for platelet or granulocyte antibodies within guidelines such as those set out in England by the National Health Service Blood and Transplant (NHSBT) in their Histocompatibility and Immunogenetics user guide [54]. The main indication here would be persistence of severe reactions despite the use of platelets where the plasma has been removed and replaced by suspension medium

Action: HTTs, Histocompatibility and Immunogenetics laboratories

- Outpatient departments and day case units should ensure patients have information about what to do if they experience a transfusion reaction after leaving the unit

Action: HTTs, Day case wards

Recommendations from previous years: still active

- 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 also applies when the hospital performs its own bacterial testing of the component

Action: Hospital Transfusion Committees (HTC)

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

Action: Haematologists

- Transfusions should only be performed where there are facilities to recognise and treat anaphylaxis, according to UK Resuscitation Council (UKRC) guidelines. This recommendation is also relevant for other transfusion-related emergencies such as respiratory distress caused by transfusion-associated circulatory overload (TACO) or transfusion-related acute lung injury (TRALI). In supplying to community hospitals or for home transfusions, providers must ensure that staff caring for patients have the competency and facilities to deal with this reaction. This is particularly relevant in the light of proposed increase in treatment of patients outside the secondary care setting

Action: HTTs, Royal College of General Practitioners

Recommendations still active from previous years are available in the 2013 Annual SHOT Report Supplement located on the SHOT website, www.shotuk.org under SHOT Annual Reports and Summaries, Report, Summary and Supplement 2013.