16 Acute Transfusion Reactions (ATR) (Allergic, Hypotensive and Severe Febrile)

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Definition:

Acute transfusion reactions (ATR) 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: 372

Implicated components		Mortality/morbidity	
Red cells	250	Deaths due to transfusion	0
FFP	29	Deaths probably/likely due to transfusion	0
Platelets	79	Deaths possibly due to transfusion	0
Cryoprecipitate	3	Major morbidity	68
Granulocytes	2	Potential for major morbidity (Anti-D or K only)	0
Anti-D Ig	0		
Multiple components	9		
Unknown	0		

Gender		Age		Emergency vs. routine and core hours vs. out of core hours		Where transfusion took place	
Male	183	≥18 years	342	Emergency	28	Emergency department	2
Female	183	16 years to <18 years	2	Urgent	76	Theatre	17
Not known	6	1 year to <16 years	22	Routine	246	ITU/NNU/HDU/Recovery	44
		>28 days to <1 year	2	Not known	22	Wards	218
		Birth to ≤28 days	2			Delivery Ward	12
		Not known	2	In core hours	276	Postnatal	3
				Out of core hours	92	Medical Assessment Unit	17
				Not known	4	Community	3
						Outpatient/day unit	51
						Hospice	1
						Antenatal Clinic	0
						Unknown	4

A total of 372 cases have been included in the analysis. This includes 5 cases transferred from 'haemolytic transfusion reactions' (HTR), 10 from the unclassifiable group, 5 from 'transfusion-transmitted infections' (TTI), 2 from TRALI, 1 from 'incorrect blood component transfused' (IBCT), and 1 from 'right blood right patient' (RBRP). A further 11 cases with predominantly respiratory features were transferred to TAD and 14 to TACO. Twenty cases were withdrawn as the reporters subsequently attributed the clinical features to other causes. A total of 169 were classified as mild: 76 febrile, 88 allergic and 5 mixed febrile/allergic and these have now been excluded from the main analysis, according to recent SHOT guidance (see revised definitions on SHOT website[23]).

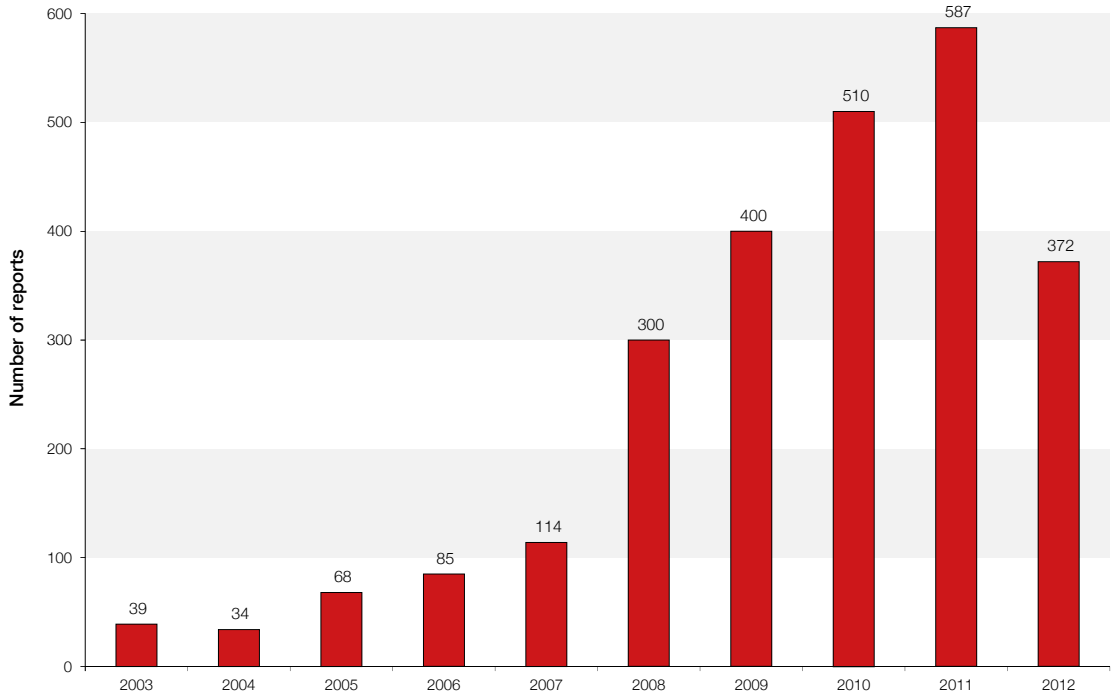


Figure 16.1: Numbers of cases of acute transfusion reactions 2003 to 2012

Introduction

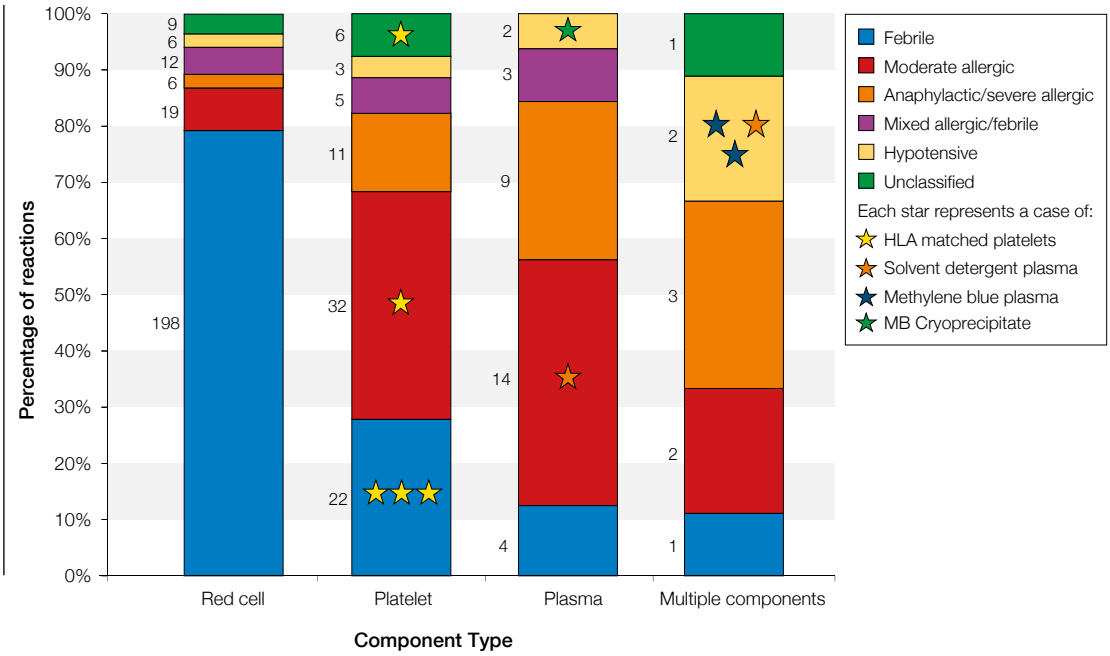
The total number of ATR cases reported has fallen slightly since last year, from 587 to 541 (including mild reactions). Withdrawal of 169 mild reactions leaves 372 for analysis. The pattern of reactions remains similar (see Figure 16.2, reactions by component type) and numbers for anaphylaxis and severe reactions are similar. Where possible, reactions have been classified according to the latest International Haemovigilance Network/International Society for Blood Transfusion (IHN/ISBT) draft definitions which have recently been published[1] and which were used in the recent British Committee for Standards in Haematology (BCSH) guideline on acute transfusion reactions[68]. 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, and this particularly appears to be the case for reactions where multiple components were given and where patients are likely to have complex clinical problems.

Types of reactions

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

- 226 febrile (210 moderate, 16 severe)
- 97 allergic (67 moderate and 30 anaphylactic or severe allergic)
- 20 mixed allergic/febrile
- 13 hypotensive
- 16 unclassifiable

Figure 16.2: Reaction by component type



In addition to the 370 cases in this figure, there was one anaphylactic reaction to granulocytes of unspecified type and one febrile reaction to buffy coat granulocytes.

Reactions in children

There were 28 reactions in children aged less than 18, and these are covered in the Paediatric chapter (Chapter 27).

Imputability

Reporters were asked to assess imputability in the case of adverse reaction or death.

Imputability was given as:

- Certain in 14 cases (12 minor morbidity, 2 major)
- Likely/probable: in 68 (54 minor morbidity, 14 major)
- Possible: 140 (121 minor morbidity, 18 major, 1 no reaction – fever only)
- Excluded/unlikely, not assessable or left blank: 150 (134 minor morbidity, 12 major, 4 no reaction – fever only)

There are clearly many cases where reporters experience difficulty in determining whether clinical features are due to the component or other factors, in what are often complex clinical situations, as in Case 3, described in the section on severe febrile reactions.

Deaths n=0

Whilst there were 8 deaths reported in patients having ATRs, none were thought to be related to the transfusion. There was one case of anaphylaxis where the reporter stated that the patient recovered from the reaction, but later died of their underlying illness.

Severe reactions n=68

The 372 cases included 68 which were considered as having severe reactions. 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[1].

Reactions were classified as severe in 50 cases, according to IHN/ISBT/BCSH/SHOT guidelines (not all of which had been categorised as severe/life-threatening or associated with major morbidity by reporters). These included 30 cases of anaphylaxis an example of which is given in Case 1 below, or severe allergy, 11 severe febrile reactions, an example of which is given in the vignette below (Case 3), 7 severe hypotensive reactions and 2 mixed febrile and allergic reactions.

In addition to these 50 cases, a further 18 were included under the 'severe' heading as they fulfilled the SHOT definition of major morbidity: they either required high dependency admission and/or ventilation; or they required dialysis and/or had renal impairment (n=18). One patient was reported as needing to start dialysis but their underlying clinical condition was described as 'unstable'. Eight patients were reported as requiring transfer to the intensive therapy unit (ITU) but this included three with massive haemorrhage and two others with acute blood loss. The imputability that the transfusion had caused the reaction was reported as likely in one case, possible in 5 cases, and was not given in two cases.

These cases demonstrate that ascribing major morbidity can be difficult in acute transfusion reactions. Morbidity may be due to the underlying illness. In other cases signs and symptoms of the reaction can be severe, but they are often transient.

Of note, 29 patients were admitted from the outpatient setting, and two were admitted who had received transfusions in the community. This number includes 19 outpatients for whom the imputability that the transfusion caused the symptoms was given as 'certain' or 'likely/probable'. These cases indicate that transfusion reactions, although rarely associated with prolonged morbidity, may nevertheless have an impact on the patient and on hospital resources. Clinicians and managers who arrange for blood transfusion to take place in an out of hospital setting should follow recent guidelines to ensure appropriate policies are in place for the management of adverse incidents (http://www.transfusionguidelines.org.uk/docs/pdfs/bbt-01_sp_tx-framework-v3.pdf).

Specific types of reactions

Anaphylactic reactions n=30

Anaphylaxis is defined by the UK Resuscitation Council (UKRC) [69] and National Institute for Health & Care Excellence (NICE)[70] 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'.

Thirty reactions were consistent with anaphylaxis or severe allergy. Only three of these were in paediatric patients. Thirteen reactions occurred on wards, 6 in theatre, 5 in ITU, 2 in recovery, 2 in outpatients, and 1 each in delivery suite and medical admissions unit (MAU). Only 15 patients with anaphylaxis were recorded as being given adrenaline (or noradrenaline), the former stated as being the first line drug treatment in anaphylaxis by the UKRC.

Case 1: Anaphylaxis in the setting of massive obstetric haemorrhage

A young woman experienced a massive obstetric haemorrhage requiring over 30 units of red cells, 8 adult platelet doses and 12 units of plasma including solvent detergent plasma (not implicated), prothrombin complex concentrates, 6 L crystalloid and 2 L colloid. When the 12th unit of plasma was transfused during surgery, she developed sudden urticaria, dropped her mean arterial pressure to 40 mm (normal 70-110 mm) and had reduced tidal volumes and wheeze. The anaesthetist experienced difficulty giving adequate sedation due to the hypotension. The blood pressure improved with boluses of metaraminol, noradrenaline and hydrocortisone and colloids. Despite the severity of this event, the patient recovered rapidly and was able to be discharged one week later. IgA level was normal.

Moderate allergic reactions n=67

These include reactions with respiratory symptoms that are not severe enough to be termed anaphylaxis, or those with angioedema.

Hypotensive reactions n=13

Thirteen reactions were classified as being hypotensive, 7 being severe. Details of treatment were available for 6/7 who had experienced severe hypotensive reactions. Six of the reports were associated with cardiothoracic procedures, including two patients on extracorporeal membrane oxygenation (ECMO): one adult and one neonate. Six reactions occurred in ITU/high dependency unit (HDU), two in the operating theatre and one on the neonatal ward. Four occurred on general wards. Three of the severe cases involved children aged 1 year or less.

Three reactions were associated with methylene blue-treated components, plasma in two cases and cryoprecipitate in one case. The underlying condition of the patients was very severe: meningococcal septicaemia in a 1 year old child, one cardiac surgery, and one ECMO, both in neonates.

The diagnosis of a hypotensive reaction can be difficult, especially in a patient in whom haemorrhage is suspected. There was evidence of haemorrhage in only two of the cases of hypotensive reaction, including Case 2, below.

Case 2: Reaction associated with hypotension in an obstetric patient

An obstetric patient suffered a post partum haemorrhage and was transfused with red cells in theatre. Towards the end of one unit, she became faint and was noted to have mottled skin. Her diastolic blood pressure was unrecordable. As anaphylaxis was suspected, she was given adrenaline, with supplementary hydrocortisone and antihistamine: however serial mast cell tryptase measurements were normal.

Severe febrile reactions n=16

Sixteen febrile reactions were classifiable as severe: 10 cases were associated with red cell transfusion, 5 with platelet transfusions (two of which were human leucocyte antigen (HLA)-matched) and one with plasma. In contrast to last year's report, only one patient had a temperature >39°C (40°C). The additional factors which led to a classification as 'severe' were hypotension and/or hypoxia. In 7 cases, the unit was cultured. No cases of transfusion-transmitted bacterial infection were identified. Patient blood cultures were performed in 6 cases (5 patients had both unit and blood cultures). One blood culture grew coagulase negative staphylococci. Four patients had no cultures. In the majority of these cases, the patient's underlying condition may have caused the clinical features which led to the reaction being classified as severe. Case 3 demonstrates the diagnostic difficulty.

Case 3: Severe febrile symptoms during removal of retained products of conception

Two weeks after delivery, a young woman experienced heavy vaginal loss and severe abdominal pain, and was found to have retained products of conception. Her Hb was 69 g/L. She was transfused with red cells, then surgery was performed, with spinal anaesthetic. During surgery she experienced myalgia, nausea and vomiting, loin pain and flushing. Her blood pressure at one point was unrecordable. Blood or unit cultures were not performed. The reaction occurred two hours after the red cell transfusion: it cannot be determined whether the reaction was related to the red cells or to a concealed haemorrhage.

Mixed febrile/allergic reactions n=20

These included 2 severe and 18 moderate reactions. This classification was usually made because of the combination of rigors and a rash. This type of reaction was seen with approximately equal frequency with all components.

Speed of onset

The time of onset of symptoms from the start of transfusion was recorded in 155 cases. The median time was 45 minutes (range 1–270 minutes).

Management of transfusion reactions

Stopping the transfusion

In the case of a suspected transfusion reaction it is important to stop the transfusion temporarily, to 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 2012, the following actions were recorded:

- 263 reports mentioned stopping the transfusion completely
- 6 transfusions were continued then stopped as symptoms recurred or worsened
- 3 continued at same rate
- 5 continued at slower rate
- 13 were stopped temporarily for observation: it was not clear what the subsequent management was
- 65 reports stated that the transfusion had been completed already
- 17 reports did not state how the transfusion was managed

Treatment

In 253 cases the reports indicated that medication was given, in most cases in combinations of two drugs or more. Treatment for febrile reactions did differ from allergic reactions, as can be seen in Figure 16.3. Only allergic reactions received adrenaline, whilst proportionately more paracetamol was given to patients with febrile reactions. However, considerable numbers of patients in each group were given hydrocortisone. Hydrocortisone and antihistamine are recommended as having a role in second line treatment of anaphylaxis[69] but outside this clinical indication, hydrocortisone does not have a clear role.

Additional medication included antibiotics and diuretics. Of the 6 patients with severe hypotensive reactions, 4 received adrenaline and/or noradrenaline, one vasopressin and one a plasma expander. One patient classified as having anaphylaxis, and two patients with moderate febrile reactions, received pethidine.

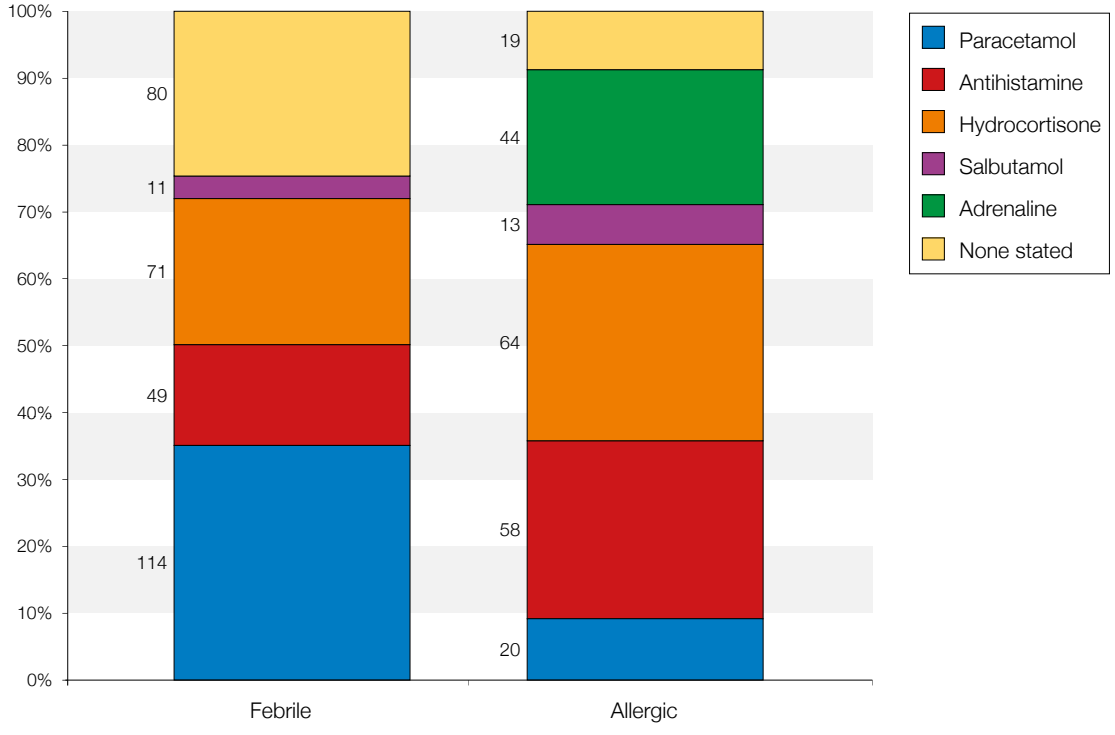


Figure 16.3: Treatments given and type of reaction. Most patients received more than one drug

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. Data for 2012 show a positive finding: that, in many cases, investigations are directed towards the patient's presenting condition. However, there is still evidence that inappropriate testing for HLA, human platelet antigen (HPA) and granulocyte antibodies is being carried out.

Respiratory investigations

A chest X-ray was reported to have been taken in 19 cases. Three cases showed pulmonary oedema, one was consistent with infection and one showed pleural effusions. Oxygen saturations were reported as performed in 61 patients (24 allergic, 30 febrile, 5 mixed allergic/febrile and 2 other reactions) and results were given in 49 reports: saturations were low in 29 cases.

Investigations for IgA deficiency

Immunoglobulin A levels were measured in 54 patients: 22 with allergic, 19 febrile, 8 mixed allergic/febrile, 3 hypotensive and 2 other reactions. Four patients were reported to have very low levels. One had anti IgA antibodies at a high titre of 1280, two had low titre antibodies and one had none. All had received red cells: the patient with high titre anti IgA antibodies experienced anaphylaxis, another case had a severe febrile reaction, one a moderate febrile reaction and one a mixed allergic/febrile reaction. IgA deficiency has not been described as being associated with febrile reactions, but rather with anaphylaxis. It is not known whether the IgA deficiency was implicated in the three patients' reactions that were not anaphylaxis.

Immunologists define IgA deficiency as an IgA level <0.07 g/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. Severe allergic transfusion reactions have been linked to severe IgA deficiency, <0.0016 g/L, often in the presence of anti-IgA antibodies. In practice, about 1 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[71]. IgA levels are now frequently measured as part of the investigation of coeliac disease and other auto-immune diseases and, in the absence of a history of transfusion reactions, even a very low level is not considered to be a risk factor for reactions[72].

Mast cell tryptase

There were only two reports showing a slight 'rise and fall pattern': one in a patient with anaphylaxis and one with a moderate allergic reaction. Several reports contained only one elevated result, and in one case three serial results were moderately high, a situation often seen with chronic pruritus, which did not seem to be the case in this patient. Mast cell tryptase testing is not routinely required, but if needed because the clinical diagnosis of anaphylaxis is in doubt, to be of value, serial mast cell tryptase levels are needed: a single result is of little diagnostic value.

HLA/HPA/granulocyte antibodies

Twenty one patients were tested for HLA antibodies (8 after red cell transfusion, 12 after platelets including 3 receiving HLA-matched platelets, and one after plasma transfusion) and antibodies were detected in 9 cases. A further 6 had HPA antibodies tested including one patient who was also tested for granulocyte antibodies. These investigations are rarely indicated in investigation of ATRs, unless there is evidence of platelet refractoriness or in rare reactions associated with sudden onset of neutropenia or thrombocytopenia[68].

Investigations to exclude bacterial contamination

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 three years (including 2012), bacterial contamination should remain 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. Patient blood cultures were performed in 154 cases, the majority having febrile reactions (112 cases). These were positive in 23 instances: 20 febrile, 1 allergic and 2 'other' reactions.

In 146 reports the unit was cultured: in 98 cases by the hospital laboratory and in 41 cases by the Blood Service (and unknown in 7 cases). Although information is not available from the reports, in the experience of the authors, sometimes initial hospital cultures of the unit have been positive but negative on re-testing by Blood Services, and the initial positive finding was thought to be due to contamination on culturing. In this group of 146 reports of units cultured, the investigation was not always appropriate, for example, there were 16 pack cultures for moderate allergic reactions and 11 for severe allergic/anaphylaxis. Seven packs associated with severe febrile reactions were not cultured, although it probably would have been appropriate to do so.

Learning point

- Where appropriate, units causing reactions that could be a result of bacterial contamination should be sent for microbiological culture. In such instances the reaction must be discussed with a Blood Service consultant in case a recall of associated components is required (see also Chapter 21, Transfusion-Transmitted Infections)

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 three reactions: one severe hypotensive reaction in a neonate who was given methylene blue-treated cryoprecipitate immediately post cardiac surgery. She then received SD-FFP without problems. Another neonate, who experienced bleeding whilst undergoing ECMO, also experienced a severe hypotensive reaction shortly after receiving MB-FFP and a unit of platelets. The imputability was given by the reporter as low. A 1 year old child with meningococcal septicaemia had hypotensive reactions to MB-FFP as well as to platelets and SD-FFP. Investigations as to the cause are still continuing. IgA level was normal.

Solvent detergent plasma

In addition to the reaction in the 1 year old patient described above, there was also a moderate allergic reaction in a young woman undergoing plasma exchange for haemolytic uraemic syndrome.

COMMENTARY

Despite removing mild cases from analysis, the pattern of reactions according to components appears similar to previous years.

Reactions to MB-FFP are unusual, and not increased compared to standard FFP[73] but when they do occur, appear to be severe and associated with hypotension.

Historically, hypotensive reactions are stated to be more common in patients on angiotensin converting enzyme (ACE)-inhibitors and in patients with abnormal bradykinin metabolism[74,75].

SHOT data suggest that hypotensive reactions frequently occur during or shortly after cardiac bypass procedures. The factors surrounding these reactions should be examined more closely.

Recommendations

- Transfusions should only be performed where there are facilities to recognise and treat anaphylaxis, according to UK Resuscitation Council (UKRC) guidelines[69,76]. 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 adverse incidents. This is particularly relevant in the light of proposed increase in treatment of patients outside the secondary care setting

Action: Hospital Transfusion Teams (HTT), General Practitioners

- In anaphylaxis, mast cell tryptase testing is not routinely required, but if needed because the clinical diagnosis of anaphylaxis is in doubt, to be of value, serial mast cell tryptase levels are needed: a single result is of little diagnostic value

Action: HTT

- Mild acute transfusion reactions (ATRs) as defined by International Haemovigilance Network/ International Society for Blood Transfusion (IHN/ISBT) (i.e. fever ≥38°C and a rise of 1–2°C from pre-transfusion values, but no other symptoms; or transient flushing, urticaria or rash) should not be reported to SHOT

Action: Reporters, HTT

Recommendations from previous years are available in the Annual SHOT Report 2012 Supplement located on the SHOT website, www.shotuk.org under SHOT Annual Reports and Summaries, Report, Summary and Supplement 2012.