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 IBCT, HTR, TRALI, TACO, TAD or those due to bacterial contamination of the component.

DATA SUMMARY

Total number of cases	**510**

Implicated components	
Red cells	**353**
FFP	**45**
Platelets	**95**
Other (granulocyte)	**1**
Multiple components	**14**
Unknown	**2**

Mortality/morbidity	
Deaths due to transfusion	**1**
Deaths *probably/likely* due to transfusion	**0**
Deaths *possibly* due to transfusion	**2**
Major morbidity	**57**

Gender	
Male	**240**
Female	**254**
Not known	**16**

Age	
≥18 years	**451**
16 years to <18 years	**9**
1 year to <16 years	**35**
>28 days to <1 year	**6**
Birth to ≤28 days	**3**
Not known	**6**
Total	**510**

Emergency vs. routine and core hours vs. out of core hours	
Emergency	**86**
Routine	**390**
Not known	**34**
In core hours	**366**
Out of core hours	**126**
Not known	**18**

Where transfusion took place	
A&E	**2**
Theatre	**19**
ITU/NNU/HDU/recovery	**89**
Wards	**337**
Community	**8**
Outpatient/day unit	**35**
Not known	**20**

Introduction

There has been a further 27% increase in the number of reports of ATRs (increased from 400 reports in 2009 to 510 in 2010). The 510 cases reviewed in this chapter are unlikely to represent all ATRs seen in the UK in 2010. The incidence of febrile reactions to pre-storage leucoreduced red cells has been quoted as 0.19%[1,2] and that of allergic reactions to leucoreduced platelets as 2.2%.[3] Personal communications from several reporting hospitals indicate that many reporters choose to include only the more severe reactions. This would be in keeping with the fall in the number of mild cases reported, both in percentage terms and absolute numbers, while the number of reports has increased.

Many of the reports in this chapter may not in fact have resulted from a transfusion reaction as defined in Table 36. The symptoms and signs of ATRs are not unique and may be related to the patient's underlying condition or to other treatments. Classification therefore tends to be subjective. Nevertheless, it is worthwhile recording the clinical features, management and investigation of all cases in which the presentation led to reporters identifying possible transfusion reactions, in order to promote best practice.

Figure 8
ATR cases 1996–2010

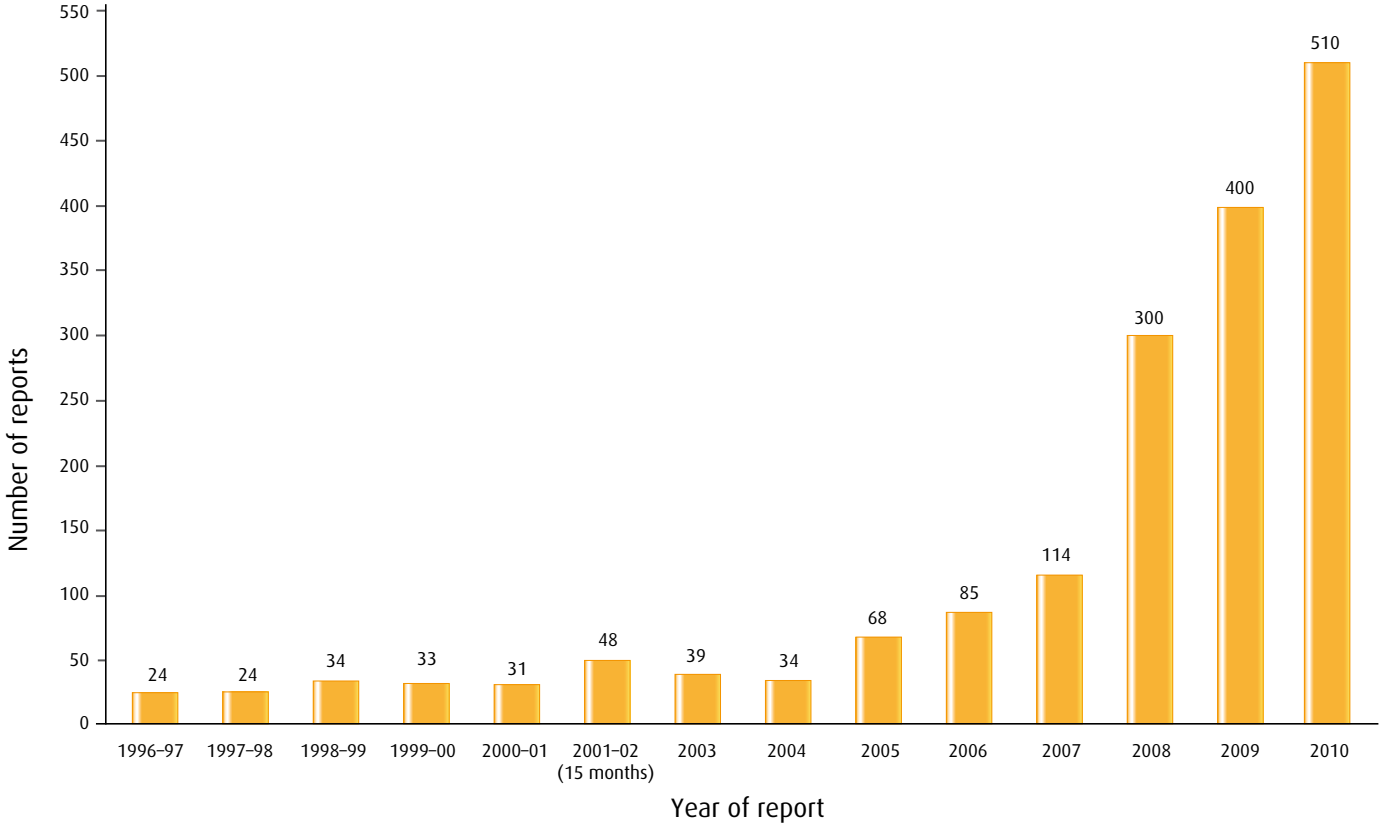

Table 36
Draft BCSH classification of ATRs

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 such as myalgia, hypotension or nausea, which precipitate stopping the transfusion	A rise in temperature of 2°C or more, and/or rigors, chills and other inflammatory symptoms/signs such as myalgia, hypotension or nausea that precipitate stopping the transfusion, prompt medical review AND/OR directly result 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 that 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[4])
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 or diastolic pressure of 30 mm or more[5] in the absence of allergic or anaphylactic symptoms No/minor intervention required	Hypotension leading to shock (e.g. acidaemia, impairment of vital organ function) without allergic or inflammatory symptoms Urgent medical intervention required

The classification of ATRs can be problematic, 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.

In addition to the SHOT classification of ATRs by death or major morbidity, it has been noted that the International Society for Blood Transfusion (ISBT) and the International Haemovigilance Network (IHN) are developing standard definitions for non-infectious ATRs in order to help haemovigilance organisations generate data that will be comparable at an international level. In the meantime, the above definitions have been put forward by the writing group of the forthcoming BCSH guideline on the investigation and management of ATRs. The SHOT annual report has therefore also shown ATRs according to this classification.

Types of reactions

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

- 283 febrile
- 122 allergic
- 34 anaphylactic
- 27 mixed allergic/febrile
- 19 hypotensive
- 25 unclassifiable.

The data in Figure 9 show that reports of febrile reactions are less common with plasma than with red cell or platelet transfusions, and that allergic reactions are much more frequent with plasma-rich components. The incidence by component type is summarised in Table 37.

Figure 9
Reaction by component type *(excluding 6 reactions that could not be attributed to a particular component)*

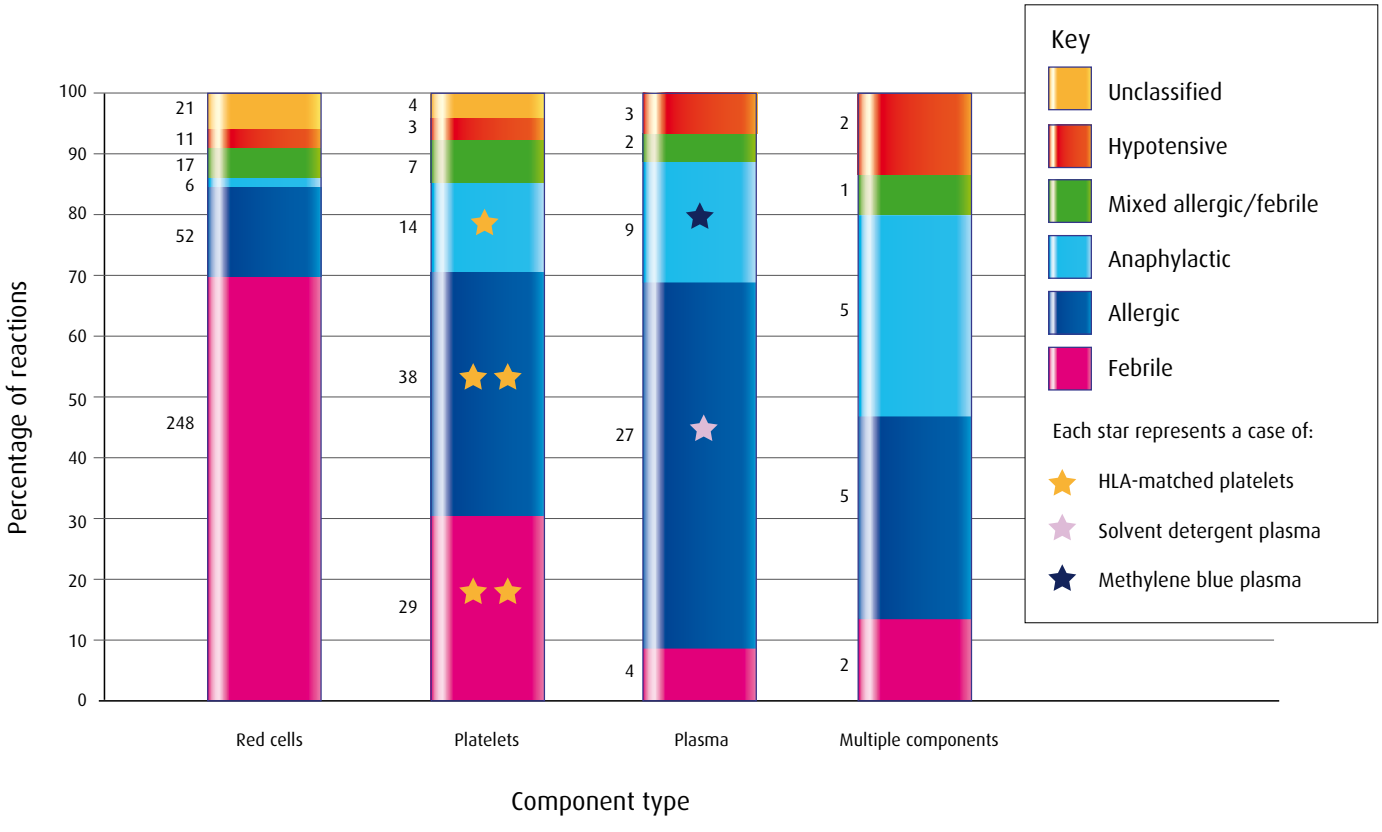

Table 37
Incidence of reactions by component type

Component	Febrile reactions, incidence per 100,000 units	Allergic or anaphylactic reactions, incidence per 100,000 units
Red cells	11.2	2.4
Platelets	10.5	13.8
Plasma	0.9	6.4
SD-FFP	0.0	0.17

Five reactions were reported with HLA-matched platelets, all from England, where 14,174 HLA-matched platelets were issued in 2010, therefore giving an incidence of 35 per 100,000.

Deaths

Although death occurred at around the time of, or shortly after, transfusion in 21 cases, in all but 3 the reporter concluded the reaction was not implicated. The majority of these patients had severe intercurrent illness or were very frail.

Case 1
Death stated to be solely attributed to transfusion reaction (imputability 3)
An elderly patient was found to be unconscious and not breathing 4 hours into the first unit of a red cell transfusion for anaemia of unknown cause. Resuscitation was unsuccessful. A post-mortem mast cell tryptase (MCT), taken several days later, was stated to be markedly raised. Unit cultures were negative. It was concluded that the patient had died of anaphylaxis due to the transfusion.

A review of post-mortem findings in deaths due to anaphylaxis, none of which was related to transfusions, found that 23/56 cases had no signs indicative of allergy.[6] Of the 16 cases that had MCT measured, 14 had raised levels. The review concludes that physical and laboratory findings must be considered along with the clinical history. This case has been included in the anaphylactic section.

Two cases are included on the website (www.shotuk.org) in which the possibility that a transfusion reaction contributed to a patient's death could not be excluded.

Major morbidity *n* = 57

Applying the criterion of 'life-threatening acute reaction requiring immediate medical intervention', there were 57 reports in which a transfusion reaction had symptoms or signs that were sufficiently severe to imply that delay in treatment could be life-threatening. However, in 4 cases of hypotension this may equally have been due to underlying bleeding or sepsis. The remaining 53 cases included 34 anaphylactic and 1 angioedema reaction, 11 allergic reactions with bronchospasm, 6 severe hypotensive reactions (including 2 cases of transfusion associated with the onset of arrhythmias) and 1 supraventricular tachycardia with a fever.

Case 2

Anaphylaxis during FFP

An elderly male patient received the first unit of FFP to correct a coagulopathy. Half-way through the unit, he developed marked hypotension (from 100/60 to 50/20) and a widespread urticarial rash and shortness of breath (SOB). He recovered following treatment for anaphylaxis and subsequently received the second unit of FFP uneventfully.

Cases 3 and 4 illustrate the difficulty in determining whether a reaction is due to transfusion or the patient's underlying condition, which was the conclusion in these two cases.

Case 3

Hypotension due to red cells or bleeding?

A male child undergoing surgery developed a marked tachycardia and hypotension 45 minutes into transfusion of red cells, after 300 mL had been given, but because of ongoing bleeding, transfusion could not be withheld while investigations were undertaken. MCT was normal and bacterial cultures of the unit were negative.

Case 4

Apparent FFP-related anaphylaxis, twice on starting FFP

An adult male patient underwent cardiothoracic surgery and received red cells and 1 unit of FFP without problems. However, 1 minute into the second unit of FFP, his blood pressure (BP) dropped from normal to unrecordable with anaphylaxis. He recovered after adrenaline, hydrocortisone and antihistamine were given. Later, a further unit of FFP resulted in the same reaction after just a few minutes, as witnessed by the same consultant anaesthetist. IgA levels were normal. No other causes of anaphylaxis (e.g. drugs) were identified. A few days later, the patient returned to theatre and, following surgery, a further similar anaphylactic episode occurred, this time without recovery. However, on this occasion, no blood components had been given within the preceding 24 hours, therefore, on review, transfusion was unlikely to have been the cause of the first two episodes of anaphylaxis.

Learning point

- In the acute situation, it can be difficult to determine whether new adverse clinical features are due to an ATR, to other complications of transfusion or to the patient's illness. The over-riding priority is to manage the clinical condition, whether or not the cause is clear.

Severity of reactions

Of the 485 reactions that could be classified, 59 (12.2%) were considered to be severe, 346 (71.3%) moderate and 80 (16.5%) mild. The comparable figures for 374 classifiable reactions in 2009 were 12.1%, 52.6% and 35.3%, respectively. This may represent a change in reporting practice, with fewer mild reactions being reported.

Severe reactions

Although ATRs are rarely associated with death or long-term morbidity, they may present with severe symptoms in the acute situation. Of the 59 severe reactions, 57 were the life-threatening reactions in the section on major morbidity and a further 2 were febrile, causing prompt medical review and prolonged hospital stay: 1 was a fever of 40ºC in a 1-year-old child and 1 was a FNHTR with vomiting in a 79-year-old. Reactions can present in any patient, irrespective of whether they have experienced reactions previously. This highlights the need for patients to be transfused where there are adequate resources for managing acute reactions, particularly anaphylaxis. This also applies to transfusions carried out in community hospitals or at home. Additional vignettes of severe reactions are available on the SHOT website.

Anaphylactic reactions

This year, 34 reactions with features suggestive of anaphylaxis were reported, including a fatality, as described above. Additional vignettes are available on the website.

Six reports were related to red cell transfusions, 9 to plasma, 14 to platelets (including 1 with an HLA-matched platelet) and 4 to multiple transfusions. As in 2009, the mean time to onset was shorter than for other reactions at 26 minutes. The reaction occurred during the transfusion in 15/34 cases. In 22 cases it was thought to have certain or probable imputability (65%) compared to 172/510 of the total number of reactions (34%).

Case 5

Anaphylactic reaction to MB-FFP

A young female patient was transfused with MB-FFP to correct a coagulation abnormality prior to surgery. She developed a rash and angioedema, as well as some lumbar pain and rigors, and required treatment with 2 doses of IM adrenaline, steroids, antihistamine and inotropes. She required overnight admission to the HDU but recovered within 24 hours.

Symptoms and signs

Hypotension was reported in all but 7 cases, and in 15/33 this was recorded as a drop of over 30 mm of systolic or diastolic blood pressure. The 7 cases in which hypotension was not mentioned included 3 in which a rash was associated with malaise of rapid onset and vomiting, 2 which the reporting team stated were anaphylaxis, 1 who sustained a cardiac arrest and the patient in whom death was attributed solely to an anaphylactic transfusion reaction. The most common combination of signs was hypotension and rash (13 cases).

Case 6

Collapse of unknown cause

A female patient in her 60s with leukaemia received a unit of apheresis platelets as a day case, for prophylaxis. Hydrocortisone and chlorpheniramine were given prior to transfusion. She developed a rash, initially on her arm then spreading further. She was given more chlorpheniramine and then lost consciousness. The cardiac arrest team were called. Fluids were given, as well as more hydrocortisone, and the patient recovered. MCT was slightly raised, but no baseline sample was performed. A decision was made to use washed platelets for future transfusions. Intravenous chlorpheniramine can lead to transient hypotension, particularly in older patients.

Management

Despite the severity of most of these reactions, only 2 patients required transfer to ITU and 1 day case required admission. In 1 case the cardiac arrest team was called but the patient recovered within 1 hour. Only 13 patients were treated with adrenaline, the recommended first-line therapy.

Learning point

- It is worth repeating that the UK Resuscitation Council (UKRC) recommends that IM adrenaline is the first-line treatment for anaphylaxis of whatever cause.[4]

Severe febrile reactions

There were 33 severe febrile reactions: 27 of these were related to red cell transfusions, 5 to platelets and 1 to red cells and platelets. Two cases required transfer to ITU, and in 22 day-case patients the reaction led to an overnight stay. The other cases were classified as severe as they required immediate clinical intervention. Two patients died, of unrelated causes. Three patients had sepsis at the time of the reaction, with positive blood cultures likely to be due to underlying infection rather than to TTI.

Case 7

Severe febrile reaction

A young female patient with acute myeloid leukaemia experienced violent shaking, cyanosis, nausea, tachycardia and a slight rise in temperature during a transfusion of apheresis platelets, which were being given prophylactically as her platelet count was <10. She had experienced a similar, milder reaction 3 days previously. She was managed with paracetamol. Patient and unit cultures were not performed.

Hypotensive reactions

There were 18 reactions involving severe falls in blood pressure, and in 14 of these cases the reporting team stated that hypotension was the predominant clinical feature. It is worth noting that 7/18 of these reactions occurred in the operating theatre (39%) as compared to 19 of the 510 total acute reactions reported (4%). Of the reactions outside theatre, 3 were described in patients having major bleeds and 2 were in postoperative patients.

Risk factors for hypotensive reactions include exposure of the blood to negatively charged filters, prostatic surgery, cardiac procedures involving bypass, use of angiotensin converting enzyme (ACE) inhibitors and patient factors such as a defect in kinin metabolism.[7] However, in several of the current reports, given the clinical setting, the possibility that haemorrhage contributed to the hypotension could not be excluded.

Moderate/mild reactions

The remaining moderate and mild reactions included many febrile non-haemolytic transfusion reactions (FNHTRs) or fevers only; however, a number of these required precautionary admission, e.g. in immunosuppressed haematology patients (11) or elderly patients living alone (3). A further 3 patients with an allergic rash alone required admission following transfusion in community hospital or hospice settings. Although not severe in terms of symptoms and signs, such reactions can have implications for management in susceptible patients.

Reactions that were not possible to classify further

There are 25 cases included in this chapter in which the HTTs, using the information present at the time, decided that a diagnosis of ATR 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 8

Imputability unknown

An elderly female patient was admitted with probable pneumonia and severe iron deficiency. She was transfused 3 units of red cells. During the third unit, she became more dyspnoeic, with oxygen saturation of 88%, and her BP dropped to 86/44 mm. Imputability was given as unlikely, and the possibility of symptoms being related to the underlying condition, or to TACO, cannot be ruled out.

Investigations

The value of investigations in ATR was discussed in the 2008 SHOT annual report. In 2010:

- 27 cases had HLA antibodies performed, with antibodies demonstrated in 7 cases – none of these results was recorded as leading to the use of HLA-matched components
- 20 cases had HPA antibodies performed and in 1 case antibodies were found but did not influence future component choice.

It is worth reiterating that HLA, HPA or human neutrophil antigen (HNA) investigations of the patient should only be performed after discussion with a Blood Service consultant. The primary indication for HLA testing should be platelet refractoriness, with or without evidence of a transfusion reaction.[8]

- IgA levels were measured in 62 patients and low levels were detected in 2 cases: 1 with an allergic reaction and 1 with a febrile reaction. In neither of these cases did the result appear to influence the choice of future components.

The significance of IgA levels does not appear to be as great as has been previously stressed, especially as the incidence of IgA deficiency is said to be approximately 1 in 700 of the UK population and therefore present in many transfusion recipients who do not experience reactions.[9] Nevertheless, as it has been considered to play an important role in the aetiology of anaphylaxis in the past, it is recommended that levels should be checked in cases of severe allergic or anaphylactic transfusion reactions as IgA deficiency may be part of the spectrum of common variable immunodeficiency.

Table 38
Summary of investigations for suspected ATRs

Mild febrile reaction (isolated pyrexia, otherwise no change in symptoms/signs) or mild allergic reaction (rash/itch)	No tests required
Features of anaphylaxis/angioedema, other severe allergy	■ Test for IgA deficiency; if present test for anti-IgA antibodies ■ Consider causes other than blood components ■ Serial MCT tests may subsequently confirm diagnosis
Fever with any of: increased heart rate (HR), decreased blood pressure, increased respiratory rate (RR)	If not clearly severe allergic/anaphylactic reaction, consider: ■ checking for 'wrong blood'; if indicated, perform G&S, DAT (G&S and DAT investigations should not be done universally in all ATRs, but are indicated as above or in the presence of haemoglobinuria, loin pain or venous pain at the cannula site) If symptoms are severe, consider: ■ bacterial contamination of blood component; blood cultures from patient; notify Blood Service (for consideration of other components from donor) and culture unit(s)
Shortness of breath	■ If not associated with anaphylaxis, consider TAD, TACO, TRALI and causes unrelated to blood components ■ Pulse oximetry/blood gases ■ CXR

COMMENTARY

The number of ATRs reported has increased further this year, mainly because of the increased numbers of febrile or allergic reactions reported. The number of anaphylactic reactions has stayed fairly constant over the last 3 years. Mild reactions have reduced, both in percentage terms and absolute numbers.

Several cases initially reported as ATRs have been transferred into the TAD section. Differentiation between ATR and TAD is difficult and it would be helpful, where possible, to know which clinical feature predominated in the reaction, as respiratory symptoms may point to TAD.

This year, hypotensive reactions appear to have increased. Many reports are of patients undergoing major surgery or who are bleeding. This highlights the inherent difficulties in making a diagnosis of a transfusion reaction. Risk factors said to contribute to hypotensive reactions include exposure of blood to negatively charged surfaces such as bedside filters, ACE-inhibition[10] and genetic predisposition. However, careful assessment of a presumed hypotensive reaction is required, for example in patients who are bleeding in whom the hypotension may be caused by haemorrhage, in which case continuation of the transfusion may be life saving.

Recommendation

- Transfusions should only be performed where there are facilities to recognise and treat anaphylaxis, according to UK Resuscitation Council (UKRC) guidelines. In supplying to community hospitals or for home transfusions, providers must ensure that staff caring for patients have the competency and facilites to deal with this adverse reaction.[4]

  Action: HTCs

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