16 Febrile, Allergic and Hypotensive Reactions (FAHR) n=238

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Definition:

The reactions assessed are isolated febrile type (not associated with other specific reaction categories), allergic and hypotensive reactions occurring up to 24 hours following a transfusion of blood or components, for which no other obvious cause is evident.

Introduction

These reactions are classified according to the International Society for Blood Transfusion/International Haemovigilance Network (ISBT/IHN) definitions, which are summarised below in Table 16.2, available online (ISBT/IHN 2011) and have been adopted by the British Society for Haematology (BSH) (BSH Tinegate et al. 2012).

Key SHOT messages

- It is fundamental for all staff involved in transfusion practice to understand the basic mechanism of reactions so that immediate treatment and future management is rational rather than traditional
- Reporters will be informed if SHOT experts change the reaction classification submitted. Such a process will allow challenge, learning and a more skilled work force within hospitals to improve both the understanding and management of patients experiencing reactions
- For febrile reactions alone, give paracetamol. For allergic reactions give an antihistamine as first line; give adrenaline if anaphylaxis is suspected. The effect of steroids is delayed by several hours, will have no immediate effect, and should only be used to prevent a late recurrence. The use of steroids may further immunosuppress already immunocompromised patients and increase the risk of side effects such as infection

Key recommendations from previous years

- Pooled platelets suspended in platelet additive solution (PAS) are associated with a reduction in allergic response (BSH Estcourt et al. 2017). Hospitals should consider preferential use of readily available pooled platelets suspended in PAS in patients with a history of allergic reactions. This should include paediatric patients where apheresis platelets are usually the platelet component of choice. If reactions continue, despite antihistamine cover, then platelets re-suspended in 100% PAS can be supplied
- Give appropriate targeted treatment and if needed, preventative cover for future transfusion (BSH Tinegate et al. 2012), as indicated in Table 16.1:

Reaction	Treatment	Prevention of recurrent reactions
Febrile	Paracetamol	Paracetamol 60 minutes before anticipated time of reaction
Allergic	Antihistamine (steroid should not be used routinely) If anaphylaxis, adrenaline is essential	If previous reaction with apheresis platelets try pooled platelets in PAS If reactions continue, give pre-transfusion antihistamine If reactions continue, consider washed platelets/red cells; for fresh frozen plasma (FFP) try a pooled component e.g. solvent-detergent treated plasma

- Outpatient departments and day care units, including those in the community, should ensure patients have information about what to do if they experience a reaction after leaving the unit
- The treatment of reactions and management of subsequent transfusions should be directed by recognised guidelines e.g. BSH guidelines on the investigation and management of acute transfusion reactions (BSH Tinegate et al. 2012)

Action: Hospital Transfusion Teams (HTT)

- 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 are featured. The International Society for Blood Transfusion/International Haemovigilance Network (ISBT/IHN) classification should be used to grade severity (Table 16.2)
- SHOT has a role in identifying trends in reactions and events, including the monitoring of new components. It is therefore important to identify the implicated component e.g. standard/washed red cells; pooled/apheresis and or washed or human leucocyte antigen (HLA)-matched platelets; standard/virally inactivated (including type) plasma

Action: SHOT reporters

- 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 (NHSBT 2015/16). The main indication, other than platelet refractoriness, is persistence of severe reactions despite the use of platelets where the plasma has been removed and replaced by suspension medium

Action: HTT, Histocompatibility and Immunogenetics laboratories

- Transfusions should only be performed where there are facilities to recognise and treat anaphylaxis, according to United Kingdom Resuscitation Council (UKRC) guidelines (Resuscitation Council 2008). 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). When supplying to community hospitals or for home transfusions, providers must ensure that staff caring for patients have the competency and facilities to deal with reactions. This is particularly relevant in the light of proposals to increase patient treatment outside of secondary care

Action: HTT, Royal College of General Practitioners

Table 16.2: Classification of reactions

	1 = Mild	2 = Moderate	3 = Severe
Febrile-type reaction	A temperature ≥38°C and a rise between 1 and 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 mmHg or more occurring during or within one hour of completing transfusion **and** a systolic blood pressure 80 mmHg 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

Number of reactions and reaction rates n=238

In addition to the 235 reactions that comply with the definition of febrile, allergic and isolated hypotensive reactions, this section also includes 3 cases associated with IgA deficiency because of the previous association of this condition with allergy.

Total number of FAHR reactions n=235

Reactions have been classified as in Table 16.3. Severe reactions, as described in Table 16.2, are used to define major morbidity.

Table 16.3: Classification of FAHR in 2018

	Moderate	Severe	Total
Febrile	85	18	103
Allergic	62	35	97
Mixed allergic/febrile	27	7	34
Hypotensive	1	0	1
Total	**175**	**60**	**235**

NB: in 22 of the 60 reactions classified as severe this was primarily because the patient was admitted overnight

The percentage of severe reactions remains similar to previous years at 25.5%. Many, largely febrile-type, reactions continue to be difficult to classify because of insufficient information, the ISBT/IHN grade of reaction not being used and because of the difficulty, distinguishing true transfusion reactions from symptoms and signs associated with the patient's underlying condition.

Table 16.4 identifies the total number of cases submitted for review into the category of FAHR over the last five years. In total, fewer cases were reported compared to previous years. The number of cases withdrawn, as not consistent with the ISBT/IHN definition of moderate or severe febrile, allergic or hypotensive reactions, was larger. Of these, 25/125 cases were referred for consideration of inclusion into alternative categories of reaction.

Cases reported	2014	2015	2016	2017	2018
Total reported	434	407	357	390	360
Included	312	296	253	284	235
Excluded (withdrawn or unclassifiable)	122	111	104	106	125
% Excluded	**28.1%**	**27.3%**	**29.1%**	**27.2%**	**34.7%**

Table 16.4: Total FAHR cases reviewed over a five-year period

Hyperacute reactions n=3

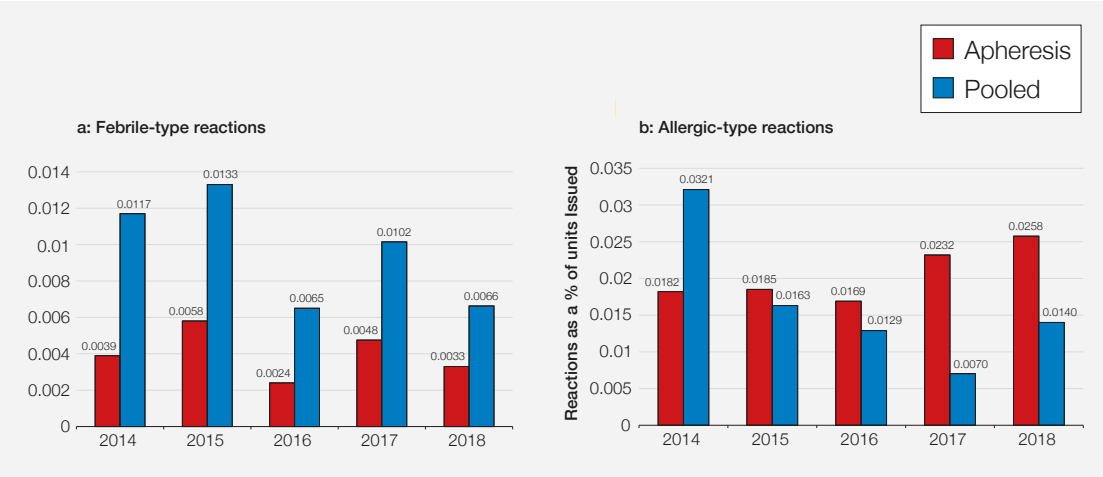
There were 3 reported cases of hyperacute transfusion reactions associated with IgA deficiency; two of which were observed in the same patient. One patient had confirmed IgA antibodies; the remaining patient had not yet been tested. For all 3 cases, the reaction occurred after transfusion of a small volume of packed red cells (between 17 and 40mL).

The transfusion reactions observed were characterised by the hyperacute onset of symptoms including tachycardia, shortness of breath without wheeze, severe anxiety, rigors and pain. Chest, loin, back and abdominal pain were all reported.

As the characteristics of these acute transfusion reactions related to IgA deficiency did not conform to those of allergy/anaphylaxis, work is underway to determine the most appropriate SHOT reporting category for such cases.

Type of reactions by component

The incidence of allergic reactions linked to pooled platelets (suspended in PAS) continues to be lower than the incidence of allergic reactions linked to apheresis platelets and, as previously reported, this is likely associated with the reduction in plasma content. The incidence of febrile reactions continues to be higher with pooled platelets compared to apheresis. Overall, there were fewer reactions reported with pooled platelets than apheresis platelets (0.02% and 0.03% respectively) as the incidence of febrile reactions to platelets is lower than allergic reactions. Reactions to platelets are at least in part caused by release of substances from the platelets themselves and therefore cannot be completely eliminated (Garraud et al. 2016, Maurer-Spurej et al. 2016). (Figures 16.1a and b).

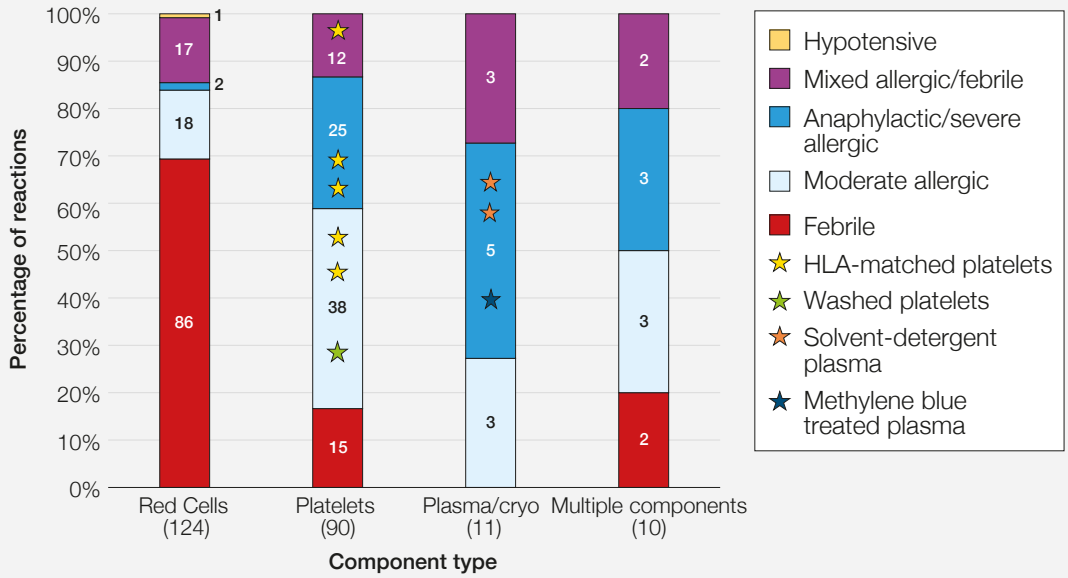


Figures 16.1: Percentage of reactions to apheresis and pooled platelets 2014 to 2018

Reactions by all component types remain similar to previous Annual SHOT Reports; see Figure 16.2. Red cells are usually associated with febrile-type reactions (~70%) whereas plasma and platelets more commonly cause allergic reactions (~70%). There were 2 reactions associated with solvent-detergent (SD)-FFP and 1 reaction was associated with methylene blue-treatment. It is notable that despite an almost certain increase in the use of virally inactivated components the number of reactions remains very low.

This year reporters were asked to state the number of days shelf life remaining at the time of the reaction if only one component was implicated. There were more pure allergic and pure febrile reactions associated with red cells but no obvious link with the age of the unit. Apheresis and pooled platelets were more likely to be associated with these reactions if there was only 2 days shelf life remaining or less, compared to fresher units, 29/38 (76.3%) and 9/14 (64.3%) respectively. However, as the number of platelet units transfused during these time periods is unknown this could simply reflect that the majority of units are used towards the end of their shelf life.

Figure 16.2: Reactions by component type



HLA=human leucocyte antigen; cryo=cryoprecipitate

NB: There were no reported febrile, allergic or hypotensive reactions associated with granulocyte transfusion

Analysis of reactions remains comparable to previous years in the following characteristics.

Table 16.5: Characteristics of FAHR

Characteristic	Occurrence
Age distribution	86% of patients were aged 18 years or over
Gender	54% male and 46% female cases
Urgency of transfusion	73% were given routinely
Timing of transfusion	43% occurred within standard hours
Location	66% were on wards and 16% in outpatient/day case units

Treatment of reactions

An antihistamine with or without steroid continues to be used inappropriately to treat reactions with only febrile/inflammatory type symptoms and/or signs; see Table 16.6. In addition to no evidence of benefit, the use of steroids may further immunosuppress already immunocompromised patients and increase the risk of side effects such as infection.

Subsequent management; an antihistamine with or without steroids to treat a subsequent pure febrile reaction remains a problem (Table 16.7). On a more positive note in 6 cases pooled platelets continued to be recommended instead of apheresis, in 3 cases discussion with a consultant haematologist/ paediatrician was advised prior to further transfusion of plasma/platelets, in 2 cases alternative treatment to blood components was suggested and in one case a single unit transfusion was advised.

	Number	Medication stated	Antihistamine +/- steroid
Febrile			
2018	103	88/103 (85.4%)	39/88 (44.3%)
2017	140	121/140 (86.4%)	46/121 (38.0%)
2016	124	102/124 (82.3%)	51/102 (50.0%)
2015	142	101/142 (71.1%)	57/101 (56.4%)
2014	144	97/144 (67.4%)	42/97 (43.3%)

Table 16.6: Treatment of reported reaction

	Number where treatment stated	Antihistamine +/- steroid stated
2018	27	8/27 (29.6%)
2017	22	5/22 (22.7%)
2016	21	9/21 (42.9%)
2015	9	7/9 (77.8%)
2014	24	9/24 (37.5%)

Table 16.7: Planned treatment of subsequent febrile reactions

Illustrative cases

Case 16.1: Febrile reaction inappropriately treated with an antihistamine and steroid

A day case patient in their 60s with myelodysplasia, haemolysis and neutropenia developed a temperature rise to 39.7°C, rigors and nausea during a red cell transfusion. They were treated with hydrocortisone, chlorphenamine, paracetamol, antibiotics and admitted on to a ward. Future transfusion management was stated to be pre-medication with an antihistamine and steroid. Although it is not clear if steroid treatment may be beneficial for the management of their haemolysis it is unlikely to prevent a further febrile-type reaction and may make infection more likely in a vulnerable, neutropenic patient.

Case 16.2: Reducing the number of units given at each transfusion episode as a reaction prevention strategy

A patient in their 60s with chronic transfusion dependent anaemia received a red cell transfusion as an inpatient. During the transfusion, they developed a temperature of 38°C associated with chills and rigors. The rate of the transfusion was reduced and they were given paracetamol, however their symptoms reoccurred therefore the transfusion was discontinued. Future management was to limit transfusion episodes to a single unit of red cells and was reported to be effective.

Case 16.3: Use of iron to avoid the need for red cell transfusion

A patient in their 80s was admitted to the ambulatory care unit for a two-unit red cell transfusion for symptomatic iron deficient anaemia. Chlorphenamine and ondansetron were given pre transfusion. On completion of the first unit the patient developed a temperature rise of more than 2°C, rigors, nausea and was treated with paracetamol. They were discharged later the same day and intravenous iron agreed as future management. It is unclear what the expected benefit was of pre-transfusion chlorphenamine, however treatment with paracetamol and future management with intravenous iron are rational. If intravenous iron is given prior to the development of symptoms this is likely to prevent the need for further urgent admission and red cell transfusion.

References

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