16 Febrile, Allergic and Hypotensive Reactions (FAHR) n=288

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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.

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 are informed if SHOT experts change the reaction classification submitted. Such a process allows 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, steroids will have no immediate effect. Give an antihistamine as first line; give adrenaline if anaphylaxis is suspected

Abbreviations used in this chapter

BSH	British Society for Haematology
FAHR	Febrile, allergic and hypotensive reactions
FFP	Fresh frozen plasma
HLA	Human leucocyte antigen
HTR	Haemolytic transfusion reaction
HTT	Hospital transfusion teams
IHN	International Haemovigilance Network
ISBT	International Society for Blood Transfusion
IV	Intravenous
PAS	Platelet additive solution
SABRE	Serious adverse blood reactions and events
SD	Solvent detergent
TACO	Transfusion-associated circulatory overload
TAD	Transfusion-associated dyspnoea
TTI	Transfusion-transmitted infection

Summary of 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. If reactions continue, despite antihistamine cover, then platelets re-suspended in 100% PAS can be supplied

Action: Hospital transfusion teams (HTT)

- Give appropriate targeted treatment and if needed, preventative cover for future transfusion (BSH Tinegate et al. 2012), as indicated below:

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 (SD) treated plasma

Table 16.1: Targeted treatment for febrile and allergic transfusion reactions

Action: HTT

Previous recommendations for all years can be found on the SHOT website: https://www.shotuk.org/shot-reports/previous-recommendations/.

Introduction

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).

	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

Table 16.2: Classification of reactions

Death n=0

Major morbidity n=72

The ISBT/IHN classification of a severe reaction has been used to define major morbidity.

Reactions are categorised in Table 16.3. This included no hyperacute cases associated with confirmed IgA deficiency.

Table 16.3: Classification of FAHR in 2019

	Moderate	Severe	Total
Febrile	127	19	146
Allergic	58	41	99
Mixed allergic/febrile	29	11	40
Hypotensive	2	1	3
Total	**216**	**72**	**288**

NB: in 24 of the 72 reactions classified as severe this was primarily because the patient was admitted/kept in overnight

The percentage of severe reactions remains similar to previous years at 72/288, 25.0%. 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 in distinguishing true transfusion reactions from symptoms and signs associated with the patient's underlying condition. In 112/288 (38.9%) cases, the type of reaction initially reported was reclassified according to the information provided (Table 16.4). Any changes were communicated back to the reporters.

Table 16.4: Reclassification of FAHR in 2019

		Confirmed FAHR category			
		Anaphylaxis/allergic	Febrile	Mixed febrile/allergic	Hypotensive
Reported category on SABRE	Anaphylaxis/allergic	87	30	28	-
	Febrile	3	78	1	-
	Mixed febrile/allergic	4	12	8	-
	Hypotensive	1	4	-	3
	Other/FAHR	3	6	2	-
	Other	1	11	1	-
	Other/TACO	-	1	-	-
	Other/TAD	-	1	-	-
	Other/HTR	-	2	-	-
	TTI	-	1	-	-
	Total	**99**	**146**	**40**	**3**

SABRE=serious adverse blood reactions and events online reporting system

TACO=transfusion-associated circulatory overload; TAD=transfusion-associated dyspnoea; HTR=haemolytic transfusion reaction; TTI=transfusion-transmitted infection

Correct category	**176**	**61.1%**
Changed category	**112**	**38.9%**

Hyperacute reactions n=0

Two cases of confirmed IgA deficiency (<0.0005g/L) were reported in 2019. One case had confirmed anti-IgA antibodies. Neither case demonstrated the typical hyperacute transfusion reaction which we have previously associated with this diagnosis.

Type of reactions by component

This remains similar to previous reports; see Figure 16.1. Red cells are usually associated with febrile-type reactions 121/152 (79.6%) whereas plasma and platelets more commonly cause allergic reactions

(18/24, 75.0% and 54/97, 55.7%). There were 6 reactions associated with SD-FFP. It is notable that despite an almost certain increase in the use of virally inactivated components the number of reactions remains low.

The number of days' shelf life remaining at the time of the reaction if only one component was transfused were analysed. Analysis was limited to red cell and platelet units as plasma is usually stored frozen. Reactions were associated with older units with 71/93 (76.3%) of red cells having less than 20 days shelf life and 43/65 (66.2%) of platelets having less than 3 days shelf life. There was no significant difference if allergic reactions and febrile reactions were considered separately. It is accepted that until data on the age of blood at the time of use is available this may simply reflect that the majority of units are given towards the end of shelf life.

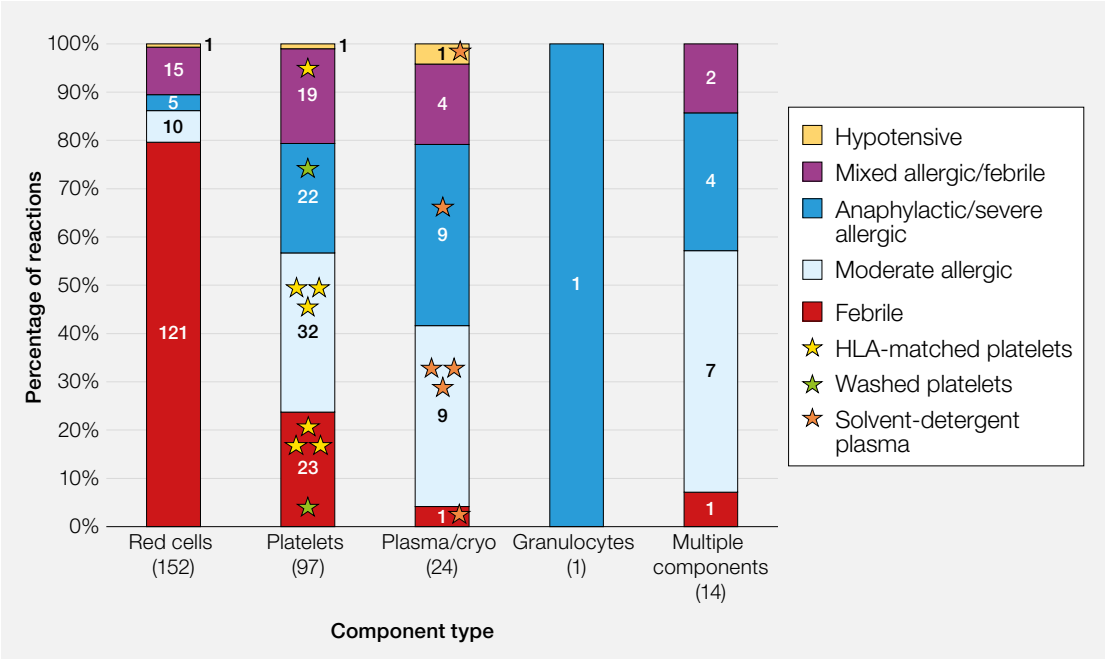
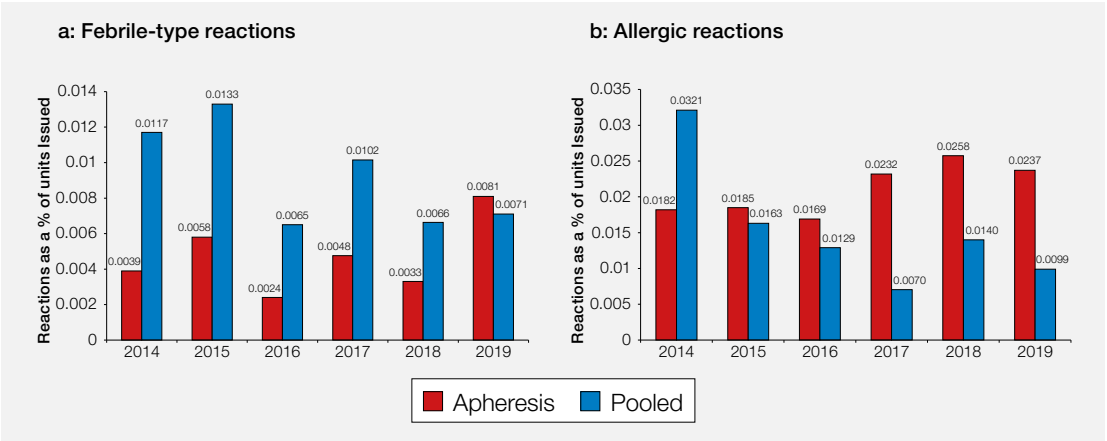


Figure 16.1: Reactions by component type

HLA=human leucocyte antigen; cryo=cryoprecipitate

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. This year there was little difference in the incidence of febrile reactions with pooled platelets compared to apheresis. Overall, there were fewer reactions reported with pooled platelets than apheresis platelets (0.02% and 0.03% respectively) and the incidence remains consistent. 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 16.2a and 16.2b).



Figures 16.2: Percentage of reactions to apheresis and pooled platelets 2014 to 2019

Analysis of reactions remains comparable to previous years in the following characteristics (Table 16.5).

Table 16.5: Characteristics of FAHR

Age distribution	84% of patients were aged 18 years or over
Gender	50% male and 50% female cases
Urgency of transfusion	*64% were given routinely
Timing of transfusion	*39% occurred within standard hours
Location	63% were on wards and 16% in outpatient/day case units

**Lower % of transfusions than in previous years likely associated with more cases reported as unknown*

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

The use of antihistamine with or without steroids to treat a subsequent pure febrile reaction may be reducing, although the single largest management category included treatment not stated or premedication. In some, avoidance of transfusion was advised and included use of a lower haemoglobin threshold, intravenous (IV) iron, and the discontinuation of prophylactic platelet transfusion (Table 16.7).

Table 16.6: Treatment of febrile reported reaction

Year	Number	Medication stated	Antihistamine and/or steroid
2019	146	130/146 (89.0%)	62/130 (47.7%)
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 16.7: Planned treatment of subsequent febrile reactions

Year	Number where treatment stated	Antihistamine +/- steroid stated
2019	42	7/42 (16.7%)
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%)

Illustrative cases

Three cases were selected where transfusion may have been avoided.

Case 16.1: Febrile reaction occurring with platelets given for an erroneous result

A patient in her 80s was admitted for symptoms relating to a pulmonary embolism. She was prescribed two units of platelets for a low platelet count (reported as 29x10^9/L). During the second unit she developed rigors, a fever of 39.2°C and an elevated heart and respiratory rate. The laboratory had noted platelet clumping and had revised the report on the system however the medical team had already acted on this initial result.

Caution should be taken when acting on unexpected blood results.

Case 16.2: Severe allergic reaction when given platelets to reverse aspirin

A patient in his 70s was transfused two doses of platelets in theatre. He was undergoing surgery for an acute subdural haematoma and platelets were given as he was on aspirin. Fifteen minutes after his second dose, the patient developed a rapid rash covering his body and hypotension unresponsive to vasopressors. The patient was treated for anaphylaxis and rapid stability was achieved.

Evidence for use of platelets to reverse aspirin effects is lacking.

Case 16.3: Avoid unnecessary transfusion

A female in her 60s was found to have a haemoglobin of 48g/L when routine blood tests were carried out at her general practice surgery. She experienced severe rigors, back pain, breathlessness and felt very cold 15 minutes after being transfused a unit of red cells for symptomatic anaemia. Paracetamol alone was used to treat this reaction. Future management will be with IV iron.

Although this demonstrates appropriate management of a febrile transfusion reaction, iron deficiency anaemia should be treated with iron in the absence of haemodynamic instability (Royal College of Pathologists 2020). All patients presenting with iron deficiency anaemia should be investigated for an underlying cause.

Conclusion

Over a third of cases reported in this chapter were re-classified according to the information provided. Nearly half of pure febrile reactions were given an antihistamine and/or a steroid inappropriately.

It is important to reiterate that there is a need to differentiate the signs and symptoms of separate reaction types, a pure allergic reaction is not associated with fever and finally treatment with an antihistamine and/or steroid should be limited to reactions with allergic features. It is recognised that in a sick patient with acute symptoms identifying different reaction types is difficult. It is encouraging to note that when future medication was stated for reactions classified as purely febrile only 16.7% stated the inappropriate use of a steroid and/or antihistamine, compared to 77.8% in 2015.

The incidence of allergic reactions to apheresis platelets compared to pooled platelets (suspended in PAS) remains higher. Although the incidence is unlikely to change, it will be interesting to note any changes in reaction reporting in 2020 following publication of the Department of Health and Social Care document 'Risk assessment of the transmission of vCJD by blood components' which states that apheresis platelets are no longer preferentially recommended for patients born after 1995.

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