16 Febrile, Allergic and Hypotensive Reactions (FAHR) n=294

Authors: Catherine Booth and Jayne Peters

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.

Abbreviations used in this chapter

BSH	British Society for Haematology	**IHN**	International Haemovigilance Network
FAHR	Febrile, allergic and hypotensive reactions	**ISBT**	International Society for Blood Transfusion
FFP	Fresh frozen plasma	**PAS**	Platelet additive solution

Key SHOT message

- Inappropriate use of steroids and antihistamines continue to be seen with staff not using the patient's symptoms and signs to differentiate allergic from febrile reactions. These reactions are distinct and require different investigations and treatment

Recommendations

The recommendations from previous years continue to be relevant and are included here again:

- Give appropriate targeted treatment and if needed, preventative cover for future transfusion (Soutar et al. 2023), as indicated below:

Table 16.1: Targeted treatment for febrile and allergic transfusion reaction

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 (suspended in PAS) If reactions continue, give pre-transfusion antihistamine; If reactions continue, consider washed platelets/red cells; for FFP try a pooled component e.g., solvent-detergent treated plasma

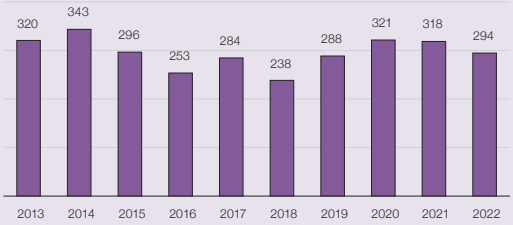
- Transfusion teams should audit appropriateness of treatment given for acute transfusion reactions
- Transfusion reaction reporting forms should be designed to help reporters classify the type of reaction, to guide appropriate investigation
- The possibility of a febrile or allergic reaction should be explained to patients/guardians when taking consent for transfusion with provision of relevant patient information leaflets

Action: Hospital transfusion teams

Headline data 2022

Number of reports n=294
Deaths n=1
Major morbidity n=77

FAHR reports by year



Demographic data

Male n=151
Female n=142
Unknown n=1

Adults n=257
Paediatric n=35
Unknown n=2

Blood component data

Red cells n=140
Platelets n=114
Plasma n=22
Cryoprecipitate n=8
Multiple components n=10

Introduction

Reactions are classified according to the ISBT/IHN definitions, which are summarised below in Table 16.2, available online (ISBT/IHN 2011) and have been adopted by the BSH (Soutar et al. 2023). Mild reactions are not reportable to SHOT.

Table 16.2: Classification of reactions

CURRENT IHN/SHOT/B(C)SH CLASSIFICATION OF ACUTE TRANSFUSION REACTIONS				SABRE classification
	1=Mild	**2=Moderate**	**3=Severe**	
Febrile type reaction	A temperature > 38°C and a rise between 1°C 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	**Other/febrile FAHR**
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)	**Anaphylaxis/ hypersensitivity/ allergic/FAHR**
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.	***Other/mixed febrile/allergic FAHR**
Hypotensive reaction		Isolated fall in systolic blood pressure of 30 mm Hg or more occurring during or within one hour of completing transfusion **and** a systolic blood pressure 80 mm or less in the absence of allergic or anaphylactic systems. 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	**Other/ hypotensive FAHR**

**This category may include mild symptoms/signs of one reaction type providing the other category is either moderate or severe*

As the reporting categories on SABRE can cause confusion, since 2022, the SHOT definitions document has been updated to clearly map which category to select when submitting a report.

Total number of FAHR reactions n=294

After 2 years with increasing number of reports of febrile reactions, the number reported in 2022 is similar to 2019 and previous years.

In 11 cases, the reporter deemed that transfusion was not clinically indicated according to the relevant BSH guidelines. In a further 28 cases this was 'unknown' and in another 7 cases, not stated. Febrile, allergic or hypotensive reactions are unpredictable and largely unpreventable, illustrating the importance of giving transfusion only when there is no suitable alternative.

Deaths related to transfusion n=1

There was 1 death possibly related to transfusion (imputability 1). A patient in his late 50s with relapsed leukaemia suffered an allergic reaction during a platelet transfusion, followed by airway obstruction requiring intubation and then cardiac arrest. Prior to the transfusion the patient was gravely unwell, being managed in the intensive care unit and had recently received emergency chemotherapy. Various factors may have contributed to the acute deterioration and outcome in this patient.

Major morbidity n=77

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

Reactions are categorised in Table 16.3.

Table 16.3: Classification of FAHR in 2022

	Moderate	Severe	Death	Total
Febrile	118	14	0	132
Allergic	62	54	1	117
Mixed allergic/febrile	25	7	0	32
Hypotensive	11	2	0	13
Total	**216**	**77**	**1**	**294**

NB: in 15 of the 77 reactions classified as severe this was primarily because the patient was admitted/kept in overnight/re-presented to hospital after discharge

Reactions in IgA deficient patients n=5

There were 5 reactions reported in patients who were subsequently discovered to have severe IgA deficiency (IgA levels <0.07g/L). Three were confirmed to have anti-IgA antibodies; in the other 2 the result was not stated. Three occurred within the first 15 minutes of transfusion and the remaining 2 within 30 minutes. Four were febrile reactions involving marked systemic upset, with other features including hypo- or hypertension, myalgia and vomiting. One presented with significant hypotension alone. None of the reactions had allergic features.

It is recommended that these patients receive washed components for future red cell or platelet transfusions, provided this does not risk delaying an urgent transfusion (NHSBT 2019).

Anaphylactic reactions n=36

Thirty-six severe allergic reactions were reported which required the use of adrenaline. Seventeen were routine transfusions, 17 occurred on general wards and 2 in an outpatient or day care setting. Children were disproportionately represented: 9/36 (25.0%) cases were in patients under 18 years.

One reaction followed a prophylactic transfusion of platelets prior to a bone marrow biopsy (contrary to guidelines) (BSH Estcourt et al. 2017) and 1 followed transfusion of cryoprecipitate postoperatively to a non-bleeding patient with marginally low fibrinogen. A patient given a red cell transfusion for iron deficiency anaemia suffered a cardiac arrest due to probable anaphylaxis, resulting in hypoxic brain injury.

All clinical areas administering blood components need to be equipped and staff trained to manage a severe acute reaction and transfusion decisions must be made after taking into account risks and benefits to patients. Where transfusions are concerned, less is often more.

Type of reaction by component

This remains similar to previous Annual SHOT Reports; see Figure 16.1. Red cells are usually associated with febrile-type reactions, 96/140 (68.6%) whereas plasma components and platelets more commonly cause allergic reactions, 26/30 (86.7%) and 62/114 (54.4%) respectively.

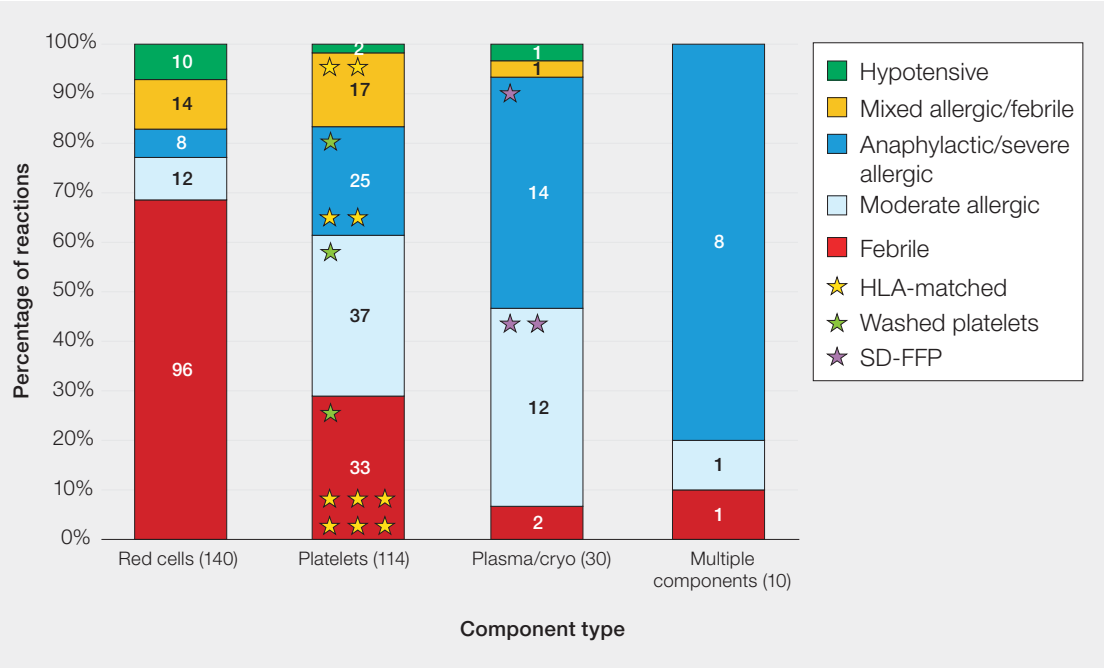


Figure 16.1: Reactions by component type

HLA=human leucocyte antigen; cryo=cryoprecipitate; SD-FFP=solvent detergent treated fresh frozen plasma

The overall incidence of reactions of all types combined is greater for apheresis (46/137,932=0.033%) than for pooled (33/147,904=0.026%) platelet components. Fewer allergic reactions were reported with pooled platelets in PAS than apheresis platelets, which is linked to the lower plasma content (Figure 16.2) (BSH Estcourt et al. 2017).

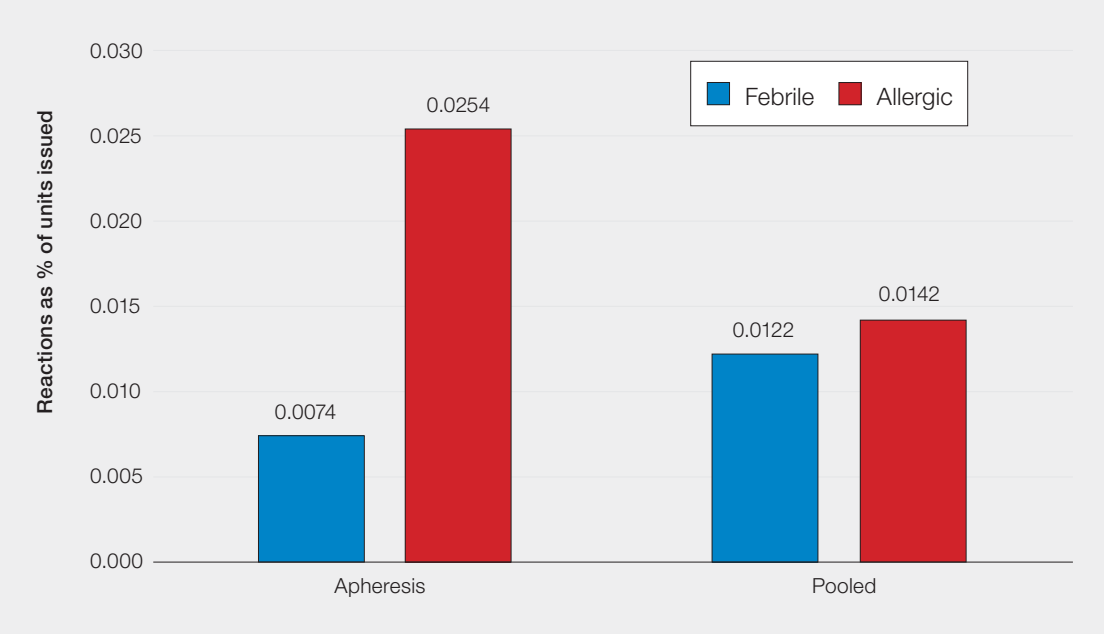


Figure 16.2: Incidence of reactions as a percentage of platelet units issued

Analysis of reactions remains comparable to previous years in the following characteristics (Table 16.4).

Table 16.4: Characteristics of FAHR

Recipient or transfusion characteristic	Percentage
Age distribution	88% of patients were aged 18 years or over
Sex	52% were male
Urgency of transfusion	62% were given routinely
Timing of transfusion	72% occurred within standard hours
Location	61% were on wards and 14% in outpatient/day case units

Over the last 3 years, a higher proportion of reactions have been reported occurring during standard working hours. This might reflect a move away from transfusing outside standard hours except in emergencies, in line with recommendations.

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 16.5. In addition to no evidence of benefit, the repeated use of steroids may further immunosuppress already immunocompromised patients and increase the risk of side effects such as infection.

Table 16.5: Reported treatment of febrile reaction

Year	Number of febrile reactions	Medication stated	Antihistamine & /or steroid
2022	132	130/132 (98.5%)	61/130 (46.9%)
2021	174	155/174 (89.1%)	61/155 (39.3%)
2020	166	140/166 (84.3%)	58/140 (41.4%)
2019	146	130/146 (89.0%)	62/130 (47.7%)
2018	103	88/103 (85.4%)	39/88 (44.3%)

Subsequent management

A plan for subsequent treatment of febrile reactions was only given in 15 cases, likely reflecting that many patients are not expected to need further transfusion. While only 4 reports explicitly gave a plan to use antihistamine with or without steroids to treat a subsequent pure febrile reaction (Table 16.6), a further 3 stated 'premedication'. The largest planned management category was use of washed blood components, 6/15 (40.0%).

Table 16.6: Planned treatment of subsequent febrile reactions

Year	Number where treatment stated	Antihistamine +/- steroid stated
2022	15	4/15 (26.7%)
2021	18	3/18 (16.7%)
2020	33	7/33 (21.2%)
2019	42	7/42 (16.7%)
2018	27	8/27 (29.6%)

Case 16.1: Misclassification of a febrile reaction results in inappropriate immediate and future management

A child with aplastic anaemia receiving a platelet transfusion developed a fever of 39.2°C with rigors, hypertension and tachycardia. There were no allergic features. He was given an antihistamine and hydrocortisone and a plan was made for prophylactic chlorphenamine before future platelet transfusions.

Learning points

- Antihistamines and steroids have no role in treating or preventing febrile reactions
- Chlorphenamine is a sedating antihistamine and repeated prophylactic dosing may potentially have an adverse effect on a child receiving regular platelet transfusions

Investigation

Laboratory investigations should be tailored to the reaction type. If a febrile reaction is sufficiently severe to warrant discontinuing transfusion completely, repeat compatibility testing should be performed. Repeat compatibility testing is not required in reactions with purely allergic features (Soutar et al. 2023).

Transfusion was discontinued completely in 95 of the 132 febrile reactions. In 22/95 of these (23.2%), there was no mention of repeat compatibility testing.

Of the 117 reactions with purely allergic features, 47/117 (40.2%) were unnecessarily investigated with repeat compatibility testing and in 29/117 (24.8%) blood cultures were taken from the patient. The unit was sent for culture in 3 cases.

Case 16.2: Unnecessary investigations for an allergic reaction

A male in his 30s with thalassaemia, who had a history of allergic reactions in other settings, developed rash, urticaria, facial swelling and mild hypotension after 60mL of his third unit of red cells had been transfused. Transfusion was discontinued, he was given an antihistamine and hydrocortisone and his symptoms settled. He was investigated with IgA levels, mast cell tryptase, repeat group and screen, direct antiglobulin test and blood cultures, none of which showed any abnormality.

Learning points

- Allergic symptoms during transfusion are not caused by red cell antibodies or bacterial sepsis
- Unnecessary investigations add to the demand on the laboratory at a time when staffing is almost universally stretched

Conclusion

Febrile, allergic and hypotensive reactions are an unavoidable and unpredictable risk relating to transfusion. While most are minor, anaphylaxis can be life-threatening, and this emphasises the need to ensure that transfusion is only given when clinically indicated and there is fully informed patient consent. Suboptimal management of acute transfusion reactions continue to be reported, particularly the inappropriate use of antihistamine and/or steroids to treat febrile reactions (in 46.9% of cases). There is a lack of selectivity in investigations following the event, with compatibility testing frequently performed unnecessarily following allergic reactions. The key message remains the need to use the patient's symptoms and signs to distinguish febrile from allergic reactions and to tailor investigation and management accordingly.

Recommended resources

SHOT Bite No. 5: FAHR
https://www.shotuk.org/resources/current-resources/shot-bites/

SHOT Video: FAHR
https://www.shotuk.org/resources/current-resources/videos/

JPAC – Guidance for UK health professionals on consent for blood transfusion
https://www.transfusionguidelines.org/transfusion-practice/consent-for-blood-transfusion/guidance-for-healthcare-practitioners-involved-in-this-role

References

BSH Estcourt LJ, Birchall J, Allard S, et al. on behalf of the British Committee for Standards in Haematology. Guidelines for the use of platelet transfusions. *Br J Haematol.* 2017;**176**(3):365-394.

ISBT/IHN. Haemovigilance Working Party of the ISBT: Proposed standard definitions for surveillance of non-infectious adverse transfusion reactions (2011). https://onlinelibrary.wiley.com/doi/pdf/10.1002/9781118338179.app2 [accessed 30 April 2023].

NHSBT. Investigation and clinical management of suspected reactions to immunoglobulin A (IgA). NHSBT clinical guideline (2019). https://hospital.blood.co.uk/clinical-guidelines/nhsbt-clinical-guidelines/ [accessed 30 April 2023].

Soutar R, McSporran W, Tomlinson T, et al. Guideline on the investigation and management of acute transfusionreactions. *Br J Haematol.* 2023;**201**(5):832-844 https://doi.org/10.1111/bjh.18789. [accessed 27 June 2023].