17 Febrile, Allergic and Hypotensive Reactions (FAHR) n=336

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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.

Abbreviations used in this chapter

BSH	British Society for Haematology	**HLA**	Human leucocyte antigen
EASL	European Association for the Study of the Liver	**IgA**	Immunoglobulin A
FAHR	Febrile, allergic and hypotensive reactions	**IHN**	International Haemovigilance Network
FFP	Fresh frozen plasma	**ISBT**	International Society for Blood Transfusion

Key SHOT messages

- The number of FAHR cases reported to SHOT is increasing, with a higher proportion of severe cases
- 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
- Repeat compatibility testing is often carried out unnecessarily following allergic reactions or reactions to platelets or plasma components

Recommendations

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

Table 17.1: 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

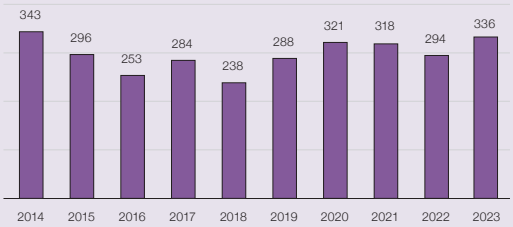
- Haematology registrars should receive training in classification, appropriate investigation and management of transfusion reactions in the laboratory induction at the start of their programme

Action: Hospital transfusion team, Haematology training programme directors

Headline data 2023

Number of reports n=336
Deaths n=0
Major morbidity n=119

FAHR reports by year



Demographic data

Male n=175
Female n=161
Unknown n=0

Adults n=300
Paediatric n=36
Unknown n=0

Blood component data

Red cells n=192
Platelets n=99
Plasma n=28
Cryoprecipitate n=1
Multiple components n=14
Granullocytes n=2

Introduction

Reactions are classified according to the ISBT/IHN definitions, which are summarised below in Table 17.2, and have been adopted by BSH (Soutar, et al., 2023). Mild reactions are not reportable to SHOT.

Table 17.2: 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*

Total number of FAHR reactions n=336

The total number of reports submitted in 2023 was the highest in the last 5 years. This was due to an increase in reported febrile reactions to red cells in adults. There was no change in the total number of allergic reactions, or in reactions in children.

While there has been an increase in the absolute number of cases reported in 2023, no significant difference was noted in the proportion of FAHR cases to the total reports received (336/3833, 8.8% in 2023 as compared to 294/3499, 8.4% in 2022).

Deaths related to transfusion n=0

There were no transfusion-related deaths reported in 2023.

Major morbidity n=119

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

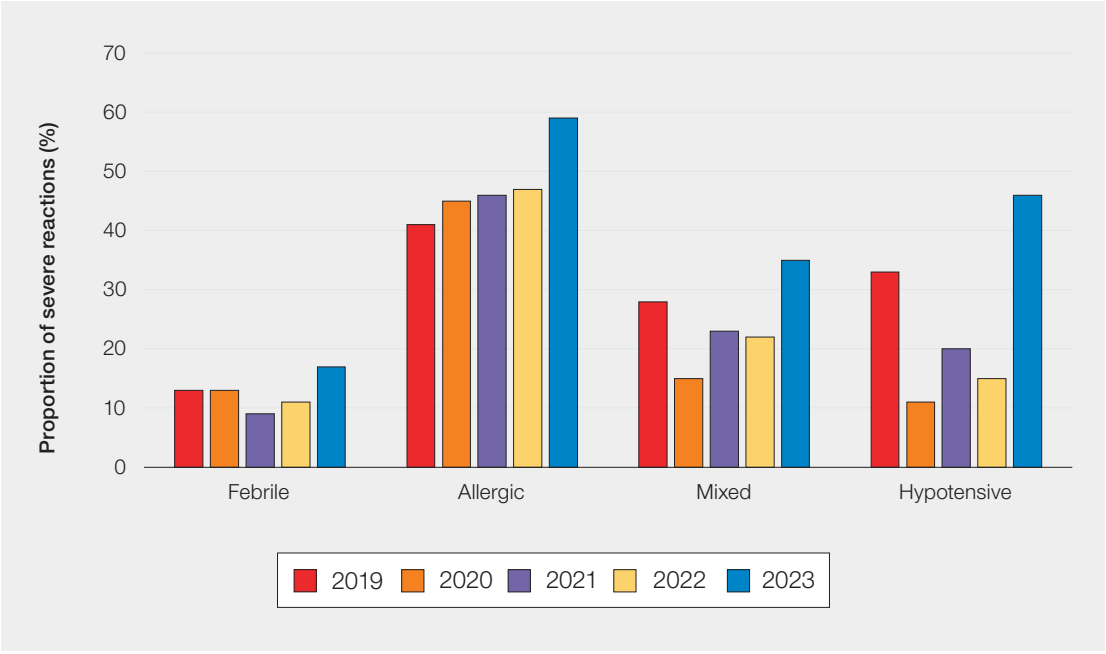
Reactions are categorised in Table 17.3.

Table 17.3: Classification of FAHR in 2023

	Moderate	Severe	Total
Febrile	136	27	**163**
Allergic	50	73	**123**
Mixed allergic/febrile	24	13	**37**
Hypotensive	7	6	**13**
Total	**217**	**119**	**336**

In all reaction types, there has been an increase in the number and proportion of reactions classified as severe. The overall proportion of severe reactions rose from 77/294 (26.2%) in 2022 to 119/336 (35.4%) in 2023.

Figure 17.1: Proportion of reactions classified as severe 2019-2023



Of note, in 24 of the 119 reactions classified as severe in 2023, this was primarily because the patient was admitted, or hospital stay was prolonged. This proportion is similar to 2022.

Reactions in IgA deficient patients n=4

There were 4 reactions, all to red cells, reported in 3 patients who were subsequently discovered to have severe IgA deficiency. Two were confirmed to have anti-IgA antibodies; the 3rd patient had not

been tested. All 3 patients suffered febrile-type reactions with marked systemic upset. Two were classic hyperacute reactions which presented within 10 minutes of starting transfusion. One of these patients gave a history of reaction to transfusion 6 years previously. The 3rd patient developed fever, rigors, tachycardia, hypotension, and a drop in oxygen saturations after 100mL had been transfused. They developed an identical reaction when a second transfusion was attempted 24 hours later.

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 (Latham, 2019).

Anaphylactic reactions n=50

Fifty severe allergic reactions were reported which required the use of adrenaline, compared to 36 in 2022. Of these, 22 were routine transfusions; 24 occurred on general wards, 2 in outpatients and 1 in a community setting. Children were disproportionately represented: 12/50 (24.0%) cases were in patients under 18 years.

Case 17.1: Inappropriate use of FFP prior to liver biopsy results in an anaphylactic reaction

A patient was given FFP prophylactically prior to liver biopsy due to prolonged international normalised ratio. They developed itching, wheeze, angioedema, and a drop in oxygen saturations requiring the anaphylaxis pathway.

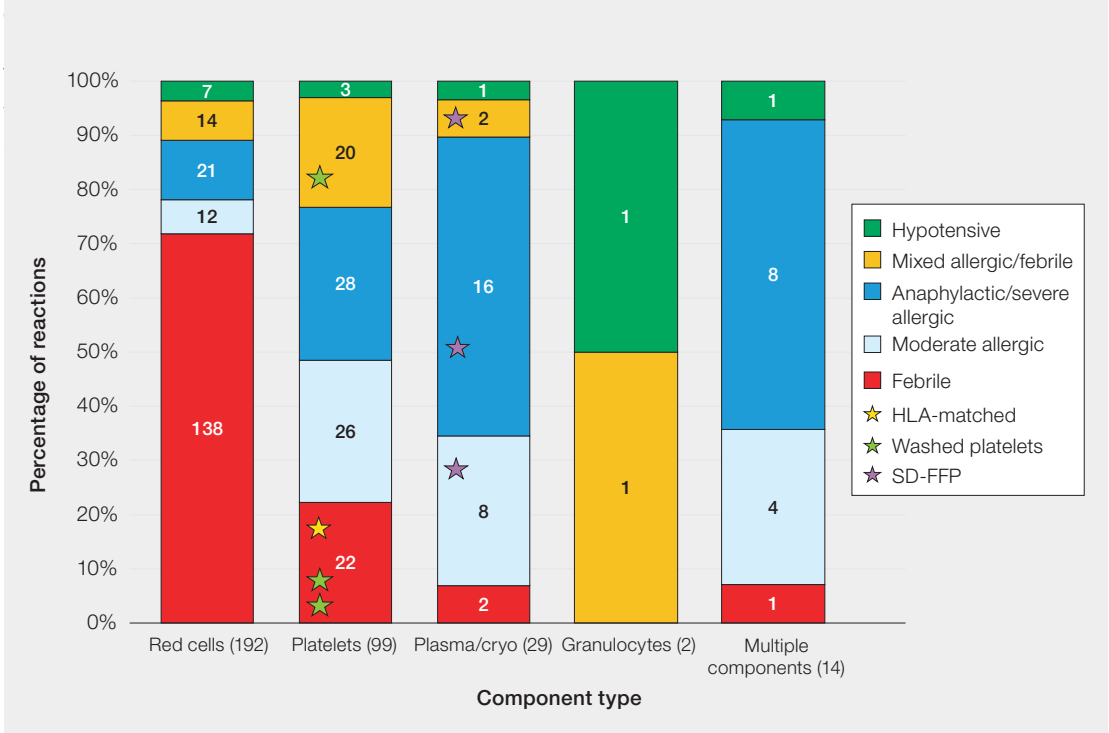
Learning points

- All areas administering blood components need to be appropriately equipped and staff trained to manage a severe acute reaction. This includes settings where transfusion is given in the community
- FFP should not be given in patients with chronic liver disease and deranged clotting tests prior to invasive procedures, as these tests do not correlate well with bleeding risk (Bent & Das, 2023; EASL, 2022)

One patient was reported to have suffered life-threatening reactions to multiple transfusions. In response, the Blood Service worked to develop a series of non-standard components to systematically reduce exposure to potential allergens, including triple-washed, mannitol free units. Eventually it was established that the reactions were unrelated to transfusion and were in fact felt to be self-induced.

This highly unusual case demonstrates the importance of careful consideration of the categorisation and pathogenesis of transfusion reactions, and of sometimes unexpected diagnoses. It also demonstrates the potential to develop and transfuse non-standard components if required in extreme situations.

Figure 17.2: Reactions by component type in 2023 (n=336)

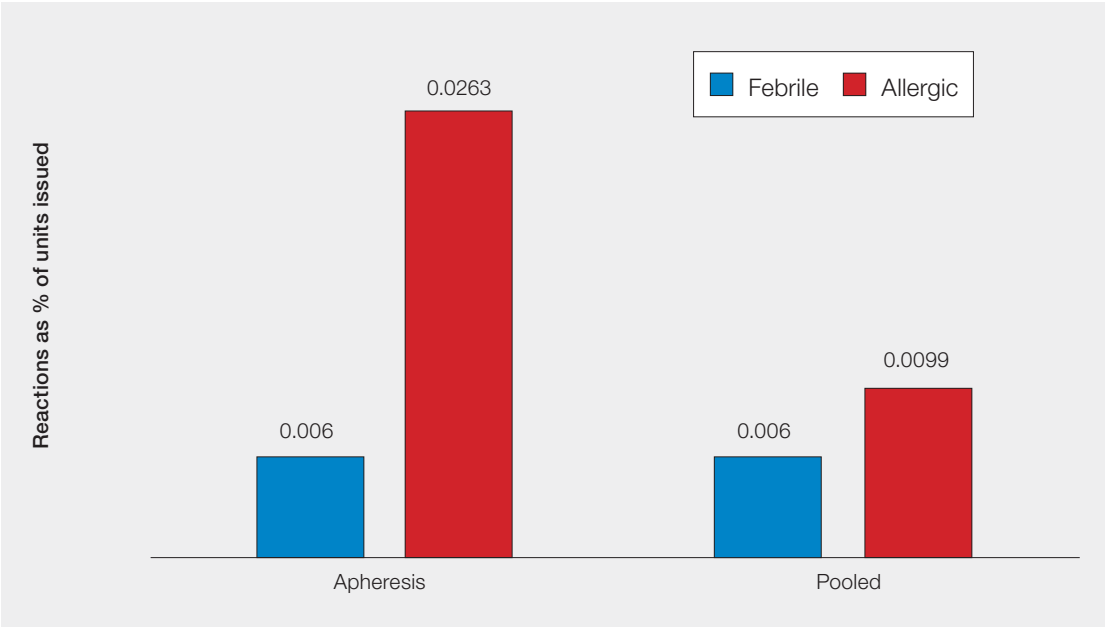


HLA=human leucocyte antigen; cryo=cryoprecipitate; SD-FFP=solvent detergent treated fresh frozen plasma

The incidence of allergic reactions was 2.7 times higher in apheresis platelets compared to pooled platelets, which relates to their higher plasma content (Estcourt, et al., 2017). The incidence of febrile reactions was identical in the two component types (Figure 17.3).

The first step for subsequent transfusions for a patient experiencing a mild to moderate allergic reaction to apheresis platelets should be to switch to a pooled component.

Figure 17.3: Incidence of reactions as a percentage of platelet units issued in 2023



Analysis of reactions remains comparable to previous years in the following characteristics (Table 17.4).

Recipient or transfusion characteristic	Percentage
Age distribution	89% of patients were aged 18 years or over
Sex	52% were male
Urgency of transfusion	58% were given routinely
Timing of transfusion	68% occurred within standard hours
Location	60% were on wards and 12% in outpatient/day case units

Table 17.4: Characteristics of FAHR

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. The proportion of patients mismanaged in this way was the lowest for the last 5 years; see Table 17.5.

Year	Number of febrile reactions	Medication stated	Antihistamine and/or steroid
2023	163	163/163 (100%)	61/163 (37.4%)
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%)

Table 17.5: Reported treatment of febrile reactions 2019-2023

Subsequent management

In 20 cases, a plan was made to give antihistamine and steroid prior to future transfusions, and in a further 7 cases, the report suggested use of 'pre-medication'. Three of these patients had experienced febrile reactions.

Learning points

- Steroids are not recommended for the prevention of allergic reactions, and neither steroids nor antihistamine have any role in preventing febrile reactions
- Repeated doses of steroids can cause immunosuppression and other complications such as diabetes (Yeates & Charlton, 2023)

Investigation

Laboratory investigations should be tailored to the reaction type.

Of the 123 reactions with purely allergic features, 51 (41.5%) were unnecessarily investigated with repeat compatibility testing and in 31 (25.2%) blood cultures were taken from the patient. The blood component was sent for culture in 10 cases, all of which were negative.

Inappropriate red cell serological testing was performed in 46/135 (34.1%) patients having reactions to platelets or plasma components.

Case 17.2: Inappropriate investigation and management of a febrile platelet reaction

A patient with lymphoma developed fever and rigors on their way home after an outpatient platelet transfusion. They returned to hospital and were treated with hydrocortisone and chlorphenamine. Repeat group and screen was sent but no blood cultures were performed.

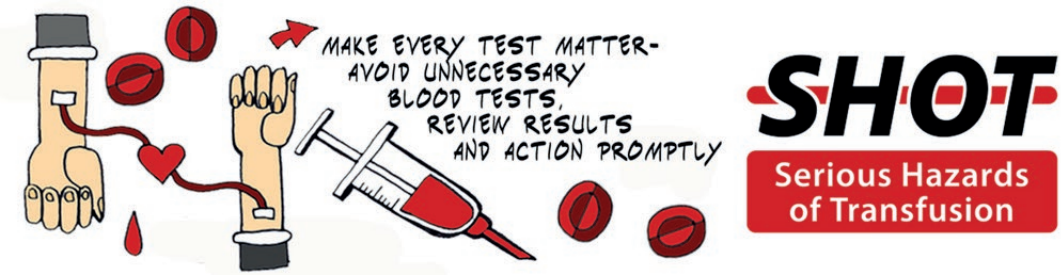
The treatment given for this febrile platelet reaction was directed against an allergic reaction, while investigation was for a febrile reaction to red cells. In a febrile potentially immunocompromised patient, blood cultures to exclude an intercurrent infection would have been appropriate.

Case 17.3: Inappropriate investigation and follow-up plans for a patient after an allergic reaction to FFP

A patient developed itching and eye swelling during transfusion of FFP in the context of major haemorrhage. They were appropriately treated with an antihistamine and their symptoms settled. They were investigated with a repeat group and screen and because of this reaction, a flag was placed on their record to require a serological crossmatch (rather than electronic issue) for future transfusions.

Learning points

- Red cell antibodies do not cause allergic transfusion reactions or reactions to platelets or plasma components. Repeat compatibility testing is not required in these scenarios
- Unnecessary investigations add to the demand on the laboratory at a time when staffing is almost universally stretched and cause avoidable delays in provision of blood components for future transfusions



Conclusion

Febrile, allergic, and hypotensive reactions are an unavoidable and unpredictable risk of transfusion. Although all patients recovered fully from the acute episode, 2023 saw a higher proportion of clinically severe reactions. Clinicians have a duty not to cause additional harm by giving inappropriate treatment. Haematology teams need to be well educated so they are confident to advise on appropriate, immediate, and subsequent management and relevant investigations. A survey of UK haematology registrars in 2023 found that only 53% felt that their training equipped them to give safe clinical transfusion advice to colleagues in other specialties (Booth 2024, personal communication. 13 March).

It is encouraging that the proportion of febrile reactions treated inappropriately with antihistamine and/or steroids has reduced in 2023, and it is hoped this improvement will be maintained in future years. There remains overuse of hydrocortisone for prevention of reactions, contrary to guidelines, and unnecessary

repeat compatibility testing for allergic and non-red cell 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 FAHR video
https://www.shotuk.org/resources/current-resources/videos/

Haematology Curriculum for Higher Medical Training Blood Transfusion Training Guidance
https://www.thefederation.uk/training/specialties/haematology

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