17 Febrile, Allergic and Hypotensive Reactions (FAHR) n=321

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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

- When assessing a patient having a transfusion reaction, staff must use the symptoms and signs to classify the reaction type. This is fundamental to providing the correct treatment, both immediately and in future transfusion episodes. Training should emphasise that 'reaction to transfusion' is not a single diagnosis requiring a uniform standard treatment
- For febrile reactions alone, give paracetamol. If anaphylaxis is suspected, give adrenaline; for less severe allergic reactions, give antihistamine first line. 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
- 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

Abbreviations used in this chapter

AML	Acute myeloid leukaemia
BSH	British Society for Haematology
CCP	COVID-19 convalescent plasma
DHSC	Department of Health and Social Care
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
MB	Methylene blue treated
MDS	Myelodysplastic syndrome
PAS	Platelet additive solution
SABRE	Serious adverse blood reactions and events
SD	Solvent detergent treated
TACO	Transfusion-associated circulatory overload
TAD	Transfusion-associated dyspnoea
TRALI	Transfusion-related acute lung injury
TTI	Transfusion-transmitted infection
vCJD	variant Creutzfeldt–Jakob disease

Key recommendations

- 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 for 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

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

Table 17.1: Targeted treatment for febrile and allergic transfusion reactions

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 FFP try a pooled component e.g. solvent-detergent treated plasma

Action: HTT and clinical staff managing patients receiving transfusions

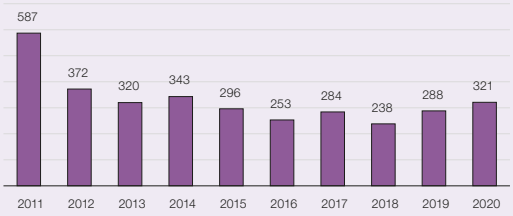
These recommendations have not changed in recent years and remain pertinent. They should be incorporated into hospital policies and routine practices.

For previous recommendations in full, see https://www.shotuk.org/shot-reports/previous-recommendations/

Headline data 2020

Number of reports n=321
Deaths n=0
Major morbidity n=80

FAHR reports by year



Demographic data

Male n=167
Female n=154
Adults n=267
Paediatric n=54

Blood component data

Red cells n=165
Platelets n=112
Plasma n=28
Multiple Components n=13
Granulocytes n=3

Introduction

Reactions are classified according to the ISBT/IHN definitions, which are summarised below in Table 17.2. These are also available online (ISBT/IHN 2011) and have been adopted by the BSH (BSH Tinegate et al. 2012).

Table 17.2: 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

Total number of FAHR reactions n=321

The number of reactions reported represents an 11% increase over last year and the highest number reported for several years. This is remarkable given the decline in blood use in 2020 caused by the COVID-19 pandemic.

Deaths n=0

There were no deaths related to FAHR reactions reported in 2020.

Major morbidity n=80

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 2020

	Moderate	Severe	Total
Febrile	145	21	**166**
Allergic	65	54	**119**
Mixed allergic/febrile	23	4	**27**
Hypotensive	8	1	**9**
Total	**241**	**80**	**321**

NB: in 20 of the 80 reactions classified as severe this was primarily because the patient was admitted/kept in overnight

There were 469 cases initially reported as FAHR with 133 cases withdrawn and 15 transferred to other categories, leaving 321 for analysis. Of the withdrawn cases, 81/133 (60.9%) were withdrawn where 'mild' appears in the 'reason for withdrawal'. Mild reactions have not been reportable to SHOT since 2012. In 136/321 (42.4%) of FAHR cases, the type of reaction stated was reclassified according to the information provided (Table 17.4). This was communicated back to the reporter. The percentage of

severe reactions remains similar to previous years (80/321, 24.9%). 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.

Table 17.4: Reclassification of FAHR in 2020

		Confirmed FAHR category			
		Anaphylaxis/allergic	Febrile	Mixed febrile/allergic	Hypotensive
Reported category on SABRE	Anaphylaxis/allergic	74	16	9	1
	Febrile	2	96	3	-
	Mixed febrile/allergic	17	15	8	-
	Hypotensive	12	6	1	7
	Other / FAHR	6	15	1	-
	Other	4	9	4	1
	Other / TRALI	2	-	-	-
	Other / TACO	-	1	-	-
	Other / TAD	1	-	-	-
	Other / HTR	1	2	-	-
	TTI	-	6	1	-
	Total	**119**	**166**	**27**	**9**

Correct category	**185**	**(57.6%)**
Changed category	**136**	**(42.4%)**

Hyperacute reactions n=0

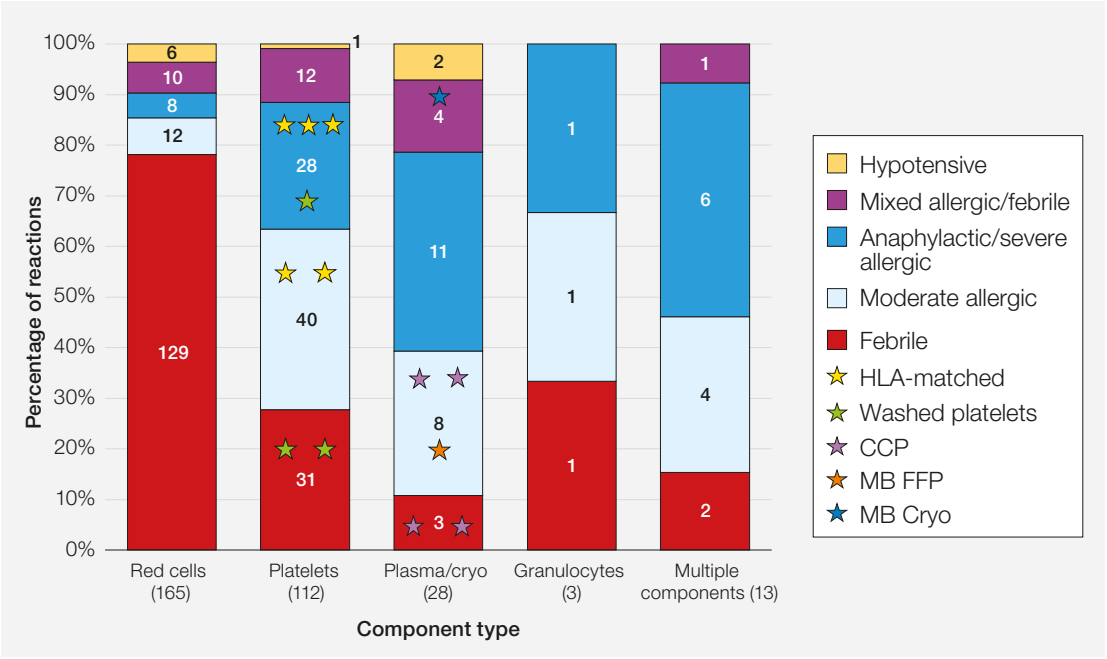
There were no allergic, febrile, or hypotensive cases clearly associated with IgA deficiency in 2020.

Type of reactions by component

This remains similar to previous Annual SHOT Reports; see Figure 17.1. Red cells are usually associated with febrile-type reactions (129/165, 78.2%) whereas plasma components and platelets more commonly cause allergic reactions (19/28 (67.9%) and 68/112 (60.7%) respectively). There were 4 reactions reported with the use of CCP, 1 with MB-FFP and 1 with MB-cryoprecipitate. None were associated with SD-FFP.

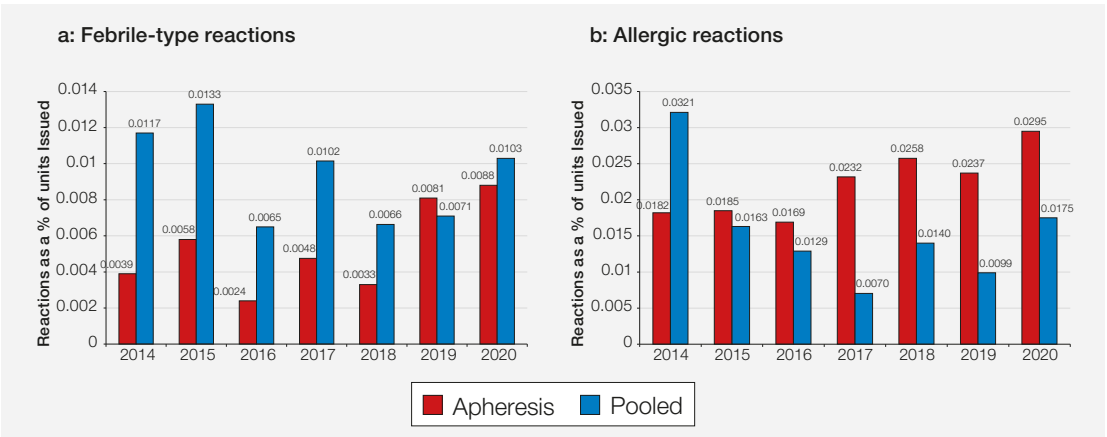
When FAHR reactions occur following transfusion of a single component unit, reporters are asked to provide the expiry date of the transfused unit. Analysis was limited to red cell and platelet units as plasma is usually stored frozen. Reactions were seen in 67/98 (68.4%) transfusions of red cells with less than 20 days' shelf life and in 52/75 (69.3%) transfusions of platelets with less than 3 days' shelf life. There was no obvious 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 for all transfusions, this may simply reflect that the majority of units are given towards the end of shelf life.

Figure 17.1: Reactions by component type



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 to be associated with the reduction in plasma content. There remains little difference in the incidence of febrile reactions with pooled platelets compared to apheresis. Overall, there were fewer reactions (allergic and febrile reactions combined) reported with pooled platelets than apheresis platelets (0.03% [35/125715] and 0.04% [52/135776] respectively) and the incidence remains consistent. Reactions to platelets are partly 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 17.2).

Figures 17.2: Percentage of reactions to apheresis and pooled platelets 2014 to 2020



Analysis of reactions remains comparable to previous years in the following characteristics (Table 17.5).

Table 17.5: Characteristics of FAHR

Recipient or transfusion characteristic	Percentage
Age distribution	83% of patients were aged 18 years or over
Gender	52% male and 48% female cases
Urgency of transfusion	*63% were given routinely
Timing of transfusion	^67% occurred within standard hours
Location	59% were on wards and 15% in outpatient/day case units

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

^Higher % of cases than last year likely associated with fewer 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 17.6. 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.

Year	Number	Medication stated	Antihistamine and/or steroid
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%)
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 17.6: Treatment of reported febrile reactions

Subsequent management

The prophylactic use of antihistamine with or without steroids to treat a subsequent purely febrile reaction appears to be reducing, although this data was not available in most cases (the single largest management category included treatment not stated or 'premedication'). Across both febrile and allergic reaction categories avoidance of transfusion was advised by some reporters and included: the cessation of routine platelet transfusions (n=2), 'only transfuse where necessary' (n=1), limit transfusion to 1 unit/day (n=1) and use of intravenous iron (n=2) (Table 17.7).

Year	Number where treatment stated	Antihistamine and/or steroid stated
2020	33	7/33 (21.2%)
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%)

Table 17.7: Planned treatment of subsequent febrile reactions

Illustrative cases

Cases managed generically as 'transfusion reactions' illustrate a failure to correctly classify the reaction and appropriately treat potentially serious causes.

Case 17.1: Inappropriate treatment of a febrile reaction

A patient in his 50s with AML attended the haematology day unit for a routine platelet transfusion. On completion he developed rigors, fever, and breathlessness. His temperature rose to 40.1°C from a baseline of 37.4°C and oxygen saturations fell to 94% on oxygen. He was given IV hydrocortisone and antihistamine with little effect. He was subsequently administered 1mg adrenaline, 4.5g piperacillin with tazobactam (tazocin) (antibiotic) IV, 1g paracetamol and IV fluids. His symptoms settled over the following hour, but he was admitted for observation. Blood cultures were negative and there was no rise in mast cell tryptase.

There were no clinical features in this case to suggest an allergic reaction. The range of treatments he received illustrates a failure to attempt to classify the reaction type, with possible delay in treating the most serious potential cause of this presentation – which in an immunocompromised patient would be infection (related or unrelated to transfusion). Adrenaline and hydrocortisone may be harmful in this scenario.

Case 17.2: Inappropriate treatment in the presence of a potential haemolytic transfusion reaction

A lady in her 70s with MDS and known alloantibodies attended for a scheduled two-unit blood transfusion. The units had been crossmatched at the reference laboratory due to slight reaction on crossmatch when performed in-house. Halfway through the second unit the patient developed rigors, a rise in temperature (38.4°C from baseline 37.7°C) and elevated blood pressure (130/60 to 167/88 mmHg). The nurse stopped the transfusion and asked for medical review. The registrar prescribed 10mg antihistamine and 100mg hydrocortisone and told the nurse to continue the transfusion in 30 minutes. However, the patient's symptoms worsened, and she complained of pain in her kidneys. She was given a further 100mg hydrocortisone and 1g paracetamol. Her symptoms resolved within a few hours. Samples sent for serological investigation revealed no evidence of a haemolytic transfusion reaction.

Here again hydrocortisone and antihistamine were used despite no symptoms of allergy. The use of empirical treatment suggests initial medical assessment failed to consider the possibility of a haemolytic transfusion reaction. This would have been the most serious differential to exclude, given the history of alloantibodies and concern about a reactive crossmatch. Even for an allergic reaction, there is never any rationale for giving a second dose of hydrocortisone in short succession, as this drug takes several hours to act.

Appropriate clinical assessment and management of a febrile reaction may allow a necessary transfusion to safely continue, without unnecessary interventions.

Case 17.3: Appropriate treatment

A man in his 20s who had suffered polytrauma received a postoperative blood transfusion. After 30 minutes, routine observations revealed a temperature rise from 37.6 to 39°C. He was treated with IV paracetamol and transfusion was continued. His temperature continued to reduce until returning to baseline around 12 hours post transfusion.

Conclusion

Over 40% of cases reported in this chapter were re-classified according to the information provided and similarly, when medication was stated over 40% of purely febrile reactions were given an antihistamine and/or a steroid. The key messages this year remain that; firstly, there is a need to differentiate the symptoms and signs of the separate reaction types, secondly a pure allergic reaction is not associated with fever, and thirdly treatment with an antihistamine and/or steroid should be limited to those with allergic features. It is recognised that in a sick patient with acute symptoms, it is not always easy to separate different reaction types at the time. It is encouraging to note that there is a downward trend in inappropriate antihistamine/steroid use, when future medication was stated for reactions classified as purely febrile (since 2014).

The incidence of allergic reactions due to apheresis platelets compared to pooled platelets (suspended in PAS) remains higher. Following publication of the Department of Health and Social Care document 'Risk assessment of the transmission of variant Creutzfeldt–Jakob disease (vCJD) by blood components' apheresis platelets are no longer preferentially recommended for patients born from 1996 (DHSC 2019).

Recommended resources

Resuscitation Council (2008) Emergency treatment of anaphylactic reactions
http://www.resus.org.uk/pages/reaction.pdf

NHSBT (2015/16) Histocompatibility and Immunogenetics diagnostic services user guide
http://hospital.blood.co.uk/diagnostic-services/diagnostic-user-guides/

Choosing Wisely UK (2018) Royal College of Pathologists (2018) Recommendation 3
https://www.choosingwisely.co.uk/i-am-a-clinician/recommendations/#1572879057348-632f8063-b7b4

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Maurer-Spurej E, Larsen R, Labrie A, et al. (2016) Microparticle content of platelet concentrates is predicted by donor microparticles and is altered by production methods and stress. *Transfus Apher Sci* 2016;**55(1)**:35-43.