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GUIDELINE

Guideline on the investigation and management of acute transfusion reactions

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METHODOLOGY

This guideline was compiled according to the British Society for Haematology (BSH) process at https://b-s-h.org.uk/media/19922/bsh-guidance-development-process-july-2021.pdf. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations.[1] The GRADE criteria can be found in Appendix S3 of the above BSH document.

LITERATURE REVIEW

The literature search was performed in January 2021 and updated in January 2022. With the assistance of the Oxford Systematic Reviews Initiative (SRI), the following databases were searched for relevant publications in English: MEDLINE (from 1950), EMBASE (from 1980), CINAHL (from 1982), The Cochrane Library, DARE (CRD website) and SRI hand search databases. The initial search and filtering produced 1693 systematic reviews, randomised controlled trials and observational studies from which relevant publications were extracted by the members of the Writing Group. Search terms include Transfusion AND ('TACO' OR 'TRALI' OR 'TAD' OR 'pulmonary complication' OR 'lung' OR 'pulmonary oedema' OR 'respiratory' OR 'ARDS' OR 'reaction' OR 'anaphylaxis' OR 'febrile reaction' OR 'allergic reaction' OR 'non haemolytic reaction' OR 'haemolytic reaction'), wrong blood to wrong person, incompatible transfusion reaction, ABO-related incompatible transfusions.

PURPOSE AND OBJECTIVES

The purpose of this document is to provide clear guidance on the recognition, investigation and management of acute adverse reactions to blood components. It is clinically focused and recognised that the precise nature of reactions may not be apparent at presentation. The emphasis is on the immediate management of potentially life-threatening reactions, but it also makes recommendations around appropriate investigation and prophylactic strategies. The key objectives are to:

1. Provide a flow diagram to aid recognition of acute transfusion reactions (ATRs) and their immediate clinical management;
2. Advise on further management of the patient during the reaction;
3. Provide advice on investigations;
4. Discuss management of subsequent transfusions;

5. Present recommendations for reporting adverse reactions to UK haemovigilance organisations, to blood services and within the hospital.

The guideline does not cover the detailed medical management of ATRs such as treatment of cardiac/respiratory failure or bacterial sepsis. Measures that might be employed for primary prevention of ATRs are outside the scope of the guideline. Readers may also find it useful to cross reference to other related British Society for Haematology guidelines such as The Administration of Blood Components and Pre-Transfusion Compatibility Procedures in Blood Transfusion Laboratories; all are available at https://b-s-h.org.uk/guidelines.

The full guideline with appendices providing detailed information on symptoms and signs, laboratory investigations, the International Society for Blood Transfusion (ISBT)/International Haemovigilance Network (IHN) classification of ATRs, a table describing differences between transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) and an algorithm for investigating and categorising pulmonary complications of transfusion can also be found on the BSH guidelines website.

Summary of key recommendations	Strength	Quality of evidence
Recognition of ATRs)		
Initial treatment of ATR should be directed by symptoms and signs. Treatment of severe reactions should not be delayed while waiting for the results of investigations.	1	C
All patients should be transfused in clinical areas where they can be directly observed and where staff are trained in the administration of blood components and the management of transfused patients, including the emergency treatment of anaphylaxis.	1	C
The recognition and immediate management of ATR should be incorporated into local transfusion policies and there should be mandatory transfusion training requirements for all clinical and laboratory staff involved in the transfusion process.	1	C
Patients should be asked to report symptoms which develop following completion of the transfusion.	1	C
Immediate management of ATR		
If a patient develops new symptoms or signs during a transfusion, this should be stopped temporarily but venous access should be maintained. Identification details should be checked between the patient, their identity band and the compatibility label of the blood component. The component should be inspected visually and the patient should be assessed with standard observations.	1	C
For patients with mild reactions, such as a temperature rise of 1–2°C leading to pyrexia ≥38°C but <39°C, **and/or** pruritus or rash but **without** other features, the transfusion may be continued with appropriate treatment and direct observation.	2	B
Patients with mild isolated febrile reactions may be treated with oral paracetamol (500–1000 mg in adults). Patients with mild allergic reactions may be managed by slowing the transfusion and treatment with an antihistamine. Corticosteroids should not be used routinely.	2	C
Anaphylaxis should be treated with intramuscular adrenaline (epinephrine). Patients who are thrombocytopenic or who have deranged coagulation should also receive intramuscular adrenaline if they have an anaphylactic reaction.	1	A
If a patient being transfused for haemorrhage develops hypotension, careful clinical risk assessment is required. If the hypotension is caused by haemorrhage, continuation of the transfusion may be life-saving. In contrast, if the blood component is considered the most likely cause of hypotension, the transfusion must be stopped or switched to an alternative component and appropriate management and investigation commenced.	1	C
If a patient develops sustained febrile symptoms or signs of moderate severity (temperature ≥39°C **or** a rise of ≥2°C **and/or** systemic symptoms such as chills, rigors, myalgia, nausea or vomiting), bacterial contamination or a haemolytic reaction should be considered.	1	C
Diagnostic investigations		
In all moderate and severe transfusion reactions, standard investigations including full blood count, renal and liver enzymes should be performed. Patients with respiratory symptoms not due to allergy should also have a chest X-ray.	1	C
If febrile symptoms of moderate severity are sustained, implicated units should be returned to the laboratory for further investigation and the blood service contacted immediately so that associated components from the implicated donation can be withdrawn if appropriate. Samples should be taken for repeat compatibility testing and culture and urine assessed for haemoglobin.	1	C
Patients who have experienced anaphylactic reactions or recurrent severe febrile/inflammatory reactions within the first 15 min should have IgA levels measured. Patients with IgA deficiency diagnosed after an ATR should be discussed with an expert in transfusion medicine regarding future management.	2	C

Summary of key recommendations	Strength	Quality of evidence
In an ATR with only allergic features, repeat compatibility testing is not required.	1	B
In the absence of platelet transfusion refractoriness or acute post-transfusion thrombocytopenia or leucopenia, investigation of the patient with ATR for leucocyte, platelet or neutrophil-specific antibodies is not indicated.	1	B
Patients with respiratory symptoms not caused by anaphylaxis or allergy should have investigations for left atrial hypertension (e.g. echocardiography and pre- and post-transfusion NT-Pro BNP) to help distinguish the type of pulmonary complication to assist diagnosis and haemovigilance reporting.	2	B
Subsequent management of the patient		
Patients who have experienced an anaphylactic reaction should be discussed with an allergist or immunologist if there is uncertainty about the causative agent (e.g. if other drugs were administered at the same time as the transfusion).	2	C
For patients with recurrent febrile reactions, we recommend a trial of premedication with oral paracetamol given 1 h before the reaction is anticipated (or non-steroidal anti-inflammatory drugs in patients with predominant chills or rigors—but an assessment of the risks of medication against the severity of reaction should be made in each case). Patients who continue to have recurrent moderate or severe febrile reactions despite premedication should have a trial of washed blood components (i.e. red cells and platelets). There is no role for prophylactic antihistamine or corticosteroids in the absence of allergic symptoms.	2	C
For recurrent mild allergic reactions, there is no evidence to support routine prophylaxis with antihistamines or corticosteroids. Alternative causes such as allergy to drugs or latex gloves should be excluded.	2	C
For patients with recurrent moderate or severe allergic reactions, options for further transfusion include:		
• If prior reactions were to apheresis platelets, consider pooled platelets (suspended in platelet additive solution).	2	B
• Consider antihistamine prophylaxis (although the evidence for efficacy is low, the risks are also low).	2	B
• Routine prophylaxis with corticosteroids is not recommended.	2	C
• Transfusion of washed red cells or platelets	2	C
• The use of pooled solvent–detergent-treated fresh frozen plasma (FFP) when there are recurrent allergic reactions to FFP in patients undergoing plasma exchange.	2	B
• If further transfusion is urgent and withholding blood is a greater risk, transfuse standard components under direct monitoring in a clinical area with resuscitation facilities.	2	C
Patients with confirmed IgA deficiency (IgA <0.07 g/L):		
• with a history of reaction to blood components should receive washed components for elective transfusion but life-saving transfusion should not be delayed if these are not immediately available. The patient must be monitored closely for an acute reaction.	1	C
• with no history of blood transfusion reactions should receive standard components with a higher frequency of monitoring. Those with a history of allergy/anaphylaxis in other settings should be discussed with a transfusion medicine or clinical immunology or allergy specialist if time allows.	2	C
Reporting of ATR		
All transfusion reactions except mild febrile and/or allergic reactions must be reported to appropriate regulatory and haemovigilance organisations and should also be reviewed within the hospital.	1	C

INTRODUCTION

Acute transfusion reactions (ATRs) are defined as those occurring within 24 h of the administration of blood or blood components.[2]

ATRs vary in severity from minor febrile reactions to life-threatening allergic, haemolytic or hypotensive events. Allergic and febrile non-haemolytic transfusion reactions (FNHTR) are those most commonly reported, but the true incidence of ATR is uncertain as most haemovigilance systems only collect information on the more serious reactions, there are wide variations in institutional reporting rates and the introduction of new processes may differentially alter reaction rates over time (e.g. prestorage leucodepletion reduces the rate of FNHTR but not allergic reactions).[3,4] ATR rates of 0.5–3% of transfusions are commonly quoted.[5] The 2020 Serious Hazard of Transfusion (SHOT) report reviewed 10 years of reporting data and calculated the risk of a febrile, allergic or hypotensive reaction as 1:7704 and the risk of a haemolytic reaction as 1:57425. Pulmonary complications were the foremost cause of morbidity and mortality accounting for 65% of reported transfusion-related deaths. Platelets are the components with the highest number of reported reactions per 10 000 transfusions.[6]

There is uncertainty about the cause of ATRs. There is good evidence, supported by the impact of leucodepletion, that many febrile reactions are caused by reactions to donor white cells or accumulation of biological response modifiers during component storage.[7] Except in rare cases, a specific allergen will not be identified in patients with allergic transfusion reactions,[8] although plasma reduction may lower their frequency.[9] It is increasingly recognised that

recipient factors, particularly underlying diagnosis and allergic predisposition, may be paramount in predicting allergic transfusion reactions.[10–13] It is possible that genetic polymorphisms play a role.[14,15] Patients' age, physical characteristics and baseline observations may be significant risk factors for development of febrile reactions.[16–18] Preventative strategies should be directed at the minority of patients who have a propensity to severe reactions.

Although it is useful to categorise ATR for reporting and research purposes and for international comparison,[19] patients with severe ATR often present with an overlapping complex of symptoms and signs, the differential diagnosis of which includes potentially life-threatening allergy or anaphylaxis, acute haemolytic transfusion reactions, bacterial transfusion-transmitted infection, transfusion-associated acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). Transfusion-associated dyspnoea (TAD) may be suspected when respiratory distress has a temporal association with transfusion and does not meet the criteria for allergic reaction, TRALI or TACO. The initial clinical picture is also often obscured by factors related to the patient's underlying medical conditions, such as febrile septic episodes in neutropenic patients who also happen to be receiving a blood component transfusion. For this reason, this guideline will consider all causes of a possible reaction during blood transfusion and focus on initial recognition and general management of the *clinical* problem, guided in the main by symptoms and clinical signs and assessment of the *severity* of the problem. This allows appropriate investigation, specific treatment and, where possible, prevention of future episodes.

RECOGNITION AND INITIAL MANAGEMENT OF ATR

To minimise the risk of harm, early identification of transfusion reactions and rapid clinical assessment are essential.

RECOMMENDATIONS

- All patients should be transfused in clinical areas where they can be directly observed and where staff are trained in the administration of blood components and the management of transfused patients, including the emergency treatment of anaphylaxis. (1C)
- The recognition and immediate management of ATR should be incorporated into local transfusion policies and there should be mandatory transfusion training requirements for all clinical and laboratory staff involved in the transfusion process. (1C)

If transfusions are administered at a patient's home, these should only be conducted in accordance with well-developed policies in patients deemed to be at low risk of ATR while otherwise abiding by the above recommendations.

Although anaphylactic and haemolytic reactions can present after only a small volume of blood has been transfused,[20] reactions can present much later, on occasion several hours after completion of the transfusion.[21] Delayed haemolytic reactions can present after days to weeks. Therefore, observation and monitoring are required throughout the transfusion episode and patients should be asked to report symptoms which develop after transfusion, particularly fever, dark urine, jaundice or symptoms suggestive of anaemia.[22] Unconscious patients, or those unable to report symptoms, require direct monitoring. The evidence on the use of early warning scores (EWS) to aid recognition of reactions is limited; however, when changes from the baseline are seen in EWS during or post-transfusion, consideration should be given to a possible transfusion reaction. Retrospective analysis has shown that in cases of patient deterioration the link to the transfusion is not always recognised and in particular pulmonary complications may not be identified.[23]

RECOMMENDATION

Patients should be asked to report symptoms which develop following completion of the transfusion. (1C)

INITIAL CLINICAL ASSESSMENT

Initial clinical assessment seeks to quickly identify those patients with serious or life-threatening reactions so that immediate treatment/resuscitation can be initiated. Figure 1 provides a practical guide to recognition and initial management of suspected ATR.

In *all* cases, the transfusion must be stopped temporarily and venous access should be maintained with physiological saline. The patient's airway, breathing and circulation ('ABC') must be assessed.[24] Their core identification details must be checked to ensure that they correspond with those on the blood component compatibility label—is the reaction due to transfusion of a component intended for another patient?[22] The component must be examined for unusual clumps or particulate matter, or discolouration suggestive of bacterial contamination. Provided that the reaction is not severe or life-threatening, as defined in the flow diagram (Figure 1), standard observations on the patient are then performed.

RECOMMENDATION

- If a patient develops new symptoms or signs during a transfusion, this should be stopped temporarily, but venous access should be maintained. Identification details should be checked between the patient, their identity band and the compatibility label of the blood component. The component should be inspected visually and the patient should be assessed with standard observations. (1C)

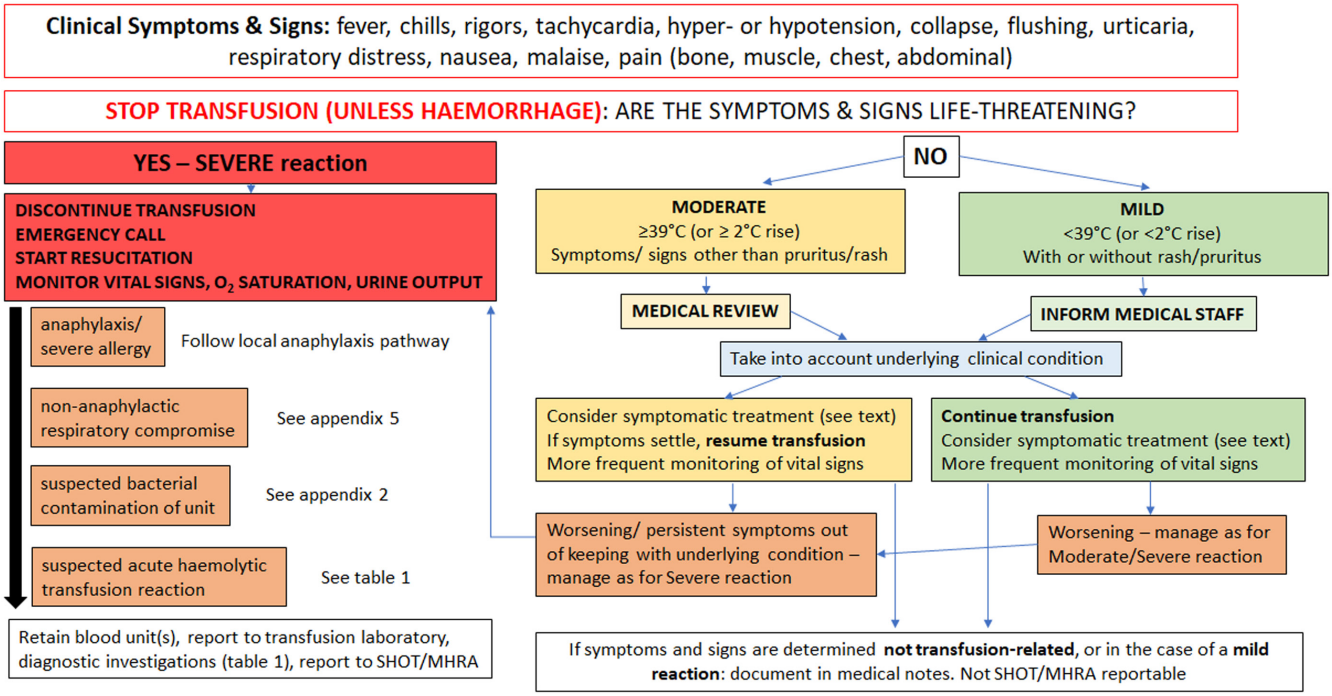

FIGURE 1 Flow diagram for recognition, initial management and subsequent management and investigations.

Severe reactions

If the presumed ATR is *severe or life-threatening*, a doctor should be called immediately and the blood transfusion should be discontinued. Caution is required in bleeding patients where hypotension may be associated with haemorrhage and continuing the transfusion may be life-saving.

RECOMMENDATIONS

- If a patient being transfused for haemorrhage develops hypotension, careful clinical risk assessment is required. If the hypotension is caused by haemorrhage, continuation of the transfusion may be life-saving. In contrast, if the blood component is considered the most likely cause of hypotension, the transfusion must be stopped or switched to an alternative component and appropriate management and investigation should be commenced. (1C)

Mild or moderate reactions

If the reaction is *mild*, for example an isolated rise in temperature without chills, rigors or other change in observations, medical staff should be informed but the transfusion may be restarted under direct supervision. In the case of reactions considered *moderate*, urgent medical advice should usually be sought before the transfusion is restarted. Exceptions to this would include reactions where there is an obvious alternative explanation for the symptoms/signs or the patient has a history of similar, previously investigated, non-serious transfusion reactions.

RECOMMENDATION

- For patients with mild reactions, such as a temperature rise of 1–2°C leading to pyrexia ≥38°C but <39°C, and/or pruritus or rash but WITHOUT other features, the transfusion may be continued with appropriate treatment and direct observation. (2B)

STANDARD OBSERVATIONS

The patient's pulse rate, blood pressure, temperature and respiratory rate should be monitored,[22] and abnormal clinical features such as fever, rashes or angioedema should be frequently assessed. A patient who has experienced a transfusion reaction should be observed directly until the clinical picture has improved.

SYMPTOMS AND SIGNS OF ATR

ATRs can present with a range of symptoms and signs of varying severity. These include the following:

- Fever and related inflammatory symptoms or signs such as chills, rigors, myalgia, nausea or vomiting
- Cutaneous symptoms and signs including urticaria (hives), other skin rashes and pruritus

- Angioedema (localised oedema of the subcutaneous or submucosal tissues), which may be preceded by tingling
- Respiratory symptoms and signs including dyspnoea, stridor, wheeze and hypoxia
- Hypotension
- Pain
- Severe anxiety or 'feeling of impending doom'
- Bleeding diathesis with acute onset

Rapidly developing features of ABC problems, usually associated with skin and mucosal change would suggest anaphylaxis.[25]

The symptoms and signs of reactions are discussed in more detail in Appendix S1. A table incorporating both the ISBT/IHN and SHOT classifications and gradations of severity can be found in Appendix S3. Both these appendices can be found on the BSH website.

MANAGEMENT OF ATRS

Management is guided by rapid assessment of symptoms, clinical signs and severity of the reaction rather than laboratory investigations.

RECOMMENDATION

- Initial treatment of ATR should be directed by symptoms and signs. Treatment of severe reactions should not be delayed until the results of investigations are available. (1C)

Severe reactions

Medical support should be given as appropriate for an acutely ill patient.[26] In all cases, disconnect the component and giving set from the patient and retain for further investigation, maintaining venous access with intravenous physiological saline. If the patient is *severely dyspnoeic*, ensure the airway is patent and give high flow oxygen through a mask with a reservoir. If wheeze is present without upper airways obstruction, consider nebulising a short-acting, inhaled, beta-2 agonists such as salbutamol.[27] Position *hypotensive* patients flat with leg elevation, or in the recovery position if unconscious or nauseated and at risk of vomiting. Further management is dependent on expert medical assessment and appropriate specialist support, such as the *resuscitation team* or *critical care outreach team*, who should be alerted according to local policies. Prompt treatment may be life-saving, and it may not be appropriate to wait for the results of investigation. A rational outline of management is provided below.

Shock/severe hypotension associated with wheeze or stridor

This is strongly suggestive of ***anaphylaxis*** with airways obstruction, especially if examination reveals angioedema and/or urticaria. This requires immediate intervention to ensure the airway is patent and the administration of adrenaline (epinephrine) is according to the UK Resuscitation Council (UKRC) guidelines.[25] Intramuscular (IM) adrenaline is rapidly effective and prevents delay in attempting to get venous access in a patient with peripheral venous shutdown. It should not be prohibited in patients with thrombocytopenia or coagulopathy. Intravenous adrenaline should only be given by expert practitioners such as intensive care specialists or anaesthetists.

For adults and children over 12 years, administer IM adrenaline: 0.5 mL of 1:1000 adrenaline (500 μg) into the anterolateral aspect of the middle third of the thigh.

For children between 6 and 12 years, give 0.3 mL of 1:1000 IM adrenaline (300 μg).

For children less than 6 years, give 0.15 mL of 1:1000 IM adrenaline (150 μg).

Adrenaline is repeated, if necessary, at 5-minute intervals according to blood pressure, pulse and respiratory function under the direction of appropriately trained clinicians.

Supportive care of anaphylaxis includes the following:

- Rapid fluid challenge of 500–1000 mL crystalloid
- Administration of 10 mg of chlorphenamine IM or by slow intravenous (IV) injection *following initial resuscitation* if there are also skin symptoms
- If the patient has continuing symptoms of asthma or wheeze, inhaled or intravenous bronchodilator therapy should be considered

Patients who have had an anaphylactic reaction should be discussed with an allergist or immunologist regarding further assessment and investigation if there is uncertainty about the cause (e.g. if other drugs had been administered at the same time as transfusion). A policy for future blood component therapy must be formulated (see section *Subsequent Management*).

RECOMMENDATION

- Anaphylaxis should be treated with intramuscular adrenaline (epinephrine). Patients who are thrombocytopenic or who have deranged coagulation should also receive intramuscular adrenaline if they have an anaphylactic reaction. (1A)

Shock/severe hypotension without clinical signs of anaphylaxis or fluid overload

Consider ABO blood group incompatibility or bacterial contamination. Both require supportive care with fluid

resuscitation, expert evaluation for inotropic, renal and/or respiratory support and blood component therapy for disseminated intravascular coagulation with bleeding. Isolated hypotension can occur in anaphylaxis and severe hypotension can occur in TRALI. In the latter, the clinical picture is usually dominated by dyspnoea.

If the identity check suggests ABO incompatibility due to transfusion of a unit intended for another patient, contact the transfusion laboratory immediately.

If bacterial contamination is suspected, take blood cultures from the patient (peripheral vein and through central line, if present) and then start broad spectrum intravenous (IV) antibiotics (the local regimen for patients with neutropenic sepsis would be appropriate). Immediately notify the transfusion laboratory staff and haematologist. The blood transfusion service should be contacted to arrange the recall of the implicated unit and for this to be cultured. They will also arrange recall and quarantine of all other components manufactured from the implicated donation.

Severe dyspnoea without shock

Consider TACO, TRALI or TAD where allergic reaction has been excluded as a cause for dyspnoea. Ensure the airway is patent and high-flow oxygen therapy started while urgent expert medical assessment is obtained. Initial investigation should include chest X-ray and oxygen saturation. Detailed investigation and treatment of TRALI (non-cardiogenic pulmonary oedema) and TACO (left atrial hypertension due to fluid overload) are beyond the scope of this guideline. The distinction is clinically important as the primary treatment of TRALI is ventilatory support and mortality/morbidity may be increased by loop diuretic therapy in patients who already have depleted intravascular volume.[28] Appropriate medical management should be initiated promptly. Cases where TRALI is strongly suspected should be discussed with a haematologist at the national blood service as investigation of donors may be required. It should be noted that TACO and TRALI may coexist[29] and pathobiology may be similar.[30] Appendix S4 provides a comparison of the pulmonary complications of transfusion[31] and Appendix S5 provides guidance on differentiating TACO, TRALI and TAD.

Moderate reactions

The differential diagnosis and investigation are similar to severe ATR. Unless there is an obvious alternative explanation for the symptoms/signs or the patient has a history of comparable, previously investigated, non-serious transfusion reactions, transfusion of the implicated unit should only be resumed after full clinical evaluation.

Moderate febrile symptoms

Symptoms and signs are defined as a temperature ≥39°C or a rise of ≥2°C from baseline and/or systemic symptoms such as chills, rigors, myalgia, nausea or vomiting in keeping with ISBT/IHN criteria. Bacterial contamination or a haemolytic reaction is very unlikely if the reaction is transient and the patient recovers with only symptomatic intervention. If the reaction is sustained, however, these possibilities should be considered. Management of bacterial contamination and haemolysis due to ABO incompatibility (also occasionally due to non-ABO antibodies, e.g. Wr^a) are described above under severe reactions and symptomatic treatment of febrile reactions is included in section Mild reactions.

RECOMMENDATION

If a patient develops sustained febrile symptoms or signs of moderate severity (temperature ≥39°C OR a rise of ≥2°C from baseline AND/OR systemic symptoms such as chills, rigors, myalgia, nausea or vomiting), bacterial contamination or a haemolytic reaction should be considered. (1C)

Moderate allergic symptoms

Signs and symptoms may include angioedema and dyspnoea, but not sufficiently severe to be life-threatening. Antihistamines such as chlorphenamine orally or IV may be effective and in addition oxygen therapy and a short-acting inhaled beta-2 agonists such as salbutamol may be useful for respiratory symptoms.[27] Corticosteroids act only to down-regulate the late-phase inflammatory response and have no role in managing acute symptoms.

Moderate respiratory symptoms

The decision to continue transfusion will depend on the clinical assessment of the probable cause of the symptoms, response to initial therapy and the urgency of transfusion.

Mild reactions

These are defined as having no or limited change in observations, for example an isolated fever ≥38°C but <39°C and rise of ≥1°C but <2°C from baseline and/or pruritus or rash but without other features (Figure 1). In these cases, it is reasonable to restart the transfusion under direct observation.

There are no randomised controlled trials (RCTs) which consider the symptomatic treatment of febrile symptoms associated with transfusion. Experience with paracetamol suggests that it is a useful antipyretic agent but less effective for

the management of symptoms such as chills or rigors. A systematic review of the use of non-steroidal anti-inflammatory drugs (NSAIDs) in fever unrelated to transfusion suggests that they may be more effective for this purpose.[32] An assessment of the risks of medication against the severity of the reaction should be made in each case. Caution would be required in the use of NSAIDs in patients with thrombocytopenia, reduced platelet function or renal impairment.

There are no reported trials of treatment of skin symptoms but clinical experience suggests that patients with skin reactions such as itch or rash with no other features may continue to receive the transfusion. Reducing the rate of transfusion and the use of a systemic antihistamine may be helpful.

RECOMMENDATION

- Patients with mild isolated febrile reactions may be treated with oral paracetamol (500–1000 mg in adults). Patients with mild allergic reactions may be managed by slowing the transfusion and treatment with an antihistamine. Corticosteroids should not be used routinely. (2C)

LABORATORY INVESTIGATION OF ATR

(See Appendix S2 for detailed discussion).

This is largely determined by the pattern of symptoms and clinical signs and the severity of the reaction. We recommend that all reactions considered to be a result of the transfusion, except minor allergic or febrile reactions, and without a history of comparable, non-serious reactions, be investigated with a standard battery of tests together with additional investigations based on the symptom complex (Table 1). The urgency of investigations and clinical details must be communicated to the laboratory. If febrile symptoms of moderate severity are sustained, bacterial contamination or a haemolytic reaction should be considered. Implicated units should be returned to the laboratory for further investigation and the blood service contacted immediately so that any associated components from the implicated donation can be withdrawn. If however, febrile symptoms are transient and the patient recovers with only symptomatic treatment, further investigation to exclude these possibilities is unlikely to be required.

Standard investigations

Standard investigations provide a baseline in case of subsequent clinical deterioration and may give an early indication of whether haemolysis has occurred.

RECOMMENDATION

- In all moderate and severe transfusion reactions, standard investigations, including full blood count, renal and liver enzymes should be performed. Patients with respiratory symptoms not due to allergy should also have a chest X-ray. (2C)

Investigations dependent on symptom complex

Further investigations should be guided by the clinical symptoms and signs, rather than the presumed category of reaction.

RECOMMENDATIONS

- If febrile symptoms of moderate severity are sustained, implicated units should be returned to the laboratory for further investigation and the blood service contacted immediately so that associated components from the implicated donation can be withdrawn if appropriate. Samples should be taken for repeat compatibility and culture and urine assessed for haemoglobin. (1C)
- In an ATR with only allergic features, repeat compatibility testing is not required. (1C)

Testing the patient for human leucocyte antibodies (HLA), human platelet antibodies (HPA) or human neutrophil-specific antibodies (HNA)

These are usually an incidental finding in patients with ATR and routine screening is not recommended (see Appendix S2 for detailed discussion and references).

RECOMMENDATION

- In the absence of platelet transfusion refractoriness or acute post-transfusion thrombocytopenia or leucopenia, investigation of the patient with ATR for leucocyte, platelet or neutrophil-specific antibodies is not indicated. (1B)

MANAGEMENT OF PATIENTS WITH REPEATED REACTIONS

This section focuses on the management of recurrent febrile and allergic reactions. In the small number of patients with repeated reactions, premedication and/or component manipulation by washing or plasma removal is usually considered, although the evidence base is weak[33]

Febrile non-haemolytic transfusion reactions

Reports on prevention of FNHTRs using premedication with paracetamol (acetaminophen), usually in a dose of 500–650 mg, are of inadequate quality, include both primary and secondary prevention, and report contradictory results. Studies suggesting a reduced incidence of febrile reactions in

TABLE 1 Investigation of Moderate or Severe Acute Transfusion Reactions (for detailed guidance and references, see Appendix S2).

Symptoms	Investigations
Fever (≥2°C rise or ≥39°C), and/or chills, rigors, myalgia, nausea or vomiting and/or loin pain	Standard investigations[a] If febrile reaction sustained: Return unit to laboratory Take samples for repeat compatibility testing and DAT on both the pre- and post-transfusion samples. If the DAT is positive or stronger on the post-transfusion sample, elution studies should be performed[b] Haptoglobin, LDH[b] Coagulation screen Assessment of urine for haemoglobin[b] Blood cultures from patient
Dyspnoea, wheeze, or features of anaphylaxis	Standard investigations[a] Check oxygen saturation or blood gases. Chest X-ray (mandatory if symptoms are severe) If severe allergy/anaphylaxis suspected, consider measurement of serial mast cell tryptase (plain tube) (immediate, 1–2 h and 24 h) Patients with respiratory symptoms not caused by anaphylaxis or allergy should have investigations for left atrial hypertension (e.g. echocardiography and pre- and post-transfusion NT-Pro BNP) to help distinguish the type of pulmonary complication to assist diagnosis and haemovigilance reporting
Hypotension (isolated fall systolic of ≥30 mm Hg resulting in level ≤80 mm Hg)	Investigate as for fever If severe allergy/anaphylaxis, consider measurement of serial mast cell tryptase, as above

Abbreviations: DAT, direct antiglobulin test; LDH, lactate dehydrogenase; NT-Pro BNP, N-terminal-pro hormone B-type natriuretic peptide.

[a]Standard investigations: full blood count, renal and liver enzymes.

[b]Note that in adults, platelets and plasma components are unlikely to cause significant haemolysis and so haemolysis screen is of limited value.

patients premedicated with paracetamol[34–37] are counterbalanced by studies with negative results.[38–42] Studies on patients with a previous febrile reaction showed no difference in reaction rates compared to those with no previous reaction.[39,40] There is little information on the timing of administration of paracetamol (peak activity is 30–60 min after oral administration). Several studies show that paracetamol does not prevent inflammatory symptoms such as chills and rigors.[35,37–40] Plasma removal was reported to reduce the incidence of FNHTR before the introduction of prestorage leucodepletion,[43,44] but there are no recent publications to support this practice.

In the absence of clear evidence, if recurrent reactions occur, options include premedication with oral paracetamol given 1 h before the reaction is anticipated (first option) or the use of washed blood components. NSAIDs may be useful in patients with chills or rigors associated with red cell transfusions but must be used with caution in patients with thrombocytopenia or renal impairment. An assessment of the risks of medication against the severity of reaction should be made in each case.

RECOMMENDATION

- For patients with recurrent febrile reactions, we recommend a trial of premedication with oral paracetamol given 1 h before the reaction is anticipated (or NSAIDs in patients with predominant chills or rigors—but an assessment of the risks of medication against the severity of reaction should be made in each case). Patients who continue to have moderate or severe febrile reactions despite premedication should have a trial of washed blood components (i.e. red cells and platelets). There is no role for prophylactic antihistamine or corticosteroids in the absence of allergic symptoms. (2C)

Allergic reactions

There are several studies of prevention/prophylaxis, including one large RCT.[37–40,42] None showed that premedication with an antihistamine (diphenhydramine), as widely used in the United States, was effective whether or not patients had experienced a previous reaction. There are no studies which assess the use of corticosteroids. The use of plasma-reduced (washed) components was shown to reduce the incidence of allergic complications in two before and after cohort studies[45,46] and in a post hoc analysis of a RCT investigating transfusion reactions to platelets (compared with prestorage leucodepletion).[35]

Mild allergic reactions

In the absence of evidence that prophylaxis is beneficial, patients who have experienced a mild allergic reaction may receive further transfusions without prior intervention and any subsequent mild reaction can be managed by reducing the rate of transfusion and by the use of a systemic antihistamine such as chlorphenamine orally or IV, which is effective in some patients with mild reactions.[2]

Alternatively, intervention as described for more severe reactions, detailed below in recommendation, may be used.

Moderate and severe allergic reactions

In patients with previous severe reactions who need urgent transfusion, infusion of standard components with or without antihistamine premedication with direct monitoring is justified.[47] Pooled platelets (suspended in platelet additive solution) are associated with fewer allergic reactions than apheresis platelets, which have a higher plasma content.[48–51] Recurrent allergic transfusion reactions to fresh frozen plasma (FFP) in patients treated with plasma exchange for conditions such as thrombotic thrombocytopenia purpura are reduced by the use of pooled solvent–detergent-treated FFP.[47,52–55]

RECOMMENDATIONS

For recurrent mild allergic reactions, there is no evidence to support routine prophylaxis with antihistamines or corticosteroids. Alternative causes such as allergy to drugs or latex gloves should be excluded. (2C)

For patients with recurrent moderate or severe allergic reactions, options for further transfusion include the following:

1. If prior reactions were to apheresis platelets, pooled platelets should be considered (suspended in platelet additive solution). (2B)
2. Consider antihistamine prophylaxis (although the evidence for efficacy is low, the risks are also low). (2B)
3. Routine prophylaxis with corticosteroids is not recommended. (2C)
4. Transfusion of washed red cells or platelets. (2C)
5. The use of pooled solvent–detergent-treated plasma when there are recurrent allergic reactions to FFP in patients undergoing plasma exchange. (2B)
6. If further transfusion is urgent and withholding blood is a greater risk, transfuse standard components under direct monitoring in a clinical area with resuscitation facilities. (2C)

- Patients who have experienced an anaphylactic reaction should be discussed with an allergist or immunologist if there is uncertainty about the causative agent (e.g. if other drugs were administered at the same time as the transfusion). (2C)

Patients with IGA deficiency

Anaphylactic transfusion reactions have rarely been described in patients with severe congenital IgA deficiency, sometimes in association with anti-IgA antibodies. However, there is a lack of evidence for a causative role and the link remains unclear. Haemovigilance data do not support an increased incidence of IgA deficiency in patients experiencing anaphylaxis, and reported reactions in IgA-deficient patients more often involve inflammatory features (fever, rigors, myalgia), with rapid onset (in the first 15 min of transfusion).[56]

Low IgA levels found on screening, in the absence of generalised hypogammaglobulinaemia, should be confirmed by a more sensitive method and IgA antibodies should be checked (assays done by the national blood services). Patients with confirmed IgA deficiency (<0.07 g/L) and a history of transfusion reactions should be transfused with washed red cells and washed platelets resuspended in platelet additive solution in elective situations. If FFP is required, the UK blood services keep a small stock of IgA-deficient plasma available on a national basis. If reactions persist in spite of washed components, the case should be discussed with a transfusion medicine specialist from the national blood service. If urgent, life-saving transfusion is needed, standard blood components should be transfused with direct observation in a clinical area with the skill and facilities to manage severe acute reactions.[57]

There is no high-level evidence to guide the management of patients with IgA deficiency and no prior transfusion. Serious reactions to standard components are very rare in this group[58] and patients with no history of allergic reactions may be transfused with standard components. Occasionally, the balance of clinical risks in a patient with a history of significant allergic reactions in other settings might warrant washed components. Discussion of the case with a transfusion medicine specialist or clinical immunologist may be helpful. Urgent transfusion must not be denied because washed components are not immediately available.

RECOMMENDATIONS

- Patients experiencing anaphylactic reactions to blood transfusion, or recurrent severe febrile/ inflammatory reactions within the first 15 min should have IgA levels measured. Patients with IgA deficiency diagnosed after an ATR should be discussed with a specialist in transfusion medicine regarding future management. (2C)
- Patients with confirmed IgA deficiency and a history of reaction to blood should receive washed components for elective transfusion but life-saving transfusion should not be delayed if these are not immediately available. The patient must be monitored closely for an acute reaction. (1C)
- Patients with known IgA deficiency (IgA <0.07 g/L) and no history of reactions to blood should receive standard components with a higher frequency of monitoring. Those with a history of allergy/anaphylaxis in other settings should be discussed with a transfusion medicine or clinical immunology or allergy specialist if time allows. (2C)

Patients with antibodies to HLA, HPA or HNA

There is little evidence that the use of HLA-, HNA- or HPA-matched components is of benefit in reducing the incidence

of transfusion reactions and these are not required unless there is evidence of platelet refractoriness (See Appendix S2).

Hypotensive reactions

Patients with otherwise unexplained hypotensive reactions should be given a trial of washed red cells or platelets resuspended in platelet additive solution.

In rare cases, it is thought to be due to bradykinin release, ACE inhibitors should be stopped before transfusion if clinically safe to do so.

ATR IN CHILDREN AND NEONATES

Symptoms and signs of ATR may be less easily recognised in children or neonates,[59] although they may have a higher prevalence than in adult transfusion recipients.[60] A high degree of vigilance by treating clinicians is needed. Protocols for drug management should be written in close collaboration with paediatric specialists. In the case of anaphylaxis, UKRC guidelines should be followed.[25] Appropriate paediatric doses of adrenaline are given above.

REPORTING ATR

Reporting to national haemovigilance schemes

Moderate and severe ATRs, as defined in this guideline, meet the criteria for serious adverse reactions and there is a legal requirement to report them to the Medicines and Healthcare Products Regulatory Agency (MHRA) (the UK Responsible Body under the Blood Safety and Quality Regulations, 2005).[61]

They should also be reported to the UK SHOT haemovigilance scheme to contribute to analysis of transfusion hazards and recommendations for improved safety. The latter is not a legal requirement but is mandated by laboratory accreditation and hospital quality assurance schemes and should therefore be considered a professional requirement. Reporters may wish to classify the reaction, as set out in Appendices S3 and S4. However, as classification can be difficult, the SHOT organisation will aid in classification into the appropriate category and provide a tool 'definitions of current SHOT reporting categories and what to report' (available on SHOT website).

Reporting to the blood transfusion service

This is essential when bacterial contamination of transfused components may have occurred, when TRALI is suspected or there is severe neutropenia or thrombocytopenia associated with an ATR, as associated components from the implicated donation must be removed from the blood supply.[62] A transfusion medicine specialist will also be available to give advice on the choice of components for future transfusion and the need for investigation of donors. Hospitals should have clear mechanisms in place to ensure prompt and effective communication with the blood service.

Reporting within the hospital

All healthcare organisations should have clear and effective systems in place for reporting transfusion incidents through local risk management and clinical governance structures and review by the Hospital Transfusion Committee. Patients with moderate or severe ATR should be reviewed by the Hospital Transfusion Team to:

1. Assess the appropriateness of management and investigations;
2. Plan management of future transfusions for the patient;
3. Ensure the suspected reaction has been reported to the MHRA, SHOT and blood service as appropriate;
4. Review the appropriateness of the transfusion;
5. Identify practice concerns, lessons to be learnt and any training requirements;
6. Identify and monitor trends.

RECOMMENDATION

- All transfusion reactions except mild febrile and/or allergic reactions must be reported to appropriate regulatory and haemovigilance organisations (MHRA and SHOT) and should also be reviewed within the hospital. (1C)

SHOT provides resources to support reporting and structured review of reaction incidents. See "Current Resources" section of the SHOT website, www.shotuk.org

TOPICS FOR AUDIT

Audit of acute transfusion reactions within a hospital, including documentation, management, internal and external reporting and planning of subsequent transfusions.

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CONFLICT OF INTEREST STATEMENT

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a full declaration of interests to the BSH and Task Force Chairs which may be viewed on request. None of the authors have any relevant conflicts of interest to declare.

REVIEW PROCESS

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines).

DISCLAIMER

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

AUDIT TOOL

Blank Audit template can be found on the www.b-s-h.org.uk

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

[Corrections made on 13 December 2023, after first online publication: The Supporting Information was corrected in this version.]

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