bjh guideline

Guideline on the investigation and management of acute transfusion reactions Prepared by the BCSH Blood Transfusion Task Force

Hazel Tinegate[1] (Writing group lead), Janet Birchall,[2] Alexandra Gray,[3] Richard Haggas,[4] Edwin Massey,[5] Derek Norfolk,[6] Deborah Pinchon,[7] Carrock Sewell,[8] Angus Wells[9] and Shubha Allard[10]

[1]Consultant Haematologist, NHS Blood and Transplant, Newcastle upon Tyne, UK, [2]Consultant Haematologist, NHSBT Filton, UK and North Bristol NHS Trust Bristol, UK, [3]Programme Director, Better Blood Transfusion, Scottish National Blood Transfusion Service, Edinburgh, UK, [4]Blood Transfusion Quality Manager, Leeds Teaching Hospitals, Leeds, UK, [5]Associate Medical Director-Patient Services, NHS Blood and Transplant, Filton, UK, [6]Consultant Haematologist, NHS Blood & Transplant and Leeds Teaching Hospitals, Leeds, UK, [7]Transfusion Nurse Specialist, Hull and East Yorkshire NHS Trust, Hull, UK, [8]Visiting Professor, Department of Immunology, University of Lincoln, Lincoln, UK, [9]Clinical Director Supply Chain, Scottish National Blood Transfusion Service, Edinburgh, UK and [10]Consultant Haematologist NHSBT and Chair, BCSH Transfusion Task Force, London, UK

Summary

Although acute non-haemolytic febrile or allergic reactions (ATRs) are a common complication of transfusion and often result in little or no morbidity, prompt recognition and management are essential. The serious hazards of transfusion haemovigilance organisation (SHOT) receives 30–40 reports of anaphylactic reactions each year. Other serious complications of transfusion, such as acute haemolysis, bacterial contamination, transfusion-related acute lung injury (TRALI) or transfusion-associated circulatory overload (TACO) may present with similar clinical features to ATR.

This guideline describes the approach to a patient developing adverse symptoms and signs related to transfusion, including initial recognition, establishing a likely cause, treatment, investigations, planning future transfusion and reporting within the hospital and to haemovigilance organisations.

Key recommendations are that adrenaline should be used as first line treatment of anaphylaxis, and that transfusions should only be carried out where patients can be directly observed and where staff are trained in manging complications of transfusion, particularly anaphylaxis. Management of ATRs is not dependent on classification but should be guided by symptoms and signs. Patients who have experienced an anaphylactic reaction should be discussed with an allergist or immunologist, in keeping with UK resuscitation council guidelines.

Keywords: transfusion reaction, anaphylaxis, febrile, allergic, non-haemolytic.

Correspondence: Dr Hazel Tinegate, Consultant Haematologist, NHSBT Newcastle, Holland Drive, Newcastle upon Tyne, NE2 4NQ.
E-mail: hazel.tinegate@nhsbt.nhs.uk

Background and methods

The guideline group was selected to be representative of UK-based medical experts. 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 1080 systematic reviews and randomized controlled trials (RCTs) and 878 observational studies, from which relevant publications were extracted by the members of the Writing Group.

Criteria used to quote levels and grades of evidence are according to the GRADE system (Guyatt *et al*, 2006). Strong recommendations (grade 1, 'recommended') are made when there is confidence that the benefits either do or do not outweigh the harm and burden and costs of treatment. Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation ('suggested') is made. Grade 1 recommendations can be applied uniformly to most patients whereas grade 2 recommendations require judicious application. The quality of evidence is graded as A (high quality randomized clinical trials), moderate (B) or low (C).

This publication reports the key recommendations of the Writing Group. The full version of the guideline, including appendices containing background information (can be found at http://www.bcshguidelines.com/documents/ATR_final_version_to_pdf.pdf.

Purpose and objectives

The purpose of this document is to provide clear guidance on the recognition, investigation and management of acute

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adverse reactions to blood components. It is clinically focused and recognizes that the precise nature and severity of reactions may not be apparent at presentation. It is intended to provide a framework for the development of institutional policies. The emphasis is on the immediate management of potentially life-threatening reactions but it also makes recommendations around appropriate investigation and strategies for prevention and prophylaxis. The key objectives are to:

- Provide a flow diagram to aid recognition of acute transfusion reactions and their immediate clinical management.
- Advise on further management of the patient during the reaction.
- Provide advice on the use of investigations.
- Discuss management of subsequent transfusions.
- Present recommendations for reporting adverse reactions to UK haemovigilance organizations, to blood services, and within the hospital.

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 acute transfusion reactions, and a table describing differences between transfusion-related acute lung injury (TRALI) and transfusion associated circulatory overload (TACO) can be found on the BCSH website (www.bcshguidelines.com/).

Introduction

Although acute transfusion reactions (ATR) are defined by the UK Serious Hazards of Transfusion group (SHOT) as those occurring within 24 h of the administration of blood or blood components *excluding* cases of acute reactions due to transfusion of the incorrect component, haemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-related circulatory overload (TACO) and those due to bacterial contamination of the component (Davies, 2008), this guideline includes these additional complications in the initial recognition and management, and use of investigations sections. We have adopted the international definitions for ATR proposed by the International Haemovigilance Network (IHN) and the International Society for Blood transfusion (ISBT) (IHN/ISBT, 2011) [see Appendix 3 of the full guideline (http://www.bcshguidelines.com/documents/ATR_final_version_to_pdf.pdf)].

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 (for example: prestorage leucodepletion reduces the rate of FNHTR but not allergic reactions (Paglino *et al*, 2004)). ATR rates of 0·5–3% of transfusions are commonly quoted (Fry *et al*, 2010). Data from SHOT annual reports, which tend to have fewer reports of mild FNHTR, suggest an incidence of more clinically serious ATR of around 14/100 000 components transfused, ranging from 11/100 000 for red cells to 29/100 000 for platelets (Knowles *et al*, 2011).

There is also 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 (Heddle, 2007). Except in rare cases, a specific allergen will not be identified in patients with allergic transfusion reactions (Sandler & Vassallo, 2011), although plasma reduction may lower their frequency (Tobian *et al*, 2011). Recent evidence suggests that *recipient* factors may be paramount in predicting allergic transfusion reactions and that preventative strategies should be directed at the minority of patients who have a propensity to severe reactions (Savage *et al*, 2011).

Whilst it is useful to categorize ATR for reporting and research purposes, and for international comparison, (British Thoracic Society/Scottish Intercollegiate Guideline Network guidelines on the management of asthma, 2011) 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, TRALI and TACO. Where the predominant clinical feature is respiratory distress, transfusion-associated dyspnoea (TAD) may be suspected. (British Thoracic Society/Scottish Intercollegiate Guideline Network guidelines on the management of asthma, 2011) The initial clinical picture is also often obscured by factors related to the patient's underlying medical condition, 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 prevention, where possible, of future episodes.

Recognition and initial management of acute transfusion reactions

To minimize the risk of harm, early identification of reactions and rapid clinical assessment is essential.

Recommendation

All patients should be transfused in clinical areas where they can be directly observed, and where staff are trained

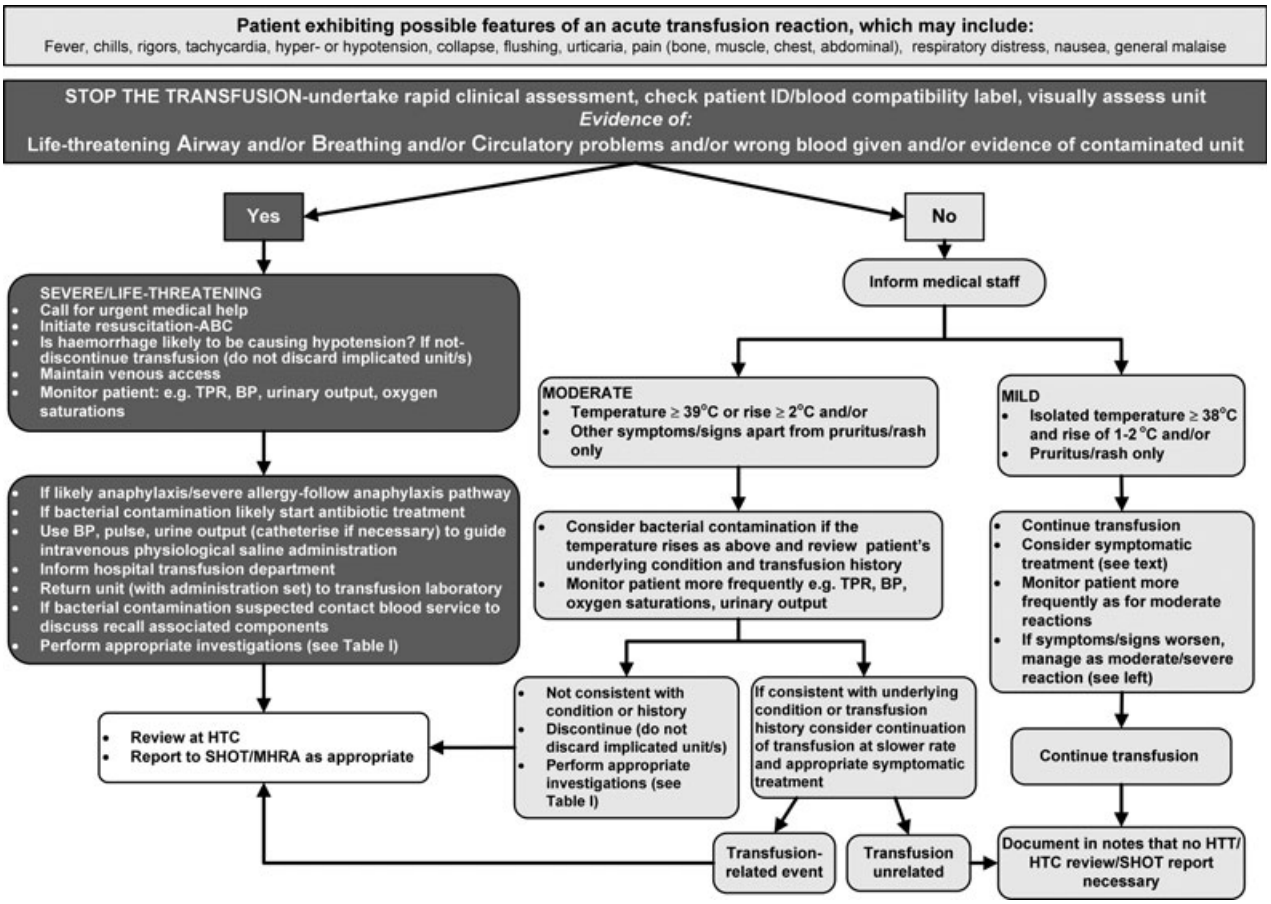

Fig 1. Flow diagram to guide the recognition and initial management of suspected acute transfusion reactions. ID, identification details; ABC, airway, breathing and circulation; TPR, temperature, pulse and respiratory rate; BP, blood pressure; HTT, hospital transfusion team; HTC, hospital transfusion committee; SHOT, serious hazards of transfusion; MHRA, medicines and healthcare products regulatory agency.

in the administration of blood components and the management of transfused patients, including the emergency treatment of anaphylaxis. (1C)

Recommendation

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. (2C)

Although anaphylactic and haemolytic reactions can present after only a small volume of blood has been transfused (Heddle, 2009), reactions can present much later, on occasion several hours after completion of the transfusion (Taylor *et al*, 2009). Therefore, observation and monitoring is required throughout the transfusion episode and patients should be asked to report symptoms that develop during the next 24 h (BCSH, 2009). Unconscious patients, or those unable to report symptoms, require direct monitoring.

Recommendation

Patients should be asked to report symptoms that develop within 24 h of completion of the transfusion. (2C)

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 the recognition and initial management of suspected ATR.

In *all* cases, the transfusion must be stopped temporarily and venous access maintained with physiological saline. The patient's Airway, Breathing and Circulation ('ABC') must be assessed (Resuscitation Council (UK), 2008). Their core identification details must be checked to ensure they correspond with those on the blood component compatibility label – is the reaction due to transfusion of a component intended for another patient (British Committee for Standards in Haema-

tology, 2009)? 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 Fig 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 maintained. Identification details should be checked between the patient, their identity band and the compatibility label of the blood component. Perform visual inspection of the component and assess the patient with standard observations. (1C)

Severe reactions

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

Recommendation

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. (1C)

Mild or moderate reactions

If the reaction is *mild*, for example an isolated rise in temperature without chills, rigours or other change in observations (Fig 1), 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 pyrexia (temperature of $\geq$38°C AND rise of 1–2°C from baseline), 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 (British Committee for Standards in Haematology, 2009), and abnormal clinical features, such as fever, rashes or angioedema, frequently assessed. A patient who has experienced a transfusion reaction should be observed directly until the clinical picture has improved.

Symptoms and signs of acute transfusion reactions

Acute transfusion reactions can present with a range of symptoms and signs of varying severity. These include:
Fever and related inflammatory symptoms or signs, such as chills, rigours, myalgia, nausea or vomiting.
Cutaneous symptoms and signs including urticaria (hives), other skin rashes and pruritus.
Angioedema (localized 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 airway, breathing or circulation problems, usually associated with skin and mucosal change would suggest anaphylaxis (Resuscitation Council (UK), 2008)

The symptoms and signs of reactions are discussed in more detail in Appendix 1 of the full guideline (http://www.bcshguidelines.com/documents/ATR_final_version_to_pdf.pdf). A table incorporating both the ISBT/IHN and SHOT classifications, and gradations of severity, can be found in Appendix 3 of the full guideline (http://www.bcshguidelines.com/documents/ATR_final_version_to_pdf.pdf). Both these appendices can be found on the BCSH website (www.bcshguidelines.com).

Management of Acute Transfusion Reactions

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

Recommendation

Initial treatment of ATR is not dependent on classification but 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

Whilst awaiting medical support, the patient should be managed as appropriate for an acutely ill patient (National Insti-

tute of Clinical Excellence (NICE) 2007) (see Fig 1). 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 nebulizing a short-acting inhaled beta-2 agonist, such as salbutamol (British Thoracic Society/Scottish Intercollegiate Guideline Network guidelines on the management of asthma, 2011). 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) according to the UK Resuscitation guidelines (Resuscitation Council (UK), 2008). 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 <6 years give 0·15 ml of 1:1000 IM adrenaline (150 μg).
  Adrenaline is repeated, if necessary, at 5-min intervals according to blood pressure, pulse and respiratory function under the direction of appropriately trained clinicians.

- Supportive care of anaphylaxis includes:
  - Rapid fluid challenge of 500–1000 ml crystalloid.
  - Administration of 10 mg of chlorphenamine IM or by slow intravenous (IV) injection *following initial resuscitation*.
  - Administration of 200 mg of hydrocortisone IM or by slow IV injection *following initial resuscitation*.
  - 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 to blood should be discussed with an allergist or immunologist regarding further assessment and investigation. A policy for future blood component therapy must be formulated (see section on *Subsequent Management*).

Recommendations

Anaphylaxis should be treated with intramuscular adrenaline (epinephrine) according to Resuscitation Council (UK) guidelines. Patients who are thrombocytopenic or who have deranged coagulation should also receive IM adrenaline if they have an anaphylactic reaction. (1A)

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

- Consider ABO 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 (see section on Subsequent management).
- If the identity check shows ABO incompatibility due to transfusion of a unit intended for another patient, contact the transfusion laboratory immediately to prevent a further 'wrong' blood incident.
- If bacterial contamination is suspected, take blood cultures from the patient (peripheral vein and through central line, if present) and start broad-spectrum IV antibiotics (the local regimen for patients with neutropenic sepsis would be appropriate). Immediately notify the transfusion laboratory staff and haematologist to arrange culture of the implicated unit/units and contact the blood service so that any other components from the implicated donation can be recalled and quarantined.

Severe dyspnoea without shock.

- Consider TRALI or TACO, although dyspnoea can be a feature of allergic reactions and occasionally occurs as an unexplained complication of transfusion and may be designated TAD (Davies, 2008; British Thoracic Society/Scottish Intercollegiate Guideline Network guidelines on the management of asthma, 2011). 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-car-

diogenic pulmonary oedema) and TACO (left ventricular failure due to fluid overload) is beyond the scope of this guideline. However, 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 (Kopko & Holland, 1999). Appendix 4 of the full guideline (http://www.bcshguidelines.com/documents/ATR_final_version_to_pdf.pdf), summarizes the major diagnostic features of, and differences between, these conditions.

Moderate reactions

The differential diagnosis and investigation is 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. In most cases it is prudent to discontinue or switch to an alternative unit.

Moderate febrile symptoms. Symptoms and signs are defined as a temperature $\geq$39°C or a rise of $\geq$2°C from baseline and/or systemic symptoms, such as chills, rigours, myalgia, nausea or vomiting in keeping with IHN/ISBT. Bacterial contamination or a haemolytic reaction are 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 are described above under severe reactions and symptomatic treatment of febrile reactions is included below under mild reactions.

Recommendation

If a patient develops sustained febrile symptoms or signs of moderate severity (temperature $\geq$39°C OR a rise of $\geq$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. 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 agonist, such as salbutamol, may be useful for respiratory symptoms (McClelland, 2007; BTS/SIGN guideline, 2011).

Mild reactions

These are defined as having no or limited change in vital signs for example an isolated fever $\geq$38°C and rise of 1–2°C from baseline and/or pruritus or rash but without other features (Fig 1). In these cases it is reasonable to restart the transfusion with direct observation.

There are no RCTs that consider the symptomatic treatment of febrile symptoms associated with transfusions. Experience

Table I. Investigation of moderate or severe acute transfusion reactions [for detailed guidance and references see Appendix 2 of the full guideline (http://www.bcshguidelines.com/documents/ATR_final_version_to_pdf.pdf)].

Symptoms	Investigations
Fever ($\geq$2°C rise or $\geq$39°C), and/or chills, rigors, myalgia, nausea or vomiting and/or loin pain	Standard investigations* Take samples for repeat compatibility testing, DAT, LDH and haptoglobin Take blood cultures from patient Coagulation screen Do not discard implicated unit *If febrile reaction sustained*, return unit to laboratory, repeat serological investigations (compatibility testing, antibody screen and DAT), haptoglobin and culture unit *If loin pain*, perform serological investigations as above
Mucosal swelling (angio-oedema)	Standard investigations* Measure IgA level (EDTA sample)- if <0·07 g/l, and no generalized hypogammaglobulinaemia, perform confirmatory test with sensitive method and check for IgA antibodies
Dyspnoea, wheeze, or features of anaphylaxis	Standard investigations* Check oxygen saturation or blood gases. Chest X-ray (mandatory if symptoms severe) If severe or moderate allergy suspected measure IgA level. If severe allergy/anaphylaxis suspected, consider measurement of serial mast cell tryptase (plain tube) (immediate, 3 h and 24 h)
Hypotension (isolated fall systolic of $\geq$30 mm resulting in level $\leq$80 mm)	Investigate as for fever If allergy suspected measure IgA level. If severe allergy/anaphylaxis consider measurement of serial mast cell tryptase, as above

DAT, direct antiglobulin test; Ig, immunoglobulin; LDH, lactate dehydrogenase.
*Standard investigations: full blood count, renal and liver function tests, and assessment of urine for haemoglobin

with paracetamol suggests 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 in fever unrelated to transfusion suggests that they may be more effective for this purpose (Kim *et al*, 2009). 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 or reduced platelet function

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. (2C)

Laboratory investigation of ATR

[see Appendix 2 of the full guideline (http://www.bcshguidelines.com/documents/ATR_final_version_to_pdf.pdf) 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 I). The urgency of investigations and clinical details must be communicated to the laboratory so that, where necessary, results can be obtained rapidly and contribute to decisions regarding the risk of continued transfusion and the management of the acute event. Samples must be collected and labelled in line with local and national guidelines. 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 or platelet transfusion refractoriness has occurred.

Recommendation

In all moderate and severe transfusion reactions, standard investigations, including full blood count, renal and liver function tests and assessment of the urine for haemoglobin should be performed. (2C)

Investigations dependent on symptom complex

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

Recommendation

If febrile symptoms of moderate severity are sustained, implicated units should be returned to the laboratory for further investigation, the blood service contacted immediately so that associated components from the implicated donation can be withdrawn and the patient sampled for repeat compatibility and culture. (1C)

Recommendation

Patients who have experienced moderate or severe allergic reactions should have IgA levels measured. Low levels found on screening, in the absence of generalized hypogammaglobulinaemia, should be confirmed by a more sensitive method and IgA antibodies should be checked. Patients with IgA deficiency diagnosed after an ATR should be discussed with an allergist or immunologist regarding future management. (2C)

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 2 of the full guideline (http://www.bcshguidelines.com/documents/ATR_final_version_to_pdf.pdf) for detailed discussion and references].

Recommendation

In the absence of platelet or granulocyte 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)

Subsequent management of patients with repeated reactions

This section focuses on the management of recurrent febrile and allergic reactions and those patients who have experienced anaphylaxis. 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. Transfusion premedication has been reviewed (Tobian *et al*, 2007).

Febrile non-haemolytic transfusion reactions (FNHTR)

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 patients premedicated with paracetamol (Heddle *et al*, 1993, 2002; Ezidiegwu *et al*, 2004; Kennedy *et al*, 2008) are counterbalanced by studies with negative results (Patterson *et al*, 2000; Wang *et al*, 2002; Sanders *et al*, 2005). Studies on patients with a previous febrile reaction showed no difference in reaction rates compared to those with no previous reaction (Wang *et al*, 2002; Sanders *et al*, 2005). There is little information on the timing of administration of paracetamol (peak activity is 30–60 min after oral administration). Several studies showed that paracetamol does not prevent inflammatory symptoms, such as chills and rigors (Patterson *et al*, 2000; Heddle *et al*, 2002; Wang *et al*, 2002; Sanders *et al*, 2005; Kennedy *et al*, 2008). Plasma removal was reported to reduce the incidence of FNHTR before the introduction of prestorage leucodepletion (Heddle *et al*, 1999; Vo *et al*, 2001), 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 one hour before the reaction is anticipated (first option) or the use of washed blood components. Non-steroidal anti-inflammatory drugs may be useful in patients with chills or rigors associated with red cell transfusions, but must be used with extreme caution in patients with thrombocytopenia. 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 one hour 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 react should have a trial of washed blood components. (2C)

Allergic reactions

There are several studies of prevention/prophylaxis, including one large RCT (Patterson *et al*, 2000; Wang *et al*, 2002; Sanders *et al*, 2005; Kennedy *et al*, 2008). 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 that assess the use of steroids. Use of plasma-reduced (washed) components was shown to reduce the incidence of allergic complications in one before and after cohort study (Azuma *et al*, 2009) and in an *ad hoc* analysis (Heddle *et al*, 2002) of a RCT investigating transfusion reactions to platelets (compared with prestorage leucodepletion).

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 (McClelland, 2007). Alternatively intervention as described for more severe reactions, detailed below in the recommendation, may be used.

Moderate and severe allergic reactions (other than IgA deficiency). In patients with previous severe reactions who need urgent transfusion, infusion of standard components with or without antihistamine premedication with direct monitoring is justified (Gilstad, 2003).

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 (Gilstad, 2003); Scully *et al*, 2007; BCSH, 2004)

Recommendation

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

Recommendation

For patients with recurrent moderate or severe allergic reactions, other than those in which the patient is IgA-deficient, options for further transfusion include:

- **Use of directly monitored transfusion of standard components in a clinical area with resuscitation facilities. Consider antihistamine prophylaxis (although the evidence for efficacy is low, the risks are also low). This may be the only option when further transfusion is urgent and withholding blood is a greater risk. (2C)**
- **Transfusion of washed red cells or platelets. (2C)**
- **The use of pooled solvent detergent-treated FFP when there are recurrent allergic reactions to FFP in patients undergoing plasma exchange. (2B)**

Recommendation

Patients who have experienced an anaphylactic reaction associated with transfusion must be discussed with an allergist or immunologist, in keeping with Resuscitation Council (UK)guidelines. (1C)

Patients with IgA deficiency

There are occasional, fully investigated patients with severe IgA deficiency, anti-IgA antibodies and a history of allergic reactions to blood components. However, there is a much larger group of patients with confirmed IgA deficiency, often picked up during antibody screening for coeliac disease, with or without known IgA antibodies, who present for their first transfusion or have been previously transfused with standard components without adverse reaction.

The former group should be transfused with blood components from IgA-deficient donors in elective situations if available (the UK blood services keep a small stock of IgA-deficient red cells available on a regional or national basis and a small panel of IgA-deficient platelet and plasma donors can be contacted). If IgA-deficient components are not available *in a clinically relevant time frame*, then washed red cells should be used (NB, washed platelets resuspended in platelet additive solution still contain significant amounts of IgA-containing plasma). 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 allergic reactions (Sandler, 2006).

There is no high level evidence to guide the management of IgA-deficient patients with no history of ATR. Experience suggests that serious reactions to standard components are very rare in this group. Factors that should influence the choice of component include urgency of transfusion, indication for IgA testing, history of allergy or anaphylaxis, level of confirmation of the diagnosis and whether repeated transfusions will be needed. Urgent transfusion must not be denied because IgA-deficient or washed components are not immediately available. Discussion of the case with a transfusion medicine expert or clinical immunologist may be helpful.

Recommendation

Patients with confirmed IgA deficiency and a history of reaction to blood should be transfused with components from IgA-deficient donors (first choice) or washed red cells (second choice) if time allows. (1C)

Life-saving transfusion should not be denied or delayed if these are not immediately available but the facilities and skills to manage severe allergic reactions must be present. (1C)

Recommendation

Patients with known IgA deficiency (IgA < 0·07g/l) and no history of reactions to blood must be assessed on an individual basis, taking into account the urgency of transfusion, the indication for IgA testing, the anticipated frequency of transfusion, and history of allergy/anaphylaxis in other settings. Most will receive standard components without problems, but discussion with a transfusion medicine or clinical immunology or allergy specialist is advisable if time allows. (2C)

Patients with leucocyte antibodies (HLA), platelet antibodies (HPA) or neutrophil-specific antibodies (HNA)

There is no evidence that the use of HLA-, HNA- or HPA-matched components are of benefit in reducing the incidence of transfusion reactions unless there is evidence of platelet refractoriness [See Appendix 2 of the full guideline (http://www.bcshguidelines.com/documents/ATR_final_version_to_pdf.pdf)].

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 the rare cases thought to be due to bradykinin release, angiotensin-converting-enzyme (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 recognized in children or neonates (Gauvin *et al*, 2006) although they may have a higher prevalence than in adult transfusion recipients (Stainsby *et al*, 2008; Knowles *et al*, 2011). Hence, 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 (Resuscitation Council (UK), 2008) and appropriate paediatric doses of adrenaline are given in section 6. Children with severe allergic or anaphylactic reactions to a blood component should be discussed with a paediatric allergy specialist regarding further assessment and investigation. If the reaction is associated with methylene blue plasma, specific investigations of possible methylene blue allergy should be considered.

Reporting ATR

Reporting to national schemes

Moderate and severe ATR, 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, http://www.opsi.gov.uk/si/si2005/20050050.htm). 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 the SHOT/IHN/ISBT table [Appendix 3 of the full guideline (http://www.bcshguidelines.com/documents/ATR_final_version_to_pdf.pdf)], however, as classification can be difficult, the SHOT organization will aid in classification into the appropriate category.

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. 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 Centre.

Reporting within the hospital

All healthcare organizations 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:

- Assess the appropriateness of management and investigations,
- plan management of future transfusions for the patient,
- ensure the suspected reaction has been reported to the MHRA, SHOT or regional Blood Centre as appropriate,
- review the appropriateness of the transfusion,
- identify practice concerns, lessons to be learnt and any training requirements,
- identify and monitor trends.

Recommendation

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

Topics for audit

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

Disclaimer

While the advice and information in these guidelines are believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of the guidelines.

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Author contributions

HT led the writing group and contributed the section on investigations and classifications. JB wrote the section on recognition and management, and designed the flow diagram with AG, who also contributed to recognition and immediate management. RH, DP, EM and AW contributed to all sections of the guideline. CS advised on immunological investigations and management of anaphylaxis. SA, as chair of the Transfusion Task Force and DN as past chair, both advised on the scope and format of the document.

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