Guideline on the investigation and management of acute transfusion reactions

Prepared by the BCSH Blood Transfusion Task Force

Address for correspondence:
BCSH Secretary
British Society for Haematology
100 White Lion Street
London N1 9PF
e-mail bcsh@b-s-h.org.uk

Writing Group:

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

Table of Contents

1. 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 randomised controlled trials 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 randomised 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 is accessible on www.bcshguidelines.com.

2. 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 recognises 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 organisations, 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)

3.

Summary of Key Recommendations	Strength	Quality of Evidence
Recognition of acute transfusion reactions (ATR)		
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.	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.	2	C
Patients should be asked to report symptoms which develop within 24 hours of completion of the transfusion.	2	C
Immediate management of ATR		
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.	1	C
For patients with mild reactions, such as pyrexia (temperature of $\geq$ 38 ^{o}C **and** rise of 1-2^{o}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 (500-1000mg in adults). Patients with mild allergic reactions may be managed by slowing the transfusion and treatment with an antihistamine.	2	C
Anaphylaxis should be treated with intramuscular adrenaline (epinephrine) according to UKRC guidelines. 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	1	C

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.		
If a patient develops sustained febrile symptoms or signs of moderate severity (temperature $\geq$ 39^{o}C **or** a rise of $\geq$ 2^{o}C **and/or** systemic symptoms such as chills, rigors, myalgia, nausea or vomiting), bacterial contamination or a haemolytic reaction should be considered.	1	C
Laboratory Investigations		
In all moderate and severe transfusion reactions, standard investigations, including full blood count, renal and liver function tests and assessment of the urine for hemoglobin should be performed.	2	C
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.	1	C
Patients who have experienced moderate or severe allergic reactions should have IgA levels measured. Low levels found on screening, in the absence of generalised 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.	2	C
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.	1	B
Subsequent management of the patient		
Patients who have experienced an anaphylactic reaction associated with transfusion must be discussed with an allergist or immunologist, in keeping with UKRC guidelines.	1	C
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.	2	C
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.	2	C
For patients with recurrent moderate or severe allergic reactions, other than those in which the patient is IgA deficient, options for further transfusion include:	2	C

• 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. • Transfusion of washed red cells or platelets • The use of pooled solvent-detergent treated FFP when there are recurrent allergic reactions to FFP in patients undergoing plasma exchange.	 2 2	 C B
• 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. • 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. • 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.	1 1 2	C C C
Reporting of ATR		
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	1	C

4. Introduction

Although acute transfusion reactions (ATR) are defined by the UK Serious Hazards of Transfusion group (SHOT) as those occurring within 24 hours 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, 2011). (see Appendix 3.

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 JL *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 & Cohen, 2010)

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 *et al*, 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, 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 categorise ATR for reporting and research purposes, and for international comparison, (IHN, 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, transfusion-associated acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). Where the predominant clinical feature is respiratory distress, transfusion-associated dyspnoea (TAD) may be suspected. (IHN, 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.

5. Recognition and initial management of acute transfusion reactions

To minimise 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 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 *et al*, 2009), reactions can present much later, on occasion several hours after completion of the transfusion (Taylor *et a*l, 2009). Therefore, observation and monitoring is required throughout the transfusion episode and patients should be asked to report symptoms which develop during the next 24 hours (BCSH, 2009). Unconscious patients, or those unable to report symptoms, require direct monitoring.

Recommendation
Patients should be asked to report symptoms which develop within 24 hours of completion of the transfusion. (2C)

5.1 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 (flow diagram) provides a practical guide to 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. (UKRC guidelines, 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? (BCSH, 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 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 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)

5.2 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)

5.3 Mild or moderate reactions
If the reaction is *mild*, for example an isolated rise in temperature without chills, rigors or other change in observations, (see Fig 1 Flow Diagram) 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 ^{o}C AND rise of 1-2^{o}C from baseline), and/or pruritus or rash but WITHOUT other features, the transfusion may be continued with appropriate treatment and direct observation. (2B)

5.4 Standard observations The patient's pulse rate, blood pressure, temperature and respiratory rate should be monitored, (BCSH, 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.

6. 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, 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 airway, breathing or circulation problems, usually associated with skin and mucosal change would suggest anaphylaxis (UKRC, 2008)

The symptoms and signs of reactions are discussed in more detail in Appendix 1. A table incorporating both the ISBT/IHN and SHOT classifications, and gradations of severity, can be found in Appendix 3. Both these appendices can be found on the BCSH website.

7. 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)

7.1 Severe reactions

Whilst awaiting medical support manage the patient as appropriate for an acutely ill patient (National Institute for Clinical Excellence, 2007) (see Figure 1 Flow Diagram). 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 agonist such as salbutamol. (British Thoracic Society/SIGN guideline 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.

7.1.1 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. (UKRC guidelines, 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 1:1,000 adrenaline (500mcg) into the anterolateral aspect of the middle third of the thigh.
  For children between 6 and 12 years give 0.3 ml of 1:1,000 IM adrenaline (300mcg)
  For children less than 6 years give 0.15 ml of 1:1,000 IM adrenaline (150mcg)
  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:
  - Rapid fluid challenge of 500-1000ml 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*).

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

7.1.2 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 7.1.3).
- 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 with the blood service so that any other components from the implicated donation can be recalled and quarantined.

7.1.3 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 (SHOT Toolkit, 2010; IHN 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-cardiogenic 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 and Holland, 1999). Appendix 4, on the BCSH website summarises the major diagnostic features of, and differences between, these conditions.

7.2 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.

7.2.1 Moderate febrile symptoms

Symptoms and signs are defined as a temperature $\geq 39^{o}C$ **or** a rise of $\geq 2^{o}C$ from baseline **and/or** systemic symptoms such as chills, rigors, myalgia, nausea or vomiting in keeping with ISBT/IHN. 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 ≥ 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)

7.2.2 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).

7.3 Mild reactions
These are defined as having no or limited change in vital signs for example an isolated fever ≥ 38 °C **and** rise of 1-2°C from baseline **and/or** pruritus or rash but **without** other features (Figure 1 Flow Diagram). In these cases it is reasonable to restart the transfusion with direct observation.
There are no randomised controlled trials which consider the symptomatic treatment of febrile symptoms associated with transfusions. Experience 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)

8. Laboratory investigation of ATR (see Appendix 2 on the BCSH website 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 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.

8.1 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)

8.2 Investigations dependent on symptom complex

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

Table 1 Investigation of Moderate or Severe Acute Transfusion Reactions (for detailed guidance and references see Appendix 2 on the BCSH website)

Symptoms	Investigations
Fever (>2°C rise or ≥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 <0.07g/L , and no generalised 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 ≥30 mm resulting in level ≤80mm)	Investigate as for fever If allergy suspected measure IgA level. If severe allergy/anaphylaxis consider measurement of serial mast cell tryptase, as above

* Standard investigations: full blood count, renal and liver function tests, and assessment of urine for haemoglobin

Abbreviations: DAT, direct antiglobulin test; Ig, immunoglobulin; LDH, lactate dehydrogenase;

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 generalised 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)

8.3 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 on the BCSH website 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)

9. 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. Transfusion premedication has been reviewed by Tobian (2007)

9.1 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; Heddle *et al*, 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 (Sanders *et al* 2005; Wang *et al* 2002). There is little information on the timing of administration of paracetamol (peak activity is 30-60 minutes after oral administration). Several studies show that paracetamol does not prevent inflammatory symptoms such as chills and rigors (Kennedy *et al*; 2008; Heddle *et al*; 2002, Wang *et al*; 2002; Patterson *et al*; 2000; Sanders *et al*, 2005). Plasma removal was reported to reduce the incidence of FNHTR before the introduction of prestorage leucodepletion, (Heddle 1999 *et al*; 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)

9.2 Allergic Reactions
There are several studies of prevention/prophylaxis, including one large randomised controlled trial (RCT) (Kennedy *et al*, 2008; Sanders *et al*, 2005; Wang *et al*, 2002; Patterson *et al*, 2000). 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 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).

9.2.1 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 (Handbook of Transfusion Medicine 4th Edition, 2007). Alternatively intervention as described for more severe reactions, detailed below in recommendation, may be used.

9.2.2 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, 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 UKRC guidelines. (1C)

9.3 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)

9.4 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).

9.5 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, ACE inhibitors should be stopped before transfusion if clinically safe to do so.

10. ATR in children and neonates

Symptoms and signs of ATR may be less easily recognised 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 & Cohen, 2010). 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 (UKRC, 2008) and appropriate paediatric doses of adrenaline are given in section 7. 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.

11. Reporting ATR

11.1 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 (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 Serious Hazards of Transfusion (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, on BCSH website) However, as classification can be difficult, the SHOT organisation will aid in classification into the appropriate category.

11.2 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.

11.3 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:

- 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 organisations (MHRA and SHOT) and should also be reviewed within the hospital. (1C)

12. Topics for audit

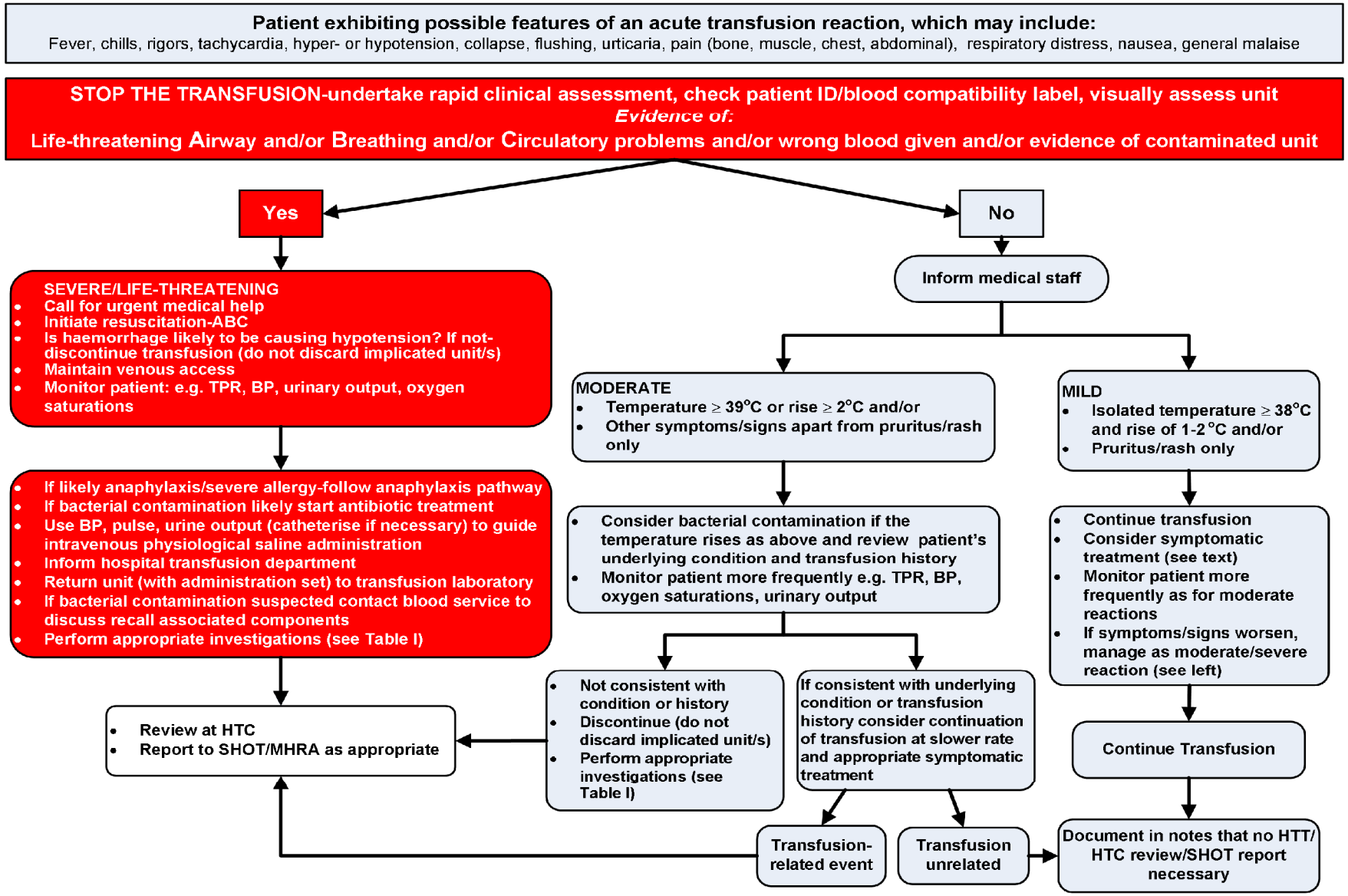
Audit of acute transfusion reactions within a hospital: including the documentation, management, internal and external reporting, and planning of subsequent transfusions.

13. Acknowledgements

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.

The authors are also grateful to Dr Susan Knowles for her help in planning the guideline, Helen New for advice on paediatric management, Susan Henderson and Sandra Hodgkins for their help in formatting the document, and to the BCSH Transfusion Task Force, Sounding Board and other colleagues for their advice.

Figure 1 Flow Diagram for recognition, initial management and subsequent management and investigations.



Appendix 1

Symptoms and signs of acute transfusion reactions

Fever and related symptoms or signs

Although characteristic of FNHTR, pyrexia and other symptoms or signs of an inflammatory response (myalgia, malaise, nausea, chills or rigors) may also occur in acute haemolysis, TRALI and bacterial transfusion-transmitted infection (TTI) (Heddle et al, 1993; 2002). Transfusion can often be continued in patients with mild FNHTR but differentiation from other causes is not always straightforward. Life-threatening haemolysis due to ABO incompatibility is unlikely if the correct unit of blood has been given. Acute haemolysis due to other antibodies may occasionally present with immediate clinical features suggesting a severe or moderate febrile reaction during the transfusion, with signs of haemolysis appearing later. (Taylor et al, 2009). TRALI can be reasonably excluded if the patient has no respiratory symptoms.

The possibility of bacterial TTI should always be considered as early appropriate treatment is life-saving. Several authors report this to be more likely if the rise in temperature is 2ºC or more (Heddle et al, 2007; Hewitt, 2009). In the 16 confirmed reports of bacterial TTI to SHOT between 2005 and 2010, all patients had symptoms or signs in addition to pyrexia and, in the five cases where a specific temperature was stated this was either 39ºC or above or associated with a rise of greater than 2ºC (personal communication from National Bacteriology Laboratory, England). Inspection of the implicated unit is important as discolouration or abnormal particles are suggestive of contamination (Handbook of Transfusion Medicine, 4th edition, 2007).

Skin lesions and rashes

Urticaria is commonly seen with allergic reactions but other types of skin change may occur, such as maculopapular rashes, erythema or flushing. In some transfusion reactions there is no visible rash but itching is reported by the patient (Domen and Hoeltge, 2003).

Angio-oedema

This describes localized, non-pitting, oedema of the subcutaneous or submucosal tissues and usually indicates an allergic reaction. The eyelids and mouth are most often affected, less commonly throat and tongue (Kaplan and Greaves, 2005). If angio-oedema occurs, the transfusion must be stopped immediately and the patient promptly assessed and treated.

Dyspnoea

Shortness of breath is a non-specific symptom and successful management relies on careful clinical examination supported by the results of investigations such as radiology and measurement of oxygen saturation/blood gases. Possible causes include allergy, TRALI, TACO and TAD. Stridor and wheeze suggest an allergic reaction but also occur in patients with TACO and have been reported once, associated with chills and rigors, in bacterial TTI. (Taylor et al, 2008). Pulmonary oedema with clinical signs of basal crackles and radiological evidence suggest a diagnosis of TACO or TRALI and helps exclude allergy. Low oxygen saturation is not diagnostic of a specific condition, although it gives information on severity. The possibility that clinical features are related to the patient's underlying illness must be kept in mind.

Anaphylaxis

The UK Resuscitation Council advises that a precise definition of anaphylaxis is not important for emergency treatment. An anaphylactic reaction involves a severe, life-threatening, generalised or systemic hypersensitivity reaction characterised by rapidly developing airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes.

Hypotension
This is defined as a drop in systolic and/or diastolic blood pressure of greater than 30 mm Hg. It is a common and non-specific feature of acute haemolysis, severe allergic reaction, bacterial contamination or TRALI (Kopko & Holland, 1999). It occurs rarely as an isolated finding and some cases have been attributed to the generation of bradykinin and angiotensin when blood components were exposed to the charged surface of leucoreduction filters. (Klein et al, 2007) Patients taking ACE inhibitors and those with a genetic defect which prevents bradykinin breakdown were most at risk. (Mair and Leparc, 1998; Arnold et al, 2004) In addition hypotension may be associated with the patient's underlying condition, especially haemorrhage, so careful clinical risk assessment is required when deciding to stop the transfusion for this indication.

Bleeding diathesis of acute onset
This is highly suggestive of disseminated intravascular coagulation (DIC) especially when there is oozing from wounds or intravenous line insertion sites. It is most likely in severe acute haemolysis (especially ABO incompatibility) or bacterial contamination and is an alert that the transfusion must be stopped immediately and rapid clinical assessment undertaken.

Tingling around the face and lips
This is a recognised herald symptom of angioedema (Zuraw, 2008) but may also occur in patients who are hyperventilating or during a plasma or red cell exchange procedure with citrate anticoagulant due to a fall in ionised calcium.

Pain
Patients with febrile reactions often complain of generalised muscular and bone aches, probably due to release of inflammatory cytokines. Acute haemolytic reactions, particularly those due to ABO incompatibility, may be characterised by pain at the infusion site, abdomen, chest and loins. Chest pain can also be an occasional feature of anaphylactic reactions, possibly due to myocardial ischaemia (UKRC, 2008)

Severe Anxiety
This is often reported in serious transfusion reactions. A "feeling of impending doom" has been described in acute haemolysis, (Hendrickson and Hillyer, 2009) and bacterial transfusion-transmitted infection (Taylor et al, 2008) and should always initiate urgent review of the patient. However, mild anxiety is common in patients being transfused, especially for the first time.

Appendix 2
Laboratory investigation of ATR

The 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

Microbiological investigations

Clinically significant transfusion of bacterially contaminated blood components is a rare but serious event, carries a high mortality and is particularly associated with platelets (Taylor et al, 2008). Clinical severity may be influenced by the type of bacteria involved (Gram-negative organisms cause more severe reactions with rapid onset), bacterial load infused (which may be dependent on component storage time) and the recipient's clinical status (Ramirez-Arcos et al, 2007). To reduce the risk, UK blood services have now introduced automated bacterial screening of platelet components.

Bacterial reactions may present as a severe febrile ATR and a high index of suspicion is important. There is usually a sustained reaction with a temperature rise of 2^{o}C or more and/or rigors and the onset is usually rapid (Blajchman & Goldman, 2001). Nausea, vomiting, severe hypotension leading to shock and pain in the chest, back, abdomen or transfusion site often occur (Hewitt, 2009). In those where a decision is made to perform bacterial testing of the unit, whether by the hospital or by a blood service laboratory, the blood service should be informed so that associated components from the donation can be withdrawn.

Visual inspection of the component for discoloration, abnormal clumps or signs of leaks or damage is important, but many contaminated units appear normal.

Blood cultures from a peripheral vein and any central lines should be performed. The component should be sealed and transported to the transfusion laboratory as soon as possible. The transfusion laboratory should have an agreed policy for culture of the component in the hospital microbiology laboratory or referral to a blood transfusion service laboratory. The microbiology laboratory should have standard operating procedures for sampling the pack with minimal risk of contamination.
Where the hospital site does not consider suitable local facilities for microbiological sampling and testing are present the implicated blood component, appropriately secured, should be sent to the relevant transfusion service bacteriology laboratory. Referral to a blood transfusion service reference laboratory should also be considered if bacterial contamination is the most likely cause of the reaction. Clinically significant local culture results should be confirmed by the blood service reference laboratory, where molecular typing of the organism to assist investigation of the donor can be performed.

Whenever culture of an implicated unit is performed for a severe or sustained moderate febrile transfusion reaction, the local haematologist must be informed and the blood service contacted ***immediately*** so that any associated components from the implicated donation can be withdrawn and other patients protected from harm. All UK blood services provide access 24/7 to expert transfusion medicine advice.

Compatibility testing
When the patient presents with moderate or severe febrile symptoms, hypotension or back/loin pain, compatibility testing should be performed. Testing should include repeat ABO/D grouping of the patient repeat antibody screen, crossmatch and a direct antiglobulin test. (Milkins, 2011)

Mast cell tryptase
Serum levels of mast cell tryptase (MCT) are transiently raised after serious allergic/anaphylactic reactions. Although the clinical value of serum MCT is controversial, the current UK guidelines on the management of anaphylactic reactions recommend its measurement (UKRC, 2008). Its utility lies in retrospective *confirmation* that an ATR was anaphylactic, rather than assisting immediate management of the patient and is particularly useful in a patient who is unable to describe their symptoms or where signs may be masked: e.g. by anaesthesia. (Payne & Kam, 2004) Ideally, blood samples are taken as soon as possible after the reaction, (without delaying resuscitation), then at 3 and 24 hours. Levels rise within 30-60 minutes of the onset of anaphylaxis, peak at 3-4 hours and fall to baseline (<13 mcg/L) by 6-8 hours. Post-mortem sampling may help in the differential diagnosis of patients who die of a suspected ATR (Yunginger et al, 1991) but persistent elevation of MCT may occur in myelodysplastic syndromes, systemic mastocytosis and patients with chronic kidney disease and pruritus (Payne and Kam, 2004).

Immunoglobulin A deficiency
IgA deficiency in transfusion recipients was commonly held to be the most common identifiable cause of severe allergic or anaphylactic transfusion reactions. However, this was based on case reports published before 1985, when diagnostic criteria for IgA deficiency were not well-defined, and some of these cases might now be classified as TRALI (Sandler, 2006). Since 1996, there have only been ten reports of ATR associated with IgA deficiency to SHOT, and in one of these the reaction was febrile in type rather than allergic (Knowles & Cohen, 2010). However, IgA levels were not measured in many of the other reported cases of anaphylaxis. A recent unpublished review of cases referred to NHS Blood and Transplant in England and North Wales found very few cases of confirmed IgA deficiency among patients who had experienced transfusion reactions.

IgA deficiency is most common in Caucasians, occurring in around 1 in 700 of the UK population (Munks et al, 1998). It is defined as a selective deficiency of IgA with a serum level of less than 0.07 g/L (in patients above 4 years of age), in whom other causes of hypogammaglobulinemia have been excluded (European Society for Immunodeficiencies, 2005). Reactions to IgA in blood components are thought to occur particularly in IgA deficient patients who have anti-IgA antibodies, but a review of published data suggests the presence of antibodies is of low predictive value (Lilic and Sewell, 2001).
As there remains significant concern that IgA deficiency presents a transfusion risk, and the relationship between deficiency and transfusion reactions is unclear, we recommend that serum IgA is measured in all patients who have moderate or severe allergic transfusion reactions. Low results, especially if measured by nephelometric assay, should be confirmed by an alternative method, provided generalised hypogammaglobulinaemia has been excluded and investigation for IgA antibodies should be requested. Patients with confirmed IgA deficiency after ATR should be discussed with a clinical immunologist for expert assessment and advice about the need for IgA-deficient blood components. Follow up may be appropriate as IgA deficiency may be associated with the development of subsequent health problems including chronic infections and autoimmune disease. (Lilic and Sewell, 2001; Latiff and Kerr, 2007)

Haptoglobin deficiency
Haptoglobin deficiency, with haptoglobin antibodies, is said to be found in 1 in 60 cases of transfusion-related anaphylaxis in Thai or Japanese patients (Shimada et al, 2002) and should be considered in patients of appropriate ethnic origin.

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

The association of these antibodies and ATR, mainly febrile reactions, is problematic. HLA class I or II antibodies are found in 1-2% of male and 9 -17% of female blood donors (MacLennan et al 2004; Reil 2008 et al; Triulzi et al, 2009). HPA and HNA antibodies develop in 2-10% of patients receiving repeated transfusions (Kiefel et al, 2001; TRAP, 1997). Hence, they may be an incidental finding in patients or donors who are investigated in the setting of transfusion reactions. Indeed, ATR occurred at a similar frequency when HLA-matched or single donor, non-HLA-matched platelets were transfused (Chambers et al, 1990; Mangano et al, 1991) and most studies of HLA antibodies and platelet refractoriness do not show a link with ATR. In contrast leucocyte depletion is known to reduce the likelihood of transfusion reactions (TRAP 1997; Yazeret al, 2004; Paglino et al, 2004; King et al, 2004; Tobian et al, 2011) and plasma removal appears to have been a useful strategy prior to prestorage leucodepletion (Heddle et al, 1999; Vo et al, 2001). This suggests that HLA matching of leucocyte depleted components would have limited impact in reducing ATR (although there is anecdotal experience of patients with alloimmune platelet refractoriness and recurrent ATR who achieved good increments with HLA-matched platelets and ceased to have reactions).
In patients with recurrent troublesome reactions to leucocyte-depleted components, plasma reduction (washing of red cells or resuspension of platelets in platelet additive solution) to remove residual soluble leucocyte or platelet antigenic material and inflammatory mediators is the logical first step. Testing for leucocyte, platelet and neutrophil-specific antibodies should be reserved for patients with evidence of refractoriness and/or who do not respond to plasma reduction as management of reactions (Robson et al, 2008).

Investigation of "high risk" donors
Blood components from some donors may be associated with a high rate of acute transfusion reactions in different recipients, often associated with a transient severe fall in neutrophil count caused by donor HNA antibodies (Fadeyi et al, 2007; Wallis et al, 2002; Kopko et al, 2002). Passive transfer of HPA antibodies has also been linked with acute severe thrombocytopenia in rare cases (Pavenski et al, 2008). These reactions usually occur with plasma or platelet components and may be under-recognised and reported.

Appendix 3: ISBT/IHN classification of ATRs

	1 = Mild	2 = Moderate	3 = Severe
Febrile type reaction	A temperature ≥ 38 ^{o}C and a rise between 1and 2^{o}C from pretransfusion values, but no other symptoms/signs	A rise in temperature of 2^{o}C or more, or fever 39 ^{o}C or over and/or rigors, chills, other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion	A rise in temperature of 2^{o}C or more, and/or rigors, chills, or fever 39 ^{o}C or over, or other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion, prompt medical review AND/OR directly results in, or prolongs hospital stay.
Allergic type reaction	Transient flushing, urticaria or rash	Wheeze or angioedema with or without flushing/urticaria/rash but without respiratory compromise or hypotension	Bronchospasm, stridor, angioedema or circulatory problems which require urgent medical intervention AND/OR, directly result in or prolong hospital stay, or **Anaphylaxis** (severe, life-threatening, generalised or systemic hypersensitivity reaction with rapidly developing airway and/or breathing and/or circulation problems, usually associated with skin and mucosal changes
Reaction with both allergic and febrile features	Features of mild febrile **and** mild allergic reactions	Features of both allergic and febrile reactions, at least one of which is in the moderate category.	Features of both allergic and febrile reactions, at least one of which is in the severe category.
Hypotensive reaction		Isolated fall in systolic blood pressure of 30 mm or more occurring during or within one hour of completing transfusion **and** a systolic blood pressure 80 mm. or less in the absence of allergic or anaphylactic symptoms. No/minor intervention required.	Hypotension, as previously defined, leading to shock (e.g., acidaemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required.

Febrile and allergic reactions may present within 4 hours, whilst hypotensive reactions are considered as presenting within one hour

Appendix 4: Comparison of TRALI and TACO

For patients who develop respiratory distree during or shortly after transfusion, and who do not have evidence of wheeze or stridor, the following table may be of help in determining a cause. (Sources: NHSBT, 2011; Popovsky, 2008, 2010; Kopko & Holland, 1999)

	TRALI	**TACO**
Patient characteristics	More frequently reported in haematology and surgical patients	May occur at any age, but characteristically age > 70
Type of component	Usually plasma or platelets	Any
Speed of onset	During or within 6 hours of transfusion, usually within 2 hours.	Defined as occurring within 6 hours of transfusion
Oxygen saturation	Reduced	Reduced
Blood pressure	Often reduced	Often raised
JVP	Normal	Raised
Temperature	Often raised	Usually unchanged
CXR findings	Often suggestive of pulmonary oedema with normal heart size: may be a “whiteout”	Cardiomegaly, signs of pulmonary oedema
Echo findings	Normal	Abnormal
Pulmonary wedge pressure	Low	Raised
Full blood count	May be fall in neutrophils and monocytes followed by neutrophil leucocytosis	No specific changes
Response to fluid load	Improves	Worsens
Response to diuretics	Worsens	Improves

In addition to the categories of TRALI and TACO, SHOT is now collecting cases of transfusion associated dyspnoea (TAD). The International Haemovigilance Network defines TAD as “being characterized by respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO, or allergic reaction. Respiratory distress should be the most prominent clinical feature and should not be explained by the patient’s underlying condition or any other known cause.” (IHN, 2011) There are currently no other known distinguishing features to aid diagnosis of TAD.

References

1. Arnold, D., Molinari, G., Warkentin, T., DiTomasso, J., Webert, K., Davis, I., Lesiuk, L., Dunn, G., Heddle, N., Adam, A. & Blajchman, M. (2004) Hypotensive transfusion reactions can occur with blood products that are leukoreduced before storage. *Transfusion,* **44,** 1361-1366
2. Azuma, H., Hirayama, J., Akino, M., Miura, R., Kiyama, Y., Imai, K., Kasai, M., Koizumi, K., Kakinoki, Y., Makiguchi, Y., Kubo, K., Atsuta, Y., Fujihara, M., Homma, C., Yamamoto, S., Kato, T. & Ikeda, H. (2009) Reduction in adverse reactions to platelets by the removal of plasma supernatant and resuspension in a new additive solution (M-sol) *Transfusion,* **49,** 214-218
3. Blajchman, M. & Goldman, M. (2011) Bacterial contamination of platelet concentrates: Incidence, significance and prevention. *Seminars in Hematology,* **38s11,** 20-26
4. British Committee for Standards in Haematology (2009) Guidelines on the administration of blood components http://www.bcshguidelines.com/documents/Admin_blood_components_bcsh_05012010.pdf
5. British Committee for Standards in Haematology (2004) Guidelines for the use of fresh frozen plasma, cryoprecipitate and cryosupernatant. *British Journal of Haematology,* **126,** 11-28
6. British Thoracic Society/Scottish Intercollegiate Guideline Network guidelines on the management of asthma (2011) http://www.brit-thoracic.org.uk/Portals/0/Guidelines/AsthmaGuidelines/sign101%20Jan%202012.pdf
7. Chambers, L.A., Kruskall, M.S., Pacini, D.G. & Donovan, L.M. (1990) Febrile reactions after platelet transfusion: the effect of single versus multiple donors.*Transfusion,* **30**,219-221
8. Davies, T. SHOTToolkit, SHOT, Manchester 2008 http://www.shotuk.org/wp-content/uploads/2010/03/SHOT-Toolkit-Version-3-August-2008.pdf
9. Domen, R. and Hoeltge, G. (2003) Allergic transfusion reactions: an evaluation of 273 consecutive reactions. *Arch Pathol Lab Med,* **127,** 316-320
10. ESID European Society for Immunodeficiencies (2005) Definition of IgA deficiency http://www.esid.org/downloads/IgA%20Deficiency
11. Ezidiegwu, C., Lauenstein, K., Rosales, L., Kelly, K., Henry, J.(2004) febrile Nonhemolytic transfusion reactions. Management by premedication and cost implications in adult patients *Arch Pathol Lab Med* **128,** 991-995
12. Fadeyi, E., Muniz, M., Wayne, A., Klein, H., Leitman, S. and Stroncek, D. (2007) The transfusion of neutrophil-specific antibodies causes leukopenia and a broad spectrum of pulmonary reactions. *Transfusion,* **47,** 545-550
13. Fry, J.., Arnold, D.., Clase, C.., Crowther, M.., Holbrook, A.., Traore, A.., Warkentin, T., Heddle, N. (2010) Transfusion premedication to prevent acute transfusion reactions: a retrospective observational study to assess current practices. *Transfusion*, **50**:1722-1730
14. Gauvin, F., Lacroix, J., Robillard, P., Lapointe, H. and Hume, H. (2006) Acute transfusion reactions in the pediatric intesive care unit. *Transfusion,* **46,** 1899-1908
15. Gilstad, C. (2003) Anaphylactic transfusion reactions *Current Opinion in Hematology,* **10,** 419-423
16. Guyatt, G., Vist, G., Falck-Ytter, Y., Kunz, R., Magrini, N. & Schunemann, H. (2006) An emerging consensus on grading recommendations? *ACP Journal Club*, **144**, A8–A9.
17. Handbook of Transfusion Medicine 4th edition (2007) ed McClelland, D. pub The Stationery office, p61 http://www.transfusionguidelines.org.uk/?Publication=HTM&Section=9&pageid=1145#lnk01
18. Heddle, N., Klama, L., Roberts, R., Shukla, G. and Kelton, J. (1993) A prospective study to identify the risk factors associated with acute reactions to platelet and red cell transfusions. *Transfusion,* **33,** 794-797
19. Heddle, N., Klama, L., Meyer, R., Walker, I., Boshkov, L., Roberts, R. Chambers, S., Podlosky, L., O'Hoski, P. and Levine, M., (1999) A randomized controlled trial comparing plasma removal with white cell reduction to prevent reactions to platelets. *Transfusion,* **39,** 231-238
20. Heddle, N., Blajchman, M., Meyer, R., Lipton, J., Walker, I. Sher, G., Constantini L., Patterson, B.,Roberts, R., Thorpe, K. & Levine, M. (2002) A randomized controlled trial comparing the frequency of acute reactions to plasma-removed platelets and presorage WBC-reduced platelets. *Transfusion,* **42,** 556-566
21. Heddle, N. (2007) Febrile Nonhemolytic Transfusion reactions. *In: Transfusion Reactions 3rd edition*, ed Popovsky, M. AABB press, ISBN 978-1-56395-244-9

22. Heddle, N. (2009) Investigation of acute transfusion reactions *in: Practical Transfusion Medicine 3rd edition,* eds Murphy, M. & Pamphilon, D. Wiley-Blackwell ISBN 978-1-4051-8196-9
23. Hendrickson, J. and Hillyer, C. (2009) Non-infectious Serious Hazards of Transfusion, *Anesthesia and Analgesia,* **108,** 759-769
24. Hewitt, P. (2009) Bacterial Contamination *in:*: *Practical transfusion medicine 3rd edition,* eds Murphy, M., Pamphilon, D. Wiley-Blackwell ISBN 978-1-4051-8196-9
25. International Haemovigilance Network/ International Society for Blood transfusion (2011) Proposed standard definitions for surveillance of non-infectious adverse transfusion reactions http://www.isbtweb.org/fileadmin/user_upload/WP_on_Haemovigilance/ISBT_definitions_final_2011__4_.pdf
26. Kaplan, A. and Greaves, M. (2005) Angioedema *Journal of the American Academy of Dermatology,* **53,** 373-388
27. Kennedy, L., Case, D., Hurd, D., Cruz, J. and Pomper, D. (2008) A prospective, randomized, double-blind controlled trial of acetominaphen and diphenhydramine pretransfusion medication versus placebo for the prevention of transfusion reactions. *Transfusion*, **48**, 2285-2291
28. Kiefel V, Konig C, Kroll H, Santoso S. (2001) Platelet alloantibodies in transfused patients. *Transfusion,* **41,** 766-70.
29. Klein, H., Spahn, D. & Carson, J. (2007) Red blood cell transfusion in clinical practice *The Lancet,* **370,** 415-426
30. Kim, S., Cho HM, Hwang, Y., Moon, Y. & Chang, Y. Non-steroidal anti-inflammatory drugs for the common cold. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD006362. DOI: 10.1002/14651858.CD006362.pub2
31. King, K., Shirey, R., Thoman, S., Bensen-Kennedy, D., Tanz, W. & Ness, P. (2004) Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs *Transfusion,* **44,** 25-29
32. Kopko, P. & Holland, P. (1999) Transfusion-related lung injury. *Br J Haematol*, **105,** 322-329
33. Kopko, P., Marshall, C., MacKenzie, M., Holland, P. and Popovsky, M. (2002) Transfusion-Related Acute Lung Injury-report of a clinical look-back investigation *JAMA,* **287**, 1968-1971
34. Knowles, S. & Cohen, H. on behalf of of the Serious Hazards of transfusion (SHOT) Steering Group (2011) The 2010 Annual SHOT Report ISBN 978-0-9558648-3-4
35. Latiff, A. & Kerr, M. (2007) The clinical significance of IgA deficiency. *Ann Clin Biochem*, **44,** 131-139
36. Lilic, D. and Sewell, C. (2001) IgA deficiency: what we should-or should not-be doing, *J Clin Pathol,* **54,** 337-338
37. MacLennan, S., Lucas, G., Brown, C., Evans, R., Kallon, D., Brough, S., Contreras, M., Navarrete, C. 2004) Prevalence of HLA and HNA antibodies in donors: correlation with pregnancy and transfusion history. *Vox Sanguinis,* **87S3,** 4
38. Mair, B. & Leparc, G. (1998) Hypotensive reactions associated with platelet transfusions and angiotensin-converting enzyme inhibitors. *Vox Sanguinis,* **74,** 27-30
39. Mangano MM, Chambers LA, Kruskall MS 1991Limited efficacy of leukopoor platelets for prevention of febrile transfusion reactions. *American Journal of Clinical Pathology,* **95,** 733-8.
40. Milkins, C. (2011), The minimum requirements for red cell serological testing. *ISBT Science Series,* **6,** 189–192.
41. Munks, R., Booth, J., and Sokol, R. (1998) A comprehensive IgA service provided by a blood transfusion center. *Immunohematology,* **14,** 155-160
42. National Institute for Health and Clinical Excellence (2007) Acutely ill patients in hospital. http://www.nice.org.uk/CG50
43. NHSBT (2011) TRALI information document http://hospital.blood.co.uk/library/pdf/INF271_3.pdf
44. Paglino, J., Pomper, G., Fisch, G., Champion, M. and Snyder, E. (2004) Reduction of febrile but not allergic reactions to RBCs and platelets after conversion to universal prestorage leukoreduction. *Transfusion,* **44,** 16-24
45. Patterson, B., Freedman, J., Blanchette, V., Sher, G., Pinkerton, P., Hannach, J., Meharchand, J., Lau, W., Boyce, N., Pinchefsky, E., Tasev, T., Pichefsky, J., Poon, S., Shulman, S., Mack, P., Thomas, K.,Blanchette, N., Greenspan, D. and Panzarella, T.(2000) Effect of premedication guidelines and leucoreduction on the rate of febrile nonhaemolytic transfusion reactions. *Transfusion medicine,* **10,** 199-206

46. Pavenski, K., Webert, K., and Goldman, M. (2008) Consequences of transfusion of platelet antibody: a case report and literature review. *Transfusion* **48** 1981-1989
47. Payne, V. and Kam, P. (2004) Mast cell tryptase: a review of its physiology and clinical significance. *Anaesthesia,* **59,** 695-703
48. Popovsky, M. (2010) To breathe or not to breathe: that is the question. Pulmonary complications of transfusion. *Transfusion,* **50**, 2057-2062
49. Popovsky, M. (2008) transfusion-Associated Circulatory overload, *ISBT Science Series*, **3,** 166-169
50. Ramirez-Arcos, S., Goldman, M. and Blajchman, M (2007) Bacterial Contamination, in: Transfusion Reactions, 3rd edition, *Pub AABB Press,* p163-206,ISBN 978-1-56395-244-9
51. Reil, A., Keller-Stanislawski, B., Gunay, S. and Bux, J. (2008) Specificities of leucocyte alloantibodies in transfusion-related acute lung injury and results of leucocyte antibody screening of blood donors *Vox Sanguinis,* **95,** 313-317.
52. Resuscitation Council (UK), (2010) Resuscitation Guidelines. http://www.resus.org.uk/pages/guide.htm
53. Resuscitation Council (UK), (2008) Emergency treatment of anaphylactic reactions. http://www.resus.org.uk/pages/reaction.pdf
54. Robson P. Lucas G, Green F, Bourn R, Massey E. (2008)The investigation of severe non-haemolytic febrile transfusion reactions: an audit of adherence to NBS guidelines.http://www.optimalblooduse.eu/_assets/pdf/39_UK%20Report%20AUDIT%20OF%20TRANSFUSION%20REACTIONS.pdf
55. Sanders, R., Maddirala, S., Geiger, T., Pounds, S., Sandlund, J., Ribeiro, R.Pui, C. and Howard, S. (2005) Premedication with acetaminophen or diphenhydramine for transfusion with leucoreduced blood products in children. *British Journal of Haematology*, **130**, 781-787
56. Sandler, S.G. (2006) How I manage patients suspected of having had an IgA anaphylactic transfusion reaction *Transfusion,* **46,** 10-13
57. Sandler, S & Vassallo, R. (2011) Anaphylactic transfusion reactions. *Transfusion,* **51,** 2265-2266
58. Savage, W., Tobian, A., Fuller, A., Wood, R., King, K. & Ness, P. (2011) Allergic transfusion reactions to platelets are associated more with recipient and donor factors than with product attributes. *Transfusion,* **51,** 1716-1722
59. Scully, M., Longair, I., Flynn, M., Berryman, J. and Machin, S. (2007) Cryosupernatant and solvent-detergent fresh-frozen plasma (octaplas) usage at a single centre in acute thrombotic thrombocytopenic purpura. *Vox Sang,* **93,** 154-158
60. Shimada, E., Tadokoro, K., Watanabe, Y., Ikeda, K., Niihara, H., Maeda, I., Isa K , Moriya, S., Mitsunaga, S., Nakajima, K. and Juji, T(2002) Anaphylactic transfusion reactions in haptoglobin-deficient patients with IgA and IgG haptoglobin antibodies. *Transfusion,* **42,** 766-773
61. Stainsby, D., Jones, H., Wells, A., Gibson, B. and Cohen, H. (2008) Adverse outcomes of blood transfusion in children: analysis of UK reports to the serious hazards of transfusion scheme 1996-2005. *British Journal of Haematology,* **141,** 73-79
62. Taylor, C.(Ed.) Cohen, H., Mold, D., Jones, H, *et al*, on behalf of the Serious Hazards of transfusion (SHOT) Steering Group (2009) The 2008 Annual SHOT Report ISBN 978-0-9558648-1-0
63. Taylor, C.(Ed.) Cohen, H., Mold, D., Jones, H, *et al*, on behalf of the Serious Hazards of transfusion (SHOT) Steering Group (2010) The 2009 Annual SHOT Report ISBN 978-0-9558648-2-7
64. The Trial to Reduce Alloimmunisation to Platelets Study Group (TRAP) (1997) . Leukocyte reduction and ultraviolet B irradiation to prevent alloimmunisation and refractoriness to platelet transfusions. *New England Journal of Medicine,* **337,**1861-1869.
65. Tobian, A., King, K. and Ness, P. (2007) Transfusion premedications: a growing practice not based on evidence *Transfusion,* **47,** 1089-1096
66. Tobian, A., Savage, W., Tisch, D., Thoman, S., King, K. & Ness, P. (2011) Prevention of allergic transfusion reactions to platelets and red blood cells through plasma reduction. *Transfusion,* **51,** 1676-1683
67. Triulzi, D., Kleinmann. S., Kakaiya, R., Busch, M. P. Norris, P., Steele, W., Glynn, S., Hillyer, C., Carey, P., Gottschall, J., Murphy, E., Rios, J., Ness, P., Wright, D., Carrick, D. & Schreiber, G. (2009) The effect of previous pregnancy and transfusion on HLA alloimmunization in blood donors: implications for a transfusion-related acute lung injury risk reduction strategy. *Transfusion,* **49,** 1825-1835

68. Vo, T., Cowles, J., Heal, J. and Blumberg, N. (2001) Platelet washing to prevent recurrent febrile reactions to leucocyte-reduced transfusions. *Transfusion medicine,* **11,** 45-47
69. Wallis, J., Haynes, S., Stark, G., Green, F., Lucas, G. and Chapman, C. (2002) Transfusion-related alloimmune neutropenia: an undescribed complication of blood transfusion. *Lancet,* **360,** 1073-1074
70. Wang, S., Lara, P., Lee-Ow, A., Reed, J., Wang, L., Palmer, P., Tuscano, J., Richman, C., Beckett, L. and Wun, T. (2002) Acetaminophen and diphenhydramine as premedication for platelet transfusions: A prospective randomized double-blind placebo-controlled trial *American Journal Hematology,* **70,** 191-194
71. Yazer M, Podlosky L, Clarke G & Nahirniak, S. (2004) The effect of prestorage leukoreduction on the rates of febrile nonhemolytic transfusion reactions to PC and RBC. *Transfusion,* **44**,10-15
72. Yunginger, J., Nelson, D., Squillace, D., Jones, R., Holley, K, Hyma, B., Biedrzycki, L., Sweeney, K., Sturmer, W. and Schwartz, L. (1991) *J Forensic Sci,* **36,** 857-865
73. Zuraw, B. (2008) Hereditary Angioedema, *NEJM,* **359,** 1027-1036