INVESTIGATION AND MANAGEMENT OF ACUTE TRANSFUSION REACTIONS

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Haemovigilance
NATIONAL BLOOD AUTHORITY AUSTRALIA

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Introduction

This guide is intended as a resource to provide advice or support to clinical staff regarding acute transfusion reactions (ATRs). It 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 health service organisation (HSO) and pathology laboratory and to haemovigilance organisations.

The guidance is clinically focused and recognises that the severity of suspected ATRs may not be apparent at presentation. The emphasis is on the immediate management of potentially life-threatening reactions; however, there are also recommendations around appropriate investigation and strategies for prevention and prophylaxis. It may be helpful in providing a framework for the development of institutional policies. The key objectives are:

- Supplementing the *Acute Transfusion Reaction* flowchart (see Appendix 1) provided as a separate resource to aid junior medical officers (JMOs) in the recognition of ATRs and their immediate clinical management.
- Advising on further management of the patient during the reaction.
- Providing advice on the use of investigations.
- Discussing management of subsequent transfusions.
- Presenting recommendations for reporting adverse reactions within the health service organisation and pathology laboratory, to Australian Red Cross Lifeblood (Lifeblood), the jurisdictional health department and the national haemovigilance program.

This guide is based (with permission) on the British Society for Haematology (BSH) *Guideline on the Investigation and management of acute transfusion reactions* (2012)[1]. The full original version (which includes references) and accompanying supplementary information can be found on the BSH website (http://www.b-s-h.org.uk/guidelines).

Summary of Recommendations

Key recommendations are:

- Transfusions should only be performed where patients can be directly observed and where staff are trained in managing complications of transfusion, particularly anaphylactic reactions and use of adrenaline as the first line treatment of anaphylaxis.
- Patients who have experienced an anaphylactic reaction should be discussed with an allergy specialist or immunologist, in keeping with national and/or institutional guidelines.
- Management of ATRs is not dependent on classification and should be guided by symptoms and signs.

The criteria used for strength and quality of evidence are in accordance with the GRADE system[2] and are taken from the recommendations in their original form in the British Society for Haematology *Guideline on the investigation and management of acute transfusion reactions*[1]. Some recommendations have been modified for the Australian audience.

Table 1: Summary of recommendations

#	Recommendation	GRADE
Recognition and initial management of acute transfusion reactions		
1	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 (i.e. red cells, platelets or plasma) and the management of transfused patients, including the emergency treatment of anaphylactic reactions.	***1C***
2	The recognition and immediate management of acute transfusion reactions (ATRs) 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***
3	Patients should be asked to report symptoms that develop within 24 hours of completion of the transfusion.	***2C***
4	If a patient develops new symptoms or signs during a transfusion, the transfusion should be stopped, 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	If a patient being transfused for critical bleeding develops hypotension, careful clinical risk assessment is required. If the hypotension is caused by critical bleeding, 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***
6	For patients with mild reactions, such as fever (temperature of <39°C and/or rise of 1–2°C from baseline), and/or transient flushing, urticaria or rash but WITHOUT other features, the transfusion may be recommenced after appropriate treatment and with direct observation.	***2B***
Management of acute transfusion reactions		
7	Initial treatment of an acute transfusion reaction 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***

#	Recommendation	GRADE
8	Anaphylactic reactions should be treated with intramuscular (IM) adrenaline according to institutional or Australian resuscitation guidelines. http://www.anzaag.com/Mgmt%20Resources.aspx https://www.allergy.org.au/hp//papers/acute-management-of-anaphylaxis-guidelines Patients who are thrombocytopenic or who have deranged coagulation should also receive IM adrenaline if they have an anaphylactic reaction.	***1A***
9	If a patient develops sustained febrile symptoms or signs of moderate severity (temperature of ≥ 39°C OR a rise of ≥ 2°C from baseline AND/OR systemic symptoms, such as chills, rigors, myalgia, nausea or vomiting and/or loin pain), bacterial contamination or a haemolytic reaction should be considered.	***1C***
10	After initial stopping and assessment, 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 acute transfusion reactions		
11	For all moderate or severe transfusion reactions, in a patient without an obvious alternative explanation for the symptoms and/or signs or a history of similar non-serious transfusion reactions, a standard set of tests e.g. full blood count (FBC), bilirubin, electrolytes, creatinine and urinalysis should be performed.	***2C***
12	In patients with febrile symptoms of moderate severity, implicated units should be returned to the laboratory for further investigation and the patient sampled for repeat serological tests and culture. Contact Lifeblood so that associated components from the implicated donation(s) can be withdrawn.	***1C***
13	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 the patient should be tested for the presence of anti-IgA antibodies. Patients with IgA deficiency (< 0.07 g/L) diagnosed after an ATR should be discussed with a haematologist or transfusion medicine specialist regarding future transfusion management. Referral to allergy specialist or immunologist may also be considered. https://www.allergy.org.au/hp//papers/acute-management-of-anaphylaxis-guidelines	**2C**
14	In the absence of platelet or granulocyte transfusion refractoriness, or acute post-transfusion thrombocytopenia or leucopenia, investigation of the patient with an ATR for leucocyte, platelet or neutrophil-specific antibodies is not indicated.	***1B***
Management of patients with repeated reactions		
15	For patients with recurrent febrile reactions, it is recommended that a trial of premedication with oral paracetamol is 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 be discussed with a haematologist or transfusion medicine specialist to determine if washed red cells may be beneficial.	***2C***
16	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, should be excluded.	***2C***

#	Recommendation	GRADE
17	For patients with recurrent moderate or severe allergic reactions, other than those in which the patient is IgA-deficient, options for further transfusion include:	
	• Transfusion of standard components, with close direct monitoring, in a clinical area with resuscitation facilities. Consider antihistamine prophylaxis (although the evidence for efficacy of this premedication is low, the risks of it are also low). This may be the only option when further transfusion is urgent and withholding blood is a greater risk.	***2C***
	• Provision of washed red cells (following consultation with a haematologist or transfusion medicine specialist.	***2C***
	Patients undergoing plasma exchange with recurrent allergic reactions to fresh frozen plasma (FFP) should be discussed with a haematologist or transfusion medicine specialist.	***2B***
18	Patients who have experienced an anaphylactic reaction associated with transfusion should be discussed with a haematologist or transfusion medicine specialist. Referral to an allergy specialist or immunologist should also be considered as recommended by the Australasian Society of Clinical Immunology and Allergy (ASCIA) guidelines. https://www.allergy.org.au/hp//papers/acute-management-of-anaphylaxis-guidelines	***1C***
19	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); in consultation with a haematologist or transfusion medicine specialist 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***
20	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/anaphylactic reaction in other settings. Most will receive standard components without problems, but discussion with a transfusion medicine specialist (or clinical immunology or allergy specialist) is advisable if time allows.	***2C***
Reporting acute transfusion reactions		
21	All transfusion reactions, except mild febrile reactions and/or allergic reactions and moderate reactions consistent with the patient's condition and/or not related to transfusion, must be reported and reviewed within the health service organisation and pathology laboratory and then reported to the appropriate jurisdictional health department and national haemovigilance program.	***1C***

Background

For the purposes of this guide acute reactions are broadly defined as those occurring during, or within 24 hours of, administration of blood or blood components (i.e. red cells, platelets or plasma components) and includes cases due to transfusion of the incorrect component, haemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and bacterial transfusion transmitted infection (TTI) from a bacterially contaminated component. Reactions to plasma-derived (or fractionated) products are not described here. However, it is important these events are managed appropriately and investigated and reported in accordance with the manufacturer, regulator (Therapeutic Goods Administration), institutional or jurisdictional health department requirements.

The definitions used in this guide are those proposed by the International Haemovigilance Network (IHN)/International Society for Blood Transfusion (ISBT)[5] and the UK Serious Hazards of Transfusion (SHOT) group to which the Australian Haemovigilance Minimum Data Set (AHMDS)[6] guides Australian haemovigilance data collection.

ATRs vary in severity, from minor febrile reactions to life-threatening anaphylactic reactions, haemolytic or hypotensive events. Febrile and allergic reactions are commonly experienced by transfusion recipients and often result in little or no morbidity. However prompt recognition and management of suspected reactions is essential so that more serious reactions are not overlooked.

In some cases it may be desirable to seek advice from a haematologist or transfusion medicine specialist. Lifeblood has transfusion medicine specialists available 24/7 who can be contacted for advice.

Whilst it is useful to categorise ATRs for reporting and research purposes, and for international comparison[5], patients with severe ATRs often present with an overlapping complexity of symptoms and signs. The differential diagnosis includes potentially life-threatening anaphylactic reactions, acute haemolytic transfusion reactions (AHTR), bacterial TTI, TRALI and TACO. Where the predominant clinical feature is respiratory distress, transfusion-associated dyspnoea (TAD) may be suspected[5]. The initial clinical picture is also often obscured by factors related to the patient's underlying medical condition, such as febrile episodes in neutropenic patients who also happen to be receiving a blood component transfusion.

Consequently this guide will consider all causes of a possible reaction during transfusion and focus on initial recognition and general management of the clinical problem, guided by symptoms, clinical signs and assessment of their severity. This allows appropriate investigation, specific treatment and prevention, where possible, of future episodes.

1 Recognition and initial management of acute transfusion reactions

To minimise the risk of harm to the patient, early identification and rapid clinical assessment of suspected transfusion reactions is essential (see Section 2).

Recommendation 1
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 (i.e. red cells, platelets or plasma) and the management of transfused patients, including the emergency treatment of anaphylactic reactions.

Recommendation 2
The recognition and immediate management of acute transfusion reactions (ATRs) should be incorporated into local transfusion policies and there should be mandatory transfusion training requirements for all clinical and laboratory staff involved in the transfusion process.

1.1 Observing the patient

Whilst anaphylactic and haemolytic reactions can present after only a small volume of blood has been transfused[7], reactions may occur several hours after completing the transfusion[8].

Patient observations (pulse rate [PR], blood pressure [BP], temperature and respiratory rate [RR]) should be taken prior to starting the transfusion, to provide a baseline for comparing subsequent measurements against. Once started, regular observation and monitoring is required throughout the transfusion episode. The patient should also be asked to report symptoms that develop during the 24 hours following the transfusion[9]. Unconscious patients, or those unable to report symptoms, require direct monitoring.

Recommendation 3
Patients should be asked to report symptoms that develop within 24 hours of completion of the transfusion.

Additional assessment should include observing for abnormal clinical features, such as pain (abdominal, flank, back, along the intravenous [IV] line), jaundice, dark urine, nausea, diarrhoea, bleeding from IV lines, respiratory distress, rashes or angioedema. A patient who has experienced a transfusion reaction should continue to be observed directly until the clinical picture has improved.

In some cases, especially moderate or severe reactions, it may be desirable to seek medical advice from a haematologist or transfusion medicine specialist.

1.2 Initial clinical assessment

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

- In all cases, the transfusion must be stopped and venous access maintained with normal saline. The patient's airway, breathing and circulation (ABC) must be assessed[10]. The key patient identification details must be checked to ensure they correspond with those on the blood component compatibility label. This is to ensure that the correct blood component is being transfused to the correct patient[9].

- The blood 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 and being managed accordingly, the patient should continue to be monitored with standard observations.

Recommendation 4
If a patient develops new symptoms or signs during a transfusion, the transfusion should be stopped, 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.

1.3 Severe reactions

For severe or life-threatening reactions a doctor should be called immediately and the transfusion stopped. Caution is required in bleeding patients where hypotension may be associated with critical bleeding and continuing the transfusion may be life-saving.

Advice from a haematologist or transfusion medicine specialist should be sought before transfusion is restarted. Exceptions to this would include reactions where there is an obvious alternative explanation for the symptoms and signs or the patient has a history of similar, previously investigated, non-serious transfusion reactions.

Recommendation 5
If a patient being transfused for critical bleeding develops hypotension, careful clinical risk assessment is required. If the hypotension is caused by critical bleeding, continuation of the transfusion may be life-saving. In contrast, if the blood component is considered the most likely cause of hypotension, the transfusion must be stopped or switched to an alternative component and appropriate management and investigation commenced.

1.4 Mild and moderate reactions

If the reaction is mild, for example an isolated rise in temperature without chills, rigors or other changes in observations (see flow chart, Appendix 1), medical staff should be informed but the transfusion may be restarted with appropriate treatment under direct supervision.

In the case of reactions considered moderate or severe reactions, urgent medical advice (from a haematologist or transfusion medicine specialist) should be sought before the transfusion is restarted. Exceptions to this would include reactions where there is an obvious alternative explanation for the symptoms and signs or the patient has a history of similar, previously investigated, non-serious transfusion reactions.

Recommendation 6
For patients with mild reactions, such as fever (temperature of <39°C and/or rise of 1–2°C from baseline), and/or transient flushing, urticaria or rash but WITHOUT other features, the transfusion may be recommenced after appropriate treatment and with direct observation.

2 Symptoms and signs of acute transfusion reactions

ATRs can present with a range of symptoms and signs of varying severity and may be present in more than one type of reaction. The initial clinical presentation is also often obscured by factors related to the patient's underlying medical condition, such as febrile episodes in neutropenic patients who also happen to be receiving a transfusion.

Rapidly developing features of airway obstruction or circulation problems, usually associated with skin and mucosal change, would suggest an anaphylactic reaction[10]. The following table identifies major symptoms and signs of ATRs and the possible types of reactions that should be considered.

Table 2: Symptoms and signs of acute transfusion reactions

Symptoms and signs	Possible reaction type(s)
Fever and related symptoms or signs <39°C and temperature rise of 1 to 2°C from baseline, and/or systemic symptoms such as chills, rigors, myalgia, nausea or vomiting and/or loin pain	***FNHTR, AHTR, TRALI or bacterial TTI*** • 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, bacterial TTI, and TRALI[11,12]. • Bacterial TTI should always be considered. A temperature of either 39°C or above or a rise in temperature of 2°C or more is considered suggestive of bacterial TTI. • 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[8]. • TRALI can be reasonably excluded if the patient has no respiratory symptoms.
Skin lesions and rashes Urticaria (hives) or other types of skin change such as maculopapular rashes, erythema or facial flushing	***Allergic reaction*** • Urticaria is commonly seen with allergic reactions but other types of skin change may occur. • In some reactions there is no visible rash but itching is reported by the patient[13].
Angioedema Localised, non-pitting, oedema of the subcutaneous or submucosal tissues	***Allergic reaction*** Usually indicates an allergic reaction with the eyelids and mouth most often affected, less commonly throat and tongue[14].

Symptoms and signs	Possible reaction type(s)
Dyspnoea Shortness of breath (SOB), stridor, wheeze, pulmonary oedema, low oxygen saturation	***Allergic reaction, TRALI, TACO , TAD or bacterial TTI*** • SOB is a non-specific symptom and association with transfusion requires careful clinical examination supported results of investigations such as radiology or O_2 saturation/blood gases. • Stridor and wheeze suggest an allergic reaction however also occur in patients with TACO and may be associated with chills and rigors in bacterial TTI. • Pulmonary oedema with clinical signs of basal crackles and radiological evidence suggest a diagnosis of TACO. Clinical and chart review of fluid balance can help support a diagnosis of TACO. • Low oxygen saturation is not diagnostic of a specific condition, although it gives information on severity. • Distinguishing characteristics of TRALI, TACO and TAD - see Appendix 2.
Anaphylaxis	***Anaphylactic reaction*** • Typically 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 A fall in systolic and/or diastolic BP of greater than 30 mm Hg (in adults) or a fall of greater than 25% of baseline level (in paediatrics)	***AHTR, severe allergic reaction, bacterial TTI, TRALI or hypotensive reaction*** • A common and non-specific feature of acute haemolysis, severe allergic reactions, bacterial contamination or TRALI[15]; rarely occurs as an isolated finding. • Bradykinin is believed to play a major role in generating hypotension, with patients taking ACE inhibitors and those with a genetic defect preventing bradykinin breakdown most at risk[16,17]. • May also be associated with the patient's underlying condition, especially critical bleeding, so careful clinical risk assessment is required when deciding to stop the transfusion for this indication.
New unexpected bleeding	***Severe AHTR or bacterial infection*** • Highly suggestive of acute disseminated intravascular coagulation (DIC) especially when there is oozing from wounds or IV line insertion sites. • It is most likely in severe acute haemolysis (especially ABO incompatibility) or bacterial TTI.

Symptoms and signs	Possible reaction type(s)
Tingling around the face and lips	***Angioedema (see above), citrate toxicity or hyperventilation*** A recognised herald symptom of angioedema[18] however, 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 Abdominal, flank, back, IV infusion site	***FNHTR, AHTR or anaphylactic reaction*** • Patients with FNHTR 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[19].
Severe anxiety	***AHTR, bacterial TTI*** • Often reported in serious reactions. • A "feeling of impending doom" has been described in acute haemolysis[20] and bacterial TTI[8] and should always prompt urgent review of the patient. However, mild anxiety is common in patients being transfused, especially for the first time.

3 Management of acute transfusion reactions

Management of the patient should be guided by rapid assessment of symptoms, clinical signs and severity of the reaction. Please refer to Appendix 1 for flowchart.

> ***Recommendation 7***
> Initial treatment of an acute transfusion reaction 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.

3.1 Severe reactions

In severe, potentially life-threatening reactions, prompt recognition and supportive management of the patient is vital until specialist medical care is available:

- In all cases STOP the transfusion, disconnect the blood component and giving set from the patient, leaving the IV line in situ, and retain for further investigation. Maintain venous access with intravenous normal (0.9%) saline.
- Check patient's identification (ID), blood component compatibility label and visually assess component.
- If the patient is severely dyspnoeic, ensure the airway is patent and give high flow oxygen. If wheeze is present without upper airway obstruction, consider administering nebulised salbutamol[21].
- Position hypotensive patients flat with leg elevation, or in the recovery position if unconscious or nauseated and at risk of vomiting.

Ongoing management is dependent on expert medical assessment and appropriate specialist support, such as the rapid response Medical Emergency Team (MET) (or equivalent), 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. An outline for management of severe reactions is provided below.

3.1.1 Severe hypotension associated with wheeze or stridor

- A patient presenting with severe hypotension, wheeze or stridor accompanied by allergic symptoms such as rash, urticaria, or angioedema strongly suggests an anaphylactic transfusion reaction with airway obstruction. This requires immediate intervention with intramuscular (IM) adrenaline according to institutional or Australian resuscitation guidelines[3,4].
- Intramuscular (IM) adrenaline is rapidly effective and prevents delay in attempting to get subsequent venous access in a patient with peripheral venous shutdown. It should not be withheld in patients with thrombocytopenia or coagulopathy. Intravenous (IV) adrenaline should only be given by expert practitioners, such as intensive care specialists or anaesthetists.
- Adrenaline is repeated, if necessary, at 5 minute intervals according to BP, pulse and respiratory function under the direction of appropriately trained clinicians.
- Supportive management of severe anaphylactic transfusion reactions should be in accordance with local health service organisation and pathology laboratory/site policy and be delivered by trained staff[3,4].
- On-going transfusion requirements for patients experiencing an anaphylactic transfusion reaction should be discussed with a haematologist or transfusion medicine specialist. A policy for future blood component therapy must be formulated (see *Section 5: Management of patients with repeated acute transfusion reactions*). Consider referring the patient to an allergy specialist or immunologist (as per Australian Society for Clinical Immunology and Allergy (ASCIA) guidelines)[4].

Recommendation 8
Anaphylactic reactions should be treated with intramuscular (IM) adrenaline according to institutional or Australian resuscitation guidelines.

http://www.anzaag.com/Mgmt%20Resources.aspx

https://www.allergy.org.au/hp//papers/acute-management-of-anaphylaxis-guidelines

Patients who are thrombocytopenic or who have deranged coagulation should also receive IM adrenaline if they have an anaphylactic reaction.

3.1.2 *Severe hypotension without clinical signs of anaphylaxis or fluid overload*

- For severe hypotension in the absence of anaphylaxis or fluid overload, ABO incompatibility or bacterial TTI should be considered. Both require supportive care with fluid resuscitation, evaluation for inotropic, renal and respiratory support. Further blood component therapy may be needed to treat DIC with bleeding.
- Isolated hypotension can occur in anaphylactic reactions and severe hypotension in TRALI. For TRALI the clinical picture is usually dominated by dyspnoea (see 3.1.3).
- If the identity check shows transfusion of a unit intended for another patient, contact the transfusion laboratory immediately to prevent a further 'wrong blood' incident.
- If bacterial TTI 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(s). Lifeblood should also be notified, usually by the transfusion laboratory, so that any other components from the implicated donation(s) can be recalled and quarantined.

3.1.3 Severe dyspnoea

- Isolated severe dyspnoea can be seen in TRALI, TACO, and dyspnoea can also be a feature of allergic reactions. Occasionally occurs as an unexplained complication of transfusion and in this context may be designated transfusion-associated dyspnoea (TAD)[5,22].
- 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, pulse oximetry, arterial blood gas, fluid balance and urine output. Measurement of brain natriuretic peptide (BNP) or pro-BNP levels may be useful in differentiating suspected TRALI or TACO, if testing is available locally.

The diagnosis of transfusion reactions involving dyspnoea can be challenging. The table in Appendix 2 provides a comparison of TRALI and TACO which may be useful in distinguishing between these two events.

3.2 Moderate reactions

The differential diagnosis and investigation of moderate reactions is similar to severe reactions. Unless there is an obvious alternative explanation for the symptoms and signs or the patient has a history of similar 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 stop the transfusion or switch to an alternative unit.

3.2.1 Moderate febrile reactions

Defined as a temperature of ≥ 39°C OR a rise of ≥ 2°C from baseline AND/OR systemic symptoms, such as chills, rigors, myalgia, nausea or vomiting and/or loin pain.

- Bacterial TTI or haemolytic reactions are very unlikely if the reaction is transient, the patient is haemodynamically stable and the patient recovers with only symptomatic intervention. If the reaction is sustained, these possibilities should be considered.
- Management of bacterial TTI 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 9

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

3.2.2 Moderate allergic reactions

Symptoms of a moderate allergic reaction may include angioedema and dyspnoea (without wheeze or stridor), but not sufficiently severe to be considered life-threatening. The use of antihistamines (given either orally or IV) may provide relief and, additionally, oxygen therapy and a short-acting beta$_2$-agonist, such as salbutamol, may be useful for respiratory symptoms[21,23]. Corticosteroids (prednisolone or hydrocortisone) may reduce the possibility of relapse.

3.3 Mild reactions

Mild reactions are those with no change or limited change in vital signs such as fever (temperature of <39°C and/or rise of 1–2°C from baseline), and/or transient flushing, urticaria or rash but WITHOUT other features. In these cases it is reasonable to recommence the transfusion after appropriate treatment and with direct observation.

There are no randomised controlled trials (RCT) that consider the symptomatic treatment of febrile symptoms associated with transfusions. Experience with paracetamol suggests it is a useful antipyretic agent but less effective in managing chills or rigors whereas non-steroidal anti-inflammatory drugs (NSAIDs) may be more effective for symptoms of chills or rigors[24]. An assessment of the risks of medication against the severity of the reaction should be made in each case. Caution is required in the use of NSAIDs in patients with thrombocytopenia or reduced platelet function.

There are no reported trials of treatment of skin symptoms; however, 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 10

After initial stopping and assessment, 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.

4 Laboratory investigation of acute transfusion reactions

The extent of laboratory investigation for presumed ATRs is largely determined by the pattern of symptoms and clinical signs and the severity of the reaction.

- All presumed transfusion reactions except allergic reactions or mild febrile reaction, in a patient without an obvious alternative explanation for the symptoms and/or signs or a history of similar non-serious transfusion reactions, should be investigated with a standard set of tests e.g. full blood count (FBC), bilirubin, electrolytes, creatinine and urinalysis with additional investigations based on the observed symptoms (Table 3).
- The urgency of investigations must be communicated to the laboratory so that 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 guidelines and national requirements.
- In patients experiencing moderate or severe febrile reactions, bacterial TTI or a haemolytic reaction should be considered.
    - Implicated units should be returned to the laboratory for further investigation.
    - Contact Lifeblood immediately if TTI is suspected so that any associated components from the implicated donation(s) can be withdrawn.
    - If however, febrile symptoms are transient and the patient is haemodynamically stable and recovers with only symptomatic treatment, further investigation to exclude bacterial TTI or a haemolytic reaction is unlikely to be required.

4.1 Standard investigations

Standard investigations provide a baseline in case of subsequent clinical deterioration.

4.1.1 Investigations dependent on observed symptoms

Further investigations should be guided by the clinical symptoms and signs, rather than the presumed category of reaction. Table 2 describes typical laboratory investigation of suspected ATR.

Recommendation 11
For all moderate or severe transfusion reactions, in a patient without an obvious alternative explanation for the symptoms and/or signs or a history of similar non-serious transfusion reactions, a standard set of tests e.g. full blood count (FBC), bilirubin, electrolytes, creatinine and urinalysis should be performed.

Recommendation 12
In patients with febrile symptoms of moderate severity, implicated units should be returned to the laboratory for further investigation and the patient sampled for repeat serological tests and culture. Contact Lifeblood so that associated components from the implicated donation(s) can be withdrawn.

Recommendation 13
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 the patient should be tested for the presence of anti-IgA antibodies.

Patients with IgA deficiency (< 0.07 g/L) diagnosed after an ATR should be discussed with a haematologist or transfusion medicine specialist regarding future transfusion management.

Referral to an allergy specialist or immunologist may also be considered.
https://www.allergy.org.au/health-professionals/papers/acute-management-of-anaphylaxis-guidelines

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

This is usually an incidental finding in patients experiencing an ATR and routine screening is not recommended.

Recommendation 14
In the absence of platelet or granulocyte transfusion refractoriness, or acute post-transfusion thrombocytopenia or leucopenia, investigation of the patient with an ATR for leucocyte, platelet or neutrophil-specific antibodies is not indicated.

Table 3: Investigation of a moderate or severe acute transfusion reaction based on symptoms

Symptoms	Investigations
Fever *Temperature of ≥ 39°C OR rise of ≥ 2°C from baseline, AND/OR systemic symptoms such as chills, rigors, myalgia, nausea or vomiting and/or loin pain*	• Standard investigations: FBC, bilirubin, electrolytes, creatinine and urinalysis • Take samples for repeat serological investigations (blood group and antibody screen, crossmatch, and DAT), LDH and haptoglobin • Take blood cultures from patient • Coagulation screen – aPTT, PT, fibrinogen and D-dimer (or FDP) • Do not discard implicated unit(s) • If *febrile reaction* return unit(s) to laboratory; repeat serological investigations on pre and post transfusion patient samples; confirm blood group of unit(s) and culture unit(s) • If *haemolysis* – LDH and haptoglobin • If *loin pain* perform serological investigations as above
Mucosal swelling (angioedema)	• Measure IgA level (EDTA tube) • If <0.07g/L and no generalised hypogammaglobulinaemia, confirm with sensitive test method and test for anti-IgA antibodies

Symptoms	Investigations
Dyspnoea, wheeze, or features of anaphylaxis	• Pulse oximetry or arterial blood gases • Chest X-ray (mandatory if symptoms severe) • Measurement of brain natriuretic peptide (BNP) or pro-BNP levels may be useful in differentiating suspected *TACO or TRALI*, if testing is available locally • If *bacterial TTI or haemolytic reaction* suspected investigations as for *fever* • If *severe or moderate allergic reaction* suspected measure IgA level • If <0.07g/L and no generalised hypogammaglobulinaemia, confirm with sensitive test method and test for anti-IgA antibodies • If *severe allergic/anaphylactic reaction* consider measurement of serum tryptase levels (plain tube) - 1 hr, 4 hrs and 24 hrs*
Hypotension	• Investigate as for *fever* • If *allergy* suspected measure IgA level • If <0.07g/L and no generalised hypogammaglobulinaemia, confirm with sensitive test method and test for anti-IgA antibodies • If *severe allergy/anaphylactic reaction* consider measurement of serial mast cell tryptase, as above

* Australian and New Zealand College of Anaesthetists (ANZCA) / Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) (2016) Anaphylaxis Management Guidelines (http://www.anzaag.com/Mgmt%20Resources.aspx)[3]

5 Management of patients with repeated acute transfusion reactions

In the small number of patients with recurrent febrile and allergic reactions and those patients who have experienced an anaphylactic reaction, premedication and/or component manipulation by washing or plasma removal may be considered although the evidence base is weak[25].

5.1 Febrile non-haemolytic transfusion reactions (FNHTR)

In the absence of clear evidence, if recurrent reactions occur, options include firstly premedication with oral paracetamol given one hour before the reaction is anticipated (first option), or otherwise the use of washed blood components in consultation with a haematologist or transfusion medicine specialist[11,12,26,27,28,29,30,31,32].

Non-steroidal anti-inflammatory drugs may be useful in patients with chills or rigors associated with red cell transfusions, however, 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 15
For patients with recurrent febrile reactions, it is recommended that a trial of premedication with oral paracetamol is 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 be discussed with a haematologist or transfusion medicine specialist to determine if washed red cells may be beneficial.

5.2 Allergic reactions

Prophylactic premedication with paracetamol and antihistamine does not reduce the incidence of allergic reactions[28,29,30,32,33]. However, patients who experience repeated allergic reactions and who require chronic transfusion therapy may benefit from premedication with antihistamines.

5.2.1 Mild allergic reactions

Patients who have experienced a mild allergic reaction may receive further transfusions without prior intervention such as premedication. Any subsequent mild reaction can be managed by reducing the rate of transfusion and by the use of a systemic antihistamine (given orally or IV) or steroids which is effective in some patients with mild reactions[23]. Alternatively, intervention as described in Recommendation 17 for more severe reactions may be used.

5.2.2 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[34].

Recurrent allergic transfusion reactions to fresh frozen plasma (FFP) in patients treated with plasma exchange for conditions such as thrombotic thrombocytopenia purpura should be discussed with a haematologist or transfusion medicine specialist.

Recommendation 16
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, should be excluded.

Recommendation 17

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

- Transfusion of standard components, with close direct monitoring, in a clinical area with resuscitation facilities. Consider antihistamine prophylaxis (although the evidence for efficacy of this premedication is low, the risks of it are also low). This may be the only option when further transfusion is urgent and withholding blood is a greater risk.
- Provision of washed red cells (following consultation with a haematologist or transfusion medicine specialist).

Patients undergoing plasma exchange with recurrent allergic reactions to fresh frozen plasma (FFP) should be discussed with a haematologist or transfusion medicine specialist.

Recommendation 18

Patients who have experienced an anaphylactic reaction associated with transfusion should be discussed with a haematologist or transfusion medicine specialist. Referral to an allergy specialist or immunologist should also be considered as recommended by the Australasian Society of Clinical Immunology and Allergy (ASCIA) guidelines.

https://www.allergy.org.au/health-professionals/papers/acute-management-of-anaphylaxis-guidelines

5.2.3 Patients with IgA deficiency and history of ATR

There are occasional, fully investigated patients with severe IgA deficiency, anti-IgA antibodies and a history of allergic reactions to blood components. However, clinically this is a difficult area with limited high quality evidence to guide practice and the following is largely based on haemovigilance data and expert opinion[35,36]. Patients with confirmed IgA deficiency after ATR should be discussed with a haematologist or transfusion medicine specialist (or clinical immunologist) for expert assessment and advice about the need for IgA-deficient blood components.

These patients should be transfused with washed red cells or blood components from IgA-deficient donors in elective situations if available (Lifeblood has a panel of IgA-deficient platelet and plasma donors and should therefore be contacted if IgA-deficient components are being considered).

If urgent, life-saving transfusion is needed, standard blood components should be transfused with direct observation in a clinical area with the skills and capacity to manage severe allergic reactions[37].

Urgent transfusion must not be denied because IgA-deficient or washed components are not immediately available.

Follow up of the patient may also be appropriate as IgA deficiency can be associated with the development of subsequent health problems including chronic infections and autoimmune disease.

Recommendation 19

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); in consultation with a haematologist or transfusion medicine specialist 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.

5.2.4 Patients with IgA-deficiency with no history of ATR

There is a larger group of patients with confirmed IgA deficiency (often picked up incidentally during antibody screening for another condition, such as 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.

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 20***
> 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/anaphylactic reaction in other settings. Most will receive standard components without problems, but discussion with a transfusion medicine specialist (or clinical immunology or allergy specialist) is advisable if time allows.

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

There is no evidence that the use of HLA-, HPA- or HNA-matched components are of benefit in reducing the incidence of acute transfusion reactions.

5.4 Hypotensive reactions

In patients with otherwise unexplained recurrent hypotensive reactions, a trial of washed red cells could be considered for future transfusions.

In the rare cases thought to be due to bradykinin release, angiotensin-converting-enzyme (ACE) inhibitors should be stopped before the transfusion if clinically safe to do so.

Discussion with a transfusion medicine specialist may be helpful.

6 Acute transfusion reactions in children and neonates

There is limited haemovigilance and other data available focusing on transfusion adverse events in children and neonates[38]. Symptoms and signs of ATR may be less easily recognised in children or neonates[39], although febrile and allergic reactions appear to have a higher prevalence than in adult transfusion recipients[40,41]. Hence, a high degree of vigilance by treating clinicians is needed.

Investigation and on-going management of children or neonates experiencing ATRs may need to be modified from what is used in the adult setting. Specific protocols, in particular those for drug management, should be written in close collaboration with paediatric specialists. In the case of anaphylactic reactions, appropriate paediatric doses of adrenaline should be given as per the Australian Society for Clinical Immunology and Allergy (ASCIA) guidelines[4].
https://www.allergy.org.au/health-professionals/papers/acute-management-of-anaphylaxis-guidelines

Children with severe allergic or anaphylactic reactions to blood components should be discussed with a haematologist, transfusion medicine specialist (or paediatric allergy specialist) regarding further assessment and investigation.

7 Reporting acute transfusion reactions

7.1 Reporting within the health service organisation and pathology laboratory

National Safety and Quality Health Service Standards (NSQHS) Standard 7: *Blood Management Standard*[42] requires that 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 Blood Management (or Hospital Transfusion/equivalent) Committee. Reporting should be in accordance with the national haemovigilance framework and the state or territory health departments will advise on their reporting requirements.

Cases of moderate or severe ATR should be reviewed by the Hospital Transfusion Team, a haematologist, or a transfusion medicine specialist 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 jurisdictional health department or Lifeblood as appropriate
- Review the appropriateness of the transfusion
- Identify practice concerns, lessons to be learnt and any training requirements
- Identify and monitor trends.

> ***Recommendation 21***
> All transfusion reactions, except mild febrile reactions and/or allergic reactions and moderate reactions consistent with the patient's condition and/or not related to transfusion, must be reported and reviewed within the health service organisation and pathology laboratory and then reported to the appropriate jurisdictional health department and national haemovigilance program.

7.2 Reporting to Lifeblood

This is essential when a bacterial TTI 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(s) 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.

Health service organisations and pathology providers should have clear mechanisms in place to ensure prompt and effective communication with Lifeblood.

7.3 Reporting to product manufacturers

For adverse reactions to plasma-derived (or fractionated) products, report in accordance with the product manufacturer, regulator (Therapeutic Goods Administration), institutional or jurisdictional health department requirements. Links to suppliers (product manufacturers) are on the NBA website.

7.4 National haemovigilance reporting

The National Blood Authority (NBA) is responsible for governance of haemovigilance reporting at a national level in Australia in line with the *Strategic Framework for the National Haemovigilance Program*[43]. https://www.blood.gov.au/haemovigilance-reporting

The National Haemovigilance Program reports on serious transfusion-related adverse events occurring in public and private health service organisations and pathology laboratories, with data provided by the jurisdictional health departments. To ensure consistent reporting the NBA has produced the Australian haemovigilance minimum data set (AHMDS)[6]. In Australia, health service organisations use processes for reporting adverse events in accordance with national guidelines and criteria.

7.5 Topics for audit

Audit of acute transfusion reactions within a health service organisation and pathology laboratory can provide useful information both from understanding the degree and accuracy of reporting as well as identifying areas for staff and patient education. Areas to audit include:

- staff training
- patient consent
- documentation of adverse reactions, observations, transfusion history, and management
- internal and external adverse event reporting
- management and outcomes of subsequent transfusions.

Example audit templates are available from:

- The British Society for Haematology[1] https://b-s-h.org.uk/guidelines/guidelines/investigation-and-management-of-acute-transfusion-reactions/
- Department of Health & Human Services Victoria Blood Matters program[44] https://www2.health.vic.gov.au/hospitals-and-health-services/patient-care/speciality-diagnostics-therapeutics/blood-matters/transfusion-audits.

Appendix 1

Figure 1: Flowchart: Acute transfusion reactions

[Note: An image of the flowchart will be inserted here after public consultation. To view the flowchart, go to the link to the PowerPoint version on the NBA public consultation webpage]

Appendix 2

TRALI, TACO and TAD

TRALI and TACO

Haemovigilance definitions of TRALI and TACO are continually under review[5,46]. Differentiating TRALI and TACO can be challenging, as can distinguishing other causes of lung injury[46,47].

For patients who develop respiratory distress 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[15,48,49].

Table 4: Diagnostic features of TRALI and TACO

Characteristic	TRALI	TACO
Patient characteristics	More frequently reported in haematology and surgical patients	May occur at any age, but most commonly reported in older patients
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 (BP)	Often reduced	Often raised
Jugular venous pressure (JVP)	Normal	Raised
Temperature	Often raised	Usually unchanged
Chest X-ray (CXR) findings	Often suggestive of pulmonary oedema with normal heart size: may be a whiteout of lung fields	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
Fluid balance	Neutral	Typically positive
Response to fluid load	Improves	Worsens
Response to diuretics	Worsens	Improves
Brain natriuretic peptide (BNP)	Low (<250)	High

Table 4 adapted from the *British Society for Haematology (2012) Guideline on the Investigation and management of acute transfusion reactions*

TAD

In addition to the categories of TRALI and TACO, another respiratory event 'transfusion-associated dyspnoea' (TAD) has been categorised, and is also reportable to the national haemovigilance program. The IHN/ISBT and the AHMDS define TAD as being characterised 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[5]. There are currently no other known distinguishing features to aid diagnosis of TAD.

Abbreviations

ABC	Airway, breathing, circulation
ACE	Angiotensin converting enzyme
AHMDS	Australian haemovigilance minimum data set
AHTR	Acute haemolytic transfusion reaction
ANZAAG	Australian and New Zealand Anaesthetic Allergy Group
ANZCA	Australian and New Zealand College of Anaesthetists
aPTT	Activated partial thromboplastin time
ASCIA	Australasian Society of Clinical Immunology and Allergy
ATR	Acute transfusion reaction
BNP / Pro-BNP	Brain natriuretic peptide
BP	Blood pressure
BSH	British Society of Haematology
CXR	Chest X-ray
DAT	Direct antiglobulin test
DIC	Disseminated intravascular coagulation
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
FBC	Full blood count
FDP	Fibrin degradation products
FFP	Fresh frozen plasma
FNHTR	Febrile non-haemolytic transfusion reaction
HLA	Human leucocyte antigen
HNA	Human neutrophil antigen
HPA	Human platelet antigen
HSO	Health service organisation
ID	Identification
IgA	Immunoglobulin A
IHN	International Haemovigilance Network
IM	Intramuscular
ISBT	International Society of Blood Transfusion
IV	Intravenous
JMO	Junior medical officer
LDH	Lactate dehydrogenase
LFT	Liver function tests
MCT	Mast cell tryptase
MET	Medical emergency team
NBA	National Blood Authority
NHS	National Health Service
NSAID	Non-steroidal anti-inflammatory drug
NSQHS	National Safety and Quality Health Service Standards
PR	Pulse rate
PT	Prothrombin time
RCT	Random controlled trial
SHOT	Serious Hazards of Transfusion
SOB	Shortness of breath
TACO	Transfusion-associated circulatory overload
TAD	Transfusion-associated dyspnoea
TGA	Therapeutic Goods Administration
TMS	Transfusion medicine specialist
TRALI	Transfusion-related acute lung injury
TTI	Transfusion transmitted infection

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