Transfusion Reactions: Diagnosis, Management and Investigation - Full Clinical Guideline

Reference no.: CG-CLIN/1757/25

1. Introduction

In addition to ensuring that patients receive the correct blood component, an important aspect of safe transfusion practice is to ensure that any adverse event or reaction are recognised and treated promptly and effectively.

The UK Blood Safety and Quality Regulations (2005) have introduced a legal requirement for serious adverse reactions (SAR) and serious adverse events (SAE) to be reported to the Medicines and Healthcare products Regulatory Agency (MHRA), the UK Competent Authority. This is done via an online reporting system: SABRE (Serious Adverse Blood Reactions & Events) by members of the Hospital Transfusion Team.

Incidents are also reported to the Serious Hazards of Transfusion (SHOT) scheme. Reporting to SHOT is required for compliance with HSC/2007/001 'Better Blood Transfusion: Safe and Appropriate Use of Blood' and is a standard for the NHS Litigation Authority – Clinical Negligence Scheme for Trusts in England.

2. Aim and Purpose

This document aims to offer clear guidance on identifying, investigating, and managing adverse reactions to blood components. It is a clinically focused guideline, acknowledging that reactions may not be immediately obvious. While its main aim is to prioritise the management of life-threatening reactions, it also advises on appropriate investigation and recommended preventive strategies.

3. Definitions, Keywords

Serious adverse event (SAE) 'Any untoward occurrence associated with the collection, testing, processing, storage and distribution, of blood or blood components that might lead to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalisation or morbidity.'

Serious adverse reactions (SAR) 'an unintended response in a donor or in a patient that is associated with the collection, or transfusion of blood or blood components that is fatal, life-threatening, disabling or incapacitating, or which results in or prolongs hospitalisation or morbidity'

These are:

- Immunological haemolysis due to ABO incompatibility
- Immunological haemolysis due to other allo-antibody
- Non-immunological haemolysis

- Transfusion-transmitted bacterial infection
- Anaphylaxis / hypersensitivity
- Transfusion related acute lung injury (TRALI)
- Transfusion-transmitted viral infection
- Transfusion-transmitted parasitical infection
- Post-transfusion Purpura
- Transfusion associated Graft-versus host disease (TA-GvHD)
- Transfusion associated circulatory overload (TACO)
- Other serious reactions, e.g.:

    - transfusion associated dyspnoea (TAD)
    - febrile reactions with a 2°c rise in temperature
    - Uncategorised unintended responses

All serious adverse events or serious adverse reactions including near miss events must be reported to blood bank as soon as possible.

4. Diagnosis, Management and Investigation

Although anaphylactic and haemolytic reactions can present after only a small volume of blood has been transfused, reactions can present much later, on occasion several hours after completion of the transfusion (Taylor et al, 2009). Therefore, observation and monitoring is required throughout the transfusion episode (BSH, 2023) and patients should be encouraged to report any symptoms that develop in up to 14 days post transfusion. All patients discharged less than 24 hours post transfusion should receive a patient information leaflet with relevant contact details. A resus trolley must also be available in any area were transfusion takes place in case of anaphylaxis. Where an unconscious patient, or patient unable to report symptoms is transfused, direct monitoring is required.

4.1- Acute Transfusion Reactions

Recognition of ATRs

→ Initial treatment should be directed by symptoms and signs.
→ Treatment of severe reactions should not be delayed while waiting for results on an investigation.
→ Transfusion should take place in clinical areas where direct observation is possible.
→ Staff should be trained in blood component administration and management of transfused patients (including emergency treatment of anaphylaxis).
→ Patients should be asked to report symptoms that develop during/following transfusion.

Immediate management of ATR

→ Where a patient develops new symptoms or signs during transfusion, this should be stopped immediately but venous access should be maintained.
→ Immediate medical review should be undertaken.
→ Identification details should be checked between patient, their ID band and component compatibility label.

→ Component should be inspected for any physical changes, and standard observations taken from patient.
→ Where a mild reaction is suspected (such as temp increase 1-2˚C leading to pyrexia ≥38°C but <39°C, and/or pruritus or rash but without other features) the transfusion may be continued with appropriate treatment and direct observation.
→ 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 lifesaving.

4.1.1 Febrile type reactions

4.1.1.1 Mild reactions

Features: Isolated fever (≥38˚C but <39˚C with a rise of ≥1˚C but <2˚C from baseline and/or Pruritus or rash without other features) usually with shivering and general discomfort occurring towards the end of the transfusion or up to 2 hours afterwards.

Management: Most mild febrile reactions can be managed by slowing or stopping the transfusion and giving an antipyretic drug, e.g. paracetamol (500–1000 mg in adults), not aspirin.

Investigation: Where continuation of transfusion is recommenced no laboratory investigation is required.

Prevention: For patients with recurrent febrile reactions, a trial of premedication with oral paracetamol (1 hr prior to transfusion start) may be considered.

4.1.1.2 Moderate/Severe Febrile reactions

Features: Temperature increase ≥39°C or a rise of ≥2°C from baseline and/or systemic symptoms such as chills, rigors, myalgia, nausea or vomiting.

Management: Immediate medical review required. The decision to continue transfusion will depend on the clinical assessment of the probable cause of the symptoms, response to initial therapy and the urgency of transfusion

Investigation: Implicated units should be immediately returned to the blood bank laboratory for further investigation. Standard investigation includes post transfusion group and screen, full blood count, renal and liver enzymes (LFTs, U&E, ALT, AST) required. Patients with respiratory symptoms not due to allergy should also have a chest X-ray.

Prevention: For patients with recurrent febrile reactions, a trial of premedication with oral paracetamol (1 hr prior to transfusion start) may be considered. Patients who continue to have moderate/severe febrile reactions may require non-standard blood components (discuss with Haematologist).

Remember: fever or rigors could be the first warning of a severe acute reaction.

4.1.2 Mild Allergic Reactions

Features: Urticaria and/or itching within minutes of starting a transfusion are quite common, particularly with components including large volumes of plasma e.g. platelet concentrates and FFP.

Investigation: For transfusion reactions with only allergic features, repeat compatibility testing is not required.

Management: Symptoms usually subside if the transfusion rate is reduced, and an antihistamine is given.

Adult: Chlorphenamine, (10mg) by slow intravenous injection or intramuscular injection in patients who are not thrombocytopenic.

Paediatric: Refer to the BNFc for current dosing as this can change and there are 4 different age ranges and doses for Chlorphenamine (<6 months, 6 months -6 yrs., 6-12 yrs. and 12-18yrs).

The transfusion may be continued if there is no progression of symptoms after 30 minutes.

Prevention: Alternative causes such as allergy to drugs or latex gloves should be excluded. Chlorphenamine (in the doses stated above) should be given as premedication 30 minutes before commencement of a transfusion if the patient has previously experienced repeated allergic reactions. If signs and symptoms fail to respond to this, discussion with haematology consultant is required prior to next transfusion. If further transfusion is urgent and withholding blood is a greater risk, transfuse standard components under direct monitoring in a clinical area with resuscitation facilities.

4.1.3 Moderate/severe Allergic Reaction or Anaphylaxis

This is a rare but potentially life-threatening complication usually occurring in the early part of a transfusion. Anaphylaxis occurs when a patient has IgE or IgG antibodies to infused allergens. A few patients with severe IgA deficiency (these patients often have a family history of IgA deficiency) develop antibodies to IgA. Some of these patients have severe anaphylaxis if exposed to IgA by transfusion. If a patient has had a moderate/severe reaction and must have further transfusions, **it is essential to use sodium chloride 0.9% solution (saline)-washed red cells or, if available, blood components from IgA-deficient donors. In these cases, the requesting doctor must inform blood bank of the situation and discussion with haematology consultant and NHSBT consultant will be required, life-saving transfusion should not be delayed if these are not immediately available.**

Severe Allergic Reactions are characterised by bronchospasm causing hypoxia, or angioedema causing respiratory distress.

Anaphylactic Reactions are characterised by hypotension with one or more of: rash, dyspnoea, stridor, wheezing, angioedema, pruritus, urticaria, during, or within 24 hrs of transfusion.

Investigation: Patients experiencing anaphylactic reactions to blood transfusion, or recurrent severe febrile/inflammatory reactions within the first 15min should have IgA levels measured.
If anaphylaxis is suspected investigation should include:

- Chest X-ray to exclude TRALI where patient is dyspnoeic
- Blood gases if patient is clinically hypoxic
- IgA level and anti-IgA
- Mast cell tryptase

Management: A resus trolley must be available in all areas where transfusions may be administered in case of anaphylaxis. Management should be according to standard protocols referring to the Trust's Anaphylaxis Guideline. Patients with no history of allergic reactions may be transfused with standard components. Patients who have experienced an anaphylactic reaction should be discussed with an allergist or immunologist if there is uncertainty about the causative agent.

4.1.4 Acute Haemolytic Transfusion Reaction (AHTR)

This is defined as fever and other symptoms/signs of haemolysis within 24 hours of transfusion. Confirmed by a fall in Hb, rise in LDH, positive DAT, positive crossmatch and possible haemoglobinuria.

N.B: These are difficult to distinguish from Haemolytic Gram Negative shock

Cause: AHTRs are potentially fatal. They are most commonly caused by an ABO incompatibility between patient and blood product. When the patient's (anti-A or anti-B) antibodies bind to the transfused red cells, the complement cascade is activated causing intravascular red cell lysis (destruction). Infusion of ABO-incompatible blood is most commonly due to errors in sample collection or labelling, collecting the wrong blood from the fridge, or failure to correctly carry out the bedside check.

If red cells are erroneously administered to the 'wrong' patient, the chance of ABO incompatibility is approximately one in three. The reaction is frequently most severe if group A red cells are infused to a group O patient.

Acute haemolysis may also occur following infusion of plasma-rich components, e.g. platelets or FFP, containing high-titer anti-red-cell antibodies, usually anti A or B.

Features: Fever, rigors, profound hypotension, acute loin pain and a sensation of "something seriously wrong", haemoglobinuria and anuria. Additional clinical signs are shock and activation of the coagulation system causing disseminated intravascular coagulopathy (DIC) leading to widespread bleeding.

Even a few milliliters of ABO incompatible blood may cause symptoms within a few minutes that will be noticed by a conscious patient. However, if the patient is

unconscious or cannot communicate, the first signs of the reaction may be bleeding, tachycardia, hypotension or hypertension.

Management: Guided by rapid assessment of symptoms, clinical signs and severity of the reaction rather than laboratory investigations. Medical support to be given as appropriate for acutely ill patient, initial treatment of ATR should be directed by symptoms and signs. Treatment of severe reactions should not be delayed until the results of investigations are available.

- Disconnect blood and put up 0.9% Normal Saline
- Call On Call Doctor urgently
- Check and record observations
- Monitor urine output/catheterize
- Maintain urine output> 100ml/hr
- Consider Ionotropic support if prolonged hypotension
- Treat DIC with appropriate blood components
- Contact on call Haem consultant and arrange Medical Registrar review
- Patient might require ITU/Outreach Team input

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

Investigation: Standard investigations including full blood count, renal and liver enzymes. Return unit to laboratory with post-transfusion group and screen sample for repeat compatibility testing and DAT. Minimum samples required for full blood count, haptoglobin, LDH, coagulation screen (including fibrinogen, d-dimer, thrombin time) send 3 EDTA,1 citrate,1 yellow top (serum), blood culture and culture of blood component pack.

4.1.5 Bacterial Contamination

Cause: Organisms associated with contamination include *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Bacillus cereus*, Group B streptococci, *E. coli*, *Pseudomonas* species and other gram negative organisms. Bacterial contamination of blood components is rare, but is more often reported with platelet concentrates (stored at 22°c) than with red cells (stored at 4–6°c).

Features: Bacterial contamination is likely to cause a very severe acute reaction with rapid onset of hyper- or hypotension, temperature rise, rigors and collapse. The signs and symptoms may be similar to acute haemolytic transfusion reactions or severe acute allergic reactions. A patient who 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 should be considered.

Management: As for acute haemolytic reactions.
Administer IV antibiotic that will cover gram-positive and gram-negative bacteria. Seek Microbiology advice and, in the interim, follow protocol for antibiotic management of neutropenic sepsis.

Investigation: Essential samples as in acute haemolytic reactions. Exclusion of all other potential causes of infection must be considered. Blood cultures required from patient, transfused blood unit returned to blood bank for further investigation and discussion with NHSBT.

4.1.6 Transfusion Related Acute Lung Injury (TRALI)

Cause: The syndrome is seen more frequently in association with plasma rich products e.g. platelets and FFP than with red cell preparations. It may be very difficult to distinguish TRALI from other causes of non-cardiogenic pulmonary oedema or cardiac failure. It is important to report any case of TRALI to NHS Blood and Transplant so that an implicated donor can be contacted and, if appropriate, taken off the donor panel.

Features: Typically, within six hours of a transfusion, the patient develops severe breathlessness and a non-productive cough. The chest X-ray characteristically shows bilateral nodular infiltrates in a bat-wing pattern, similar to adult respiratory distress syndrome. Loss of circulating volume and hypotension are common. The patient may or may not have fever or chills. Reduced Monocyte count or neutropenia may be seen.

Management: Seek urgent critical care and haematology advice. Treatment is that of adult respiratory distress syndrome from any cause. Diuretics should be avoided. Steroids are of uncertain benefit. The syndrome is self-limiting with supportive care but may require mechanical ventilation.

Investigation: For suspected TRALI reactions, NHSBT will require completion of the clinical presentation form that will determine if reaction is being investigated. The treating medic will be directed to the NHSBT consultant for further investigation. A chest X-Ray should be performed on all respiratory symptoms associated with transfusion.

4.1.7 Transfusion Associated Circulatory Overload (TACO) - Fluid Overload

Cause: When too much fluid is transfused or the transfusion is too rapid.

Features: Acute left ventricular failure (LVF) may occur with dyspnea, tachypnea, non-productive cough, raised JVP, basal lung crackles, frothy pink sputum, hypertension and tachycardia.

Management: The transfusion should be stopped and standard medical treatment, including diuretic and oxygen given. Monitor urine output. Urgent discussion with haematology consultant is required.

Prevention: Patients with chronic anaemia are usually normovolaemic or hypervolaemic and may have signs of cardiac failure before any fluid is infused. If

such a patient must be transfused, each unit should be given slowly with diuretic and the patient closely observed. e.g. **Adult...** Furosemide 20–40 mg oral or iv; **Paediatric...** refer to the BNFc for current dosing as this can change. Where possible, restricting transfusion to one unit of red cells in each 12-hour period should reduce the risk of LVF. Volume overload is a special risk with 20% albumin solutions due to sudden changes in oncotic pressure.

Investigation: Implicated units should be returned to the laboratory for further investigation immediately. Standard investigation including post transfusion group and screen, full blood count, renal and liver enzymes (LFTs, U&Es, ALT, AST) required as well as N-BNP. Patients with respiratory symptoms should also have a chest X-ray.

4.2 DELAYED TRANSFUSION REACTIONS

By definition, a delayed transfusion reaction occurs more than 24 hours after transfusion, the median being 7-9 days based on recent Serious Hazards of Transfusion reports.

4.2.1 Delayed haemolytic transfusion reaction (DHTR)

Definition: Fever and other symptoms/signs of haemolysis more than 24 hours after transfusion. Confirmed by fall in Hb, rise in bilirubin, positive DAT and positive cross-match **not detectable** pre-transfusion. Simple serological reactions (development of antibody without positive DAT or evidence of haemolysis) are excluded.

Cause: usually occurs in patients who have been sensitised to red cell antigens by prior transfusion or pregnancy. These may be undetectable when the patient is tested months or years later. However, a subsequent red cell transfusion can trigger a secondary immune response with a rapid rise in antibody levels. Antibodies of the Kidd (Jk) system are often the cause of such reactions.

Features:

- Hb falls more rapidly than expected after a red cell transfusion
- Rise in Hb is less than expected
- Sudden onset of jaundice
- Positive direct antiglobulin test (DAT)
- Haemoglobinuria

Management: Specific treatment is rarely required. Steroids are of no benefit. Antigen negative blood may be considered. Discuss with Consultant Haematologist.

Investigations: Standard investigation including Group and screen with DAT, Full blood count with reticulocyte count, renal and liver enzymes (LFTs, U&Es, ALT, AST), haptoglobin. Look for evidence of increased red cell destruction; fall in Hb, rise in LDH and/or bilirubin.

4.2.2 Transfusion-Associated Graft-Versus-Host Disease (TA-GvHD)

Cause: Transfused donor lymphocytes present in cellular blood components e.g. red cells and platelets, which recognise the recipient as foreign, can engraft and proliferate, causing TA-GvHD in susceptible recipients.

Features: Patients develop skin rash, diarrhoea and abnormal liver function and deteriorate, with bone marrow failure and death from infection usually within 2-3 weeks of transfusion.

Prevention: TA-GvHD can be prevented by gamma irradiating cellular blood components to be transfused. Please refer to the site-specific Blood Transfusion Policy.

4.2.3 Iron Overload

Transfusion-dependent patients receiving >20 units of red cells become overloaded with iron. Each unit of red cells contains 250mg of iron and tissue iron accumulation will cause multiple organ damage in particular liver, pancreas and cardiac damage.

Prevention: Iron chelation therapy e.g. with desfersirox (Exjade) can be used to prevent dangerous accumulation of iron in patients receiving long-term transfusions. Discuss with haematologist.

4.2.4 Post-Transfusion Purpura (PTP)

Cause: This is a rare but potentially lethal complication of transfusion of red cells or platelets. It is more often seen in female patients. It is caused by platelet-specific alloantibodies.

Features: Typically, five to nine days after transfusion, the patient develops an extremely low platelet count with bleeding.

Management: Seek specialist advice from a haematologist. High-dose intravenous immunoglobulin is the current treatment of choice with responses in about 85% of cases. There is often a rapid and prompt increase in the platelet count. Platelet transfusions are usually ineffective in raising the platelet count but may have to be given in large doses in the attempt to control severe bleeding in the acute phase, particularly in patients who have recently undergone surgery, before there has been a response to high-dose IV IgG.

Investigations: Platelet count, coagulation screen to exclude DIC as a cause of thrombocytopenia, HPA typing and HPA antibodies.

4.2.5 Transfusion Transmitted Infections (TTI)

The risks of blood transfusion transmitted infection in the UK are minimised by careful selection of donors and screening of all blood donations for known hazards e.g. hepatitis B, HIV There is currently no test for vCJD. The risks of transmission of known infections are very low but all non-essential transfusions should be avoided,

and clinicians and patients must be aware there is a risk of infection - perhaps previously unrecognised or unknown - that could be transmitted by transfusion. Protozoal, helminthic, spirochetal and rickettsial infections can all be transmitted through blood transfusions.

6 Reporting incidents

All adverse events relating to transfusion should be reported to Blood Bank as soon as possible, they will take the details verbally and complete an 'Investigation into a Suspected Transfusion Reaction' form.

If a severe reaction is suspected, advice from a Consultant Haematologist should be sought.

The clinician must record the reaction in the patient's notes and blood transfusion documentation. A clear management plan for future transfusion must be documented in patient notes also. It is the responsibility of the treating clinician to ensure 'Duty of Candour' is performed in the event of the adverse transfusion episode causing harm.

Enter a DATIX under the incident type tier one: Blood/Plasma Products.

All moderate/severe adverse reactions are required to be reported externally to MHRA/SHOT by a member of the Hospital transfusion Team.

7 References

https://b-s-h.org.uk/guidelines/guidelines/guideline-on-the-investigation-and-management-of-acute-transfusion-reactions BSH guidelines 2023

Annual-SHOT-Report-2023-V1.2.pdf 2023 SHOT Report

Consent for Blood Transfusion - Guidance for Healthcare Practitioners in the UK - JPAC

1. Documentation Controls

Reference Number CG-CLIN/1757/25	**Version:** 2		**Status** Final	A. Burtenshaw Transfusion Practitioner
Version / Amendment History	Version	Date	Author	Reason
	1	2016	Dr McKernan	New summary guideline- Derby only
	2	Dec 24	A Burtenshaw	Update of existing guideline to be Trustwide and cross-site
Intended Recipients: All staff with responsibility for any step of the blood transfusion process across UHDB.				
Training and Dissemination: Theory training is required by all staff involved all steps of the transfusion process. Theory training is incorporated in Trust Induction and requires 3 yearly updates. Guideline is disseminated via KOHA on NETi.				
Development of Guideline: **Job Title:**				
Consultation with:				
Linked Documents: Trust Policy for The Transfusion of Blood and Blood Components (site specific). Transfusion Reaction Clinical Guideline summary.				
Keywords: Transfusion reaction, Blood transfusion				
Business Unit Sign Off			**Group:** Hospital Transfusion Team **Date:** 28/11/2024	
Divisional Sign Off			**Group:**Trustwide CGG **Date**:January 2025	
Date of Upload			8th January 2025	
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