5: Adverse effects of transfusion

Essentials

- Modern blood transfusion is very safe but preventable death and major morbidity still occurs.
- Inappropriate decisions to transfuse put patients at unnecessary risk of transfusion errors, reactions and transfusion-transmitted infection.
- Identification errors (of patients, blood samples and blood components) by hospital staff are the root cause of most ‘wrong blood into patient’ incidents, including ABO-incompatible transfusions.
- Severe acute transfusion reactions are the most common cause of major morbidity. These include immunological reactions (predominantly allergy/anaphylaxis, haemolytic reactions and lung injury), circulatory overload and rare bacterial contamination of blood components.
- If a serious transfusion reaction is suspected – stop the transfusion; assess clinically and start resuscitation if necessary; check that the details on the patient’s ID band and the compatibility label of the blood component match; call for medical assistance; contact the transfusion laboratory.
- Transfusion-transmitted infection is now a very rare event, underpinned by voluntary donation, donor selection procedures and microbiological testing, but constant vigilance is required as new threats emerge.
- Variant CJD transmission by blood has had a major impact on transfusion practice in the UK although the risk appears to be receding.

Compared with many medical and surgical procedures modern blood transfusion is extremely safe but deaths and major morbidity still do occur. Errors in the identification of patients, blood samples and blood components are the root cause of many preventable serious adverse events (see Chapter 4). Around 1 in 13 000 blood component units is transfused to the wrong patient (not always with adverse consequences) and up to 1 in 1 300 pre-transfusion blood samples are taken from the wrong patient.

Serious acute transfusion reactions are often unpredictable but patients are put at unnecessary risk by inappropriate decisions to transfuse. In its 2012 Annual Report, the UK Serious Hazards of Transfusion haemovigilance scheme (SHOT – http://www.shotuk.org/) described 252 incidents of ‘incorrect blood component transfused’ (each underpinned by 100 near misses). Ten ABO-incompatible transfusions (all due to clinical errors) and 145 incidents of ‘avoidable, delayed or under-transfusion’ were reported. There were nine transfusion-related deaths (six associated with transfusion-associated circulatory overload) and 134 cases of major morbidity (most often following acute transfusion reactions).

Transfusion-transmitted infection is now a rare event but there is no room for complacency as the emergence of new infectious agents requires constant vigilance.
5.1: Haemovigilance

Haemovigilance is the ‘systematic surveillance of adverse reactions and adverse events related to transfusion’ with the aim of improving transfusion safety. Transfusion reactions and adverse events should be investigated by the clinical team and hospital transfusion team and reviewed by the hospital transfusion committee. SHOT invites voluntary reporting of serious adverse transfusion reactions, errors and events as well as near-miss incidents. Under the Blood Safety and Quality Regulations 2005 (BSQR) there is a legal requirement to report serious adverse reactions and events to the Medicines and Healthcare Products Regulatory Agency (MHRA). The MHRA also inspects blood establishments (transfusion centres) and hospital transfusion laboratories to ensure their processes and quality standards comply with the BSQR. SHOT and MHRA work closely together and have a joint reporting system through the SABRE IT system (http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Blood/).

Haemovigilance can identify transfusion hazards and demonstrate the effectiveness of interventions. SHOT reporting highlighted the importance of transfusion-related acute lung injury (TRALI) as a potentially lethal risk of transfusion and confirmed the benefit of sourcing fresh frozen plasma (FFP) from male donors. More recently, transfusion-associated circulatory overload (TACO) has been identified as an important preventable cause of death or major morbidity. Incidents of avoidable, delayed or under-transfusion are increasingly reported, leading to initiatives to improve the knowledge base of clinical staff and awareness of evidence-based guidelines.

Adverse effects of transfusion are commonly classified as infectious or non-infectious; acute or delayed; caused by errors or pathological reactions; and by their severity (mild, moderate or severe).

5.2: Non-infectious hazards of transfusion

5.2.1: Acute transfusion reactions

Acute transfusion reactions (ATRs) present within 24 hours of transfusion and vary in severity from mild febrile or allergic reactions to life-threatening events. They include:

- Febrile non-haemolytic transfusion reactions – usually clinically mild.
- Allergic transfusion reactions – ranging from mild urticaria to life-threatening angio-oedema or anaphylaxis.
- Acute haemolytic transfusion reactions – e.g. ABO incompatibility.
- Bacterial contamination of blood unit – range from mild pyrexial reactions to rapidly lethal septic shock depending on species.
- Transfusion-associated circulatory overload (TACO).
- Transfusion-related acute lung injury (TRALI).

Early recognition of ATRs by careful monitoring of vital signs during transfusion is important; especially the 15-minute checks (see Chapter 4). Patients should be asked to report symptoms that arise during the transfusion and for at least the next 24 hours.

Severe ATRs occur in about 1 in 7000 units transfused. Patients may present suddenly with cardiovascular collapse and the underlying cause may not be immediately apparent. The differential diagnosis of severe, life-threatening ATRs includes bacterial transfusion-transmitted infection, acute haemolytic reactions (usually due to ABO-incompatible transfusion), anaphylaxis, TRALI and TACO.

The British Committee for Standards in Haematology (BCSH) Guideline on the Investigation and Management of Acute Transfusion Reactions (Tinegate et al., 2012) (https://b-s-h.org.uk) emphasises that
Immediate management should focus on timely recognition of the event and its severity, based on clinical symptoms and signs, stopping the transfusion and resuscitating the patient. This is followed by appropriate investigation, specific treatment and prevention (where possible) of future events. The guideline provides a flowchart for the recognition and management of ATR based on presenting symptoms and clinical signs (Figure 5.1).

Key principles in the management of ATR include:

- Transfusing patients in clinical areas where they can be directly observed by appropriately trained staff (including the emergency management of anaphylaxis)
- Ensuring that the recognition and immediate management of ATR are incorporated into local transfusion policies and the training of clinical and laboratory staff.

If a patient develops new symptoms or signs during a transfusion:

- Stop the transfusion and maintain venous access with physiological saline.
- Check vital signs and start resuscitation if necessary.
- As soon as possible, check that the identification details of the patient, their ID band and the compatibility label of the component match.
- Inspect the component for abnormal clumps or discoloration.
- If the presumed ATR is severe or life threatening the transfusion must be discontinued and immediate medical review arranged.
- Note: If a patient being transfused for haemorrhage develops hypotension, careful clinical assessment is essential as this may be due to continuing blood loss and continuation of the transfusion may be life-saving.

Except for patients with mild allergic or febrile reactions, a standard battery of tests should be performed, including full blood count, renal and liver function tests and assessment of urine for Hb. Further tests are determined by the symptoms and clinical signs (Table 5.1).

5.2.2: Severe and life-threatening reactions

5.2.2.1: Acute haemolytic reactions

The most serious reactions are caused by transfusion of ABO-incompatible red cells which react with the patient’s anti-A or anti-B antibodies. There is rapid destruction of the transfused red cells in the circulation (intravascular haemolysis) and the release of inflammatory cytokines. The patient often quickly becomes shocked and may develop acute renal failure and disseminated intravascular coagulation (DIC). Transfusion of less than 30 mL of group A red cells to a group O patient has proven fatal. Acute haemolysis may also, rarely, be caused by transfusing plasma-rich blood components, such as platelets or FFP (usually group O) containing high-titre or high-potency anti-A or anti-B antibodies to a patient with group A, B or AB red cells. This has mainly been reported in infants and small children (see Chapter 10). Intravenous immunoglobulin solutions contain ABO antibodies and the 2012 annual report for SHOT includes a rare case of fatality due to haemolysis and renal failure in a group A patient.

ABO-incompatible transfusion occurs in around 1 in 180,000 red cell units transfused. It is usually caused by human error when taking or labelling pre-transfusion blood samples, collecting components from the blood bank or satellite refrigerator and/or failing to perform a correct identity check of blood pack and patient at the bedside (see Chapter 4). If red cells are transfused to the wrong patient, there is around a 30% chance they will be ABO incompatible. Major morbidity (requiring intensive care or renal dialysis) occurs in up to 30% of cases and 5–10% of episodes contribute to the death of the patient.

Conscious patients often become very unwell within the first few minutes of transfusion, complaining of flushing, loin and abdominal pain and ‘a feeling of impending doom’. If the patient is unconscious,
anaesthetised or cannot communicate, the first indication of a reaction may be tachycardia, hypotension and bleeding into the skin or from needle wounds, emphasising the importance of careful monitoring of vital signs.

Immediate clinical management of patients with suspected severe acute haemolytic transfusion should follow the steps outlined in Figure 5.1 and the investigations in Table 5.1. After disconnecting the transfusion pack and starting resuscitation:

- Maintain venous access with physiological saline and call for urgent medical support.
- Check the compatibility label on the blood pack against the patient’s ID band (and seek confirmation of identity from the patient, parent or carer if possible).
- Inform the transfusion laboratory urgently. If the wrong blood has been transfused, another patient may be at risk. Return the (sealed) transfusion pack and giving-set for investigation.
- Seek early support and advice from critical care and haematology teams and admit the patient to an intensive care unit if possible.

Figure 5.1 Clinical flowchart for the management of acute transfusion reactions (reproduced from BCSH Guideline on the Investigation and Management of Acute Transfusion Reactions, 2012, with kind permission of British Committee for Standards in Haematology)
Table 5.1 Investigation of moderate or severe acute transfusion reactions (adapted from BCSH Guideline on the Investigation and Management of Acute Transfusion Reactions, 2012)
<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Standard Investigations¹</th>
<th>Additional Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever (≥2°C rise or &gt;39°C)</strong> and/or chills, rigors, myalgia, nausea or vomiting and/or loin pain</td>
<td>Standard investigations¹</td>
<td>Samples for repeat compatibility testing, direct antiglobulin test (DAT), lactate dehydrogenase (LDH) and haptoglobins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood cultures from patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coagulation screen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not discard implicated unit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If febrile reaction sustained, return blood component to laboratory, repeat serological investigations (compatibility testing, antibody screen and DAT), measure haptoglobins and culture blood component. Contact a Blood Service consultant to discuss the need for recall of components from same donation.</td>
</tr>
<tr>
<td><strong>Mucosal swelling (angioedema)</strong></td>
<td>Standard investigations¹</td>
<td>Measure IgA level – if &lt;0.07 g/L (in absence of generalised hypogammaoglobulinaemia) perform confirmatory test with sensitive method and check for IgA antibodies</td>
</tr>
<tr>
<td><strong>Dyspnoea, wheeze or features of anaphylaxis</strong></td>
<td>Standard investigations¹</td>
<td>Check O₂ saturation or blood gases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chest X-ray (mandatory if symptoms severe)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If severe or moderate allergic reaction suspected, measure IgA level (as above)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If severe allergic/anaphylactic reaction, consider measurement of serial mast cell tryptase (immediate, 3 and 24 hours)</td>
</tr>
<tr>
<td><strong>Hypotension (isolated fall in systolic blood pressure of &gt;30 mm Hg resulting in a level &lt;80 mm Hg)</strong></td>
<td>Standard investigations¹ plus investigations as for fever</td>
<td>If allergic reaction suspected measure IgA level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If severe allergic/anaphylactic reaction suspected, consider measurement of serial mast cell tryptase</td>
</tr>
</tbody>
</table>
5.2.2.2: Transfusion of a blood component contaminated by bacteria

Although rare, this more often occurs with platelet components (which are stored at 22–24°C) than with red cells refrigerated at 2–6°C and can rapidly be fatal. Measures to reduce bacterial contamination from the donor arm have significantly reduced this risk (see section 5.3) but awareness and rapid response are important. The transfusion of a pack contaminated with highly pathogenic bacteria often causes an acute severe reaction soon after the transfusion is started. Initially, this may be indistinguishable from an acute haemolytic reaction or severe allergic reaction. Typical symptoms and signs include rigors, fever (usually >2°C above baseline), hypotension and rapidly developing shock and impaired consciousness.

Immediate management and investigation follows the principles outlined in Figure 5.1 and Table 5.1. In particular:

- Inspection of the pack may show abnormal discoloration, aggregates or offensive smell, but many packs appear normal.
- Blood cultures should be taken from the patient and treatment immediately started with an intravenous broad spectrum antibiotic combination covering gram negative and gram positive bacteria (the local empirical antibiotic regimen used in patients with neutropenic sepsis is appropriate).
- Implicated components must be sealed to avoid leakage or contamination and returned to the transfusion laboratory for further investigation.
- The blood transfusion centre must be contacted immediately so that any associated components from the implicated donation can be urgently identified and withdrawn from hospital blood banks.

National Blood Services provide comprehensive bacterial testing and typing of strains (to confirm identity of contaminating bacteria with those isolated from the patient’s blood cultures). Both SHOT and BCSH recommend that, wherever possible, implicated component packs are returned to the Blood Service for testing rather than sampled and cultured in local hospital laboratories.

5.2.2.3: Severe allergic or anaphylactic reactions

Shock or severe hypotension associated with wheeze (bronchospasm), stridor from laryngeal oedema or swelling of face, limbs or mucous membranes (angioedema) is strongly suggestive of anaphylaxis – an acute, life-threatening emergency. Other skin changes may include flushing and urticaria (‘nettle rash’ or hives) that also occur in less severe allergic reactions. Severe allergic and anaphylactic reactions may occur with all blood components but are most commonly reported with plasma-rich components such as platelets or FFP. In addition to the general resuscitation and supportive measures in Figure 5.1, specific points include:

- Staff in clinical areas carrying out blood transfusion must be trained in the emergency management of anaphylaxis, and epinephrine (adrenaline) must be available for emergency use.
- UK Resuscitation Council (UKRC) guidelines (2010 update) (http://www.resus.org.uk/pages/guide.htm) recommend the urgent administration of intramuscular (IM) epinephrine to treat anaphylaxis (adult dose 0.5 mL of 1:1000 (500 µg)). The IM route is rapidly effective (and life-saving) and prevents delay in attempting to obtain venous access in a shocked patient. It is not contraindicated in

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*a Standard investigations: full blood count, renal and liver function tests, assessment of urine for Hb*
patients with coagulopathy or low platelet count. The 2012 BCSH guideline on the investigation and management of acute transfusion reactions recommends that intravenous epinephrine is only given by expert practitioners such as anaesthetists.

- Urgent expert medical care should be called immediately (e.g. critical care outreach team or local equivalent).
- After initial resuscitation, parenteral steroids or antihistamines may be given but these should not be the first-line therapy.

After an anaphylactic reaction to blood, further investigation of the patient should be discussed with a clinical immunologist (including diagnosis of severe IgA deficiency – see below). Future transfusion policy should be discussed with a specialist in transfusion medicine. Most patients will have a single anaphylactic episode and essential transfusions should not be withheld (but must be carefully monitored). Those with recurrent episodes may benefit from using washed red cells or platelets in additive solution. There is little evidence to support the common practice of giving prophylactic antihistamines or steroids. Patients with recurrent reactions to FFP may be switched to pooled solvent detergent FFP, which rarely causes severe allergic reactions.

5.2.2.4: Severe allergic reactions associated with IgA deficiency

Only a small minority of patients with IgA deficiency are at risk of developing severe allergic reactions to blood components. Those at most risk have severe IgA deficiency (<0.07 g/L), often with anti-IgA antibodies in their plasma. Even then, most such patients do not react to blood transfusion. Patients with less severely reduced IgA levels as part of a more generalised (e.g. common variable immunodeficiency or secondary to a lymphoproliferative disorder) antibody deficiency disorder and the frequent mild cases picked up when screening for IgA coeliac antibodies are not at risk. Patients with no history of severe reactions to blood transfusion should be transfused with standard blood components.

The small group of patients with severe IgA deficiency and a clear history of serious allergic reaction to blood components should be discussed with a specialist in transfusion medicine and/or clinical immunologist. In elective situations they should be transfused with blood components from IgA-deficient donors. The UK Blood Services keep a small stock of such components on the shelf and have panels of suitable donors to call upon. If IgA-deficient components are not available within a clinically relevant time-frame (e.g. acute haemorrhage) then washed red cells should be used (washed platelets resuspended in platelet additive solution still have significant amounts of IgA in the plasma). In extreme emergency, transfusion with standard blood components should not be withheld and the patient must be transfused in a clinical area with appropriate facilities and staff to identify and treat severe allergic reactions.

5.2.2.5: Transfusion-related acute lung injury (TRALI)

Classical TRALI is caused by antibodies in the donor blood reacting with the patient’s neutrophils, monocytes or pulmonary endothelium. Inflammatory cells are sequestered in the lungs, causing leakage of plasma into the alveolar spaces (non-cardiogenic pulmonary oedema). Most cases present within 2 hours of transfusion (maximum 6 hours) with severe breathlessness and cough productive of frothy pink sputum. It is often associated with hypotension (due to loss of plasma volume), fever and rigors and transient peripheral blood neutropenia or monocytopenia. Chest X-ray shows bilateral nodular shadowing in the lung fields with normal heart size. TRALI is often confused with acute heart failure due to circulatory overload (see Table 5.2) and treatment with powerful diuretics may increase mortality.

Treatment is supportive, with high-concentration oxygen therapy and ventilatory support if required. Steroid therapy is not effective. Managed appropriately, often with intensive care, there is now a high rate of survival and most patients recover within 1 to 3 days without long-term problems.
Table 5.2 Comparison of TRALI and TACO (adapted from BCSH Guideline on the Investigation and Management of Acute Transfusion Reactions, 2012, by kind permission of British Committee for Standards in Haematology)

<table>
<thead>
<tr>
<th></th>
<th>TRALI</th>
<th>TACO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td>? More common in haematology and surgical patients</td>
<td>Most common in age &gt;70 but can occur at any age</td>
</tr>
<tr>
<td>Implicated blood components</td>
<td>Usually plasma or platelets</td>
<td>Any</td>
</tr>
<tr>
<td>Onset</td>
<td>Up to 6 hours from transfusion (usually within 2 hours)</td>
<td>Within 6 hours of transfusion</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Often low</td>
<td>Often high</td>
</tr>
<tr>
<td>Jugular venous pressure</td>
<td>Normal or low</td>
<td>Elevated</td>
</tr>
<tr>
<td>Temperature</td>
<td>Often raised</td>
<td>Normal</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Bilateral peri-hilar and nodular shadowing or ‘white out’, heart size normal</td>
<td>Enlarged heart and characteristics of pulmonary oedema</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Blood count</td>
<td>Fall in neutrophils and monocytes followed by neutrophil leucocytosis</td>
<td>No specific changes</td>
</tr>
<tr>
<td>Fluid challenge</td>
<td>Improves</td>
<td>Worsens</td>
</tr>
<tr>
<td></td>
<td>Worsens</td>
<td>Improves</td>
</tr>
</tbody>
</table>
Response to diuretics

Retrospective confirmation of TRALI requires the demonstration of antibodies in the donor’s plasma that react with antigens on the patient’s white blood cells. Suspected cases should be reported to the Blood Service and discussed with a transfusion medicine specialist who can advise on the need to investigate the implicated blood donors for antibodies to human leucocyte antigens (HLA) or human neutrophil antigens (HNA) with a view to removing them from the donor panel.

SHOT data suggest an approximate incidence of TRALI of 1 in 150,000 units transfused. It is most common after transfusion of plasma-rich blood components such as FFP or platelets and implicated donors are usually females sensitised during previous pregnancy. Since the UK Blood Services switched to using male donors for producing FFP, resuspending pooled platelets in male plasma and screening female apheresis platelet donors for leucocyte antibodies, SHOT has documented a significant fall in both reported cases and mortality from TRALI.

5.2.2.6: Transfusion-associated circulatory overload (TACO)

TACO is defined as acute or worsening pulmonary oedema within 6 hours of transfusion. Typical features include acute respiratory distress, tachycardia, raised blood pressure and evidence of positive fluid balance. It has probably been significantly under-reported in the past and may now be the most common cause of transfusion-related death in developed countries.

TACO causes significant morbidity and mortality. In 2012 SHOT received 82 reports of TACO. It contributed to the death of six patients and was responsible for 29 cases of major morbidity. Elderly patients are at particular risk and predisposing medical conditions include heart failure, renal impairment, low albumin concentration and fluid overload. Small patients, such as the frail elderly and children, are at increased risk of receiving inappropriately high-volume and rapid blood transfusions. Most reported cases involve red cell transfusions but high-volume FFP transfusions, sometimes given inappropriately for reversal of warfarin, have been identified as a risk. Poor pre-transfusion clinical assessment and inadequate monitoring during transfusion is a common feature of reported cases.

The treatment of TACO involves stopping the transfusion and administering oxygen and diuretic therapy with careful monitoring and critical care support if required. The risk of TACO is reduced by careful consideration of the need to transfuse, clinical assessment for predisposing factors, prescription of appropriate volume and flow rate, and adequate monitoring during the procedure. The common assumption that one unit of red cells produces a rise in Hb of 10 g/L only applies to patients of 70–80 kg. A dose of 4 mL/kg will produce a rise of about 10 g/L. The use of single-unit transfusions in small, frail adults or prescription in millilitres (as in paediatric practice) has been recommended.

5.2.2.7: Hypotensive reactions

Hypotensive reactions are indicated by an isolated fall in systolic blood pressure of 30 mm Hg or more (to <80 mm Hg) during, or within one hour of, transfusion with no evidence of an allergic reaction or haemorrhage. Most are transient but they occasionally progress to shock and organ dysfunction. The cause of most of these reactions is unknown, although they may be more common in patients taking ACE inhibitors. Management involves stopping the transfusion and nursing the patient flat with leg elevation (or in the ‘recovery position’ if consciousness is impaired). Other causes of severe ATR should be excluded by clinical and laboratory investigation.

Patients with recurrent hypotensive reactions may be given a trial of washed blood components.
5.2.3: Less severe acute transfusion reactions

5.2.3.1: Febrile non-haemolytic transfusion reactions (FNHTRs)

FNHTR are characterised by fever, sometimes accompanied by shivering, muscle pain and nausea. These are much less common since leucodepleted blood components were introduced. They can occur up to 2 hours after completion of the transfusion and are more common in multi-transfused patients receiving red cells.

Mild FNHTRs (pyrexia >38°C, but <2°C rise from baseline) can often be managed simply by slowing (or temporarily stopping) the transfusion. Giving an anti-pyretic, such as paracetamol, may be helpful. The patient should be monitored closely in case these are the early signs of a more severe ATR.

In the case of moderate FNHTRs (pyrexia >2°C above baseline or >39°C or rigors and/or myalgia), the transfusion should be stopped. If the symptoms worsen, or do not quickly resolve, consider the possibility of a haemolytic or bacterial reaction. In most cases it is prudent to resume transfusion with a different blood unit.

Patients with recurrent FNHTRs can be pre-medicated with oral paracetamol (or a non-steroidal anti-inflammatory drug if rigors or myalgia are a problem) given at least one hour before the reaction is anticipated, although the evidence base for effectiveness is poor. Patients who continue to react should have a trial of washed blood components.

5.2.3.2: Mild allergic reactions

Symptoms are confined to itching (pruritus) and/or skin rash ('nettle rash' or hives) with no change in vital signs. They are most common in patients receiving plasma-rich components such as FFP or platelets.

Symptoms often improve if the transfusion is slowed and an antihistamine (e.g. chlorpheniramine) is administered orally or intravenously. The patient must be monitored closely for development of a more severe reaction, in which case the transfusion must be stopped.

Several studies, including randomised controlled trials, have shown no benefit for routine pre-medication with antihistamines or steroids. Patients with recurrent mild allergic reactions who respond poorly to slowing the transfusion and administering an antihistamine should be discussed with a specialist in transfusion medicine or allergy. They may be considered for a trial of washed components. The possibility of other causes, such as latex allergy or drug reaction, should also be considered.

5.2.4: Delayed transfusion reactions

5.2.4.1: Delayed haemolytic transfusion reactions (DHTRs)

DHTRs occur more than 24 hours after transfusion in a patient who has previously been ‘alloimmunised’ to a red cell antigen by blood transfusion or pregnancy. The antibody may have fallen to a level that is undetectable by the pre-transfusion antibody screen and the patient is then inadvertently re-exposed to red cells of the immunising group. Antibodies to the Kidd (Jk) blood group system are the most common cause of DHTRs reported to SHOT, followed by antibodies to Rh antigens.

Transfusion of antigen-positive red cells causes a boost in the patient’s antibody levels (secondary immune response) leading to haemolysis of the transfused cells. Haemolysis becomes clinically apparent up to 14 days after the transfusion and signs may include a falling Hb concentration or failure to achieve the expected increment, jaundice, fever and occasionally haemoglobinuria or acute renal failure. Delayed reactions may be missed, especially if the patient has been discharged. In sickle cell disease, the clinical features of a DHTR may be misdiagnosed as a sickle cell crisis.
Clinical suspicion of DHTRs should be confirmed by laboratory investigations including blood count and reticulocytes, examination of the blood film, plasma bilirubin, renal function tests and LDH. Serological investigations should include repeat blood group and antibody screen (on pre- and post-transfusion patient samples), DAT and elution of antibodies from the patient’s red cells for identification.

Treatment of DHTRs is usually supportive, sometimes requiring further transfusion. The offending antibodies must be recorded on the transfusion laboratory computer and medical records and patients are usually issued with an ‘Antibody Card’ to carry and present to clinical staff whenever further transfusion is required. Patients investigated by Blood Services reference laboratories will also have their antibodies recorded on a central database. All DHTRs should be reported to SHOT and the MHRA.

5.2.4.2: Transfusion-associated graft-versus-host disease (TA-GvHD)

This rare and almost always fatal complication occurs when viable lymphocytes in a blood donation engraft in the patient and mount an immune response against the recipient’s cells of a different HLA type. At-risk patients usually have impaired cell-mediated immunity and are unable to reject the foreign cells. These include fetuses receiving intrauterine transfusion, patients with inherited immunodeficiency disorders affecting T-cell function, medical procedures causing very severe immunosuppression such as allogeneic stem cell transplantation or treatment with specific chemotherapy drugs such as purine analogues. TA-GvHD has occasionally been reported in non-immunosuppressed patients receiving a blood transfusion from an HLA-matched donor or a close relative with HLA types in common. Patients receiving conventional combination chemotherapy for cancer are not at increased risk of TA-GvHD and it has not been reported in HIV positive transfusion recipients. Clinical aspects of TA-GvHD prevention in haemato-oncology patients and neonates/infants are discussed in Chapters 8 and 10 respectively.

Symptoms classically occur 7 to 14 days (maximum 30 days) after transfusion with fever, skin rash, diarrhoea, disturbed liver function and worsening bone marrow aplasia. Diagnosis is based on showing the typical features of acute GvHD in biopsies of affected organs and demonstration of donor-derived cells or DNA in the patient’s blood or tissues. The UK Blood Services provide specialist diagnostic services. Only one case of TA-GvHD has been reported in the UK since 2000 (an intrauterine transfusion of non-irradiated maternal blood). Routine leucodepletion of blood components has clearly reduced the risk of TA-GvHD but it remains essential to ensure that all at-risk patients receive irradiated red cells or platelet components. The BCSH Guidelines on the Use of Irradiated Blood Components (http://www.bcshtaguidelines.com) regularly update the list of patients and therapeutic agents that require the use of irradiated blood components in the light of current research.

5.2.4.3: Post-transfusion purpura (PTP)

Affected individuals develop a very low platelet count and bleeding 5 to 12 days after transfusion of red cells. The typical patient is a parous female who is negative for a common platelet antigen, most commonly HPA-1a, and may have been initially sensitised by carrying a HPA-1a positive fetus in pregnancy. PTP is caused by re-stimulation of platelet-specific alloantibodies in the patient that also damage their own (antigen-negative) platelets by an ‘innocent bystander’ reaction. This severe, and potentially fatal, complication has become rare since the introduction of leucodepleted blood components.

Advice in diagnosis and management should be sought from transfusion medicine specialists and Blood Service laboratories. Platelet transfusions are usually ineffective (but may be given in high doses in patients with life-threatening bleeding) but most patients show a prompt and sustained response to high-dose intravenous immunoglobulin (IVIg).

5.3: Infectious hazards of transfusion
Historically, transfusion-transmitted infections (TTIs) dominated the transfusion safety agenda but they are now rare in developed countries. However, constant vigilance is required to counter the risk from established and newly emergent pathogens in the era of mass international travel. Novel transfusion-transmissible agents, such as prions, have also emerged to threaten the safety of the blood supply.

### 5.3.1: Viral infections

With modern donor selection and testing, hepatitis B, hepatitis C and HIV transmission are now very rare in the UK (Table 5.3). The current risk of an infectious donation entering the UK blood supply is now <1 in 1.2 million donations for hepatitis B, <1 in 7 million for HIV and <1 in 28 million for hepatitis C.

With the exception of hepatitis B, conventional screening tests were traditionally based on the detection of viral antibodies in donor blood. There is a small risk of infectious products entering the blood supply if a donation is made during the window period early in the course of infection before a detectable antibody response. These window periods have been much reduced by the addition of antigen testing and nucleic acid testing (NAT). Donations from new donors carry a slightly higher risk of viral positivity than repeat (previously tested) donors. Table 5.4 summarises the 23 confirmed viral transmissions (28 affected recipients) reported to the UK Blood Services between 1996 and 2012.

#### Table 5.3 Estimated risk per million blood donations of hepatitis B virus, hepatitis C virus and HIV entering the blood supply due to the window period of tests in use, UK 2010–2012 (data and information collected by the NHSBT/Public Health England Epidemiology Unit)

<table>
<thead>
<tr>
<th></th>
<th>Hepatitis B virus</th>
<th>Hepatitis C virus</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All donations</td>
<td>0.79</td>
<td>0.035</td>
<td>0.14</td>
</tr>
<tr>
<td>Donation from repeat donors</td>
<td>0.65</td>
<td>0.025</td>
<td>0.14</td>
</tr>
<tr>
<td>Donations from new donors</td>
<td>2.23</td>
<td>0.133</td>
<td>0.18</td>
</tr>
</tbody>
</table>

#### Table 5.4 Confirmed viral transfusion-transmitted infections, number of infected recipients and outcomes reported to UK Blood Services 1996–2012 (extracted from SHOT Annual Report 2012)

<table>
<thead>
<tr>
<th>Infection</th>
<th>No. of incidents</th>
<th>No. of infected recipients</th>
<th>Deaths related to infection</th>
<th>Major morbidity</th>
<th>Minor morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>11</td>
<td>13</td>
<td>0</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
### 5.3.1.1: Hepatitis A

This is primarily an acute enteric infection spread by the faeco-oral route (contaminated food or water). Transmission by transfusion is very rare as affected individuals are usually unwell and deferred from donation. There is no carrier state and blood donations are not screened for hepatitis A antibody or antigen. As a non-enveloped virus it is resistant to methods of pathogen inactivation such as solvent detergent treatment.

### 5.3.1.2: Hepatitis B

The hepatitis B virus (HBV) is readily transmitted by infectious blood or body fluids, including sexual intercourse and parenteral drug use, and perinatal transmission is common in endemic areas such as the Far East and China. Most patients recover after the initial episode of acute hepatitis but some develop a chronic carrier state, estimated at 350 million individuals worldwide, with long-term risk of cirrhosis of the liver and hepatocellular cancer. Hepatitis B remains the most commonly reported viral TTI in the UK because of window period transmissions but more sensitive screening tests for blood donations, such as HBV NAT, are increasingly effective.

### 5.3.1.3: Hepatitis C

There are around 170 million affected individuals worldwide. Initial infection is often symptomless but around 80% of patients develop a chronic carrier state with long-term risk of cirrhosis, liver failure and liver cancer. Hepatitis C was formerly a major cause of TTI, known as 'non-A non-B hepatitis', but the risk of transmission by blood transfusion has fallen dramatically since the introduction of antibody screening in 1991 and progressively more sensitive tests for hepatitis C antigen and RNA since 1999.

### 5.3.1.4: Hepatitis E

Caused by a small non-enveloped RNA virus, hepatitis E was formerly believed to be most prevalent in warmer climates and less developed countries where it is mainly spread by the faeco-oral route. In Western countries, recent studies have indicated large numbers of asymptomatic infections and up to 13% of individuals in England are seropositive for hepatitis E antibodies. Hepatitis E usually produces a self-limiting acute hepatitis but can lead to chronic infection, especially in immunocompromised patients, and may cause cirrhosis of the liver. An increase in the frequency of diagnoses of hepatitis E in patients in the UK has been seen in recent years. Transmission by blood transfusion has been confirmed with single UK cases reported to SHOT in 2004 and 2012. Blood Services are monitoring the situation closely, and working to establish the risk to transfusion recipients.

### 5.3.1.5: Human immunodeficiency virus (HIV) 1 and 2

<table>
<thead>
<tr>
<th>Virus</th>
<th>1</th>
<th>2</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis E</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HIV</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>HTLV</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Transfusion transmission by both single-donor and pooled blood components was common early in the course of the 1980s epidemic of acquired immunodeficiency syndrome (AIDS). Modern donor selection and screening has made transmission a rare event in the UK. The two incidents identified since SHOT reporting began (1996 and 2003) were both from HIV antibody negative window period donations before the introduction of HIV RNA screening.

5.3.1.6: Cytomegalovirus (CMV)

Cytomegalovirus is a common herpes virus that causes asymptomatic infection or a mild glandular fever-like illness in most healthy individuals. Despite an antibody response (seroconversion), the virus persists in blood monocytes and 50–60% of adults in the UK, including blood donors, are lifelong carriers of the virus. It can be transmitted by transfusion of cellular blood components although this may be difficult to distinguish from reactivation of previous infection. CMV can cause severe, sometimes fatal, infection in fetuses, neonates and immunocompromised adults. There has long been debate about the relative merits of donor CMV antibody screening (CMV negative components) or routine pre-storage leucodepletion in preventing transmission to patients at risk. In 2012, the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) produced an evidence-based position statement (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_133086.pdf). This can be summarised as follows:

- CMV seronegative red cells and platelets should be provided for intrauterine transfusions and neonates (up to 28 days after expected date of delivery).
- CMV seronegative granulocytes should be provided for CMV seronegative recipients.
- CMV seronegative red cells and platelets should be provided, where possible, for pregnant women. In an emergency, such as major haemorrhage, standard leucocyte-depleted components should be given to avoid delay.
- Standard pre-storage leucodepleted components are suitable for all other transfusion recipients, including haemopoietic stem cell transplant patients, organ transplant patients and immune deficient patients, including those with HIV.

5.3.1.7: Human T-cell lymphotropic virus types I and II (HTLV I and II)

These T-cell-associated RNA retroviruses are endemic in southwest Japan, the Caribbean Basin, sub-Saharan Africa and parts of South America, where they affect 15–20 million people. They are transmitted by sexual contact, breastfeeding, shared needles and blood transfusion. The clinical significance of HTLV II is uncertain but HTLV I is associated with a 1 to 4% lifetime risk of developing adult T-cell leukaemia /lymphoma (ATLL) or the chronic neurological disease HTLV I related myelopathy (HAM) many decades after infection. The combination of donor screening for antibodies to HTLV I and II plus leucodepletion of cellular blood components has virtually eliminated transmission by transfusion in the UK.

5.3.1.8: Human parvovirus B19 (HPV B19)

Infection with this common, seasonal, non-enveloped DNA virus is often asymptomatic and there is no chronic carrier state. It causes the childhood illness erythema infectiosum (‘slapped cheek syndrome’). Transient infection of red cell precursors in the marrow can cause an aplastic crisis in patients with shortened red cell survival such as sickle cell disease, thalassaemia major and chronic haemolytic anaemias. Infection of non-immune mothers in the second trimester of pregnancy may cause severe anaemia (hydrops fetalis) or death of the fetus. The virus can be transmitted by cellular blood components or frozen plasma and is resistant to pathogen inactivation techniques such as solvent detergent treatment. Although routine blood donor testing is not performed, only one TTI was reported to SHOT between 1996 and 2012. Products manufactured from large donor plasma pools, such as immunoglobulins and clotting factor concentrates, are screened for high titres of HPV B19 RNA.

5.3.1.9: West Nile Virus (WNV)
This mosquito-borne flavivirus has spread from its traditional distribution in Africa, western Asia, southern Europe and Australia in recent years and now produces seasonal epidemics across the United States and Canada, usually between May and November. Most infections are mild or asymptomatic, but around 0.5% of patients develop severe encephalitis that may be fatal. Blood donors may transmit the infection during the 3- to 15-day incubation period; therefore, individuals returning from affected areas are deferred from donation for 28 days or may be accepted for donation with the added precaution of WNV NAT screening.

5.3.2: Bacterial infections

5.3.2.1: Syphilis

All donations are routinely screened for antibodies to Treponema pallidum. Transmission is now extremely rare and no cases have been reported since SHOT surveillance began in 1996.

5.3.2.2: Other bacterial infections

Blood components may be contaminated by bacteria, most often derived from the donor arm at the time of collection, which can proliferate on storage and harm the recipient. Bacteria from the normal skin flora, such as the coagulase negative staphylococci rarely produce severe infections although febrile reactions may occur. More pathogenic gram positive bacteria, such as Staphylococcus aureus, and gram negatives, such as E. coli, Klebsiella spp. and Pseudomonas spp., may produce life-threatening reactions. Between 1996 and 2012, 40 acute transfusion reactions due to confirmed bacterial transmission were reported to SHOT, affecting 43 recipients, of whom 11 died. Thirty-three of these transmissions were from platelet packs and seven were from red cells.

Bacterial TTIs are more common with platelet components because of their storage at 20–24°C. The risk increases with storage time after donation and is the main reason for the short shelf life of platelet components. Platelet donors often give two or more adult therapeutic doses at a single apheresis session, with the risk of an infected donation affecting multiple recipients. Up to 1 in 2000 platelet packs contain detectable bacteria 5 days after donation and fatal reactions have been reported in 1 in 25 000–80 000 transfusions. By contrast, most pathogenic bacteria grow poorly in refrigerated red cell components although some gram negative organisms, such as Yersinia enterocolitica and Pseudomonas spp., can proliferate in these conditions.

5.3.2.3: Preventing bacterial transmission

Improved techniques for cleaning/decontamination of the donor arm and diversion of the first 20–30 mL of the donation into a side-pouch (this blood is used for donor testing) have produced a marked fall in the reports of bacterial TTIs in the UK. No cases were reported to SHOT between 2009 and 2012. As an additional safety measure, the UK Blood Services have introduced automated culture of all platelet donations and this may allow the safe extension of their shelf life from 5 to 7 days.

Pathogen inactivation (PI) technologies for platelets and red cells, such as the use of light-activated psoralens that kill organisms by damaging their DNA or RNA, are being developed and have the potential to eliminate both bacterial and viral TTIs. At present, the cost-effectiveness of PI is uncertain and early clinical studies of the currently licensed system have raised concerns about its effect on platelet function.

5.3.3: Protozoal infections

5.3.3.1: Malaria
Despite increasing international travel, transfusion-transmitted malaria remains a rare event in the UK. There have been two cases reported to SHOT (both *Plasmodium falciparum*) since 1996, the last in 2003, one of which was fatal. A policy of taking a travel history at the time of donation combined with deferral and, where indicated, testing for malarial antibodies has proved effective.

### 5.3.3.2: Chagas disease

This serious multi-system disease, caused by *Trypanosoma cruzi*, is endemic in Central and South America and may be transmitted by blood transfusion. No transfusion-transmitted cases have been recorded in the UK and precautions centre on donor history of residence/travel and, where appropriate, testing for antibodies to the parasite.

### 5.4: Variant Creutzfeldt–Jakob disease (vCJD)

This fatal neurological disease, due to the same agent (abnormal variant of prion protein) as bovine spongiform encephalopathy (BSE) in cattle and caused by eating beef from affected animals, was first identified in the UK in 1996. By the end of 2012 there had been 174 cases in the UK, peaking in 2000. Four cases of transfusion-transmitted vCJD infection have been identified, from three apparently healthy donors who later developed vCJD. All occurred with non-leucodepleted red cells donated before 1999. Three of the four recipients died of vCJD a few years after the implicated transfusion. The fourth recipient died of unrelated causes but had abnormal prion protein in the spleen at post-mortem examination (significance uncertain). There are still many uncertainties around the pathogenesis and epidemiology of vCJD and no practical screening test for blood donors has yet been developed. The vCJD risk-reduction measures introduced in the UK include (see also Chapter 3):

- Importation of plasma for fractionated blood products (1998)
- Leucodepletion of all blood components (1999)
- Importation (and viral inactivation) of fresh frozen plasma for all patients born on or after 1 January 1996 (when dietary transmission of vCJD is assumed to have ceased) (2002)
- Exclusion of blood donors who have received a blood transfusion in the UK since 1980 (2004)

The efficacy and safety of prion filters for blood components has been investigated but their cost-effectiveness is uncertain as the numbers of clinical cases of vCJD have reduced. There is also interest in the cohort of individuals born after measures to eliminate contaminated beef products from the UK diet were instituted in 1996 (‘class of 96’) who are becoming eligible to donate blood as they reach the age of 17.