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>Condition</th>
<th>Standard investigations&lt;br&gt;a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;2°C rise or &gt;39°C) and/or chills, rigors, myalgia, nausea or vomiting and/or loin pain</td>
<td>Samples for repeat compatibility testing, direct antiglobulin test (DAT), lactate dehydrogenase (LDH) and haptoglobins&lt;br&gt;Blood cultures from patient&lt;br&gt;Coagulation screen&lt;br&gt;Do not discard implicated unit&lt;br&gt;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>Mucosal swelling (angioedema)</td>
<td>Measure IgA level – if &lt;0.07 g/L (in absence of generalised hypogammaglobulinaemia) perform confirmatory test with sensitive method and check for IgA antibodies</td>
</tr>
<tr>
<td>Dyspnoea, wheeze or features of anaphylaxis</td>
<td>Check O₂ saturation or blood gases&lt;br&gt;Chest X-ray (mandatory if symptoms severe)&lt;br&gt;If severe or moderate allergic reaction suspected, measure IgA level (as above)&lt;br&gt;If severe allergic/anaphylactic reaction, consider measurement of serial mast cell tryptase (immediate, 3 and 24 hours)</td>
</tr>
<tr>
<td>Hypotension (isolated fall in systolic blood pressure of &gt;30 mm Hg resulting in a level &lt;80 mm Hg)</td>
<td>Standard investigations&lt;br&gt;a plus investigations as for fever&lt;br&gt;If allergic reaction suspected measure IgA level&lt;br&gt;If severe allergic/anaphylactic reaction suspected, consider measurement of serial mast cell tryptase</td>
</tr>
</tbody>
</table>

a Standard investigations: full blood count, renal and liver function tests, assessment of urine for Hb
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 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>Patient characteristics</th>
<th>? More common in haematology and surgical patients</th>
<th>Most common in age &gt;70 but can occur at any age</th>
</tr>
</thead>
<tbody>
<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>Response to diuretics</td>
<td>Worsens</td>
<td>Improves</td>
</tr>
</tbody>
</table>

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.bcshguidelines.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).