7: Effective transfusion in surgery and critical care

Essentials

- Transfusion of blood according to evidence-based guidelines improves patient safety and conserves precious blood supplies.
- The decision to transfuse should be based on clinical assessment as well as laboratory tests.
- The use of red cells in surgery has decreased but audits show many transfusions are inappropriate and there is wide variation in practice between clinical teams.
- Patient blood management programmes to improve surgical transfusion work across primary and secondary care and focus on:
  - preoperative optimisation
  - minimising blood loss at surgery
  - avoiding unnecessary transfusion after surgery
  - using blood conservation techniques (e.g. intraoperative cell salvage) and transfusion alternatives (e.g. antifibrinolytic drugs) where appropriate.
- Restrictive red cell transfusion strategies are safe in a wide variety of surgeries and in critical care patients.
- In the haemodynamically stable, non-bleeding patient transfusion should only be considered if the Hb is 80 g/L or less. A single red cell unit (or equivalent weight-related dose in children) may be transfused and the patient reassessed.
- Most invasive surgical procedures can be carried out safely with a platelet count above 50×10^9/L or international normalised ratio (INR) below 2.0.
- Successful transfusion support in major haemorrhage depends on the rapid provision of compatible blood, a protocol-driven multidisciplinary team approach and excellent communication between the clinical team and transfusion laboratory.
- The benefit of routinely transfusing fresh frozen plasma (FFP) in a fixed ratio to red cells (‘shock packs’) in traumatic haemorrhage is still uncertain but the CRASH-2 trial has proven that early administration of tranexamic acid reduces mortality.
- A restrictive red cell transfusion policy may be appropriate in many patients with acute upper gastrointestinal haemorrhage.

Blood transfusion can be life-saving and is a key component of many modern surgical and medical interventions. However, blood components are expensive, may occasionally have serious adverse effects and supplies are finite. Avoiding unnecessary and inappropriate transfusions is both good for patients and essential to ensure blood supplies meet the increasing demands of an ageing population. Clinical assessment, rather than laboratory test results, should be the most important factor in the decision to transfuse and evidence-based guidelines should be followed where available.
Surgical blood use in the UK has fallen by more than 20% since 2000, at least in part due to the various Better Blood Transfusion initiatives and increasing evidence for the benefits of restrictive transfusion policies. Less than 50% of red cell units are now given to surgical patients. However, audits show that 15–50% of red cell transfusions in a range of surgical procedures are inappropriate and there is still significant variation in the use of blood for the same operations. The fourth edition of the handbook defined good blood management as ‘management of the patient at risk of transfusion to minimise the need for allogeneic transfusion, without detriment to the outcome’. Multidisciplinary, evidence-based and patient-centred programmes to achieve this, often called patient blood management (PBM), are being set up across the UK and in other countries, such as Australia (http://www.nba.gov.au/guidelines/review.html).

7.1: Transfusion in surgery

7.1.1: Red cell transfusion

Patient blood management should start in primary care at the time of referral for surgery; working closely with the preoperative assessment clinic at the hospital. It has three key strands:

Preoperative optimisation

- Anaemia (and other relevant health problems) should be identified and treated in a timely fashion before surgery.
- Patients at increased risk of bleeding, especially those on anticoagulants or antiplatelet drugs, should be recognised.
- The use of blood conservation techniques in appropriate patients should be planned in advance.

Minimising blood loss at surgery

- Drugs that increase bleeding risk should be withdrawn if safe to do so (discuss with prescribing clinician).
- Blood-sparing surgical and anaesthetic techniques should be used.
- Antifibrinolytic drugs, tissue sealants and intraoperative cell salvage procedures should be used when appropriate.

Avoiding unnecessary transfusion after surgery

- Use restrictive ‘transfusion triggers’, balancing safety and effectiveness in individual patients.
- Minimise blood loss from blood tests.
- Use postoperative red cell salvage and reinfusion where appropriate.
- Prescribe iron and other stimulants to red cell production as needed.

Alternatives to donor blood transfusion and blood conservation techniques are detailed in Chapter 6. For further useful information about transfusion alternatives see http://www.nataonline.com/ and http://www.transfusionguidelines.org.uk/.

7.1.1.1: Preoperative anaemia

Patients who are anaemic preoperatively (Hb <130 g/L in adult males and Hb <120 g/L in adult females) are more likely to be transfused and a number of retrospective studies have shown that preoperative anaemia is an independent risk factor for increased morbidity and mortality. Ideally, a full blood count is checked at least 6 weeks before planned surgery to allow time for investigation and treatment and reduce the risk of late cancellation.
Iron deficiency is the most common anaemia revealed by preoperative screening. In men and postmenopausal women iron deficiency may be an indicator of gastrointestinal bleeding from peptic disease or cancer and should always be investigated. The speed of response to oral iron depends on the Hb deficit and the presence of continued blood loss. At least 3 months of treatment after recovery of Hb is needed to restore body iron stores. Patients intolerant of full dose oral iron may tolerate a lower dose, albeit with slower response. Oral iron is ineffective in the early postoperative period because of the inhibitory effect of inflammation on red cell production. Intravenous iron preparations, which now have a very low incidence of severe allergic reactions, may be used in patients intolerant of oral iron and may also improve the Hb when administered postoperatively (see Chapter 6). Erythropoiesis stimulating agents (ESAs) such as recombinant erythropoietin are not cost-effective in this setting.

7.1.1.2: Red cell transfusion in surgery

Clinical factors, as well as the degree of anaemia, must always be considered when making the decision to transfuse. Peripheral blood Hb concentration gives only limited information about the delivery of oxygen to vital organs. Experience of surgical patients who decline red cell transfusion, such as Jehovah’s Witnesses, show that otherwise healthy individuals can have successful outcomes down to an Hb concentration as low as 50 g/L (haematocrit approximately 15%) with good supportive care. The ‘safe’ Hb concentration is likely to be higher in patients with heart or lung disease who are less able to compensate for anaemia.

A number of studies have shown that red cell transfusion is a significant predictor of mortality after cardiac surgery, although its significance in non-cardiac surgery is less clear. Randomised trials of red cell transfusion in haemodynamically stable surgical patients have shown no benefits for liberal transfusion policies in terms of mortality, length of hospital stay or postoperative mobilisation. There is up to a 40% reduction in exposure to donor transfusions when restrictive transfusion thresholds are employed (evidence for the management of more severely ill patients is discussed in section 7.2). Most experts now agree that:

- Transfusion should be considered if Hb below 80 g/L
- If the Hb is below 70 g/L transfusion is usually indicated
- The decision to transfuse should be based on the clinical condition of the patient (higher thresholds may be appropriate in individual cases).

The same ‘transfusion triggers’ are applicable to patients with asymptomatic cardiovascular disease. Many clinicians recommend using a higher Hb threshold in patients with acute coronary syndromes, but the evidence for this is limited and a recent systematic review actually showed a higher mortality in transfused patients.

The American Association of Blood Banks (AABB) guidelines, published in 2012 (http://www.aabb.org/resources), stress the importance of considering symptoms and expected surgical blood loss as well as the Hb concentration in making the decision to transfuse. The AABB recommendations for red cell transfusion after surgery are as follows:

- Adhere to a restrictive transfusion strategy.
- Consider transfusion if Hb 80 g/L or less.
- Transfuse if symptomatic of anaemia – chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure.
- The same thresholds can be safely applied to patients with stable cardiovascular disease.

Patients who are not actively bleeding should be transfused with a single unit of red cells and then reassessed before further blood is given.

7.1.1.3: Does the age of red cells affect outcome after surgery?
Retrospective observational studies have suggested that transfusing ‘older’ stored red cells may be associated with higher mortality in patients undergoing cardiac surgery and cardiopulmonary bypass. This is controversial because of confounding factors and conflicting results from other studies. Large randomised trials are in progress to answer this important question. Unless or until there is prospective trial evidence of benefit, specific selection of fresh red cells is not recommended.

### 7.1.2: Bleeding problems in surgical patients

Patients who report abnormal bleeding, especially after dental extractions or surgery, or give a family history of bleeding problems, should be investigated before surgery wherever possible. Patients with known or suspected congenital bleeding disorders should be managed in conjunction with a comprehensive haemophilia care centre (http://www.ukhcdo.org/HaemophiliaCentres/a-c.htm). Most invasive surgical procedures can be carried out safely with a platelet count above 50×10⁹/L or international normalised ratio (INR) below 2.0.

#### 7.1.2.1: Low platelet count

Guidelines for platelet transfusion thresholds in thrombocytopenic surgical patients and patients undergoing invasive procedures are largely based on expert opinion and clinical experience.

Patients who also have impaired blood coagulation (e.g. liver disease, oral anticoagulants) or are on antiplatelet drugs, such as aspirin or clopidogrel, are at higher risk of perioperative bleeding and specialist advice should be sought if major surgery cannot be delayed. The template bleeding time is not a useful screening test for risk of surgical bleeding.

Consensus guidelines commonly used for thrombocytopenic patients requiring surgery are summarised in Table 7.1. When treatment is indicated, a single adult therapeutic dose (ATD) of platelets should be transfused shortly before the procedure and the post-transfusion count checked (10 minutes after transfusion gives a reliable indication).

#### Table 7.1 Platelet transfusion thresholds in surgery and invasive procedures

<table>
<thead>
<tr>
<th>Indication</th>
<th>Transfusion threshold or target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most invasive surgery (including post-cardiopulmonary bypass)</td>
<td>50×10⁹/L</td>
</tr>
<tr>
<td>Neurosurgery or posterior eye surgery</td>
<td>100×10⁹/L</td>
</tr>
</tbody>
</table>
| Prevention of bleeding associated with invasive procedures | Lumbar puncture 50×10⁹/L  
Central-line insertion 50×10⁹/L  
Liver, renal or transbronchial biopsy 50×10⁹/L  
Gastrointestinal endoscopy with biopsy 50×10⁹/L |
| Spinal anaesthesia                             | 50×10⁹/L                                              |
| Epidural anaesthesia                           | 80×10⁹/L                                              |
Bone marrow aspiration and trephine biopsy can be performed in patients with severe thrombocytopenia without platelet support if adequate local pressure is applied.

### 7.1.2.2: Patients on anticoagulants or antiplatelet drugs

Many older patients scheduled for surgery are on oral anticoagulants or antiplatelet drugs. A decision to temporarily stop the drug or reduce the dose must balance the risk of surgical bleeding against the indication for anticoagulation and be made in collaboration with the prescribing specialist (see 2012 British Committee for Standards in Haematology (BCSH) Guideline on the Management of Bleeding in Patients on Antithrombotic Agents (https://b-s-h.org.uk/).

#### 7.1.2.3: Warfarin

The current BCSH Guidelines on Oral Anticoagulation with Warfarin (https://b-s-h.org.uk/) provide detailed discussion of perioperative management. Minor dental procedures, joint aspiration, cataract surgery and gastrointestinal endoscopic procedures (including biopsy) can be safely carried out on warfarin if the INR is within the therapeutic range. More complex perioperative management should be guided by local protocols and specialist haematological advice. Management options are summarised in Table 7.2.

### Table 7.2 Perioperative management of warfarin anticoagulation (adapted from BCSH Guidelines on Oral Anticoagulation with Warfarin – 4th edition, 2011, with permission)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Management Options</th>
</tr>
</thead>
</table>
| Moderate/high risk of surgical haemorrhage, low risk of thrombosis (e.g. lone atrial fibrillation) | Stop warfarin 5 days preoperatively.  
Check INR on day before surgery:  
  - If INR <1.5, proceed  
  - INR 1.5 or above, give intravenous vitamin K 1–3 mg  
Restart maintenance dose of warfarin on evening of surgery if haemostasis secured. |
| Moderate/high risk of surgical haemorrhage, high risk of thrombosis (e.g. mechanical heart valve – especially mitral, venous thromboembolism within last 3 months) | Stop warfarin 5 days preoperatively and give ‘bridging therapy’ with low molecular weight heparin (LMWH) according to BCSH guideline.  
Last dose of LMWH 24 hours preoperatively.  
Restart LMWH when haemostasis secure (at least 48 hours in high bleeding risk surgery).  
Restart maintenance dose of warfarin when oral intake possible and continue LMWH until INR in therapeutic range. |
| Semi-urgent surgery (within 6–12 hours)                                  | Stop warfarin and give intravenous vitamin K 1–3 mg.  
Significant correction of INR within 6–8 hours. |
| Emergency surgery or life-threatening bleeding                            | Stop warfarin. |
7.1.3: Newer oral anticoagulants

In recent years a number of new oral anticoagulant drugs have been licensed. These include direct oral thrombin inhibitors, such as dabigatran, and direct oral Factor Xa inhibitors, such as rivaroxaban and apixaban. These drugs have no specific antidote. Their half-life is relatively short but can be prolonged in patients with reduced renal function. Wherever possible, treatment should be stopped at least 24 hours before surgery, longer if renal function is impaired (see Summary of Product Characteristics for each drug).

Management of bleeding involves stopping the drug, applying local pressure and administration of antifibrinolytic agents such as tranexamic acid. Fresh frozen plasma (FFP) does not reduce bleeding caused by these drugs. Recombinant activated Factor VII (rFVIIa, NovoSeven™), prothrombin complex concentrate (PCC) and activated PCC (FEIBA™) have been used as a treatment of last resort in uncontrollable bleeding but may increase the risk of thrombosis.

7.1.4: Heparins

Unfractionated heparins (UFHs) have a short plasma half-life, but this is increased in the presence of renal dysfunction. They can be administered by intravenous infusion or subcutaneous injection and therapeutic dosing is usually adjusted by comparison of the activated partial thromboplastin time with that of normal pooled plasma (APTT ratio). The anticoagulant effect can be rapidly reversed by injected protamine sulphate (1 mg reverses 80–100 units of UFH, maximum recommended dose 50 mg). Protamine can cause severe allergic reactions and, in most situations, simply discontinuing the UFH is all that is necessary.

Low molecular weight heparins (LMWHs) have a longer half-life, around 3 to 4 hours, which is significantly increased in renal dysfunction. The duration of anticoagulant effect depends on the particular LMWH and is only partially reversible by protamine. LMWHs have a more ‘targeted’ anticoagulant effect (mainly anti-Xa) than UFH, which may reduce the risk of bleeding, and a lower risk of heparin-induced thrombocytopenia (HIT) and osteopenia. Administration is by subcutaneous injection once or twice daily. They can be prescribed in a fixed or weight-related dose without monitoring in many clinical situations and are convenient for self-administration. Consequently, LMWHs have largely replaced UFH for many routine indications, including thromboprophylaxis for surgery. Perioperative management of patients on heparins is summarised in Table 7.3.

Table 7.3 Perioperative management of patients on heparins (general guidance only, see Summary of Product Characteristics for specific LMWH)

<table>
<thead>
<tr>
<th>Unfractionated heparins</th>
<th>Stop infusion 6 hours before surgery for full reversal (longer if renal dysfunction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low molecular weight heparins</td>
<td>Prophylactic dose: stop 12 hours before surgery</td>
</tr>
<tr>
<td></td>
<td>Therapeutic dose: stop 24 hours before surgery</td>
</tr>
</tbody>
</table>
7.1.5: Antiplatelet drugs

Aspirin and clopidogrel impair the function of platelets produced during exposure to the drug and the antiplatelet effect takes around 5 days to wear off (varies between individuals). Platelet function analysis or platelet mapping, if available, may give clinically useful information about residual antiplatelet activity. Urgent surgery should not be delayed in patients on these drugs. Many international guidelines recommend clopidogrel is stopped 3 to 5 days before elective surgery because of the risk of perioperative bleeding but the balance of risks and benefits depends on the indication for clopidogrel therapy. Aspirin can be stopped at the time of surgery in cardiac surgery and continued in many surgical procedures except in neurosurgery or operations on the inner eye.

Non-steroidal anti-inflammatory drugs (NSAIDs) produce reversible platelet dysfunction and have a short duration of action. Most guidelines suggest they are stopped at least 2 days before surgery associated with significant bleeding risk. Studies in elective orthopaedic surgery (mainly hip replacement) show increased blood loss and transfusion requirements in those who continue NSAID therapy to the time of surgery. The optimum time to discontinue NSAIDs prior to orthopaedic surgery is uncertain. Some guidelines have suggested a 2-week interval but acknowledge the evidence base for this is weak.

Inhibitors of platelet surface receptors GPIIb/IIIa may be used in patients with acute coronary syndromes. Abciximab inhibits platelet function for 12 to 24 hours after administration whereas eptifibatide and tirofiban have a short half-life of 1.5 to 2.5 hours. Invasive surgery should be delayed for 12–24 hours if possible. The drug effect is partially reversible by platelet transfusion.

7.1.6: Systemic fibrinolytic agents

‘Clot-busting’ drugs may be used in acute myocardial infarction, acute ischaemic stroke or massive pulmonary embolism. Streptokinase has a variable half-life, depending on the presence of anti-streptococcal antibodies, but can reduce fibrinogen and anti-plasmin levels for several days. With recombinant tissue plasminogen activator (e.g. alteplase) fibrinogen levels are only modestly reduced, usually returning to normal within 24 hours. Treatment for haemorrhage due to these drugs, or preparation for emergency surgery, may include antifibrinolytic agents (tranexamic acid or aprotinin – see Chapter 6), transfusion of FFP and cryoprecipitate or fibrinogen concentrate (not licensed for this indication) if the plasma fibrinogen is <1 g/L.

7.1.7: Cardiopulmonary bypass

Cardiopulmonary bypass (CPB) causes thrombocytopenia and platelet dysfunction that can increase the risk of haemorrhage. Prophylactic transfusion of platelets (or other blood components) is not beneficial but antifibrinolytic agents, such as aprotinin and tranexamic acid, may reduce blood loss. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM), usually performed in the operating room, may be helpful in guiding blood component therapy when excess bleeding occurs.

7.1.8: Liver transplantation

Transfusion requirements for liver transplantation have fallen significantly, but substantial, complex blood component support may still be necessary. Problems include preoperative coagulopathy due to liver disease, difficult surgery with the risk of high blood losses and intraoperative coagulopathy and
Transfusion Handbook / 7: Effective transfusion in surgery and critical care

hyperfibrinolysis before the transplanted liver starts to function. Intraoperative red cell salvage is effective in reducing donor blood transfusion and TEG is often used to direct blood component transfusion with FFP and platelets. Antifibrinolytic therapy with tranexamic acid or aprotinin may be beneficial in individual cases.

7.2: Transfusion in critically ill patients

Patients admitted to critical care units often receive blood transfusions but there is increasing evidence of potential harm as well as benefit. Clinical audits show that transfusions of platelets and FFP are often given for indications outside consensus guidelines.

7.2.1: Red cell transfusion in critical care

More than half of all patients admitted to critical care are anaemic and 30% of these have an initial Hb of <90 g/L. Anaemia early after admission is mainly caused by haemorrhage, haemodilution and frequent blood sampling. Later, reduced red cell production due to inflammation becomes an important factor and 80% of patients have an Hb of <90 g/L after 7 days. Around 80% of these transfusions are given to correct a low Hb rather than treat active bleeding. Blood losses from phlebotomy can be reduced by the use of blood conservation sampling devices and paediatric blood sample tubes.

Transfusion management has been strongly influenced by the 1999 Transfusion Requirements In Critical Care (TRICC) study (http://www.ncbi.nlm.nih.gov/pubmed/9971864) which randomised patients to an Hb ‘transfusion trigger’ of 100 g/L (liberal) or 70 g/L (restrictive). There was a trend to lower mortality in patients randomised to a restrictive policy (30% of whom received no transfusions). This was statistically significant in younger patients (<55 years) and those less severely ill. A restrictive transfusion policy was associated with lower rates of new organ failures and acute respiratory distress syndrome. Randomised trials in paediatric critical care, cardiac surgery, elderly patients undergoing ‘high-risk’ hip surgery and gastrointestinal haemorrhage have shown no advantages for a liberal transfusion policy.

A higher transfusion trigger may be beneficial in patients with ischaemic stroke, traumatic brain injury with cerebral ischaemia, acute coronary syndrome (ACS) or in the early stages of severe sepsis. There is no current evidence to support the use of ‘fresh’ rather than stored red cells in critically ill patients or the routine use of erythropoiesis stimulating agents.

The evidence base is reviewed in the 2012 BCSH Guidelines on the Management of Anaemia and Red Cell Transfusion in Adult Critically Ill Patients (https://b-s-h.org.uk/) and the guideline recommendations are summarised in Figure 7.1.

7.2.2: Platelet transfusion in critical care

Moderate thrombocytopenia (>50×10⁹/L) is common in critical care patients, often associated with sepsis or disseminated intravascular coagulation (DIC). ‘Prophylactic’ platelet transfusion in non-bleeding patients is not indicated, although this is the most common reason for transfusion identified in clinical audits (followed by ‘cover’ for invasive procedures). There are no high-quality randomised controlled trials to guide clinical practice and a BCSH guideline is currently in development.

The risk of bleeding in thrombocytopenic patients may be reduced by the avoidance or withdrawal of antiplatelet agents (e.g. aspirin, clopidogrel or non-steroidal anti-inflammatory drugs) and the use of antifibrinolytics such as tranexamic acid. Guidelines based on observational studies and expert opinion are summarised in Table 7.4.
Figure 7.1 Guidelines for red cell transfusion in critical care (adapted by courtesy of British Committee for Standards in Haematology)

Table 7.4 Suggested indications for platelet transfusion in adult critical care

<table>
<thead>
<tr>
<th>Indication</th>
<th>Transfusion threshold or target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not indicated</td>
<td></td>
</tr>
</tbody>
</table>

ACS – acute coronary syndrome
TBI – traumatic brain injury

Be less confident using an Hb trigger of 70 g/L if patient is elderly, has significant cardiopulmonary co-morbidities or inadequate tissue oxygenation.
Be more confident using an Hb trigger of 70 g/L if patient is <55 years and/or the severity of illness is relatively low.
Non-bleeding patients without severe sepsis or haemostatic abnormalities

Prophylaxis in non-bleeding patients with severe sepsis or haemostatic abnormalities

DIC with bleeding

Platelet dysfunction with non-surgically correctable bleeding (e.g. post-cardiopulmonary bypass or potent antiplatelet drugs)

Major haemorrhage and massive transfusion

<table>
<thead>
<tr>
<th>Condition</th>
<th>Threshold/Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-bleeding patients without severe sepsis or haemostatic abnormalities</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis in non-bleeding patients with severe sepsis or haemostatic abnormalities</td>
<td>Threshold $20 \times 10^9$/L</td>
</tr>
<tr>
<td>DIC with bleeding</td>
<td>Maintain $&gt;50 \times 10^9$/L</td>
</tr>
<tr>
<td>Platelet dysfunction with non-surgically correctable bleeding (e.g. post-cardiopulmonary bypass or potent antiplatelet drugs)</td>
<td>May bleed despite a normal platelet count. Transfusion of one adult therapeutic dose and repeat according to clinical response</td>
</tr>
<tr>
<td>Major haemorrhage and massive transfusion</td>
<td>Maintain $&gt;75 \times 10^9$/L ($&gt;100 \times 10^9$/L if multiple trauma or trauma to the central nervous system or inner eye)</td>
</tr>
</tbody>
</table>

### 7.2.3: Plasma component transfusion in critical care

A study of UK critical care units in 2011 showed that 13% of patients received transfusions of FFP. Around 40% of these transfusions were given to non-bleeding patients with normal or only mildly deranged clotting tests and many doses were subtherapeutic. Cryoprecipitate is used as a concentrated source of fibrinogen (fibrinogen concentrate is not yet licensed in the UK for this use). More research is needed to define best practice but the following pragmatic guidelines are suggested:

**Fresh frozen plasma**

- Indicated for the treatment of bleeding in patients with deranged coagulation due to deficiency of multiple clotting factors (e.g. DIC).
- Minimum dose 12–15 mL/kg (equivalent to four units in an average adult).
- Not indicated for prophylaxis in non-bleeding patients with abnormal clotting tests.
- Not indicated for the immediate reversal of warfarin (PCC should be used).
- In liver disease, there is no benefit to FFP transfusions in patients with an INR less than 1.7.

**Cryoprecipitate**

- Adult dose is two pooled units (ten donor units – approximately 3 g fibrinogen).
- Indications include:
  - acute DIC with bleeding and fibrinogen $<1.5$ g/L
  - severe liver disease with bleeding
  - prophylaxis for surgery when fibrinogen $<1.5$ g/L
  - hypofibrinogenaemia associated with massive transfusion (maintain $>1.5$ g/L).

### 7.3: Transfusion management of major haemorrhage

Major haemorrhage is variously defined as:
• Loss of more than one blood volume within 24 hours (around 70 mL/kg, >5 litres in a 70 kg adult)
• 50% of total blood volume lost in less than 3 hours
• Bleeding in excess of 150 mL/minute.

A pragmatic clinically based definition is bleeding which leads to a systolic blood pressure of less than 90 mm Hg or a heart rate of more than 110 beats per minute.

Early recognition and intervention is essential for survival. The immediate priorities are to control bleeding (surgery and interventional radiology) and maintain vital organ perfusion by transfusing blood and other fluids through a wide-bore intravenous catheter. Recent research has focused on major traumatic haemorrhage, influenced by the increased survival of military casualties using ‘damage control resuscitation’ and early transfusion of fresh plasma and red cells (see below).

Successful management of major haemorrhage requires a protocol-driven multidisciplinary team approach with involvement of medical, anaesthetic and surgical staff of sufficient seniority and experience, underpinned by clear lines of communication between clinicians and the transfusion laboratory. Useful information on the development of major haemorrhage protocols can be found on the UK Blood Transfusion and Tissue Transplantation Services website and the Association of Anaesthetists’ guideline on management of massive haemorrhage (http://www.aagbi.org/sites/default/files/massive_haemorrhage_2010_0.pdf).

Major haemorrhage protocols should identify the key roles of team leader (often the most senior doctor directing resuscitation of the patient) and coordinator responsible for communicating with laboratories and other support services to prevent time-wasting and often confusing duplicate calls. In an emergency situation it is essential to ensure correct transfusion identification procedures for patients, samples and blood components are performed (see Chapter 4) and an accurate record is kept of all blood components transfused. Training of clinical and laboratory staff and regular ‘fire drills’ to test the protocol and ensure the rapid delivery of all blood components are essential.

An example of a practical algorithm for the transfusion management of major haemorrhage is given in Figure 7.2.

7.3.1: Red cell transfusion in major haemorrhage

Red cell transfusion is usually necessary if 30–40% blood volume is lost, and rapid loss of >40% is immediately life threatening. Peripheral blood haematocrit and Hb concentration may be misleading early after major acute blood loss and the initial diagnosis of major haemorrhage requiring transfusion should be based on clinical criteria and observations (see Figure 7.2).

For immediate transfusion, group O red cells should be issued after samples are taken for blood grouping and crossmatching. Females less than 50 years of age should receive RhD negative red cells to avoid sensitisation. The use of Kell negative red cells is also desirable in this group. Group O red cells must continue to be issued if patient or sample identification is incomplete or until the ABO group is confirmed on a second sample according to local policy (see Chapter 2).

ABO-group-specific red cells can usually be issued within 10 minutes of a sample arriving in the laboratory. Fully crossmatched blood is available in 30 to 40 minutes after a sample is received in the laboratory. Once the volume of blood transfused in any 24 hour period is equivalent to the patient’s own blood volume (8–10 units for adults and 80–100 mL/kg in children), ABO and D compatible blood can be issued without the need for a serological crossmatch.

Figure 7.2 Algorithm for the management of major haemorrhage (adapted from the BCSH Practical Guideline for the Management of Those With, or At Risk of Major Haemorrhage (2014) with permission)
Recognise blood loss and trigger major blood loss protocol

Take baseline blood samples before transfusion for:
- Full blood count, group and save, clotting screen including Clauss fibrinogen
- Near-patient haemostasis testing if available

If trauma and <3h from injury, give tranexamic acid 1 g bolus over 10 minutes followed by IV infusion of 1 g over 8h (consider tranexamic acid 1 g bolus in non-traumatic)

Team leader to coordinate management and nominate a member of team to liaise with transfusion laboratory
- State patient unique identifier and location when requesting components
- To limit use of Group O NEG: until patient group known, use O NEG units in females and consider O POS in males
- Use group-specific blood as soon as available
- Request agreed ratio of blood components (e.g. 6 units RBS and 4 units FFP). Send porter to lab to collect urgently

If bleeding continues

Until lab results are available:
- Give further FFP 1L (4 units) per 6 units red cells
- Consider cryoprecipitate (2 pools)
- Consider platelets (1 adult therapeutic dose (ATD))

If lab results are available:

<table>
<thead>
<tr>
<th>IF</th>
<th>GIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falling Hb</td>
<td>Red cells</td>
</tr>
<tr>
<td>PT ratio &gt;1.5</td>
<td>FFP 15–20 mL/kg</td>
</tr>
<tr>
<td>Fibrinogen &lt;1.5 g/L</td>
<td>Cryoprecipitate (2 pools)</td>
</tr>
<tr>
<td>Platelets &lt;75x10⁹/L</td>
<td>Platelets 1 ATD</td>
</tr>
</tbody>
</table>

Continue cycle of clinical and laboratory monitoring and administration of ‘goal-directed’ blood component therapy until bleeding stops
The use of intraoperative cell salvage devices reduces the need for donor red cells in appropriate cases. When bleeding is controlled and the patient enters the critical care unit, a restrictive red cell transfusion policy is probably appropriate.

7.3.2: Coagulation and major haemorrhage

The transfusion of large volumes of red cells and other intravenous fluids that contain no coagulation factors or platelets causes dilutional coagulopathy. Major traumatic haemorrhage is often associated with activation of the coagulation and fibrinolytic systems (‘acute traumatic coagulopathy’). Plasma fibrinogen predictably falls to sub-haemostatic levels (<1.5 g/L) after 1 to 1.5 blood volume replacement (earlier in the presence of coagulopathy and hyperfibrinolysis). Coagulation is also impaired by hypothermia, acidosis and reduced ionised calcium (Ca\(^{2+}\)) concentration (which can be measured on many blood gas analysers). Ionised hypocalcaemia may be caused by rapid transfusion of blood components containing citrate anticoagulant, although this is uncommon in the presence of normal liver function.

Traditional ‘massive transfusion’ guidelines use laboratory tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT) to guide blood component replacement. The usefulness of these tests is reduced by the significant delay between sampling and returning results to the clinical team. If a PT can be made available with a rapid turnaround time that allows it to reflect the clinical situation it can be used to aid decisions regarding FFP infusion. The Clauss fibrinogen assay should be used in preference to a fibrinogen estimated from the optical change in the PT (PT-derived fibrinogen) that can be misleading in this setting.

Point of care testing (POCT) has an increasing role in providing ‘real time’ laboratory data to guide blood component replacement. It is essential to ensure appropriate calibration and quality assurance of POCT devices. Assays of clot formation, clot strength and lysis, such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM), have been used for many years to inform plasma and platelet transfusion in liver transplantation and cardiac surgery. Their value in the management of major haemorrhage is uncertain and is the subject of current research.

FFP should be transfused in doses of 12–15 mL/kg (at least four units in the average adult) to maintain the PT ratio (compared to ‘normal pooled plasma’) less than 1.5. Fibrinogen levels should be maintained above 1.5 g/L (Table 7.5).

<table>
<thead>
<tr>
<th>Table 7.5 Options for fibrinogen replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of fibrinogen</td>
</tr>
<tr>
<td>Fresh frozen plasma (FFP)</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>Fibrinogen concentrate(^{a})</td>
</tr>
</tbody>
</table>

\(^{a}\) Currently not licensed in the UK for acquired hypofibrinogenenaemia
The early transfusion of FFP in a fixed ratio to red cells (‘shock packs’) in traumatic haemorrhage, to reverse coagulopathy and reduce bleeding, has been extrapolated from military to civilian practice but the true value of this approach is uncertain. Retrospective studies are confounded by ‘survivorship bias’ (the most severely injured patients do not survive long enough to be transfused) and the non-military trauma population is older and less fit. Transfusion policy is just one component of an integrated, multidisciplinary response to major trauma. Large-volume FFP transfusion carries increased risks of circulatory overload (TACO), allergic reactions and transfusion-related acute lung injury (TRALI), and further clinical research is required to clarify its role.

Once haemostasis is secured, prophylactic anticoagulation with low molecular weight heparin should be considered because of the risk of thromboembolic complications.

7.3.3: Platelets and major haemorrhage

The platelet count usually remains above 50×10^9/L (the generally accepted haemostatic level) until 1.5 to 2.5 blood volumes have been replaced. Many hospitals do not store platelets on site and the time for transfer from the blood centre must be factored into local protocols. Therefore, an adult therapeutic dose should be requested when the count falls to 75×10^9/L.

7.3.4: Pharmacological treatments in major haemorrhage

The CRASH-2 trial published in 2010 clearly showed that early administration of the antifibrinolytic drug tranexamic acid improves the survival of patients with major traumatic haemorrhage or at risk of significant bleeding after trauma (Chapter 6). Tranexamic acid should be given as soon as possible after the injury in a dose of 1 g over 10 minutes followed by a maintenance infusion of 1 g over 8 hours. Evidence is emerging of the value of tranexamic acid in other forms of major haemorrhage, including obstetric and surgical haemorrhage. Given its good safety profile, ease of administration and low cost, tranexamic acid should be considered as a component of most major haemorrhage protocols.

Recombinant activated Factor VII (rFVIIa, NovoSeven™) is widely used off-label as a ‘last ditch’ therapy for patients with major haemorrhage (see Chapter 6). Systematic reviews and registry studies show no good evidence of improved survival, and life-threatening arterial and venous thromboembolic complications may occur, particularly in older patients with vascular disease. Several national guidelines no longer recommend its use outside research studies. Local protocols that include rFVIIa should require advice and authorisation from a haematologist or coagulation specialist and ensure that adverse effects are monitored and recorded.

7.3.5: Acute upper gastrointestinal bleeding

Acute upper gastrointestinal bleeding (AUGIB) is common and has a case fatality of around 10%. Some 35% of bleeds are caused by peptic ulcer disease but the most severe haemorrhage and highest mortality is seen in the 10% of cases presenting with bleeding from oesophageal or gastric varices. Treatment of AUGIB consumes around 14% of red cell units issued in the UK. Evidence-based guidelines for management were published in 2012 by the National Institute for Health and Care Evidence (NICE – http://www.nice.org.uk/nicemedia/live/13762/59549/59549.pdf).

Initial resuscitation of patients with massive gastrointestinal haemorrhage should include transfusion of red cells, platelets and clotting factors according to the local major haemorrhage protocol. In patients who are actively bleeding, the platelet count should be maintained >50×10^9/L, PT ratio >1.5 and fibrinogen >1.5 g/L. PCC and intravenous vitamin K should be used if immediate warfarin reversal is needed. It may be logical to administer PCC, which contains the liver-derived clotting Factors II, VII, IX and X, in bleeding patients with liver failure, but its use in this situation is off-label.
Once the patient is haemodynamically stable, and in patients with less severe initial haemorrhage, overt-transfusion may increase the risk of recurrent bleeding (probably by increasing portal venous pressure) and increase mortality. In a recent large randomised trial in patients with severe (but not massive) upper gastrointestinal haemorrhage in Spain (Villanueva et al., 2013), mortality and re-bleeding was lower in patients randomised to a restrictive rather than a liberal red cell transfusion policy (transfusion trigger 70 or 90 g/L). There were more adverse events (reactions and circulatory overload) in the liberal group. Of note, the trial excluded patients with a history of ischaemic heart disease, stroke or vascular disease and the results may not be generalisable, especially to older patients. Transfusion strategy in AUGIB is the subject of a current UK multicentre randomised trial (TRIGGER – http://www.nhsbt.nhs.uk/trigger) which is recruiting unselected cases in six hospitals.

7.3.6: Major obstetric haemorrhage

See section 9.4.

7.3.7: Audit of the management of major haemorrhage

Audit is important to assess adverse events, timeliness of blood component support, patient outcome and component wastage. There should be multidisciplinary review of cases that trigger the major blood loss protocol to ensure it is being applied appropriately and effectively. Serious adverse reactions (SAR), serious adverse events (SAE) or incidents of patient harm due to delay should be reported to the Serious Hazards of Transfusion (SHOT) scheme (http://www.shotuk.org) (SAE and SAR must also be reported to the Medicines and Healthcare Products Regulatory Agency, MHRA).