

# Guidelines

## AAGBI guidelines: the use of blood components and their alternatives 2016

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### Summary

Blood transfusion can be life-saving. Anaesthetists regularly request and administer blood components to their patients. All anaesthetists must be familiar with indications and appropriate use of blood and blood components and their alternatives, but close liaison with haematology specialists and their local blood sciences laboratory is encouraged. Considerable changes in approaches to optimal use of blood components, together with the use of alternative products, have become apparent over the past decade, leading to a need to update previous guidelines and adapt them for the use of anaesthetists working throughout the hospital system.

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## Recommendations

- 1 All patients should have their haemoglobin concentration (Hb) measured before listing for major elective surgery.
- 2 Patients who are anaemic by the World Health Organization definition (Hb **men**  $< 130 \text{ g.l}^{-1}$ , **women**  $< 120 \text{ g.l}^{-1}$ ) should be investigated before elective surgery and treated appropriately, and elective non-urgent surgery other than caesarean section should be delayed.
- 3 Where blood transfusion is anticipated, this and alternatives to transfusion should be discussed with the patient before surgery, and this should be documented.
- 4 Red blood cells should be transfused **one unit at a time**, and the patient's Hb should be checked before each unit transfused, unless there is ongoing bleeding or a large deficit that needs correcting.
- 5 The use of intra-operative cell salvage and tranexamic acid administration should be considered in all non-obstetric patients where blood loss  **$> 500 \text{ ml}$**  is possible and in traumatic and obstetric major haemorrhage.
- 6 Blood components should be prescribed for **small children** by **volume** rather than number of units.
- 7 Every institution should have a massive transfusion protocol which is regularly audited and reviewed.
- 8 Group O red cells for transfusion should be readily available in the clinical area, in case haemorrhage is life-threatening. **Group-specific red cells should be available** within a very short time (**15–20 min**) of the laboratory receiving correctly-labelled samples and being informed of the emergency requirement for blood.
- 9 During major haemorrhage due to trauma and obstetrics, consideration should be given to transfusing red cells and FFP in preference to other intravenous fluid.
- 10 Patients who continue to actively bleed should be monitored by point-of-care and/or regular laboratory tests for coagulation, fibrinogen and platelet counts or function, and a guide for transfusion should be FFP if  $\text{INR} > 1.5$ , **cryoprecipitate if fibrinogen  $< 1.5 \text{ g.l}^{-1}$**  and **platelets if platelet count  $< 75 \times 10^9 \text{ l}^{-1}$** .

## What other guidelines are available on this topic?

A number of other guidelines are available, some of which are quite recent, but none cover the breadth of UK anaesthetic practice (Appendix 1).

## Why was this guideline developed?

There is a need for a relevant up-to-date clinical guidance for practising UK anaesthetists, critical care staff and those from other specialities and backgrounds, based on evidence where possible and with a focus on safety.

## How and why does this publication differ from existing guidelines?

This is an updated guideline that also brings three previous AAGBI guidelines together (blood component therapy, 2005; massive haemorrhage, 2010; and red cell transfusion, 2008).

## Introduction

Transfusion medicine is changing rapidly in response to new developments. Considerable changes in approaches to transfusion, together with the use of alternative agents, have become apparent over the past decade. Blood transfusion can be life-saving, but this is a scarce and costly resource. There is increased focus on appropriate transfusion practice to ensure quality of service provision, and transfusion has been proposed as a quality indicator in surgical care. Blood transfusion usage remains high, particularly in trauma, obstetrics, critical care and cardiovascular surgery.

Anaesthetists are frequently involved in transfusion decisions, the administration of blood and blood components and as part of the team managing any major haemorrhage. However, the use of allogeneic blood components has serious implications and warrants careful consideration [1]. As a consequence, there has recently been an expansion of interest in safeguarding and checklists, blood conservation, preservation techniques, coagulation profiling and the use of haemostatic agents. Appropriate use of blood components in patient care is of utmost importance.

Several recent major research publications that have looked at transfusion practice were aimed at patient safety, outcomes and individualised care, including: use of restrictive transfusion protocols; adjuvant therapies; substitution of blood components with pooled factor concentrates; and use of point-of-care (POC) testing to target specific component use (see <http://onlinelibrary.wiley.com/doi/10.1111/anae.2014.70.issue-s1/issuetoc>).

It is essential that our practice of blood transfusion is safe and based on current, scientific, evidence-based knowledge. A multidisciplinary approach that aims to benefit patients by the reduction in inappropriate transfusions is paramount. This working party aims to formalise guidance on the clinical indications and risks of transfusion, blood conservation and the transfusion process.

## Patient blood management

Patient blood management is a patient-based approach aimed at reducing the utilisation of blood transfusion and improving the patient's clinical outcome and safety, and focuses on the optimisation of three factors peri-operatively: patient, surgical and anaesthetic. It has been recommended as a standard of care in the UK National Health Service [2]. It focuses on three 'pillars' of care in surgical patients: detection and treatment of peri-operative anaemia; reduction of peri-operative blood loss; and harnessing and optimising the patient-specific physiological reserve of anaemia [3] (Table 1).

### Anaemia

Pre-operative anaemia is common, occurring in up to a third of patients before surgery, and associated with

worse outcomes. All patients should have their Hb checked before listing for surgery. Patients who are anaemic (Hb in men < 130 g.l<sup>-1</sup>, women < 120 g.l<sup>-1</sup>) should be investigated and the cause treated appropriately [4]. Patient pathways and pre-assessment clinics should be established to allow timely and appropriate management, and elective surgery should be delayed if required [5].

### Cell salvage

The use of cell salvage should be considered for high- or medium-risk surgery in non-obstetric adult patients where blood loss > 500 ml is likely, and in obstetric major haemorrhage. In patients with malignancy or obstetric haemorrhage, a leucocyte filter must be used. Bacterial contamination of the surgical field remains a contra-indication. Cell salvage may also be continued in the postoperative period [6].

Other aspects of patient blood management are discussed throughout these guidelines.

**Table 1** Patient blood management – measures that should be taken in patients who are expected to bleed during surgery.

Pre-operative
-Pre-operative Hb should be measured, recorded and optimised as required
-Elective surgery should be postponed in patients with untreated anaemia
-Review and consider stopping antiplatelet and anticoagulant medication seven days before surgery
-Consider minimally invasive or laparoscopic surgical technique
-Point-of-care testing should be available with appropriate training.
Intra-operative
-Position patient carefully to maintain venous drainage
-Use patient warming to maintain temperature > 36°
-Consider cell salvage if blood loss > 500 ml anticipated
-Consider giving tranexamic acid 1 g if blood loss > 500 ml anticipated
-Apply restrictive transfusion threshold (Hb 70–80 g.l <sup>-1</sup> depending on patient characteristics and haemodynamics)
-Consider use of topical haemostatic agents.
Postoperative
-Maintain oxygen delivery, targeting oxygen saturation levels > 95%
-Single unit blood transfusion policy – re-assess Hb concentration and clinical need between units
-Postoperative drains or cell salvage.

## Process for transfusion

Administering the wrong blood type in error (with the risk of ABO incompatibility) is the most serious outcome of blood transfusion. Most of these incidents are due to the failure of the final identity checks carried out between the patient (at the patient's side) and the blood to be transfused. All members of staff involved in the administration of a blood component must be trained and competency-assessed as per local policy. Local policy will also stipulate if this is a one- or two-person bedside check, with each person performing the check independently [7]. Red cell transfusions must be completed within 4 h of removal from the blood fridge. All prescriptions for transfusion must be documented in the patient record, either on the anaesthetic chart or on the drug/fluid prescription chart. Local policy for confirmation of the transfusion must be followed – it is a legal requirement that 100% of blood components must be traceable [8]. Where blood transfusion is anticipated, this should be discussed with the patient before surgery and valid consent to receive transfusion should be documented [9]. Patients should be informed that they have received blood or blood components before discharge from hospital as they will otherwise be unaware; they should also be informed that this removes them from the donor pool. It is also important that the patient's general practitioner is informed.

The following guidance is for a manual checking process at the bedside; the preferred system is an electronic transfusion management system.

- The patient must be positively identified. All patients receiving blood components should be wearing an identification wristband containing four core identifiers – first name, last name, date of birth and patient identification number.
- Immediately before the transfusion, check the component next to the patient, against the prescription.
- Check the four core identifiers on the compatibility label attached to the blood component with the identification attached to the patient. If there are any discrepancies, do not proceed and call the transfusion laboratory.
- Check that the compatibility label attached to the blood component has the same blood group and

14-digit component donation number (or batch number for coagulation factors) as the sticker on the blood component.

- Visually check the blood component for any leakage, discolouration or presence of any clots or clumps.
- Check the expiry date and time.

### *Transfusing an unidentified patient*

All hospitals should have a clear local policy for transfusion of patients whose identity is unknown. In emergency situations or where the patient cannot immediately be identified, the patient should still have identification attached stating unknown male or female and a unique identification number. The blood sample sent to the transfusion laboratory should contain these exact details.

In the event that the patient's identity becomes known, new identification must be attached to the patient and a new transfusion sample collected and fully labelled with the known patient's details.

### *Monitoring for adverse events or reactions during transfusions*

Clinical observations should include heart rate, blood pressure, temperature and respiratory rate, as per local guidelines (national guidelines define a minimum of pre-transfusion, at the end of transfusion and 15 min after transfusion). If there are any signs of a transfusion reaction, such as tachycardia, rash, breathlessness, hypotension or fever, stop the transfusion and contact the laboratory immediately [10]. Management may include the administration of antihistamine or steroid drugs, or intramuscular/intravenous adrenaline if life-threatening [11]. Diagnosis of a transfusion reaction during ongoing haemorrhage may be difficult, but if concern arises, the documentation should be double-checked for administration errors and further analyses performed as per local protocols.

### *Transferring blood with a patient*

Blood components should be transferred with patients at high risk of requiring transfusion en route or immediately on arrival. There should be effective communication between the blood transfusion laboratories involved, according to regional policy. Blood components must be transported in a storage box suitable to

maintain their integrity, along with accompanying paperwork, and careful handover is required. When the patient arrives at their destination, the receiving transfusion laboratory should be immediately informed that blood was transported. The patient should be issued with a new identity wristband, a new sample taken for cross-match and more blood issued; until this is available, blood transferred with the patient may be administered if required.

## Red blood cell transfusion

Red blood cell (RBC) transfusion is potentially life-saving for the treatment of blood loss (Major haemorrhage – see next section). In patients who do not have active bleeding and in normovolaemic patients, the Hb should be measured before and after every unit of RBC transfused. Near-patient measurement of Hb may be particularly useful, but laboratory measurement remains the gold standard. Haemoglobin concentration is dependent on both red cell mass and plasma volume; it may fall due to haemodilution due to intravenous fluid administration. In the bleeding patient, haemoglobin concentration may remain falsely elevated despite significant blood loss due to inadequate fluid resuscitation.

Other potential indications for RBC transfusion are clinical signs and biochemical markers of inadequate oxygen delivery, such as elevated blood lactate concentration, a low Ph and low central or mixed venous oxygen saturation.

### *Optimum haemoglobin transfusion trigger*

Recent publications comparing more liberal transfusion strategies (typical transfusion trigger Hb 90–100 g.l<sup>-1</sup>) with more restrictive strategies (typical transfusion trigger Hb 70–80 g.l<sup>-1</sup>) did not show any difference in patient outcomes [12, 13]. Therefore, a general Hb threshold of 70 g.l<sup>-1</sup> should apply as a guide for red cell transfusion. Uncertainty remains for patients with ischaemic heart disease, including acute coronary syndrome and after cardiac surgery [14], and higher thresholds (80 g.l<sup>-1</sup>) may be more appropriate in such circumstances.

## Major haemorrhage

Major haemorrhage is variously defined as loss of more than one blood volume within 24 h (around

70 ml.kg<sup>-1</sup>, > 5 l in a 70 kg adult); 50% of total blood volume lost in < 3 h; or bleeding in excess of 150 ml.min<sup>-1</sup>. 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.min<sup>-1</sup>. Major haemorrhage is a significant cause of mortality and morbidity in the peri-operative setting. Appropriate and effective management integrates multiple factors, including: recognition; communication; timely delivery of blood products; and application of definitive modalities of treatment (surgery and interventional radiology) [15].

### *Major haemorrhage protocol*

Policies should be defined in an institutional major haemorrhage protocol. Activation of a protocol should result in the immediate release and administration of blood components for initial resuscitation, without prior approval from a haematologist. Such protocols perform best when specific to clinical areas such as the emergency department or the labour ward, and are designed to include robust and clearly understood activation and communication from bedside to laboratory. Their activation should also mobilise other resources, such as additional (senior) staff including portering, blood warmers, pressure infusers and cell salvage devices [16].

A clear mechanism for the escalation of a team response and for identifying individuals with sufficient seniority and experience to undertake the key roles of team leader (senior anaesthetist) and co-ordinator is essential to the process, as is enabling a single point of contact with the laboratory and other support services.

### *Initial resuscitation*

Most major haemorrhage packs will contain four units of RBCs and four units of FFP (equivalent to 15–20 ml.kg<sup>-1</sup> in a standard adult); platelet concentrate may also be provided. Administration should be via wide-bore intravenous access, or intra-osseous access until the former can be obtained.

Group O red cells should be readily available and transfused if haemorrhage is life-threatening. It is essential to give group O Rh-negative red cells to children and women of childbearing potential, but group O Rh-positive red cells may be used in adult men.



Group-specific red cells should be rapidly made available (within 15–20 min) by the laboratory after receiving a correctly labelled blood group sample and being informed of the emergency requirement for blood. Emergency Group O red cells should continue to be provided where timely and safe issue of group-specific red cells is not possible.

### **Haemostatic resuscitation**

This describes the process of restoring and sustaining normal tissue perfusion with the emphasis on preservation of effective clotting. Coagulopathy is associated with haemorrhage (consumption) and transfusion of blood products (dilution), as well as mechanism of injury in trauma; this may exacerbate the haemorrhage and resultant morbidity. Point-of-care or laboratory testing should be used to guide management.

During resuscitation, the following should be prevented/treated: hypothermia; acidosis; hypocalcaemia (aim for ionised calcium  $> 1.0 \text{ mmol.l}^{-1}$ ); and hyperkalaemia.

## **Special situations**

### **Critical care**

Anaemia is prevalent during critical illness. In addition to blood loss and sampling, haemodilution and impaired erythropoiesis may be important contributors [17]. Patients with anaemia demonstrate biochemical abnormalities similar to those with chronic inflammatory diseases.

Although biochemical markers of tissue hypoxia, notably blood lactate concentration, are frequently elevated, evidence does not support increasing oxygen delivery with RBC transfusion when the Hb is  $> 70 \text{ g.l}^{-1}$ , unless the patient has cardiac disease [18].

One important group of patients admitted to ICU are patients with haematological malignancies. Overall, patients with cancer form one of the larger groups of recipients of blood components. However, unlike other patient groups, the anaemia in patients with haematological malignancies reflects an underlying bone marrow failure, and therefore, it is unclear to what extent findings from the majority of randomised trials conducted in surgery or general critical care can be extrapolated to cancer, although the same broad principles of restrictive

use of red cells commonly apply ( $70\text{--}80 \text{ g.l}^{-1}$  for red cell transfusion).

### **Obstetrics**

Estimating blood loss at delivery is notoriously difficult, and every effort should be made to directly measure abnormal bleeding across all settings in the delivery suite [19]. Early recognition of bleeding by changing bed linen and pads immediately after delivery and systematically weighing new blood-soaked pads correlates with the fall in Hb concentration and improves outcome.

As soon as abnormal bleeding is recognised,  $> 500 \text{ ml}$  after a vaginal delivery and  $> 1000 \text{ ml}$  after a caesarean delivery, the obstetrician, anaesthetist and senior midwife should attend the mother. Blood should be taken for full blood count (Hb), clotting studies, group and screen, and a venous blood gas for rapid Hb measurement and lactate ( $> 2 \text{ mmol.l}^{-1}$  is an indicator of shock). Cell salvage is recommended if abnormal bleeding occurs during caesarean section, and a leucocyte filter should be used for autotransfusion of processed blood.

Severe early consumptive coagulopathy is associated with abruptio, amniotic fluid embolus and severe bleeding with pre-eclampsia. Early use of FFP before RBC may be required.

Postpartum haemorrhage associated with atony or trauma is unlikely to be associated with haemostatic impairment unless the diagnosis is delayed. Protocolled use of blood products will lead to overtransfusion of FFP in the majority of cases [20]. If coagulation tests are not known, then FFP should be withheld until four units of RBC have been given. If no coagulation results are available and bleeding is ongoing, then, after four units of RBC, four units of FFP should be infused and 1:1 ratio of RBC–FFP transfusion maintained until the results of haemostatic tests are known. Point-of-care (POC) testing is recommended in this setting [21].

Hypofibrinogenaemia, below normal levels for pregnancy, predicts the risks of ongoing postpartum haemorrhage. The normal plasma fibrinogen concentration in pregnancy is  $4\text{--}6 \text{ g.l}^{-1}$ , and a laboratory Clauss fibrinogen of  $< 3$  and especially  $< 2 \text{ g.l}^{-1}$ , with ongoing bleeding, is associated with progression to major obstetric

bleeding [22]. Fibrinogen replacement with cryoprecipitate or fibrinogen concentrate should be considered in these circumstances, if there is bleeding.

Monitoring of haemostatic function in obstetric haemorrhage is particularly important; laboratory testing is often too slow during obstetric haemorrhage, and therefore, POC testing is preferred. Tests should include plasma fibrinogen concentration or POC equivalent [21]. With ongoing bleeding, any abnormalities should be treated, as this indicates significant haemostatic impairment in the obstetric patient. Platelet transfusions are rarely required and should only be given once the platelet count is known.

Tranexamic acid reduces total blood loss and should be given if postpartum haemorrhage is severe (> 500 ml after a vaginal delivery and > 1000 ml after a caesarean delivery), at an initial dose of 1 g.

### Paediatrics

There is little direct evidence to guide the use of blood products in children, and generally the guidance intended for adults can be safely applied to children with some modifications (specifically in transfusion volumes). 'Restrictive' approaches to transfusion are appropriate for almost all children older than 3 months of age. Higher transfusion thresholds are often applied to neonates and children with congenital heart disease. Although thresholds are not clearly defined, there is evidence that quantities of transfusion can be reduced in these patients by applying moderately restrictive thresholds for transfusion without adverse effect on outcome [23, 24]. Neonates should receive components specified for neonatal use, including cytomegalovirus-negative blood products.

The volume of blood to be administered requires modification depending on the size of the patient. It is recommended that blood in children should be prescribed in volume rather than number of units. In practice, sensible rounding to the nearest unit will be more efficient.

- A transfusion of  $10 \text{ ml.kg}^{-1}$  of RBC should increase Hb by approximately  $20 \text{ g.l}^{-1}$ .
- Cryoprecipitate should be given in a dose of  $5\text{--}10 \text{ ml.kg}^{-1}$ .

- Platelets should be given in a dose of  $10\text{--}20 \text{ ml.kg}^{-1}$ .
- Fresh frozen plasma may be given in doses of  $10\text{--}15 \text{ ml.kg}^{-1}$ .

Tranexamic acid can be used in children: a loading dose of  $15 \text{ mg.kg}^{-1}$  followed by infusion  $2 \text{ mg.kg}^{-1}.\text{h}^{-1}$  should be used in trauma [25].

With technical refinements, cell salvage can be useful in children, even if the absolute volume of blood loss is less than 500 ml [26].

Major haemorrhage is rare in children outside of highly specialist areas of practice. The guidance suggested for adults can be generally applied, though requires an awareness of the size of the child and the clinical context of the bleeding. Blood volume of a child is estimated at  $70 \text{ ml.kg}^{-1}$  but may be as high as  $100 \text{ ml.kg}^{-1}$  in newborns. Devices for vascular access and rapid administration of blood should be appropriate for the size of the child and rate of blood loss. Children are at particular risk of electrolyte imbalance and hypothermia during rapid administration of blood products.

### Trauma

During active bleeding, follow the principles of damage control resuscitation:

#### Early haemorrhage control

Ensure clinical treatment is constantly directed towards haemorrhage control. Use temporary haemostatic devices (pressure, tourniquets, etc.) followed as soon as practically possible by surgery or interventional radiological control of haemorrhage.

#### Permissive hypotension

Do not try to normalise blood pressure during active haemorrhage. Maintain a minimum acceptable preload and blood pressure with volume resuscitation alone; this may need to be modified in the presence of trauma in head and spinal injuries. The use of vaso-pressors should be avoided during active haemorrhage.

#### Avoid crystalloid and colloid administration

During uncontrolled haemorrhage, avoid clear fluids for volume resuscitation unless there is profound

hypotension and no imminent availability of blood products.

### **Target trauma-induced coagulopathy**

Deliver blood products empirically at first, and use laboratory or point-of-care tests of coagulation to guide therapy as soon as available [27].

Give tranexamic acid 1 g immediately, but avoid if more than 3 h after injury, unless there is ongoing evidence of hyperfibrinolysis (as suggested by POC testing).

Whilst haemorrhage is being controlled, administration of RBC and FFP in a ratio of 1:1 should be used to replace fluid volume [28]. Consider the administration of cryoprecipitate (two pools) and platelets (one adult therapeutic dose) until test results are available and bleeding is controlled. Once control is achieved, blood components should be administered as guided by testing at the earliest opportunity (see Monitoring section, blood components).

## **Cardiac surgery**

Anaemic patients have an increased risk of mortality and complications following cardiac surgery [29]. Elective cardiac surgery should not be undertaken in an anaemic patient without prior investigation and treatment as considered necessary.

Viscoelastic testing is recommended to guide transfusion [30]. The use of local transfusion protocols guided by point-of-care testing may lead to appropriate transfusion with reduced costs. The evidence base for the efficacy of fresh frozen plasma is minimal and of poor quality [31].

The effect of cardiopulmonary bypass on platelet function may make the use of a higher platelet count ( $> 75 \times 10^9 \cdot l^{-1}$ ) necessary after bypass.

There is no clear evidence of the benefit of platelet function analysis except in those patients who have taken P2Y<sub>12</sub> receptor inhibitors such as clopidogrel within 5 days of surgery [32].

## **Monitoring**

### **Laboratory testing**

Traditional tests such as APTT and PT/INR have been standardised for the monitoring of anticoagulants and are designed to diagnose and manage factor deficiencies

such as haemophilia. Standardisation within laboratories has made the results very reliable.

The PT and APTT were not designed to monitor coagulation deficiencies during haemorrhage and suggested INR and APTT ratios or triggers, which are widely quoted to guide coagulation product replacement, are based on small historic studies that have little relevance today. Slow turnaround time also means that the results do not reflect the dynamic clinical situation during ongoing haemorrhage [33].

### **Point-of-care testing**

Point-of-care testing has a shorter turnaround time and represents a more global and therefore more relevant reflection of coagulation status [34]. Point-of-care testing is increasingly popular for general and cardiac surgery, trauma units, intensive care and obstetrics. Point-of-care testing for Hb concentration is commonly used, such as blood gas analysis or the HemoCue<sup>®</sup> (Ängelholm, Sweden), which both correlate well with laboratory measurements [35]. The activated clotting time (ACT) is also well validated and should be used routinely whenever heparin is administered, particularly in cardiac and vascular surgery.

Targeted blood component therapy based on POC testing has been shown to be safe and effective, and to decrease blood product usage. However, there are currently no studies that show improved patient outcome compared with standard treatment [32].

At the current time, there are two commercially available semi-automated viscoelastic machines that use similar technology: thromboelastometry (ROTEM, TEM International, Munich, Germany) and thromboelastography (TEG, Haemonetics Corp, Braintree, MA, USA). One manufacturer cannot be recommended above the other.

There are no universal algorithms across the specialities, and local protocols are required based on institutional procedures. There is limited interchangeability between TEG and ROTEM, and development and validation of separate treatment algorithms for the two devices are required [36].

There are concerns about standardisation of both assays with poor quality control and assurance and a wide variation in results between centres [37]. It is



good practice to pair coagulation samples and send a second sample for laboratory-based analysis.

## Drugs

An increasing number of patients take either anticoagulants or antiplatelet agents. All patients require careful pre-operative medication optimisation before surgery. The management of drugs related to antithrombotic therapy in the peri-operative setting is a common problem, balancing bleeding risk with thrombosis.

Patients at high risk (> 10% risk of thrombotic events per year) of thrombosis should be considered for bridging anticoagulation, or in the following circumstances:

- venous thromboembolic event within the last 3 months, or
- prosthetic (mechanical) heart valve

Bridging anticoagulation usually consists of low molecular weight heparin. The dose and type of the low molecular weight heparin depends on the patient's weight, timing of surgery, type of procedure and thrombotic risks.

### Warfarin (Vitamin K antagonist)

The international normalised ratio (INR) is used to monitor the effectiveness of warfarin. In most situations, INR is maintained between 2.0 and 2.5.

The peri-operative management of warfarin is summarised in Table 2. In patients with atrial fibrillation on warfarin, routine use of bridging anticoagulation with low molecular weight heparin before surgery is not recommended.

For emergency reversal of warfarin, prothrombin complex concentrate (PCC) 50 IU.kg<sup>-1</sup> is recommended. Intravenous vitamin K (10 mg) may also be

given, but this may preclude re-warfarinisation for a number of days. Fresh frozen plasma is an alternative if PCC is not available [37], but should not be used as elective prophylaxis in patients taking warfarin.

### Novel oral anticoagulants

Novel oral anticoagulants have more predictable pharmacodynamics and a faster onset of action with a shorter half-life than warfarin. There are currently three drugs on the market; these are increasingly used for management of patients with atrial fibrillation; after stroke and transient ischaemic attacks; and prophylaxis/management of venous thromboembolism [38].

Their half-life varies, especially in the presence of renal impairment. Currently, there are no specific routine coagulation tests to determine their effectiveness. Regarding antidotes, the United States Food and Drug Administration and the European Commission have recently approved the first of these, idarucizumab (Praxbind, Boehringer Ingelheim International, Ingelheim am Rhein, Germany), for the emergency reversal of dabigatran; other antidotes are currently undergoing clinical trials.

Dabigatran is a direct thrombin inhibitor. Half-life depends on extent of renal impairment (normally 48–72 h). For major elective surgery, neuraxial blockade and in patients with renal dysfunction, the drug should be stopped 5 days before surgery. For others, it can be stopped 3 days before surgery.

Rivaroxaban and apixaban are direct factor Xa inhibitors. Half-life is 5–13 h and is less dependent on renal function. For major elective surgery, neuraxial blockade and in patients with renal dysfunction, the

Table 2 Peri-operative optimisation of warfarin anticoagulation for major surgery. Bridging with LMWH required for high-risk patients, patients who suffered recent thromboembolic events or patients with mechanical prosthetic heart valves.

Day -5	Days -4, -3, -2	Day -1	Surgery	Postoperative
Last dose of warfarin.	Treatment dose LMWH (consider Vitamin K if INR > 2.5)	Half treatment dose LMWH	Omit LMWH. Check INR	Prophylactic LMWH until warfarin is commenced.

INR, international normalised ratio; LMWH, low molecular weight heparin.

drug should be stopped 3 days before surgery, otherwise stop 24–48 h before surgery.

If surgery is urgent, consider PCC 50 IU.kg<sup>-1</sup>, correct other abnormal coagulation tests and check platelets. Bridging anticoagulation is not required except in patients with recent (< 3 months) history of pulmonary embolism or deep venous thrombosis.

### Antiplatelet drugs

These drugs cause irreversible inhibition of platelets; replenishment of platelets occurs at a rate of 10–15% per day. The restoration of normal platelet function depends on the individual drug and dosage.

Aspirin inhibits the production of thromboxane. It should be continued for most procedures until the day before surgery. In patients at low risk of cardiovascular events having major surgery and those undergoing high-risk procedures such as intracranial surgery, aspirin should be discontinued 5 days before the procedure.

Clopidogrel is an oral, thienopyridine-class antiplatelet agent, and the active metabolites circulate for up to 18 h after the last dose. Clopidogrel should be stopped 7 days before surgery unless point-of-care testing is used to check platelet function.

The drugs prasugrel and ticlopidine are also thienopyridine-class antiplatelet drugs similar to clopidogrel. The same recommendations as for clopidogrel apply to the above drugs.

### Antiplatelet drugs and non-cardiac surgery in patients with coronary stents

The management of these drugs in patients with coronary stents in situ depends on the type of stent, time after the coronary event and surgery type (major vs minor). Communication with the cardiology team is key. Elective surgery should be postponed for at least 4–6 weeks after bare metal stent implantation and 6 months after drug-eluting stent implantation. Aspirin may be continued during the peri-operative period except in closed space surgery such as intracranial and spinal surgery.

For emergency surgery, management depends on the antiplatelet agent and when the last dose was taken. Platelet transfusion should be reserved as an additional measure for critical bleeding.

### Drugs that decrease blood loss

Tranexamic acid is a synthetic derivative of the amino acid lysine that inhibits plasminogen activation, thus preventing impairment of fibrinolysis. In the last few years, there is increased evidence that its use may reduce bleeding in trauma, cardiac surgery and other major surgery. Seizures have been reported when high doses are given, but there is little evidence of other side effects [39]. Dose is variable, but 1 g bolus is recommended, and an additional infusion of 500 mg.h<sup>-1</sup> may also be considered [40].

Aprotinin is a serine protease inhibitor antifibrinolytic which acts by inactivating free plasmin. The drug was withdrawn from the market in 2007 due to safety issues with increased incidence of renal impairment and anaphylactic reactions. Recently, regulators have licensed the drug only for myocardial revascularisation (coronary artery bypass surgery) [41].

### Blood components

Before administration of any blood component, the patient's details should be checked against those on the bag (see red blood cell transfusion section). Blood components have specific storage and expiry times. Every effort must be made to avoid wastage.

In haematological malignancy, the clinical team must be consulted before administering blood components because of the need for specific requirements. The transfusion threshold may be different to non-haematological patients. A small number of patients require transfusion with irradiated blood components to prevent them developing transfusion-associated graft-versus-host disease (TA-GVHD), which is rare, but usually fatal. Patients with the following conditions require irradiated blood: congenital immunodeficiency states, for example Di-George's syndrome; allogeneic bone marrow transplant recipients and donors; autologous bone marrow-transplanted patients; Hodgkin's lymphoma; purine analogue therapy including new agents clofarabine and bendamustine; and patients who receive antithymocyte globulin (anti-CD52) therapy (alemtuzumab) [42].

### Fresh frozen plasma

Fresh frozen plasma is leucodepleted plasma rapidly frozen to below -25 °C to maintain the integrity of labile coagulation factors. The use of FFP has

increased significantly in the past few years [38]. Given that anti-HNA and anti-HLA antibodies occur at higher frequency in multiparous women, implementation of male-only plasma in component therapy began in the UK in 2003, and this has reduced the incidence of transfusion-related acute lung injury (TRALI) [43].

Fresh frozen plasma can be thawed using a dry oven (10 min), microwave (2–3 min) or in a water bath (20 min). Thawed FFP can be used for up to 24 h as long as it is stored at 4 °C. This time has recently been extended to 5 days when stored at 4 °C for use in major haemorrhage associated with trauma. Once out of the fridge, it must be used within 30 min, and once thawed, it should never be refrozen. Approximate volume per bag is 300 ml.

Fresh frozen plasma contains all the factors of the soluble coagulation system, including the labile factors V and VIII to a varying degree. The fibrinogen content of four units of FFP is approximately 2 g, compared with approximately 4 g fibrinogen in two pools of cryoprecipitate.

Fresh frozen plasma should be the same group as the patient. If the blood group is unknown, group AB FFP is preferred, as it does not contain any anti-A or anti-B. If group O FFP is given to non-group O children, it should be high-titre (HT) negative. The recommended therapeutic dose is 15 ml.kg<sup>-1</sup>.

To reduce the risk of variant Creutzfeldt–Jakob disease, FFP for use in all those born in 1996 or later is sourced outside of the UK and has undergone viral inactivation (either with methylene blue or solvent detergent treatment).

Indications for FFP use include the following:

- replacement of coagulation factors during major haemorrhage, particularly trauma and obstetrics;
- acute disseminated intravascular coagulation (DIC) with bleeding;
- in patients who are actively bleeding and whose INR is > 1.5 (or POC equivalent);
- immediate reversal of warfarin-induced haemorrhage when PCC is not available (PCC is the first choice);
- thrombocytopenic purpura usually with plasma-pheresis preferably using pathogen-inactivated FFP; and

- replacement of coagulation factors when specific factors are not available (uncommon).

There is a very limited role for FFP in the management of (mild–moderate) coagulation abnormalities frequently seen in many non-bleeding critically ill patients before invasive procedures. Fresh frozen plasma is not recommended for routine use in patients with cirrhosis/liver disease unless significant coagulopathy is identified, as again current understanding indicates that isolated abnormalities of the PT or APPT do not reflect a 'balanced haemostasis'. Fresh frozen plasma should not be used simply as routine circulatory volume replacement.

### Cryoprecipitate

Cryoprecipitate is also a leucodepleted plasma product containing concentrated factor VIII, von Willebrand factor, fibrinogen, factor XIII and fibronectin, produced by further processing of FFP. It is stored at –25 °C; once thawed for administration, it can be kept at ambient temperature for 4 h, and should not be kept in the fridge again [42].

In the UK, it is mainly available as pooled bags of five units, 100–200 ml per bag. It is also available as one unit of 20–40 ml. Each single unit has 400–450 mg of fibrinogen, and pools of five units contain at least 2 g.

The adult dose is two pools; transfuse using a standard blood giving set with a 170- to 200-µm filter.

Indications for cryoprecipitate include the following:

- hypofibrinogenaemia due to major haemorrhage and massive transfusion. There is increased use of cryoprecipitate in major trauma, obstetric haemorrhage and cardiac surgical bleeding. During major haemorrhage, fibrinogen should be maintained > 1.5 g.l<sup>-1</sup>, except in active obstetric haemorrhage where fibrinogen should be maintained > 2 g.l<sup>-1</sup>;
- combined liver and renal failure with bleeding;
- bleeding associated with thrombolytic therapy;
- disseminated intravascular coagulation with fibrinogen < 1.0 g.l<sup>-1</sup>; and

- advanced liver disease, to maintain fibrinogen level  $> 1.0 \text{ g.l}^{-1}$ .

Cryoprecipitate for use in all those born in 1996 or later is made from FFP sourced outside of the UK and has undergone viral inactivation with methylene blue. These components are available as single units for smaller children and pooled units for older children and young adults.

### Platelets

Platelets are either made from pooled buffy coat-derived platelets from four whole blood donations, suspended in platelet additive solution and the plasma of one of the four donors (who is male), or as an adult therapeutic dose obtained from a single donor by apheresis donation. Both can be used interchangeably; NHSBT recommends that recipients born on or after 1st January 1996 should receive apheresis donation platelets where possible.

There is increased use of platelets in the last few years. The greatest demand is for haemato-oncology patients; platelets should not be administered to patients with chemotherapy-induced thrombocytopenia in the absence of bleeding, unless their platelet count is  $< 10 \times 10^9 \text{ l}^{-1}$ .

The risk of transmission of bacterial infection (1 in 12,000) is higher than other blood components because platelets are stored at  $22^\circ\text{C}$ . This risk is reduced by bacterial screening before release.

Platelets do not have to be the same group as the patient, but where group O platelets are given to a non-group O child they should be selected to be high-titre negative. D-negative children and women of childbearing potential should receive D-negative platelets because of the small risk of developing immune anti-D.

Platelet concentrate should be stored at  $22^\circ\text{C}$  with constant gentle agitation in an approved incubator. Platelets must not be placed in a refrigerator. Transfusion should ideally be commenced within 30 min of removal from the platelet storage incubator. Each pack contains 250–350 ml; platelet count in the pack is  $> 2.4 \times 10^{10} \text{ l}^{-1}$  per adult dose, and transfusion should lead to an increase in the patient's platelet count by approximately  $30 \times 10^9 \text{ l}^{-1}$ . The patient's platelet count should be repeated after transfusion.

A standard adult therapeutic dose should be infused over a period of 30 min through a standard blood administration set or platelet administration set incorporating a 170- to  $200\text{-}\mu\text{m}$  filter. Do not give through a set that has already been used for red cells. No drugs should be added directly to the unit of platelets.

Indications for platelets include the following:

- prevention and treatment of bleeding due to thrombocytopenia or platelet function defects.
- If patient is actively bleeding, transfuse to a platelet count  $> 75 \times 10^9 \text{ l}^{-1}$

If not bleeding, the following triggers should be applied:

- routine prophylactic use:  $10 \times 10^9 \text{ l}^{-1}$ ;
- prophylactic use with additional risk factors (e.g. Sepsis):  $10 - 20 \times 10^9 \text{ l}^{-1}$ ;
- other major surgery or invasive procedures:  $50 \times 10^9 \text{ l}^{-1}$ ;
- neuraxial blockade:  $50 \times 10^9 \text{ l}^{-1}$ ; and
- prophylactic use in closed compartment surgery (eye, brain):  $100 \times 10^9 \text{ l}^{-1}$ .

In the UK, the availability of platelets is centralised and will depend on the demand and distance from nearest blood centre. Clinicians need to be aware of local laboratory arrangements and normal time interval for obtaining platelets from central storage.

## Special blood components

### Prothrombin complex concentrate

Prothrombin complex concentrate (in the UK) comes as four-factor concentrate containing factors II, VII, IX and X, with protein S, C and heparin. It can be rapidly reconstituted providing a high concentration of these four clotting factors in a small volume. It is indicated in acquired factor deficiency and for urgent reversal of warfarin. There is limited evidence for use in any other setting.

### Fibrinogen concentrate

There has been considerable interest in fibrinogen concentrate. It is widely used in mainland Europe in the management of bleeding following surgery or trauma. Recent trials in cardiac surgery have not shown any



benefit from its use. It is only licensed for use in congenital hypofibrinogenaemia in the UK.

### Recombinant factor viia

Licensed for use in haemophiliacs with inhibitors. It is the **most potent thrombin generator** available at present. Late use in the exsanguinating patient is almost always associated with no benefit, a high risk of mortality and thrombotic complications. Following cardiac surgery, it has been shown to reduce re-operation rates and transfusion in the bleeding patient. However, its use **may increase the risk of thrombotic complications** and its use except under haematological direction cannot be recommended [44].

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## Appendix

### Other available guidelines.

National Institute for Health and Care Excellence (NICE) 2015 (<http://www.nice.org.uk/guidance/indevelopment/gid-CGWAVE0663?>)

British Committee for Standards in Haematology, 2012–15 ([http://www.bcsghguidelines.com/4\\_haematology\\_guidelines.html?Dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl](http://www.bcsghguidelines.com/4_haematology_guidelines.html?Dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl))

Practice Guidelines for Peri-operative Blood Management – American Society of Anesthesiologists (<http://anesthesiology.pubs.asahq.org/article.aspx?Articleid=2088825>)

Management of severe perioperative bleeding – Guidelines from the European Society of Anaesthesiology (2013) ([http://anest-rean.lt/wp-content/uploads/2013/05/Management\\_of\\_severe\\_perioperative\\_bleeding\\_2.pdf](http://anest-rean.lt/wp-content/uploads/2013/05/Management_of_severe_perioperative_bleeding_2.pdf))

Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA) (<http://www.nataonline.com>)

National Blood Authority Australia PBM Guidelines (<http://www.blood.gov.au/pbm-guidelines>)