A practical guideline for the haematological management of major haemorrhage

Beverley J. Hunt,[1] Shubha Allard,[2] David Keeling,[3] Derek Norfolk,[4] Simon J. Stanworth,[5] Kate Pendry[6] and on behalf of the British Committee for Standards in Haematology

[1]Department of Haematology, GSTT, St Thomas' Hospital, [2]Department of Haematology, Royal London Hospital, London, [3]Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals, Churchill Hospital, Oxford, [4]Department of Haematology, Leeds Hospital, Leeds, [5]NHSBT/Department of Haematology, John Radcliffe Hospital, Oxford, and [6]Patients' Clinical Team, NHSBT, Manchester, UK

Keywords: haematological management, major haemorrhage, bleeding protocols.

The aim of this guideline is to provide recommendations for the haematological management of major haemorrhage in any clinical situation, with practical guidance for Clinical Haematologists and laboratory staff on the content and delivery of major bleeding protocols, including the use of blood components and transfusion alternatives. Management of major haemorrhage in any setting requires a multidisciplinary approach. There have been advances in techniques for resuscitation as well as surgical, radiological and endoscopy interventions, to control bleeding alongside critical care support, but these are beyond the scope of this document.

These updated guidelines are based on new studies, which have provoked reassessment of the principles of managing major haemorrhage in all clinical situations, and which mandate much closer working between hospital blood banks and emergency departments to provide timely transfusion support for patients with major bleeding.

Alongside changes in the use of blood component therapy, the importance of antifibrinolytics has been demonstrated in the study by the Clinical Randomization of Antifibrinolytics in Significant Haemorrhage (CRASH-2) collaborators (2010). The recognition that tranexamic acid (TA) benefited not only those with massive haemorrhage but also the larger number of patients with, or at risk of, significant haemorrhage (i.e. not only those fulfilling the criteria for massive bleeding) has led to an expansion of our guidelines from massive to major haemorrhage so that we can include this group.

Correspondence: BCSH Secretary, British Society of Haematology, 100 White Lion Street, London N1 9PF, UK.
E-mail: bcsh@b-s-h.org.uk

Methods

The writing group was representative of UK transfusion and haemostasis experts, and consultation within the specialities of anaesthesia, trauma and critical care was made. Relevant systematic reviews were identified by searching the National Health Service (NHS) Blood and Transplant Systematic Review Initiative Transfusion Evidence Library (http://www.transfusionevidencelibrary.com). A search was performed of PubMed and Embase using the term "bleeding" and "haemorrhage" combined with 'management' and "trials". The search covered articles published up until April 2015. Only human studies were included and articles not written in English were excluded.

The quality of evidence was judged by predefined Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria (Guyatt *et al*, 2006). Strong recommendations, grade 1, are made when the group was confident that the benefits do or do not outweigh the harm and burden of cost of a treatment. Where the magnitude of benefit is less certain, grade 2, suggested recommendations are made. The quality of evidence is rated as A (high quality randomized control trial), B (moderate), C (low), D (very low, expert opinion only).

The writing group produced a draft which was revised based on input from the British Committee for Standards in Haematology (BCSH) Transfusion and Thrombosis and Haemostasis Task forces, The Royal College of Anaesthetists and the Association of Anaesthetists; it was then circulated to a wider sounding board of 50 UK Haematologists and experts in bleeding management. The guidelines cover clinical management with an Appendix on logistics and laboratory management.

Recognition of major haemorrhage and activation of protocols

While there are arbitrary definitions of massive blood loss, e.g., loss of one blood volume within a 24-h period, 50%

doi: 10.1111/bjh.13580

blood volume loss within 3 h, loss of 150 ml/min, these may be difficult to apply in the acute situation. Indeed, standard definitions are not particularly helpful because they are retrospective. Our arbitrary definition of major haemorrhage is bleeding which leads to a heart rate more than 110 beats/min and/or systolic blood pressure less than 90 mmHg. Hospitals must have locally agreed triggers.

It may not be straight forward to readily determine that major haemorrhage is occurring, for example post-partum; but early recognition of significant blood loss, ideally before major increments in pulse rate and falls in blood pressure, will allow prompt action to pre-empt shock.

Recommendation

Medical, nursing and midwifery staff involved in frontline care must be trained to recognize major blood loss early, know when to activate/trigger the local major haemorrhage protocol and take prompt and appropriate action (1D).

A: Organizational aspects – key principles

Whilst the focus is currently on practice recommendations for bleeding in trauma patients, the management of patients with bleeding in other clinical settings (e.g. gastrointestinal, obstetrical or surgical) also needs specific attention. The National Patient Safety Agency (NPSA) (2010) highlighted a recurring theme of delays in blood provision in emergencies resulting in unacceptable morbidity and mortality (NPSA/2010/RRR017). From October 2006 to September 2010, the NPSA received reports of 11 deaths and 83 incidents in patients as a result of such delays.

The provision of emergency blood to a bleeding patient requires the use of specifically designed protocols, which include robust and clearly understood communication channels between clinical staff and those in the blood transfusion laboratory. Local protocols should enable the release of blood and blood components for initial resuscitation without the prior approval of a Haematologist.

The Hospital Transfusion Committee (HTC) has a key role in overseeing protocol development and implementation (Department of Health, 2007). The smaller Hospital Transfusion Team (HTT) including the Haematology Consultant responsible for Transfusion, Transfusion Practitioner and Hospital Transfusion Laboratory Manager can help support various activities essential for effective implementation, e.g. training and audit, with clear and explicit input from leads in each clinical area required. The major haemorrhage protocols should be developed in collaboration with relevant teams managing haemorrhage and ratified by the HTC. While HTTs have a key supportive role, it is essential that each clinical area has a designated trainer responsible for ensuring on-going training for all relevant staff.

Recommendations

Hospitals must have local major haemorrhage protocols with adaptations for specific clinical areas (1D).

All medical, nursing, laboratory and support staff must know where to find the haemorrhage protocol in relevant areas and be familiar with the contents; their knowledge should be supported by training and regular drills (1D).

Communication and team working

Good communication is essential between teams to prevent poor clinical outcome, suboptimal or inappropriate transfusion practice and component wastage. Appropriate expertise for the site of bleeding is vital – vascular, general or cardiothoracic surgeons, endoscopists or others with specific expertise may be needed. Consideration should be given to early referral and, if necessary, transfer to other centres to access such expertise. In the more difficult cases, early action may be essential to pack visceral cavities, and cross clamping and tying off major vessels may be required. Radiological embolization and/or stenting also have established roles in some clinical situations. An intensive care bed may be required and early communication is advisable to ensure availability.

The switchboard can play a key role in initial alert of key *staff* followed by contact of further teams as needed as follows:

1 Porter/other support staff
2 Senior clinician depending on clinical area
3 Anaesthetist/Intensive Therapy Unit
4 Senior nurse/midwife
5 Transfusion Laboratory
6 Other laboratories (Haematology and Coagulation, Biochemistry)
7 Clinical Haematologist on call
8 Radiology including interventional radiology

A designated Team Leader, usually the most senior doctor at the scene, needs to be appointed quickly to direct and co-ordinate management.

Recommendation

Following trigger of the major haemorrhage protocol there must be a clear mechanism for contacting all relevant team members and a designated Team Leader should then co-ordinate further management (1D).

A Team Leader should be appointed and nominate a specific clinical team member to co-ordinate communication with Transfusion Laboratory staff and support services for the duration of the incident (1D).

B: Transfusion support in major haemorrhage

The management of a patient with major haemorrhage has three elements: assessment and resuscitation following

Advanced Life Support principles; local control of bleeding (surgical, radiological and endoscopic techniques); and haemostatic, including transfusion support. Table I gives an overview of the blood components available for adults. Specific paediatric requirements are outlined in section D and in more detail in updated BCSH paediatric transfusion guidelines (Helen New, personal communication). Basic principles of management are outlined in Fig 1.

Accurate documentation of blood components given and the reason for transfusion is necessary in order to satisfy the legal requirement for full traceability (Department of Health, 2005) and to enable audit of outcomes.

In a setting where patients can sustain massive blood loss, blood warmers and pressure infusers should be available and used.

Red cells

Red cells are necessary for their oxygen-carrying capacity, and also contribute to improved haemostasis through rheological effect leading to axial flow, and thus margination of platelets and plasma. The optimum target haemoglobin concentration (Hb) in the management of bleeding is not established. Although red cell transfusion can be life saving, there

Table I. A guide to blood components used in major haemorrhage in adults.

Blood component	Storage conditions and shelf life	Volume per pack	Dosing regimes	Additional points
Red cells in additive solution	Up to 35 d at +2 – +6°C	MPV: 282 ml ±32 ml	Order 4–6 units initially, see text for choice of group	Rate of administration guided by rate of blood loss and haemodynamic compromise, aiming to maintain oxygen delivery to tissues. At high rates, blood should be given through a warming device
FFP (from one donor) or MB-FFP if recipient born after 1 January 1996 OR SD-FFP (pooled)	FFP: 36 months when frozen. Once thawed: 4 h at 22°C, 24 h at 4°C SD-FFP: Once thawed: 4 h at 22°C or 8 h at 4°C	FFP MPV: 273 ml ± 17 ml SD-FFP 200 ml	FFP: order 15–20 ml/kg in first instance	Allow time for thawing – order in anticipation
Platelets. Apheresis from a single donor or pooled from 4 whole blood donations	Up to 7 d at 22 ±2°C on an agitator rack	Apheresis MPV: 215 ml ± 53 ml Pooled MPV: 310 ml ± 33 ml	Order 1 adult therapeutic dose, monitor platelet count and aim to maintain platelet count >50 × 10^9/l	Use a blood- or platelet-giving set with integral filter (170–200 μm). There should be close communication between NHSBT and the transfusion laboratory to enable timely platelet transfusion. Anticipate need for further platelets in on-going bleeding as platelet count falls below 100 × 10^9/l
Cryoprecipitate. (pooled from 5 donations) (MB cryoprecipitate for those born after 1 January 1996)	36 months when frozen. Can be stored for up to 4 h at ambient temperature	MPV: 152 ml ± 12 ml	Order 2 packs (2 × 5 unit pools) and aim to keep fibrinogen >1·5 g/l. See text for further details	Allow time for thawing – order in anticipation

FFP, fresh frozen plasma; MB-FFP, methylene blue-treated FFP; SD-FFP, solvent detergent-treated FFP; MPV, mean pack volume; NHSBT, National Health Service Blood and Transfusion.

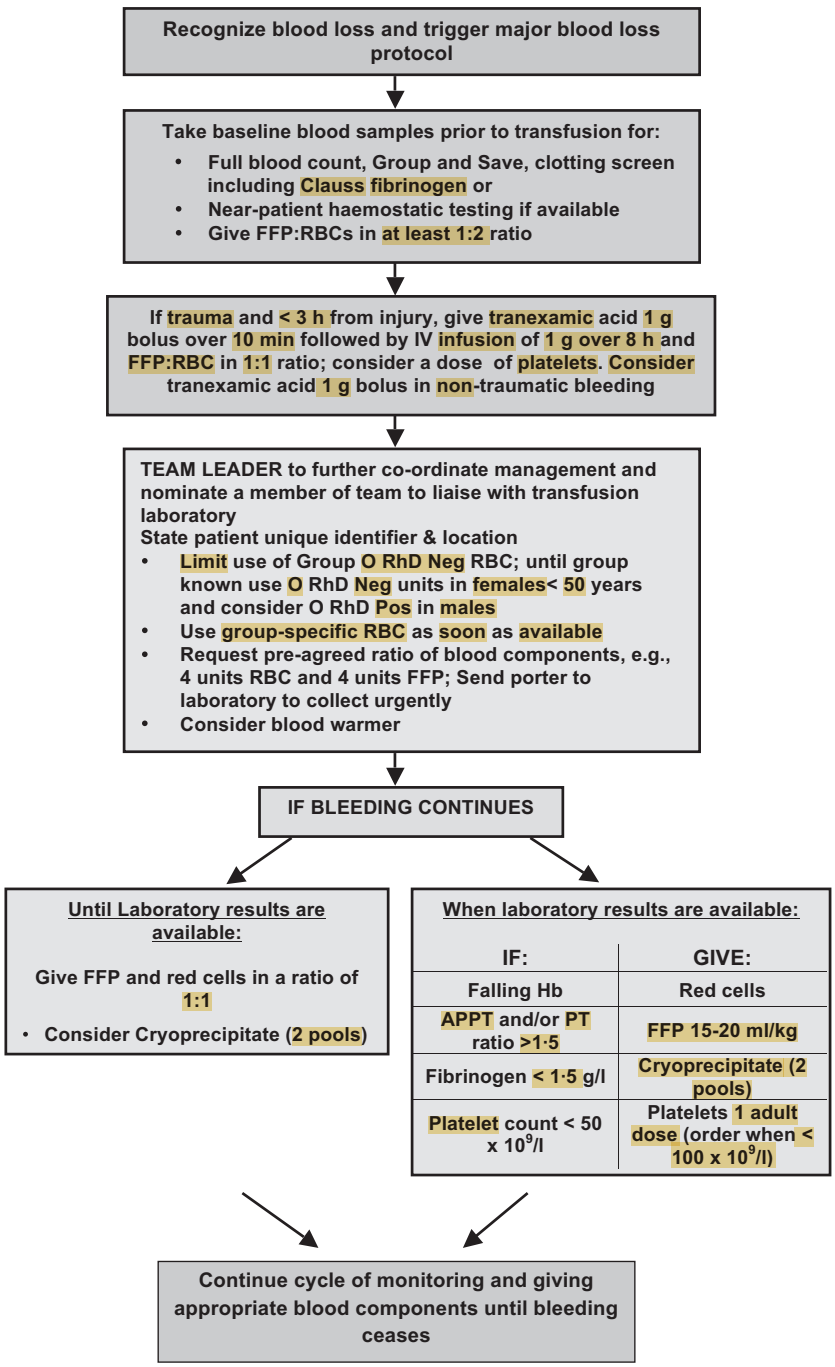

Fig 1. Algorithm for the management of major haemorrhage.

are potential risks such as increased morbidity and mortality due to organ failure and transfusion – related acute lung injury (Madjdpour & Spahn, 2005) and so exposure to red cells should be minimized. The updated European Guideline on Management of Bleeding following Major Trauma (Spahn *et al*, 2013) recommends a target Hb of 70–90 g/l based on data extrapolated from the Transfusion Requirements in Critical Care Investigators study (Hebert *et al*, 1999), which retrospectively analysed a subgroup of trauma patients: the restrictive group (Hb trigger 70 g/l) did as well as the liberal group (Hb target 100 g/l) (McIntyre *et al*, 2004). Patients with cardiorespiratory morbidity may require a higher target of 80–90 g/l. Finally, recent meta-analyses have indicated that in hospitalized patients, a restrictive red cell transfusion policy was associated with a reduced risk of health care-associated infections (Rohde *et al*, 2014). Taken with broader evidence on the risks of transfusion, recent trials in gastrointestinal bleeding (Villanueva *et al*, 2013) and meta-analyses (Hogshire & Carson, 2013), this guideline makes general restrictive recommendations for red cell transfusion in patients with bleeding, at a level to provide critical life-saving support. BCSH guidelines for red cell use in critical care

(Retter *et al*, 2013) recommend that anaemic critically ill patients with stable angina should have their Hb maintained >70 g/l, but transfusion to a Hb > 100 g/l has uncertain benefit (Grade 2B); and in patients suffering from acute coronary syndrome, the Hb should be maintained at >80–90 g/l (Grade 2C).

Haematocrit and haemoglobin levels in bleeding patients are not reliable indicators of blood loss (Kass *et al*, 1997). Red cell transfusion is usually required when 30–40% of blood volume is lost (1500 ml in a 70-kg male) and more than 40% blood volume loss (1500–2000 ml) is life threatening and requires immediate transfusion (Murphy *et al*, 2001). The rate of transfusion will be guided by the rate of blood loss and the degree of haemodynamic compromise with the aim of maintaining Hb at a level to support adequate oxygen delivery to the tissues. Every effort should be made to ensure blood is transfused through a warming device to minimize the development of hypothermia. Rapid infusion (e.g. 1 unit over 5–10 min) may be required. Once bleeding is controlled there is no indication to restore Hb to physiological levels.

Hospitals must have a strategy to ensure that red cells are readily available for life-threatening bleeding and Group O red cells are available for immediate use. In large NHS organizations using blood storage refrigerators in relevant remote clinical areas may facilitate this. The local major haemorrhage protocol must identify the location of the nearest emergency Group O red cell units. See Appendix for information on the emergency provision of blood components.

Lastly, there is controversy as to whether prolonged storage of red cells may cause adverse effects (Weinberg *et al*, 2008; Edgren *et al*, 2010). This issue was addressed in critically ill patients in the ABLE (Age of Blood Evaluation) study, which showed transfusion of fresh red cells did not affect survival (Lacroix *et al*, 2015); the preliminary results from the RECESS (Red Cell Storage Duration Study) trial suggest no difference in multiorgan system dysfunction or mortality in patients on cardiopulmonary bypass (Steiner *et al*, 2010).

Recommendation

Hospitals must have a strategy to ensure that red cells are readily available for life-threatening bleeding, through the use of emergency Group O red cells and also through the rapid provision of group-specific red cells by the transfusion laboratory (IC).

Patients must have correctly labelled samples taken before administration of emergency Group O blood (IC).

There is no indication for requesting 'fresh' red cells (e.g. under 7 d storage) in haemorrhage, whilst awaiting further publication of definitive randomized trials (2B).

Cell salvage

Cell salvage can produce a rapid supply of red cells, with 250 ml of washed salvaged red cells considered to be equivalent to one unit of packed red cells. It can be particularly useful in managing haemorrhage associated with open aortic aneurysm repair, splenic and liver trauma, pelvic and femoral fractures, abdominal and thoracic trauma and haemorrhage at caesarean section (Association of Anaesthetists of Great Britain and Ireland [AAGBI], 2009). A 24-h service is required in order for cell salvage to be useful in all emergencies.

Further information on the development of cell salvage services can be found on the UK Cell Salvage Action Group pages of the Transfusion Practice toolkit (http://www.transfusionguidelines.org.uk/transfusion-practice/uk-cell-salvage-action-group).

Recommendation

Access to 24-h cell salvage support should be available in cardiac, obstetric, trauma and vascular centres (2B).

Haemostatic testing and monitoring

It is important to establish whether the patient is receiving anticoagulant or antiplatelet medication. The coagulopathy of bleeding is related to loss of blood, consumption of coagulation factors, activation of fibrinolysis and haemodilution by resuscitation fluids. Developing hypothermia, acidosis and hypocalcaemia will further worsen coagulation. It is important to monitor haemostatic changes to guide the use of blood components after initial resuscitation, with coagulation and platelet testing performed every 30–60 min, depending on the severity of blood loss, until bleeding ceases. There is a need for rapid turnaround times for coagulation tests in a major haemorrhage and we suggest these times should be regularly audited.

Tests of coagulation. The prothrombin time (PT) and activated partial thromboplastin time (APTT) were developed to detect inherited coagulation disorders not to manage bleeding. In one study the PT was more sensitive than the APTT to low coagulation factor levels in trauma patients (Yuan *et al*, 2007). If a PT and APTT can be made available with a rapid turnaround time that allows them to reflect the clinical situation they can be used to aid the decision for infusion of fresh frozen plasma (FFP). Point-of-care whole blood coagulation tests for the PT are available but they may be dependent on the haematocrit and thus not provide an accurate assessment in a bleeding patient.

The Clauss fibrinogen assay should be used in preference to a fibrinogen estimated from the optical change in the PT (PT-derived fibrinogen), because some of these methods give falsely higher values than the Clauss in disseminated intravascular coagulation, liver disease, renal disease, dysfibrinogenaemia and in those receiving anticoagulants (Mackie *et al*, 2003). We know of no data to favour one Clauss method over another, other than the fact that the presence of colloid

plasma expander gives rise to erroneous high levels of fibrinogen by some Clauss methods (Fenger-Eriksen *et al*, 2010).

Assays of clot viscoelasticity [thromboelastography (TEG) and rotational thromboelastometry (ROTEM)] monitor developing clot strength and subsequent fibrinolysis, although they are insensitive measure of the latter (Raza *et al*, 2013). Specific parameters have been used to identify impaired platelet function, low fibrinogen levels and low coagulation factors and so have been used to guide blood component therapy. However we cannot recommend a specific TEG or ROTEM algorithm to guide transfusion practice because, despite widespread use, there are few clinical trials examining the utility of different TEG and ROTEM algorithms. A Cochrane review found evidence that transfusion guided by TEG or ROTEM may reduce bleeding but without an improvement in morbidity or mortality (Afshari *et al*, 2011). Protocols for test accuracy and prognostic reviews of TEG and ROTEM have been registered with Cochrane (Hunt *et al*, 2015), and a National Institute for Health and Clinical Care Excellence (NICE) systematic review on the use of visco-elastic devices recommended that the devices are used to manage and monitor haemostasis during and after cardiac surgery but that in other situations such as obstetric haemorrhage or trauma there was insufficient evidence for use except as part of a research study (NICE, 2014). Until evidence-based algorithms are established, we suggest that TEG and ROTEM use is confined to research.

Recommendations

Serial haemostatic tests, including platelet count, PT, APTT and fibrinogen, from before and after resuscitation should be used regularly, every 30–60 min depending on the severity of the haemorrhage, to guide and ensure the appropriate use of haemostatic blood components (1C).

Fresh frozen plasma

Fresh frozen plasma has been the component of choice to manage the coagulopathy of bleeding, but there is little high quality data to inform optimal replacement of coagulation factors in major bleeding. Previous guidelines recommended transfusion of FFP after coagulation testing showed a PT ratio >1·5 times normal (Stainsby *et al*, 2006), which typically occurs after one blood volume has been transfused (Hiippala *et al*, 1995; Hirshberg *et al*, 2003). Very few clinical studies have formally tested decisions to transfuse at different thresholds including 1·5 times mean normal (Stanworth, 2007; Haas *et al*, 2015), and many thromboplastins now have a lower International Sensitivity Index (ISI) than at the time the recommendations were made. Deitcher (2002) showed that over an International Normalized Ratio range of 1·3–1·9 inclusive, mean factor levels were not critically low, indeed they ranged from 31–65% (Factor II), 40–70% (Factor V), and 22–60% (Factor VII); consistent with adequate concentrations of coagulation factors to support haemostasis. There is very limited data on the effectiveness of different doses of FFP (Chowdhury *et al*, 2004).

It has been suggested that the key to preventing coagulopathy is FFP infusion before the PT becomes excessively prolonged (Hirshberg *et al*, 2003). Studies investigating the use of early FFP in massive traumatic haemorrhage in empirical ratios, for example 1:1 with red cells, were promising, but many were retrospective, often in the military situation, and were hampered by the effect of survivor bias (Rajasekhar *et al*, 2011). The recent PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) randomized clinical trial in trauma patients with massive blood loss (Holcomb *et al*, 2015) reported that there was no difference in overall survival between early administration of plasma, platelets and red blood cells in a 1:1:1 ratio compared to 1:1:2.

We recommend that FFP be given in the initial resuscitation process in at least a 1:2 unit ratio with red cells. However, in traumatic bleeding, we recommend aiming at an initial empiric dose ratio of 1:1,with red cells, before coagulation test results are available (although baseline tests will have been taken). After the first transfusion of FFP is complete, choice of further transfusion administration should be guided by results of conventional laboratory-based (PT, APTT, fibrinogen) or near-patient tests (e.g. TEG/ROTEM), if part of a clinical trial, to evaluate their utility. Management of haemorrhage should be carefully monitored to ensure that FFP transfusion is appropriate because it is associated with significant risks, such as circulatory overload, allergic reactions and transfusion-associated acute lung injury (MacLennan & Williamson, 2006).

Recommendation

Fresh frozen plasma (FFP) should be as part of initial resuscitation in major haemorrhage in at least a 1 unit: 2 unit ratio with red cells until results from coagulation monitoring are available (see also separate specific guidance for trauma below).

Once bleeding is under control, further FFP should be guided by abnormalities in laboratory tests with transfusion trigger of PT and/or APTT >1·5 times normal for a standard dose e.g. 15–20 ml/kg (2C).

If laboratory results are not available, and bleeding continues, further FFP may be transfused in at least a 1:2 ratio with red cells, prior to moving on to blood product use guided by laboratory results (2C).

Use of FFP should not delay fibrinogen supplementation if it is required (2C).

Fibrinogen replacement

Hypofibrinogenaemia is common in massive haemorrhage and it is reported that fibrinogen is the first factor to fall to critical levels; fibrinogen levels of ≤1 g/l are likely after

1–1·5 times blood volume replacement (Hiippala, 1998; Hirshberg *et al*, 2003). There is inadequate evidence to define critical levels of fibrinogen concentration on which to base decisions to administer fibrinogen supplementation and this may vary in different clinical settings (e.g. see later section on obstetric haemorrhage). As a pragmatic recommendation, if fibrinogen levels are <1·5 g/l, fibrinogen should be replaced in the form of cryoprecipitate. In the UK cryoprecipitate prepared from a single donor contains 300–600 mg fibrinogen, and is usually pooled into 5-unit pools (JPAC, 2013). A typical adult dose is two five-donor pools (equivalent to 10 single donor units) containing 3–6 g fibrinogen in a volume of 200 to 500 ml. One such treatment administered to an adult would typically raise the plasma fibrinogen level by about 1 g/l.

Larger doses of cryoprecipitate may be considered in patients with very low levels of fibrinogen concentration (<0·5 g/l) and/or heavier individuals. In patients with a critically low fibrinogen, the concentration of fibrinogen in FFP is insufficient to achieve the rapid rise in levels required and so fibrinogen supplementation in the form of cryoprecipitate or fibrinogen concentrate must be given early. Fibrinogen concentrate is not licensed for use in acquired bleeding disorders in the UK, but is widely used in mainland Europe; again there is a lack of clinical trials to define safe and effective use, nor any high level evidence comparing outcomes in patients receiving fibrinogen concentrate compared to cryoprecipitate.

Recommendation

Fibrinogen supplementation should be given if fibrinogen levels fall below 1·5 g/l (1C). Cryoprecipitate is the standard source of fibrinogen in the UK and two five-donor pools will increase fibrinogen in an adult by approximately 1 g/l.

Prothrombin complex concentrates

While the use of prothrombin complex concentrate (PCC) is recommended in the urgent reversal of the effect of vitamin K antagonists, there is currently no good evidence to support the use of PCC in the management of major haemorrhage and their use should be limited to clinical trials to gather evidence on their efficacy, safety and cost- effectiveness.

Recommendation

The use of PCC is not recommended in the management of major haemorrhage unless as part of a clinical trial (1D).

Platelets

Thrombocytopenia is considered a late event in massive haemorrhage, typically seen only after a loss of at least 1·5 blood volumes (Counts *et al*, 1979; Hiippala, 1998). Outside trauma and in major haemorrhage other than after cardiopulmonary bypass, there is little evidence to inform optimal use of platelet transfusion. Increasing numbers of patients are on anti-platelet medications, and there is the uncertain contributory role of platelet function defects in patients with major bleeding. The specific role of platelets in major haemorrhage in trauma is discussed later.

Platelet transfusion should be given as one adult therapeutic dose (one apheresis pack or 4 pooled units) when the platelet count falls below 50×10^9/l (Blood Transfusion Task Force, 2003). Many hospitals do not keep a stock of platelets and therefore the Transfusion Laboratory will need to order platelets from the Blood Transfusion Centre early in major haemorrhage (e.g. when the platelet count has fallen below 100×10^9/l). Practical guidance on the provision of platelets when the patient blood group is not known is described later.

Recommendation

In major haemorrhage aim to keep platelets $>50 \times 10^9$/l (1B); we suggest that platelets should be requested if there is on-going bleeding and the platelet count has fallen below 100×10^9/l (2C).

C: Pharmacological agents

Tranexamic acid

The Clinical Randomization of Antifibrinolytics in Significant Haemorrhage (CRASH-2) study was a randomized controlled trial (RCT) of TA *versus* placebo in the management of those with or at risk of significant bleeding after trauma, and recruited 20 000 patients worldwide (CRASH-2 collaborators, 2010). The primary outcome was death in hospital within 4 weeks of injury. Death in the first 4 weeks was reduced by 9% with TA: deaths due to bleeding were reduced by a third when TA was given in the first 3 h. Not only was the drug shown to be efficacious in reducing premature death, but it was also shown to be safe; there were no adverse events and, importantly for a drug that affects haemostasis, there was no increase of thrombotic events. Further analysis of the data showed that benefit was greatest the earlier that TA was given after injury and that there was a possibility of harm if given >3 h after injury (CRASH-2 collaborators, 2011).

CRASH-2 showed no reduction in the use of blood components in those treated with TA. A retrospective study of the use of TA in a military trauma suggests this is due to the higher survival rate with TA (23·9% vs. 17·9%) (Morrison *et al*, 2012), because the additional surviving patients will require further blood components.

The results of the CRASH-2 trial applied only to patients with trauma. Patients with other causes of bleeding, such as gastrointestinal (GI) bleeding, are usually older than trauma

patients, with different co-morbidities, and it is unclear whether the results of CRASH-2 should be extrapolated from trauma to GI bleeding. An on-going trial is addressing this research question [Haemorrhage Alleviation with Tranexamic acid – Intestinal system (HALT-IT); http://haltit.lshtm.ac.uk/ProtocolSummary.pdf]. A systematic review (Ker *et al*, 2012) regarding the use of TA in surgical patients, found 129 trials, totalling 10 488 patients, carried out between 1972 and 2011. In this meta-analysis, TA reduced the probability of receiving a blood transfusion by a third (risk ratio 0·62, 95% confidence interval 0·58 to 0·65; $P < 0·001$). A newly published analysis of the use of TA in hip and knee replacement in the USA has suggested that there is no increased risk of vascular occlusive events in this group of patients (Memtsoudis, 2014).

Aprotinin is bovine protein with multiple effects including an antifibrinolytic action, but cannot be recommended due to concerns about safety (Hutton *et al*, 2012).

Recommendations

Adult trauma patients with, or at risk of, major haemorrhage, in whom antifibrinolytics are not contraindicated, should be given tranexamic acid as soon as possible after injury, at a dose of 1 g intravenously over 10 min followed by a maintenance infusion of 1 g over 8 h (1A).

The use of tranexamic acid should be considered in non-traumatic major bleeding (1B).

The routine use of aprotinin is not recommended (1B).

Recombinant activated factor VIIa

Recombinant activated factor VIIa (rFVIIa) is approved in Europe for the management of haemophilia A or B with inhibitors, acquired haemophilia, inherited FVII deficiency, and Glanzmann thrombasthenia with antibodies to glycoprotein IIb/IIIa and/or human leucocyte antigen antigens and refractoriness to platelet transfusion. rFVIIa has also been used widely 'off label' in patients with massive haemorrhage after major surgery or trauma without a pre-existing coagulopathy. The first randomized placebo-controlled trial of rFVIIa in trauma patients after having been transfused eight units of red cells, showed a reduction in red cell use in those with blunt injuries (Boffard *et al*, 2005). However these findings were not replicated in further studies, and a recent Cochrane meta-analysis on the off-license use of rFVIIa (Simpson *et al*, 2012) showed only modest reductions in total blood loss or red cell requirements (equivalent to less than one unit of red cell transfusion), but for other endpoints there were no consistent indications of benefit; no trial has been powered to study effect on mortality. Levi *et al* (2010) reviewed safety of the 4468 patients entered into trials of rVIIa and found an increased rate of arterial thromboembolism, increasing with patient age: those aged over 65 years had a rate of 9% vs. 3·6% in those aged under 65 years, $P = 0·003$; those aged over 75 had a rate of 10·8% vs. 4·1% in those under 75 years of age, $P = 0·02$.

Recommendation

The use of rVIIa is not recommended in the management of major haemorrhage unless as part of a clinical trial (1D).

Thromboprophylaxis after major bleeding

Trauma patients in particular have a high rate of hospital-acquired venous thromboembolism (VTE) (Geerts *et al*, 1994) and there is also evidence from obstetrics that those who bleed excessively have a higher rate of VTE (Jacobsen *et al*, 2008). Current thromboprophylaxis protocols reduce the rate of VTE significantly and should be applied (NICE, 2010).

Recommendation

Thromboprophylaxis should be given after major haemorrhage and should be started as soon as possible after bleeding ceases (1A).

D: Specific clinical situations

Managing established bleeding in different patient subgroups

Major bleeding occurs in a number of different patient subgroups, treated by different sets of clinicians. The broad principles of management as described above should apply, but it is recognized that the pathophysiological derangements of haemostasis are likely to differ by site and different aetiologies of major bleeding. A priority for research is to understand how guidelines should be adapted for different aetiologies of bleeding. The areas where there is deviation from this or additional guidance are described below.

Patients with inherited bleeding disorders should be managed in collaboration with the local Haemophilia Centre, and bleeding in patients receiving antiplatelet medication and/or anticoagulants should be managed according to appropriate BCSH guidelines (Makris *et al*, 2013).

Obstetric haemorrhage

Postpartum haemorrhage (PPH) is usually defined as an estimated blood loss ≥1000 mL during a Caesarean section or ≥500 ml after a vaginal birth, due to diverse aetiologies. It remains a leading cause of early maternal death in both the developing and developed world, accounting for about 300 000 deaths worldwide annually. It is also a major cause of morbidity related to hysterectomy in the developed world and of anaemia and blood transfusion worldwide. PPH often

relates to uterine atony and retained placenta. Therefore guidelines recommend optimal use of obstetric intervention and uterotonic drugs initially; unless there is major blood loss, the use of blood components and haemostatic agents is not a routine first-line intervention. Recent focus on haemostatic management in PPH has been stimulated by data on fibrinogen management and TA.

Preliminary data has shown that TA may reduce blood loss in PPH but the quality of evidence is poor (Ferrer *et al*, 2009; Ducloy-Bouthors *et al*, 2011). We are awaiting completion of the WOMAN (World Maternal AntifibriNolytic) study, a double blind randomized study of TA *versus* placebo with a primary outcome measure of death, which aims to recruit 20,000 women and will report in 2016 (Shakur *et al*, 2010).

Charbit *et al* (2007) identified that low fibrinogen levels early after PPH are a predictor of the severity of PPH. Fibrinogen levels increase during pregnancy and are in the range of 4–6 g/l at delivery; therefore a fibrinogen level of 2–3 g/l which would be reassuring in a non-pregnant patient, indicates significant blood loss in PPH. A recent parallel RCT (Wikkelsø *et al*, 2015), enrolled 249 subjects with severe PPH to a single dose of fibrinogen concentrate or saline. The primary outcome was red cell transfusion up to 6 weeks postpartum. The authors reported no differences in outcomes, although limitations to the trial should be recognized including the low dose.

Management of PPH should be similar to massive haemorrhage following trauma, but particular emphasis needs to be given to measuring fibrinogen early and responding promptly to low levels and, as abnormal coagulation is less common, early empirical FFP before coagulation results may not be needed. For details of the full management of PPH, the reader is advised to read the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines (RCOG, 2009). Severe PPH increases the risk of post-partum VTE (Jacobsen *et al*, 2008) so thromboprophylaxis should be instituted as soon as possible after PPH has ceased.

Recommendations

In major obstetric haemorrhage, blood component management should follow a similar pathway as for non-pregnant patients (2C), except that meticulous attention should be paid to fibrinogen levels and consideration given to the early use of fibrinogen supplementation when fibrinogen levels are <2·0 g/l and there is on-going bleeding (1D).

In major obstetric haemorrhage, consideration should be given to using tranexamic acid (1B).

Gastro-intestinal haemorrhage

Gastro-intestinal (GI) bleeding is a common indication for transfusion of blood components. The publication of a single centre RCT (with defined inclusion/exclusion criteria) comparing liberal and restrictive policies for red cell transfusion in patients with non-massive acute upper GI bleeding showed a higher 6-week survival and lower re-bleeding rate in patients allocated to a restrictive threshold for red cell transfusion at 70 g/l (post-transfusion target 70–90 g/l) (Villanueva *et al*, 2013). Portal pressures were reported to be significantly increased in the liberal transfusion group. Although there are no comparable studies addressing changes in coagulopathy or thrombocytopenia, it seems sensible to follow a restrictive approach to the use of FFP and platelets in patients with acute upper GI bleeding unless there is massive life-threatening haemorrhage or evidence of severe derangements in laboratory tests. The role of TA in patients with GI bleeding is being addressed by the HALT-IT study (http://haltit.lshtm.ac.uk/ProtocolSummary.pdf), a large pragmatic RCT.

Recommendation

In gastro-intestinal non-massive haemorrhage a restrictive strategy of red cell transfusion is recommended for many patients (1A).

Trauma

The UK focus on improving trauma care has led to the development of regional trauma networks with designated major trauma centres. A significant proportion of trauma patients with major bleeding present with coagulopathy, which is associated with increased mortality. The definition of this 'acute traumatic coagulopathy' varies; the most commonly used is based on prolongation of the PT (Frith *et al*, 2010).

The utility of antifibrinolytics is clear and subsequent data to CRASH-2 confirms that trauma does indeed induce massive fibrinolytic activation, with the extent relating to the degree of injury (Raza *et al*, 2013). NHS England has ensured TA is available to all paramedics at the roadside. For those patients who do not receive TA pre-admission, there should be no delay in its administration once admitted to hsopital. We do not recommend waiting to test for 'TEG hyperfibrinolysis', because thromboelastography is an insensitive measure of fibrinolytic activation (Raza *et al*, 2013).

The recent PROPPR trial (Holcomb *et al*, 2015) reported that in patients who have or are at risk of massive blood loss, initial infusion with plasma, platelets and red blood cells in a 1:1:1 ratio compared to 1:1:2 ratio did not improve overall survival. However in additional analyses more patients in the 1:1:1 group were reported to achieve 'anatomic' haemostasis and fewer may have experienced death due to exsanguination by 24 h. The relative contribution of platelets or plasma to the resuscitation outcomes could not be defined in this study. We recommend that plasma: red blood cells are given initially in a 1:1 ratio, but when bleeding is under control, laboratory testing should guide blood component therapy. We suggest consideration of early use of platelets.

Recommendations

Adult trauma patients with, or at risk of, massive haemorrhage should initially be transfused empirically with a 1: 1 ratio of plasma: red blood cells (1B).

The early use of platelets should be considered (1B).

Adult trauma patients with, or at risk of major haemorrhage, should be given tranexamic acid as soon as possible after injury, at a dose of 1 g intravenously over 10 min followed by a maintenance infusion of 1 g over 8 h (1A).

The prevention of bleeding in high-risk patient groups such as cardiac and spinal surgery

Strong evidence that TA reduces blood transfusion in surgery has been available for many years (Henry *et al*, 2011; Ker *et al*, 2012). The Horrow regime of 10 mg/kg followed by 1 mg/kg/h (Horrow *et al*, 1995), originally devised for use in patients undergoing cardiopulmonary bypass, is the usual regime. Higher doses have no increase in haemostatic effect (Ker *et al*, 2012), and are associated with seizures (Kalavrouziotis *et al*, 2012).

Recommendation

In high-risk surgery tranexamic acid at a dose of 10 mg/kg followed by 1 mg/kg/h is recommended to prevent bleeding (1B).

Paediatrics

The principles of massive blood loss management in adults can be broadly applied to the care of children. There is little research evidence available to specifically guide paediatric care. Children differ from adults in anatomy and physiology as well as in size and weight. These differences require some specific modifications to the clinical care and transfusion support provided. Further details will be given in the forthcoming paediatric and neonatal transfusion BCSH guidelines.

E: Audit

Audit of major haemorrhage management is essential to assess adverse events, timeliness of blood component support, patient outcome and component wastage. There should be regular review of cases triggering the major blood loss protocol to ensure local protocols are applied appropriately and effectively, with timely delivery and transfusion to patients, including use of balanced ratios of blood components (plasma and platelets with red cells) in trauma.

All incidents should be investigated locally and, in the case of a serious adverse reaction (SAR), serious adverse event (SAE) or patient harm due to delay, should be reported to the Serious Hazards of Transfusion (SHOT) scheme (http://www.shotuk.org) and Serious Adverse Blood Reactions and Events (SABRE) for SAE and SAR (http://www.shotuk.org/wp-content/uploads/2010/03/SHOT-Toolkit-Version-3-August-2008.pdf).

Recommendation

Multidisciplinary audit and case review should be undertaken to ensure that effective systems are in place for major haemorrhage management (1A).

F: Mass casualty situations

Mass casualty events can place exceptional demand on hospitals and National Blood Services (Glasgow *et al*, 2012). Hospitals should ensure that the local policy for management of major haemorrhage is incorporated in the Major Incident Plan and, as part of contingency planning for national blood shortage situations; hospitals should also have an Emergency Blood Management Plan in place that provides guidance on clinical priorities for the use of large volumes of blood components (also see Appendix).

G: Recommendations for future research

Blood component usage has rarely been subject to clinical research regarding its effectiveness and there are concerns about safety, especially if used inappropriately. For example, FFP use has been associated with complications, especially adult respiratory distress syndrome in trauma patients whose transfusion requirements did not fulfil the definition of massive transfusion (Inaba *et al*, 2010). A number of planned or on-going RCTs will better inform the management of major bleeding or patients at risk of major bleeding. For example, the REPLACE study is a Phase III multicentre placebo-controlled randomized trial in which patients undergoing elective aortic surgery were randomized in a 1:1 ratio to treatment with fibrinogen concentrate or placebo. RCTs in major bleeding face the challenges of patient selection, consent, enrolment, randomization, treatment masking, sample size, data collection and adverse event reporting, but only these trials will have the potential to change practice on the basis of evidence (CRASH-2 trial collaborators *et al*, 2010; Holcomb *et al*, 2015). There is a need to conduct research on patient groups other than trauma patients, such as postpartum, GI or vascular bleeding, especially ruptured aortic aneurysm, including studies on cost effectiveness.

Acknowledgements

We would like to acknowledge contributions from Mr Colin Barber, Royal London Hospital and Jane Uttley, Central Manchester Hospitals for providing technical expertise and input in writing Appendix; and BCSH sounding board, The BCSH Transfusion and Thrombosis and Haemostasis task

forces, the Association of Anaesthetists and the Royal College of Anaesthetists for their helpful comments.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

References

AAGBI. (2009) AAGBI Safety Guideline. Blood transfusion and the anaesthetist. Intraoperative cell salvage. Association of Anaesthetists of Great Britain and Ireland, London. Available at: http://www.aagbi.org/sites/default/files/cell%20_salvage_2009_amended.pdf. Accessed 19 June 2015.

Afshari, A., Wikkelsø, A., Brok, J., Møller, A.M. & Wetterslev, J. (2011) Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. *Cochrane Database of Systematic Reviews*, **16**, CD007871. doi:10.1002/14651858.CD007871.pub2 Review.

Boffard, K.D., Riou, B., Warren, B., Choong, P.I., Rizoli, S., Rossaint, R., Axelsen, M. & Kluger, Y.; NovoSeven Trauma Study Group. (2005) Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *Journal of Trauma*, **59**, 8–15; discussion 15–8.

British Committee for Standards in Haematology, Blood Transfusion Task Force. (2003) Guidelines for the use of platelet transfusions. *British Journal of Haematology*, **122**, 10–23.

Chaffe, B., Glencross, H., Jones, J., Staves, J., Capps-Jenner, A., Mistry, H., Bolton-Maggs, P., McQuade, M. & Asher, D. (2014) UK Transfusion Laboratory Collaborative: minimum standards for staff qualifications, training, competency and the use of information technology in hospital transfusion laboratories. *Transfusion Medicine*, **24**, 335–340.

Charbit, B., Mandelbrot, L., Samain, E., Baron, G., Haddaoui, B., Keita, H., Sibony, O., Mahieu-Caputo, D., Hurtaud-Roux, M.F., Huisse, M.G., Denninger, M.H. & de Prost, D.; PPH Study Group. (2007) The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *Journal of Thrombosis and Haemostasis*, **5**, 266–273.

Chibber, V., Green, M., Vauthrin, M., Bailey, J. & Weinstein, R. (2014) Is group A thawed plasma suitable as the first option for emergency release transfusion? *Transfusion*, **54**, 1751–1755.

Chowdhury, P., Saayman, A.G., Paulus, U., Findlay, G.P. & Collins, P.W. (2004) Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. *British Journal of Haematology*, **125**, 69.

Counts, R.B., Haisch, C., Simon, T.L., Maxwell, N.G., Heimbach, D.M. & Carrico, C.J. (1979) Hemostasis in massively transfused trauma patients. *Annals of Surgery*, **190**, 91–99.

CRASH-2 collaborators, Roberts, I., Shakur, H., Afolabi, A., Brohi, K., Coats, T., Dewan, Y., Gando, S., Guyatt, G., Hunt, B.J., Morales, C., Perel, P., Prieto-Merino, D. & Woolley, T. (2011) The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *The Lancet*, **377**, 1096–1101, 1101.e1–2. doi:10.1016/S0140-6736(11)60278-X

CRASH-2 trial collaborators, Shakur, H., Roberts, I., Bautista, R., Caballero, J., Coats, T., Dewan, Y., El-Sayed, H., Gogichaishvili, T., Gupta, S., Herrera, J., Hunt, B., Iribhogbe, P., Izurieta, M., Khamis, H., Komolafe, E., Marrero, M.A., Mejía-Mantilla, J., Miranda, J., Morales, C., Olaomi, O., Olldashi, F., Perel, P., Peto, R., Ramana, P.V., Ravi, R.R. & Yutthakasemsunt, S. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *The Lancet*, **376**, 23–32.

Deitcher, S.R. (2002) Interpretation of the international normalised ratio in patients with liver disease. *The Lancet*, **359**, 47–48.

Department of Health. (2005) Statutory Instruments 2005 No. 50. Health and Safety. Blood Safety and Quality Regulations 2005 © crown copyright. The Stationery Office, London. Available at: http://www.legislation.gov.uk/uksi/2005/50/made. Accessed 19 June 2015.

Department of Health. (2007) Health Service Circular 2007/001: Better blood transfusion - safe and appropriate use of blood. Department of Health, London. © Crown copyright. Available at: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_080803.pdf. Accessed 19 June 2015.

Ducloy-Bouthors, A.S., Jude, B., Duhamel, A., Broisin, F., Huissoud, C., Keita-Meyer, H., Mandelbrot, L., Tillouche, N., Fontaine, S., Le Goueff, F., Depret-Mosser, S. & Vallet, B.; EXADELI Study Group, Susen, S.. (2011) High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. *Critical Care*, **15**, R117.

Edgren, G., Kamper-Jørgensen, M., Eloranta, S., Rostgaard, K., Custer, B., Ullum, H., Murphy, E.L., Busch, M.P., Reilly, M., Melbye, M., Hjalgrim, H. & Nyrén, O. (2010) Duration of red blood cell storage and survival of transfused patients (CME). *Transfusion*, **50**, 1185–1195.

Fenger-Eriksen, C., Moore, G.W., Rangarajan, S., Ingerslev, J. & Sørensen, B. (2010) Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. *Transfusion*, **50**, 2571–2576.

Ferrer, P., Roberts, I., Sydenham, E., Blackhall, K. & Shakur, H. (2009) Anti-fibrinolytic agents in post partum haemorrhage: a systematic review. *BMC Pregnancy Childbirth*, **15**, 29.

Frith, D., Goslings, J.C., Gaarder, C., Maegele, M., Cohen, M.J., Allard, S., Johansson, P.I., Stanworth, S., Thiemermann, C. & Brohi, K. (2010) Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. *Journal of Thrombosis and Haemostasis*, **8**, 1919–1925.

Geerts, W.H., Code, K.I., Jay, R.M., Chen, E. & Szalai, J.P. (1994) A prospective study of venous thromboembolism after major trauma. *New England Journal of Medicine*, **331**, 1601–1606.

Glasgow, S.M., Allard, S., Doughty, H., Spreadborough, P. & Watkins, E. (2012) Blood and bombs: the demand and use of blood following the London Bombings of 7 July 2005 – a retrospective review. *Transfusion Medicine*, **4**, 244–250.

Guyatt, G., Gutterman, D., Baumann, M.H., Addrizzo-Harris, D., Hylek, E.M., Phillips, B., Raskob, G., Lewis, S.Z. & Schünemann, H. (2006) Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. *Chest*, **129**, 174–181.

Haas, T., Fries, D., Tanaka, K.A., Asmis, L., Curry, N.S. & Schöchl, H. (2015) Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? *British Journal of Anaesthesia*, **114**, 217–224.

Hebert, P.C., Wells, G., Blajchman, M.A., Marshall, J., Martin, C., Pagliarello, G., Tweeddale, M., Schweitzer, I. & Yetisir, E. (1999) A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *New England Journal of Medicine*, **340**, 409–417.

Henry, D.A., Carless, P.A., Moxey, A.J., O'Connell, D., Stokes, B.J., Fergusson, D.A. & Ker, K. (2011) Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews*, **19**, CD001886.

Hiippala, S. (1998) Replacement of massive blood loss. *Vox Sanguinis*, **74**, 399–407.

Hiippala, S.T., Myllylä, G.J. & Vahtera, E.M. (1995) Hemostatic factors and replacement of

major blood loss with plasma-poor red cell concentrates. *Anesthesia and Analgesia*, **81**, 360–365.

Hirshberg, A., Dugas, M., Banez, E.I., Scott, B.G., Wall, Jr, M.J. & Mattox, K.L. (2003) Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation. *Journal of Trauma*, **54**, 454–463.

Hogshire, L. & Carson, J.L. (2013) Red blood cell transfusion: what is the evidence when to transfuse? *Current Opinion in Hematology*, **20**, 546–551.

Holcomb, J.B., Tilley, B.C., Baraniuk, S., Fox, E.E., Wade, C.E., Podbielski, J.M., del Junco, D.J., Brasel, K.J., Bulger, E.M., Callcut, R.A., Cohen, M.J., Cotton, B.A., Fabian, T.C., Inaba, K., Kerby, J.D., Muskat, P., O'Keeffe, T., Rizoli, S., Robinson, B.R., Scalea, T.M., Schreiber, M.A., Stein, D.M., Weinberg, J.A., Callum, J.L., Hess, J.R., Matijevic, N., Miller, C.N., Pittet, J.F., Hoyt, D.B., Pearson, G.D., Leroux, B. & van Belle, G.; PROPPR Study Group. (2015) Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*, **313**, 471–482.

Horrow, J.C., Van Riper, D.F., Strong, M.D., Grunewald, K.E. & Parmet, J.L. (1995) The dose-response relationship of tranexamic acid. *Anesthesiology*, **82**, 383–392.

Hunt, H., Stanworth, S., Curry, N., Woolley, T., Cooper, C., Ukoumunne, O., Zhelev, Z. & Hyde, C. (2015) Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma-induced coagulopathy in adult trauma patients with bleeding. *Cochrane Database of Systematic Reviews*, **2015**, CD010438.

Hutton, B., Joseph, L., Fergusson, D., Mazer, C.D., Shapiro, S. & Tinmouth, A. (2012) Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomised and observational studies. *British Medical Journal*, **345**, e5798.

Inaba, K., Branco, B.C., Rhee, P., Blackbourne, L.H., Holcomb, J.B., Teixeira, P.G., Shulman, I., Nelson, J. & Demetriades, D. (2010) Impact of plasma transfusion in trauma patients who do not require massive transfusion. *Journal of the American College of Surgeons*, **210**, 957–965.

Jacobsen, A.F., Skjeldestad, F.E. & Sandset, P.M. (2008) Ante and postnatal risk factors of venous thrombosis: a hospital-based case-control study. *Journal of Thrombosis and Haemostasis*, **6**, 905–912.

JPAC. (2013) Guidelines for the Blood Transfusion Services in the UK, 8th edn. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. Available at: http://www.transfusionguidelines.org.uk/red-book/chapter-7-specifications-for-blood-components/7-18-cryoprecipitate-pooled-leucocyte-depleted. Accessed 19 June 2015.

Kalavrouziotis, D., Voisine, P., Mohammadi, S., Dionne, S. & Dagenais, F. (2012) High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. *The Annals of Thoracic Surgery*, **93**, 148–154.

Kass, L.E., Tien, I.Y., Ushkow, B.S. & Snyder, H.S. (1997) Prospective crossover study of the effect of phlebotomy and intravenous crystalloid on hematocrit. *Academic Emergency Medicine*, **4**, 198–201.

Ker, K., Edwards, P., Perel, P., Shakur, H. & Roberts, I. (2012) Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *British Medical Journal*, **344**, e3054.

Lacroix, J., Hébert, P.C., Fergusson, D.A., Tinmouth, A., Cook, D.J., Marshall, J.C., Clayton, L., McIntyre, L., Callum, J., Turgeon, A.F., Blajchman, M.A., Walsh, T.S., Stanworth, S.J., Campbell, H., Capellier, G., Tiberghien, P., Bardiaux, L., van de Watering, L., van der Meer, N.J., Sabri, E. & Vo, D.; for the ABLE Investigators and the Canadian Critical Care Trials Group. (2015) Age of transfused blood in critically ill adults. *New England Journal of Medicine*, **372**, 1410–1418.

Levi, M., Levy, J.H., Andersen, H.F. & Truloff, D. (2010) Safety of recombinant activated factor VII in randomized clinical trials. *New England Journal of Medicine*, **363**, 1791–1800.

Mackie, I.J., Kitchen, S., Machin, S.J. & Lowe, G.D.; Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. (2003) Guidelines on fibrinogen assays. *British Journal of Haematology*, **121**, 396–404.

MacLennan, S. & Williamson, L.M. (2006) Risks of fresh frozen plasma and platelets. *Journal of Trauma*, **60**(6 Suppl), S46–S50.

Madjdpour, C. & Spahn, D.R. (2005) Allogeneic red blood cell transfusions: efficacy, risks, alternatives and indications. *British Journal of Anaesthesia*, **95**, 33–42.

Makris, M., Van Veen, J.J., Tait, C.R., Mumford, A.D. & Laffan, M.; for the British Committee for Standards in Haematology. (2013) Guideline on the management of bleeding in patients on antithrombotic agents. *British Journal of Haematology*, **160**, 35–46.

McIntyre, L., Hebert, P.C., Wells, G., Fergusson, D., Marshall, J., Yetisir, E. & Blajchman, M.J. (2004) Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? *Journal of Trauma*, **57**, 563–568.

Memtsoudis, S.G. (2014) Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *British Medical Journal*, **349**, g4829.

Milkins, C., Berryman, J., Cantwell, C., Elliott, C., Haggas, R., Jones, J., Rowley, M., Williams, M. & Win, N. (2013) British Committee for Standards in Haematology Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories. *Transfusion Medicine*, **23**, 3–35.

Morrison, J.J., Dubose, J.J., Rasmussen, T.E. & Midwinter, M.J. (2012) Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Archives of Surgery*, **147**, 113–119.

Murphy, M.F., Wallington, T.B., Kelsey, P., Boulton, F., Bruce, M., Cohen, H., Duguid, J., Knowles, S.M., Poole, G. & Williamson, L.M. (2001) British Committee for Standards in Haematology, Blood Transfusion Task Force. *British Journal of Haematology*, **113**, 24–31.

National Patient Safety Agency. (2010). Rapid Response Report NPSA/2010/RRR017. The transfusion of blood and blood components in an emergency. Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=83688. Accessed 19 June 2015.

NICE. (2010) Venous thromboembolism: reducing the risk: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE Clinical guideline 92. National Institute for Health and Clinical Care Excellence, London. Available at: http://www.nice.org.uk/guidance/cg92. Accessed 19 June 2015.

NICE. (2014) Detecting, managing and monitoring haemostasis: viscoelastometric point of care testing (ROTEM, TEG and Sonoclot systems). NICE Diagnostic Guideline 13. National Institute for Health and Clinical Care Excellence, London. Available at: http://www.nice.org.uk/guidance/dg13/chapter/1-recommendations. Accessed 19 June 2015.

Rajasekhar, A., Gowing, R., Zarychanski, R., Arnold, D.M., Lim, W., Crowther, M.A. & Lottenberg, R. (2011) Survival of trauma patients after massive red blood cell transfusion using a high or low red blood cell to plasma transfusion ratio. *Critical Care Medicine*, **39**, 1507–1513.

Raza, I., Davenport, R., Rourke, C., Platton, S., Manson, J., Spoors, C., Khan, S., De'ath, H., Allard, S., Hart, D., John Pasi, K., Hunt, B.J., Stanworth, S., Maccallum, P. & Brohi, K. (2013) The incidence and magnitude of fibrinolytic activation in trauma patients. *Journal of Thrombosis and Haemostasis*, **11**, 307–314.

RCOG. (2009) Postpartum Haemorrhage, Prevention and Management. Green-top Guideline No. 52 Royal College of Obstetricians, London, UK. Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg52/. Accessed 19 June 2015.

Retter, A., Wyncoll, D., Pearse, R., Carson, D., McKechnie, S., Stanworth, S., Allard, S., Thomas, D. & Walsh, T.; British Committee for Standards in Haematology. (2013) BCSH Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients. *British Journal of Haematology*, **160**, 419–567.

Rohde, J.M., Dimcheff, D.E., Blumberg, N., Saint, S., Langa, K.M., Kuhn, L., Hickner, A. & Rogers, M.A. (2014) Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. *JAMA*, **311**, 1317–1326.

Shakur, H., Elbourne, D., Gülmezoglu, M., Alfirevic, Z., Ronsmans, C., Allen, E. & Roberts, I. (2010) The WOMAN Trial (World Maternal

Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial. *Trials*, **11**, 40.

Simpson, E., Lin, Y., Stanworth, S., Birchall, J., Doree, C. & Hyde, C. (2012) Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database of Systematic Reviews*, **3**, CD005011.

Spahn, D.R., Bouillon, B., Cerny, V., Coats, T.J., Duranteau, J., Fernandez-Mondejar, E., Filipescu, D., Hunt, B.J., Komadina, R., Nardi, G., Neugebauer, E., Ozier, Y., Riddez, L., Schultz, A., Vincent, J.L. & Rossaint, R. (2013) Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Critical Care*, **17**, R76.

Stainsby, D., MacLennan, S., Thomas, D., Isaac, J. & Hamilton, P.J.; for the British Committee for Standards in Haematology. (2006) Guidelines on the management of massive blood loss. *British Journal of Haematology*, **135**, 634–641.

Stanworth, S. (2007) The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. *Hematology/the Education Program of the American Society of Hematology. American Society of Hematology. Education Program*, **2007**, 179–186.

Steiner, M.E., Assmann, S.F., Levy, J.H., Marshall, J., Pulkrabek, S., Sloan, S.R., Triulzi, D. & Stowell, C.P. (2010). Addressing the question of the effect of RBC storage on clinical outcomes: the Red Cell Storage Duration Study (RECESS) (Section 7). *Transfusion and Apheresis Science*, **43**, 107–116.

Villanueva, C., Colomo, A., Bosch, A., Concepción, M., Hernandez-Gea, V., Aracil, C., Graupera, I., Poca, M., Alvarez-Urturi, C., Gordillo, J., Guarner-Argente, C., Santaló, M., Muñiz, E. & Guarner, C. (2013) Transfusion strategies for acute upper gastrointestinal bleeding. *New England Journal of Medicine*, **368**, 11–21.

Weinberg, J.A., McGwin, Jr, G., Griffin, R.L., Huynh, V.Q., Cherry, 3rd, S.A., Marques, M.B., Reiff, D.A., Kerby, J.D. & Rue, 3rd, L.W. (2008) Age of transfused blood: an independent predictor of mortality despite universal leukoreduction. *Journal of Trauma*, **65**, 279–282.

Wikkelsø, A.J., Edwards, H.M., Afshari, A., Stensballe, J., Langhoff-Roos, J., Albrechtsen, C., Ekelund, K., Hanke, G., Secher, E.L., Sharif, H.F., Pedersen, L.M., Troelstrup, A., Lauenborg, J., Mitchell, A.U., Fuhrmann, L., Svare, J., Madsen, M.G., Bødker, B. & Møller, A.M.; FIB-PPH trial group. (2015). Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial. *British Journal of Anaesthesia*, **114**, 623–633.

Yuan, S., Ferrell, C. & Chandler, W.L. (2007) Comparing the prothrombin time INR versus the APTT to evaluate the coagulopathy of acute trauma. *Thrombosis Research*, **120**, 29–37.

Zielinski, M., Johnson, P.M., Jenkins, D., Goussous, N. & Stubbs, J.R. (2013) Emergency use of prethawed Group A plasma in trauma patients. *Journal of Trauma and Acute Care Surgery*, **74**, 69–75.

Appendix

The logistics and laboratory management of major haemorrhage

Introduction

While the wider principles below apply to both adults and paediatrics, dosing guidance is for adults only. Paediatrics advice will be available in a separate BCSH guideline.

Communication with the laboratory

Blood transfusion laboratory staff must be informed of major haemorrhage at the earliest opportunity so that emergency procedures can be activated in a timely manner. There should be a 'communication lead' nominated by the 'team leader' to act in a liaison role between the clinical team and the laboratory staff and support services (National Patient Safety Agency, 2010). In addition, a designated porter or 'runner' should be identified, to bring samples to the laboratory and collect blood components from the laboratory.

Before contacting the laboratory, the communication lead must document the following with the team leader:

1 Patient demographic details, full name, date of birth and unique patient identifier
2 The degree of urgency i.e. whether emergency group O red cells are required /already used or whether group-specific blood is required (15–30 min)
3 If using a Massive Haemorrhage Pack (MHP; a predefined order of blood components that will be prepared by the laboratory upon activation of the massive haemorrhage protocol), then the content should be pre-agreed between the clinical teams and laboratory staff e.g.: 4 red cell units, 4 units FFP.
4 When not using a MHP then consider the volume of initial products required e.g.: red cell units (usually 4 or 6 units) and FFP 15–20 ml/kg per dose; 4 units for an average adult

The laboratory should ensure that the above information is documented as well as the following:

1 The name and contact number of person making the call.
2 Whether the emergency Group O blood has been taken (this will need to be replaced at the earliest opportunity) – ensure the caller knows where emergency Group O blood is situated.
3 Is there a sample available or is it being sent?
4 Agree to contact the Communication Lead when components ready
5 Give the Communication Lead the name of the laboratory contact

Laboratory provision of emergency blood components

Table I gives an overview of the blood components used in the management of massive haemorhage. An emergency supply of Group O red cells must be immediately available. The major haemorrhage protocol must identify the location of the nearest emergency Group O red cell units. The patient should have a blood sample taken for pre-transfusion testing before the Group O emergency red cells are administered.

The sample and the request

In order to proceed, the transfusion laboratory must have a valid sample and a clinical request. In some situations e.g. elective surgery, the laboratory may already have a sample. In most situations, the sample will have to be collected from the patient and delivered to the laboratory urgently.

Patient identification

Positive patient identification is paramount. All patients receiving a blood transfusion must wear a patient identification (ID) band, which should hold the minimum patient identifiers: last name, first name, date of birth, unique identification number. In emergency situations, the patient's identity may be unknown. At least one unique identifier must be used [e.g. a temporary ID number such as Emergency Department (ED) number] and the patient's gender must also be used.

When taking a blood sample from a patient in a massive haemorrhage situation – the samples must be hand labelled by the bedside (unless an electronic label generated by a barcoded wrist band is used) with details as shown in Table II; the details should match the wristband and the request form.

A written/electronic request must be sent to the laboratory with a sample. If a sample is already in the laboratory (e.g., previous group and screen) then in an emergency situation, the request may be telephoned but there should be clear methods of documentation to reduce the risk of transcription error.

The minimum data on the request form should include: the core identifiers (last name, first name, date of birth, unique patient ID number, signature of person taking the sample), reason for request, urgency of request and products required.

Table II. Details required on blood samples for the transfusion laboratory.

Known patient	Unknown patient
Surname (in full) Forename (in full) Date of birth Patient Identification Number Gender Date and time of sample Signature of the person taking the sample	If the patient is unknown the following data must be included: Unknown male or unknown female Patient Identification Number Date and time of sample Signature of the person taking the sample On confirmation of patient details inform Transfusion Laboratory and re-bleed the patient labelling the samples with: Surname (in full) Forename (in full) Date of birth Patient Identification Number Gender Date and time of sample Signature of the person taking the sample

The laboratory will use the details on the request form and sample to allocate blood to the specific patient. In the case of patients with an unknown identity, the patient should continue to be transfused on the emergency ID until the record is updated and a new, fully labelled sample is collected and processed. In all cases, the details on the blood component identity tag must match the details on the patient ID band.

Laboratory procedures

Samples received by the transfusion laboratory should not be allowed to have identifiers modified. There should be zero tolerance of this, even in the emergency situation. Where possible, a second sample should be requested for confirmation of the ABO group of a first time patient because of the recognized risk of 'wrong blood in tube' events (Milkins *et al*, 2013). However, in the emergency, this may impede the delivery of group-specific red cells and components and a risk assessment should be undertaken to decide the circumstances in which one sample will suffice.

Once the blood group of the patient has been confirmed, the laboratory staff should:

1 Check availability of platelets and if no stock order 2 doses by emergency delivery
2 Check stocks of red cells and re-order when necessary

Red cells

Group O blood. Group O red cells should be used in the emergency situation until the ABO group is known. The satellite refrigerators near clinical areas where major haemorrhage can occur should have a stock of group O red cells. The exact specification of red cells will depend on the clinical specialities likely to use the emergency supply e.g. red cells for females of child-bearing potential less than 50 years of age should receive O RhD negative and Kell negative red cells.

Group-specific red cells. Determination of the ABO and D group is the main priority. Emergency grouping is often manual and the procedure must be risk assessed and additional safeguards put in place as outlined in the recent BCSH compatibility guidelines (Milkins *et al*, 2013). The result must be confirmed as soon as possible with routine methods if these differ from emergency procedures.

Antibody screening/cross matching

Blood may have to be issued without an antibody screen in an emergency. A retrospective antibody screen should be undertaken as well as routine compatibility procedures. If the antibody screen is subsequently found to be positive a recall

and reporting procedure should be in place so that the patient can be assessed for haemolysis. Once blood transfused in any 24-h period is equivalent to the patient's own blood volume, ABO and RhD compatible red cells can be issued without the need for serological cross-match, where this is part of the laboratory's routine procedure. It should be noted that in the emergency situation, red cells that, in normal circumstances might be considered unsuitable may need to be allocated.

Other blood components

If FFP is required urgently in a bleeding patient before the blood group is known then group A should be issued for adults. Data available from NHS Blood and Transplant shows that <3% of group A donors have high titre anti-B (Sheila MacLennan, personal communication, NHS Blood and Transplant). In a massively bleeding patient the risk of clinically significant haemolysis is likely to be very low (Zielinski *et al*, 2013; Chibber *et al*, 2014). In laboratories that investigate many massive haemorrhage cases, consideration should be given to having pre-thawed plasma on standby. At present this can only be used for up to 24 h post-thawing if stored at 4°C.

If platelets are required before the blood group of the patient is known, Group A should be used. RhD negative platelets should be used for females less than 50 years of age with unknown group. Hospitals with larger trauma units will need to consider the implications for inventory management of holding platelets for rapid use in emergencies. If cryoprecipitate is required before the blood group is known then group A should be issued.

In order to reduce the risk of prion transmission, it is recommended that non-UK plasma from countries with a low risk of variant Creutzfeld Jacob Disease is used for all patients born on or after 1 January 1996. Methylene blue-treated FFP, solvent detergent-treated FFP and methylene blue-treated cryoprecipitate are non-UK sourced with additional pathogen inactivation steps to also reduce the baseline risk of viral transmission. Apheresis platelets are also provided for this age group. It must however be emphasized that in emergency situations, it may not be possible to meet all standard neonatal/paediatric specifications. Accordingly, there should be a locally agreed concessionary release policy for acceptable alternatives for emergency use with a clear process for communication between the clinical and laboratory teams. More detailed guidance will be available in the forthcoming updated BCSH guidelines on paediatric and neonatal transfusion.

Staff capacity planning

There should be adequate numbers of appropriately trained laboratory staff to ensure transfusion safety (Chaffe *et al*, 2014). In an emergency situation there should be the capability to increase the number of staff through an escalation plan.

Stock management

There needs to be a robust system in place so that the transfusion laboratory staff are aware if the emergency group O red cells have been removed from a satellite refrigerator so that stocks can be replaced (electronic systems are ideal). Once the blood group of the patient is known, then stocks should be checked and appropriate supplies ordered, e.g., red cells, FFP, platelets and cryoprecipitate. In order to conserve O RhD negative stocks, consider substituting group O RhD positive red cells for O RhD negative in males and females aged 50 years or older. When MHPs are ordered, the separate components can be allocated and released when they are ready rather than waiting for all of the components to be ready before issuing.

Collection and storage

There should be a system in place to ensure that:

1 The patient's ID is documented at collection. This should be checked against the label attached to the components pack
2 There is a record of the person collecting the units
3 There is a record of the time the units are removed from the storage area.

If blood components are not required once received in the clinical area, then there should be mechanisms in place that:

1 Record the identity of the person returning the units
2 Record the date and time placed in storage location or returned to the laboratory

Unused red cells and FFP should only be returned to controlled refrigerated storage within 30 min of removal. If components have been out of their temperature control beyond this time, there should be a mechanism in place that removes these units from the supply chain. Platelets should be returned to the laboratory as soon as possible. If the unallocated emergency group O red cells are transfused, the laboratory must be informed and documentation for traceability i.e. identity of patient receiving the blood should be completed and returned to the laboratory. Emergency group O red cells should be clearly marked as such in satellite fridges and separated from other stock.

Traceability of blood and components

Hospitals must have systems for traceability, which also cover the use of blood and components in an emergency. The fate of any blood component must be documented in the clinical notes and in the Hospital Transfusion Laboratory records using the unique number of both the blood unit and the

patient. These records must be kept for 30 years for compliance with the Blood Safety and Quality Regulations (Department of Health, 2005).

Emergency planning – blood shortages

As part of contingency planning for national blood shortage situations, every hospital should have an Emergency Blood Management Plan in place that provides guidance on clinical priorities for the use of large volumes of blood components. This should include a mechanism for making decisions on an individual basis, taking into account such factors as co-morbidity, potential for control of bleeding, reversal of the underlying cause and competing demands for available blood components (http://hospital.blood.co.uk/business-continuity/contingency-planning/).