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GUIDELINE

Haematological management of major haemorrhage: a British Society for Haematology Guideline

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METHODOLOGY

This updated guideline[1] was compiled by a writing group selected to be representative of UK haematology/transfusion experts, according to the British Society for Haematology (BSH) process at [https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf].[2] An updated search (PubMed and Embase) for articles (in English, only human studies) published from July 2014 up to March 2020 was undertaken by the BSH information specialist using the terms 'bleeding' and 'haemorrhage' combined with 'management' and 'trials'. Systematic reviews were identified[3] and cross-checked by searching the National Health Service Blood and Transplant Systematic Review Initiative Transfusion Evidence Library. A total of 530 citations were screened (L.G., S.J.S.) of which, 365 citations were excluded as they were narrative reviews, case-reports, case series (without comparator groups), and studies of anticoagulation reversal; 65 citations were trial protocols; and four citations were duplicates. A total of 96 citations were included and reviewed by the members of the writing group. We reviewed a recent clinical practice guideline from the European Society of Intensive Care Medicine,[4] and recent UK Serious Hazards of Transfusion (SHOT) haemovigilance reports.[5] The writing group focused on systematic reviews and randomised controlled trials (RCTs) to formulate recommendations, although recognising that the literature underpinning laboratory and organisational aspects would likely be based on observational studies and descriptions of practice, rather than interventional trials. In areas where the evidence base was limited, the writing group presented pragmatic guidance. The following areas were considered beyond the scope of this guideline: techniques for resuscitation, surgical, radiological and endoscopic interventions to control

and monitor bleeding, the use of crystalloids and colloids for fluid resuscitation. Recommendations on thromboprophylaxis were also not considered in this guideline, but the authors recognised the importance of this topic, noting that trauma patients have high rate of hospital-acquired venous thromboembolism. The scope of this guideline included the emerging practice of pre-hospital transfusion and emergency transfusion in the context of mass casualty events (MCEs).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations (http://www.gradeworkinggroup.org).[6] The guideline was reviewed by the BSH Guidelines Committee Transfusion Task Force, and Thrombosis & Haemostasis Task Force, and placed on the members section of the BSH website for comments. Readers are referred to linked BSH guidelines on transfusion support in children and the use of viscoelastic haemostatic assays (VHAs).[7,8]

Background

Major haemorrhage is a clinical emergency that results in morbidity and mortality: practice guidance is important to reduce these risks. Delayed recognition of bleeding continues to be one factor for adverse outcomes in the management of major haemorrhage, as described in a recent SHOT report.[5] This guideline mandates a multidisciplinary approach involving the close working between laboratories, and clinical departments enabling a timely, targeted approach to transfusion support. The following sections consider the evidence for practice by components, major haemorrhage protocols (MHPs) and specific clinical settings.

Definitions

There is a spectrum of severity and presentation of major haemorrhage, which at one extreme is seen as acute major blood loss associated with haemodynamic instability and risk of shock, but also those in whom the bleeding appears controlled but still require 'massive' transfusion. Variable definitions of major haemorrhage continue to be used in the literature based on volumes of blood loss, or volume of blood transfused over a period.[9] These are retrospective definitions, arguably arbitrary, and difficult to apply in the acute situation. The current trend is towards the use of a more anticipatory or dynamic definition for major haemorrhage, based on the clinical status of the patients, their physiology and response to resuscitation therapy,[10] e.g., heart rate >110 beats/min and/or systolic blood pressure <90 mm Hg. It is important to emphasise that these physiological changes may be masked in some patient groups, e.g., the elderly or pregnancy,[11–13] potentially delaying diagnosis. The overall clinical and organisational context determines the transfusion thresholds, targets and testing. Further details of the organisational aspects are in the Supplement.

A. Use of blood components

Red blood cells (RBCs)

Haemoglobin concentration (Hb) is a surrogate measure of oxygen transfer to tissues. It is unlikely that a single universal target can be defined for all patients even with similar causes of major haemorrhage. This guideline makes general recommendations for RBC transfusion in patients with major haemorrhage, at a level to provide critical life-saving support, based on clinical judgement of the severity of bleeding, and informed by the findings of RCTs as discussed later.[14–16] Although RBC transfusion is a potential lifesaving treatment, there are risks,[5] and unnecessary exposure to excessive RBC transfusion should be minimised.

Repeated measurement of Hb through a central laboratory in a patient receiving crystalloids and fluids may not provide sufficiently timely or valid measures of RBC requirements in the face of major bleeding. RBC transfusion is usually required when 30%–40% of blood volume is lost (1500 ml in a 70 kg male). More than 40% blood volume loss (1500–2000 ml) is life threatening and requires immediate transfusion.[17] The rates of RBC (and plasma) transfusion is guided by the rate of blood loss and the degree of haemodynamic compromise, aiming at maintain critical perfusion and tissue oxygenation.[18] Haematologically, the purpose of using RBCs is to maintain Hb at a level high enough to support adequate oxygen delivery to the tissues (pragmatic target range 60–100 g/l in the face of major bleeding[19,20]). Blood should be transfused through a warming device to minimise the development of hypothermia. Rapid infusion over 5–10 min may be required, which may be facilitated using appropriate infusion devices designed for the purpose. Once bleeding is controlled, there is no indication to restore Hb to physiological levels.

Fresh Frozen Plasma (FFP)

Plasma provides a balanced source of all coagulant factors and volume expansion. In vitro data show it may have additional actions, including a protective effect on the endothelium.[21] FFP has been used as the component of choice to manage the coagulopathy of bleeding, although it is not the optimal therapy for low fibrinogen. While data support the role of early empirical use of plasma in major traumatic bleeding, in non-trauma settings the effect of high transfusion ratios of RBC and FFP on mortality is uncertain due to lack of clinical trials to assess its utility. Differential effects on mortality have been reported by ratio of RBC and FFP depending on clinical setting.[22,23] In the absence of any tests of coagulation, low ratios of empirical RBC to FFP (defined pragmatically as >2:1), with a marked excess of RBC units, should be avoided in major bleeding. After initial empirical transfusion of FFP, further plasma transfusion should be guided by serial results of coagulation tests and/or near-patient tests, which may include VHAs (for information on thresholds see BSH guideline[8]).

We suggest a general weight-adjusted recommended dose of FFP of 15–20 ml/kg, although recognising that attempting to correct coagulopathy in the face of major bleeding is challenging, and that large-volume transfusions of FFP would be required for above average body weights.[24]

Fibrinogen replacement

Hypofibrinogenaemia is common in major haemorrhage,[25,26] but there is very limited evidence to define critical levels of fibrinogen on which to base decisions to administer fibrinogen, or the role of early empirical supplementation. In patients with critical hypofibrinogenaemia (<1 g/l). FFP contains insufficient fibrinogen to achieve the rapid rise in levels required to support haemostasis, and supplementation in the form of cryoprecipitate or fibrinogen concentrate should be offered.[27]

A number of RCTs of fibrinogen supplementation have been reported in bleeding after cardiac surgery, with inconsistent results.[28,29] Clinical data do not support one form of concentrated fibrinogen replacement over the other (i.e. cryoprecipitate or fibrinogen concentrate) and there is a paucity of cost-effectiveness comparative research between fibrinogen concentrate and cryoprecipitate.[30,31] A RCT comparing the efficacy of fibrinogen concentrate with cryoprecipitate in patients undergoing cardiac surgery who developed clinically significant bleeding and hypofibrinogenaemia reported that fibrinogen concentrate was non-inferior (but not superior) to cryoprecipitate with regard to number of blood components transfused in a 24-h period post-bypass.[32]

Cryoprecipitate is the standard concentrated source of fibrinogen in the UK. Two five-donor pools may increase fibrinogen in an adult by ~1 g/l, although recognising the limitation of a non-weight adjusted dose and that the (sustained) increase in fibrinogen in patients with bleeding may be less.[33,34] Fibrinogen concentrate may also be considered as an alternative for management of bleeding in patients: 4–5 g of fibrinogen concentrate may increase fibrinogen in an adult by ~1 g/l.[32,35,36]

Platelets

A measure of platelet count does not provide an assessment of platelet dysfunction seen in patients with shock and hypotension. Significant thrombocytopenia is considered a late event in major haemorrhage, typically seen after a loss of at least 1.5 blood volumes.[37] As a pragmatic approach in cases of major bleeding, it is suggested that platelet transfusion should be given to maintain the platelet count at $>50 \times 10^9$/l, although higher thresholds may be indicated in patients with intracranial/spinal bleeding, or in actively bleeding patients with falling platelet counts.

Patients presenting with major bleeding may be on antiplatelet medications. Platelet transfusions have been considered a safe and potentially effective intervention in major haemorrhage in these patients. The results of the PATCH trial demonstrated that platelet transfusion increased the risk of death in patients receiving antiplatelet therapy (mainly aspirin) and presenting with acute spontaneous intracerebral haemorrhage (stroke),[38] although methodological limitations have been described.[39] It is unclear how these trial results should be applied to patients taking other types of antiplatelet agents, or those presenting with traumatic intracerebral haemorrhage or other types of major haemorrhage. Some data also support the cautious use of platelet transfusions in patients on antiplatelet therapy with gastrointestinal bleeding.[40]

B. Major haemorrhage protocols and transfusion testing

Establishment of MHPs form the basis of standardising transfusion support for bleeding patients. A MHP is a site-specific protocol that outlines the processes, people and blood components required to treat a patient who is bleeding. The MHP is a treatment algorithm that pre-specifies the order and ratios of how different blood components (or products) can be delivered to treat the bleeding in different clinical contexts, and are widely available in NHS hospitals.[5,41] MHPs enable rapid provision of blood components to a bleeding patient through agreed communication channels between clinical staff and the transfusion laboratory without escalation for approval.[1,42] The local MHP must identify the location of emergency blood components (RBCs, plasma and platelets) and provide clear instructions on how to access these during a major bleeding event.

While it seems intuitive that rapid and early transfusion of blood components in bleeding patients will improve survival, the impact of protocolised management (through use of MHP) on outcomes of bleeding patients and healthcare resources, has not been fully established, although there may be some evidence of clinical benefit.[42] Irrespective of the levels of evidence for transfusion support, the management principles of major haemorrhage are those of any medical emergency, where communication and co-ordination are key to optimising the delivery of a safe and effective transfusion response and enabling better use of resources.

The MHP should state the details required to activate the transfusion emergency response by providing appropriate contact numbers (through the switchboard) including the terminology for alerts that should be distinct and easily identifiable. Communication with the laboratory should be timely and targeted. A structured approach to communication between the clinical and laboratory areas is recommended (see Table S1).

Red blood cells should be readily available for life-threatening bleeding, including prompt access to group O RBCs as emergency stock. Where appropriate, NHS organisations and laboratories should risk assess the need for having pre-thawed plasma available to speed up plasma provision during major haemorrhage, particularly for trauma patients. Blood may be provided remotely to clinical areas through remote blood fridges or validated blood-boxes, to facilitate timely delivery of RBCs, which should be supported by a quality management system and governance

framework. Accurate documentation of blood components transfused is necessary to comply with the legal requirement for full traceability.[43] Laboratories should be informed when patients are moved rapidly between departments and hospitals (e.g. theatre, radiology, or transfer to another hospital). Deactivation of the MHP is also important, as delays in standing down the MHP will lead to blood wastage and prevent resumption of other laboratory services.

Baseline blood samples for an ABO group and antibody screen should be taken as early as possible, and ideally before the start of the first transfusion. Accurate patient and sample identification are fundamental to providing safe transfusion, to avoid the accidental administration of ABO incompatible RBCs. Wrong blood in tube continues to be the commonest near miss events reported to SHOT, occurring more frequently in the emergency setting.[44,45] All patients receiving a blood transfusion must wear a patient identification wristband. Further details on laboratory aspects are provided in supplementary pages.

C. Tranexamic Acid (TXA)

A meta-analysis of 216 trials (125 550 patients) found no evidence to support an overall increased risk of thromboembolic complications with use of TXA, supporting the general safety of this drug.[46] Large, pragmatic RCTs have compared TXA with placebo for the management of bleeding, establishing the benefits of TXA, with reductions in mortality in trauma and postpartum haemorrhage (PPH).[47-49] A meta-analysis of two trials showed that immediate treatment improved survival by >70% and thereafter, the survival benefit decreased by 10% for every 15 min of treatment delay until 3 h, after which there was no benefit.[50] In an effort to give TXA as early as possible, prehospital use is now supported by ambulance services in the UK. Current research is evaluating alternative doses and formulations including intramuscular TXA.[51,52] which appears more feasible for timely administration in emergencies.

D. Other haemostatic agents

Different haemostatic agents have been evaluated for benefit in major haemorrhage, including prothrombin complex concentrate (PCC), aprotinin and recombinant activated factor VII (rVIIa). Calcium levels should be monitored and supplemented as appropriate.

Prothrombin complex concentrate

Systematic reviews have identified few RCTs on the use of PCC versus FFP in adult patients with major bleeding.[31,53] While the use of PCC is safe and recommended for urgent reversal of the effect of vitamin K antagonists,[54] there is currently limited evidence to support its use in the management of major haemorrhage not related to vitamin K antagonists. Two pilot RCTs in cardiac surgery have recently been published; both were underpowered for clinical outcomes, but no safety concerns were observed.[55,56]

Aprotinin

Aprotinin is a serine protease inhibitor with multiple effects, including antithrombotic, antifibrinolytic and anti-inflammatory actions. Although efficacious in reducing bleeding in cardiac surgery, its license was suspended in 2007 following concerns about its safety, but it was later reinstated following a re-evaluation,[57] with a revised indication applies for the prevention of bleeding in adult patients at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery. Aprotinin is a bovine protein and there is a risk of allergy.

Desmopressin

Randomised controlled trials have assessed the role of desmopressin outside inherited bleeding disorders, including the perioperative setting and cardiac surgery.[58,59] Desmopressin increases the release of high molecular weight von Willebrand factor from the endothelium and has been considered as an alternative to platelet transfusions. Desmopressin has a good safety profile, although further data continue to be required including in older patients or those with cardiovascular risk factors.[60,61] Robust evidence of the clinical effectiveness of desmopressin (and/or with TXA) is not available and further studies in major bleeding are required.

Recombinant activated factor VII

Recombinant activated factor VII has been used widely 'off label' in bleeding after major surgery or trauma, but reviews of trial data have shown only modest reductions in total blood loss or transfusion requirements, with no consistent clinical benefit including mortality,[62] but an increased risk of arterial thromboembolism.[63]

E. Coagulation testing and cell salvage

Haemostatic testing and monitoring

The coagulopathy of bleeding is related to blood loss, consumption of coagulation factors, activation of fibrinolysis and haemodilution when resuscitation fluids are used.[64] Hypothermia, acidosis and hypocalcaemia will further worsen coagulation. Coagulopathy is associated with worse outcomes, and it is important to attempt its correction as part of the initial haemostatic resuscitation. We recommend performing coagulation tests and platelet counts every 30–60 min, depending on the severity of blood loss, until bleeding ceases. There is a need

to regularly undertake and improve rapid turnaround times for coagulation results in a major haemorrhage setting and we suggest these times should be regularly audited.[65]

It is important to establish early in the course of bleeding whether a patient has taken anticoagulant or antiplatelet agents, as these medications will further exacerbate bleeding. Mortality rates are high in patients with major bleeding on oral anticoagulants. Detection of oral anticoagulants or antiplatelet agents are challenging by routine testing, although types of rapid tests may be applied.[66,67] A reliable medication history remains key.

The method of assessing coagulation varies between institutions, some relying on standard coagulation screens others on near patient VHAs, including thromboelastography or rotational thromboelastometry (for thresholds for VHA, please refer to guidelines[8]). Repeated testing, with comparisons made between longitudinal tests, provides more information than a stand-alone VHA tests to aid the decision for plasma and other component transfusion.[65] Point-of-care whole blood coagulation tests for the prothrombin time 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 prothrombin time (PT-derived fibrinogen), as some of these methods give falsely high functional levels.[68]

Data to evaluate the impact of the use of VHAs on clinical outcomes in the bleeding patient[8,69–71] remain limited outside cardiac surgery and trauma.[35,72] VHA testing is less sensitive to measuring fibrinolytic activation in trauma and should not be used to withhold the use of TXA.[73]

Cell salvage

Cell salvage can produce a rapid re-supply of RBCs, with 250 ml of washed salvaged RBCs considered to be equivalent to 1 RBC unit, but requires a 24-h service to cover all emergencies.[74–76] In a RCT of >3000 women at risk of PPH, the use of cell salvage did not reduce the rate of blood transfusion, and was reported not to be cost-effective (in this context, cell salvage may also be associated with risks of increased maternal exposure to fetal blood in RhD-negative mothers).[77] Further studies continue to be needed in other clinical setting to demonstrate the (cost-) effectiveness of cell savage in the management of major bleeding. Cell salvage in emergency trauma surgery may reduce overall transfusion needs, but without an impact on overall mortality and costs.[78]

F. Specific clinical settings including emergency planning

Obstetric haemorrhage

A PPH is usually defined as an estimated blood loss of >1000 ml during a Caesarean section, or >500 ml after a vaginal birth.[13] Severe PPH of >1500 ml remains a leading cause of early maternal death and morbidity, and obstetric management should consider prevention and management including uterotonics for uterine atony and surgery.[13,79,80] There are limited RCT data on optimal strategies for RBC transfusion in obstetric bleeding,[16,81] and we suggest following general recommendations.

Overall, a coagulopathy develops only in a minority of women with PPH,[82] but is difficult to predict, and needs urgent identification and management to prevent bleeding becoming overwhelming. There is evidence that patterns of haemostatic responses differ by cause of bleeding in PPH.[83] The cut-off thresholds for defining an abnormal PT/activated partial thromboplastin time (APTT) are typically based on non-pregnant individuals and do not take into consideration the rise in clotting factors seen during pregnancy and therefore a mildly elevated PT or APTT, should it develop, can represent a more significant haemostatic deficit during PPH. Serial monitoring of coagulation tests is recommended. The evidence on the optimal ratios of RBCs to plasma in PPH remains unknown, and further studies are needed.

Fibrinogen levels increase during pregnancy (range of 4–6 g/l at delivery vs. 2–4 g/l when non-pregnant). A low fibrinogen level during PPH is an important predictor of the severity of PPH and poor clinical outcome.[84,85] RCTs do not support the early unselected use of fibrinogen concentrate replacement therapy,[86,87] and administering fibrinogen supplementation to women with PPH who have fibrinogen levels of >2 g/l is unlikely to have added benefit.[88] A recent pilot cluster RCT in severe PPH highlighted practical challenges around the early delivery of cryoprecipitate in PPH, and further trials are required to evaluate clinical outcomes.[89]

A quality improvement programme has described the role of a 'bundle of care' in PPH management (measurements of blood loss after delivery, escalated care to senior staff, timely VHA point-of-care guided fibrinogen concentration, and risk assessments) to successfully reduce transfusion requirements.[90]

The WOMAN trial showed that TXA reduces bleeding deaths and need for surgery in women with PPH.[91] However, prophylactic use of TXA did not show any benefit in a large study of women delivering vaginally who were randomised to 1 g TXA versus placebo in addition to oxytocin after delivery.[92] In both studies there were no increased rates of thrombosis.

Gastrointestinal haemorrhage

A common indication for transfusion is acute gastrointestinal bleeding.[93] The initial management of gastrointestinal bleeding involves fluid and transfusion resuscitation with pharmacological therapies and timely access to endoscopy or definitive interventional procedures.

Red blood cell transfusion policies in the haemodynamically stable patient with acute gastrointestinal bleeding have been defined by RCTs including a trial that reported a higher 6-week survival and lower re-bleeding rate in patients allocated to a restrictive threshold for RBC transfusion at Hb of 70 g/l (patients

with exsanguinating bleeding were not eligible).[14,16,94] Portal pressures were reported to be increased significantly in patients with acute variceal bleeding allocated to the liberal transfusion group. A meta-analysis across all trials reported a significant reduction in all-cause mortality and re-bleeding with restrictive transfusion practices, with no increase in ischaemic events.[6,15]

There are limited prospective studies characterising changes in coagulopathy or thrombocytopenia in gastrointestinal bleeding. In this patient population, especially those with liver disease and cirrhosis, rapid changes to vascular pressures are not desired, and there are concerns about the use of excessive plasma transfusions to achieve arbitrary reductions in PT.[95] Recent retrospective studies have described an association between use of FFP with adverse clinical outcomes, and with use of platelets in patients with gastrointestinal bleeding taking antiplatelet agents.[40,96] The results of a pragmatic trial of TXA in patients with acute gastrointestinal bleeding reported an increased risk of venous thrombosis and seizures.[97] Reasons for this result could be due to the dose and schedule for TXA (given over 24 h), and that hospital presentation in these patients may occur many hours after the onset of bleeding, missing the period where there is excess fibrinolytic activation. Patients with gastrointestinal bleeding are typically older than trauma patients and have different comorbidities including liver disease.

Trauma including pre-hospital management

The mortality rate after major haemorrhage in trauma is high unless actively managed. Transfusion support, as part of 'Damage Control Resuscitation' (DCR), is now closely integrated with all other aspects of resuscitation including haemorrhage control and surgery. Early and pre-hospital use of TXA has been discussed earlier. Time to initial transfusion is critical in trauma.[98] Early pre-hospital transfusion, before patients arrive to hospital, may improve survival, although the evidence is inconclusive and patterns of blood component use are variable.[99–101] More recently, the RePHILL trial did not show that pre-hospital RBC–LyoPlas resuscitation was superior to saline (0·9% sodium chloride) for adult patients with trauma-related haemorrhagic shock.[102] The trial had limitations including the composite primary outcome and wide confidence intervals for results. Two other RCTs reported on the effect of pre-hospital plasma transfusion on patient outcomes, including mortality, with contrasting results, one cluster trial reporting that pre-hospital plasma use led to 30-day mortality that was 10% lower compared to the standard-care group,[103] while the other individual patient randomised trial found no difference.[104] The differing results may be explained by factors including different transport times and type of injury.[105,106]

The use of RBCs in trauma follows the general principles of shock mitigation and support of Hb. The updated European Guidelines[4,17] recommend a target Hb of 70–90 g/l based on data extrapolated from the TRICC study, which retrospectively analysed a subgroup of trauma patients.[107,108] The RePHILL study showed that despite significant injury few patients (6%) receiving saline had a Hb of <80 g/l on arrival at hospital.[99] The average age of patients with traumatic major bleeding is increasing,[109] and more patients aged >60 years are being seen alongside younger patients. Some older patients have comorbidities including cardiac disease, which may affect the selection of Hb thresholds for RBC transfusion in major bleeding due to trauma.[16,110]

A significant proportion of trauma patients with major bleeding present early with coagulopathy, typically defined by abnormalities of PT,[111] which is associated with increased mortality. Early empirical plasma transfusion has been advocated to manage coagulopathy and prevent deterioration of coagulation, although methodological limitations, including survivorship bias, have been recognised in many earlier studies.[3,112] The PROPPR trial[113] reported no difference in overall survival between early administration of plasma, platelets and RBCs in a 1:1:1 ratio compared to 1:1:2 ratio; however, more patients in the 1:1:1 group achieved 'anatomic' haemostasis and fewer experienced death due to exsanguination by 24 h, although the results of the post hoc analyses has been challenged.[3,114] A smaller trial compared fixed high-dose ratios (including platelets) against laboratory testing in trauma, and established feasibility but demonstrated wastage of blood.[115] Overall, we recommend that plasma and RBCs are given initially in a 1:1 ratio (and not less than 1:2) in major traumatic bleeding, until bleeding is under control and the results of coagulation tests are available to guide further transfusion. The iTACTIC RCT in trauma bleeding patients tested whether augmenting MHPs with VHA versus Conventional Coagulation Tests, would reduce mortality or massive transfusion at 24 h; results showed no difference in overall outcomes between the two groups.[116] The thresholds for the VHA parameters used for viscoelastic tests in this trial in trauma are reproduced in a supplementary table.

Many patients with trauma have levels of fibrinogen at hospital admission around 1 g/l, which may rapidly fall further in the event of on-going blood loss.[117] The CRYOSTAT-2 trial is evaluating the effects of early empirical high-dose cryoprecipitate in adult patients with major trauma haemorrhage requiring MHP activation versus standard of care.[118]

The management of patients with traumatic brain injury (TBI) is distinct from general trauma, that may include (small volume) bleeding or re-bleeding occurring in a critical site. However, many patients with TBI have co-existing general injuries and may present with major bleeding. Optimal transfusion support in TBI is poorly defined. A factorial RCT in TBI reported that neither erythropoietin nor transfusions to maintain Hb concentration above 100 g/l resulted in improved long-term functional outcomes, and liberal transfusion threshold were associated with more adverse events.[119] By contrast a pilot trial that randomised patients with TBI to a restrictive (Hb threshold 70 g/l) versus liberal (Hb 90 g/l) transfusion strategy, reported higher hospital mortality in the restrictive group.[16,120] The presence of coagulopathy in TBI is associated with more severe injuries and increased morbidity and mortality[121] and early coagulation testing is advised.

The utility of antifibrinolytics in trauma is defined by the CRASH-2 trial,[47] and trauma induces a massive fibrinolytic

activation, the extent of which relates to the degree of injury; crucially, the benefits of TXA are not restricted to patients with only the more severe injuries, and TXA is effective in minor bleeding across all ages (patients with low baseline risk of death).[122] Strategies for TXA use need to recognise that women may be less likely to be treated with TXA.[123] The CRASH-3 trial (subgroup analyses) in adults with TBI (intracranial bleeding on computed tomography [CT] scan, and no major extracranial bleeding), reported that treatment with TXA reduced head injury-related death in patients with mild-to-moderate head injury.[49] A further RCT evaluated different dosing regimens for pre-hospital TXA in TBI, reporting no overall benefits for functional neurological outcomes at 6 months.[124] The role of TXA in other contexts, such as sub-arachnoid haemorrhage and non-traumatic intracranial bleeding is not clearly established by randomised trials.[125,126]

Different blood products continue to undergo evaluation in clinical studies, particularly in trauma. Lyophilised plasma offers logistic advantages but requires reconstitution. There may be human factor advantages of administering whole blood over separated blood components, but this remains an area of active research to establish effectiveness.[127-129] Cold-stored low-titre type O whole blood is under investigation in the UK and has a shorter shelf life (14–21 days) than RBCs in optimal additive solutions.[130] Finally, extending the use of blood for major traumatic haemorrhage into the pre-hospital environment may seem clinically intuitive,[131] but has significant implications for transfusion laboratory services at a local and national level.[131] Such challenges include the demand for use of 'universal' blood group components, the potential for wastage, and the need for regulatory compliance and associated workload.[132] Further information on the selection of blood for pre-hospital transfusion and transferring of blood between hospitals is provided in the Supplement.

Surgery

Major bleeding in the setting of surgery is generally managed in theatres rather than emergency departments, with support staff on-site including surgeons and radiology, and timely access to laboratory coagulation monitoring, which would inform the need for further blood components in addition to RBCs. In the absence of coagulation testing, an ideal ratio of RBCs to FFP, has not been defined due to lack of RCTs.[23] A large observational study in cardiac surgery patients assessed the impact of different FFP to RBC ratios in patients who had received massive transfusion (defined as ≥8 RBC units): patients with a high FFP:RBC ratio (>1:1) had improved 30-day survival when compared with those with a low ratio (<1:2), and high transfusion ratios appeared to be associated with fewer complications.[133]

Evidence that TXA reduces blood transfusion needs in surgery has been available for many years,[134] including the recent POISE-3 trial, which reported a significantly lower incidence of a composite bleeding outcome in non-cardiac surgery patients receiving TXA.[135] Information on doses of TXA as prophylaxis prior to surgery with anticipated moderate blood loss is also provided in the National Institute for Health and Care Excellence transfusion guidelines; higher doses have no greater haemostatic effect and may be associated with seizures.[136,137]

Emergency planning and mass casualty events

National emergency planning requires healthcare organisations to assess that they can deal with incidents while maintaining critical services. Organisational preparation aims to ensure an overall co-ordinated approach together that includes a good transfusion response. Many events can challenge transfusion services, including MCEs, and pandemics.[138] As part of contingency planning for any national blood shortage, every hospital should have access to the national guidance and triage tool for cellular components.[139] Hospital should also have established emergency blood management arrangements, or equivalent arrangements such as an independent multidisciplinary clinical triage team to provide further support in the context of severe blood shortage.[140,141] This should include a mechanism for making decisions on an individual basis, considering factors such as comorbidity, potential for control of bleeding, reversal of the underlying cause and competing demands for available blood components. In mass casualty events, all injured patients should receive tranexamic acid as soon as possible, which might be provided more feasibly as an IM injection as part of triage.

The aim of transfusion support during MCEs is to supply sufficient prompt blood components and diagnostic services, whilst maintaining support to other patients not involved in the event.[142] Identification of patients in need of emergency blood transfusion is a key priority of triage. Typically, the number of patients requiring massive transfusion following MCEs is low, but this cannot be predicted.[140] Evidence suggests an estimate of 2–4 RBC units per patient for all hospitalised casualties admitted with bleeding,[143,144] although the total may be increased with additional haemostatic components for those severely injured admitted to Major Trauma Centres. Consideration should be given to transfusion triage to identify those needing activation of MHPs, so that pre-agreed numbers of RBCs and plasma can be issued to patients during MCE so that overall blood supply can be controlled optimally in this setting. Most blood components are initially ordered and used within the first 6 h, although some patients may have an ongoing demand for blood over days, especially where repeat surgery may be necessary.[145-147] The main risk during MCEs is assumed to be the accidental use of ABO incompatible blood, and policies described earlier should be followed.

G. Audit and Quality Management Education (refer to Supplement)

Review and audit of major haemorrhage management is essential to assess timeliness of providing blood to bleeding patients, patient outcome and overall blood component use and wastage, e.g., comparing practices to guidelines and

outcomes.[20] Where adverse incidents occur, they should be investigated locally, and reported externally to SHOT haemovigilance scheme as required. Staffing levels have been recognised as a risk factor for adverse events, and laboratory managers should consider the acceptable staffing resources required for MHP provision and have a clear staffing capacity plan in place, with escalation routes to management of potential risks associated with staff shortages.[148,149] Training and competency assessment, and annual drills of MHP systems including mechanisms for communication to laboratories and responses by laboratories provide an important means of review. Following MHP events, the teams should hold a de-brief, to address learning points from the event, including emotional support for staff, as required.[150,151]

H. Conclusions and future research

The major risks in emergency settings of bleeding remain delays in identification of the bleed, activation of MHP and timely provision of blood components. The evidence and practice recommendations in this guideline emphasise the need for protocols that are increasingly targeted for different clinical contexts of major bleeding. A single universal or common approach to the management of all types of bleeding patients is not optimal. There is a need to conduct research on transfusion strategies for bleeding patients other than due to trauma (obstetrics, gastrointestinal, surgery), as well as to better understand the efficacy, safety and cost effectiveness of different haemostatic agents and cell salvage to manage major bleeding.

Organisational oversight by the Hospital Transfusion Committee and Patient Blood Management teams is integral for audit, governance, and growth of effective and safe transfusion support in emergencies, and implementation of a MHP.[152] An integrated electronic pathway from the Blood Service operator to the hospitals will further enhance the transfusion response during emergencies making it simpler, safer, and more resilient. The design and ongoing development of the MHP should be considered a dynamic process to allow for future evidence and developments in components/products, policy, and practice.[153,154]

RECOMMENDATIONS

General recommendations

- Hospitals must have local MHPs in relevant clinical areas that includes a clear mechanism for contacting all relevant team members and support staff. (2C)
- Clinical staff involved in frontline care must be trained to recognise major blood loss early, be familiar with the contents of MHPs and know when to activate and deactivate the local MHP. (2B)
- Hospitals must have a strategy to ensure that emergency 'universal' RBCs are readily available for treatment of life-threatening bleeding, including prompt access to group O RBC as emergency stock. Group O RhD- and K-negative RBCs should be prioritised for females of childbearing potential (aged <50 years) and in patients whose sex is unknown. (2B)
- We recommend a standard threshold and target Hb range for RBC transfusion to provide critical life-saving support in major bleeding alongside clinical judgement on the severity of bleeding (threshold Hb 70 g/l, target range for the post-transfusion HB level of 70–90 g/l. (1B)
- If major bleeding is on-going and results of standard coagulation tests or near-patient tests are not available, we suggest that units of FFP be transfused in at least a 1:2 ratio with units of RBCs. (2B)
- If major bleeding is on-going, and laboratory results are available, we suggest further FFP be administered aiming to maintain the PT ratio at <1.5-times mean normal (or equivalent). (2C)
- We suggest that serial haemostatic tests should be checked regularly, every 30–60 min depending on the severity of the haemorrhage, to guide and ensure the appropriate use of haemostatic blood components. (1B)
- We suggest fibrinogen supplementation should be given if fibrinogen concentrations fall below 1.5 g/l (non-pregnant women). (2B)
- If major bleeding is on-going, we suggest using platelet transfusions to maintain platelet counts at $>50 \times 10^9$/l. (2C)
- We suggest that VHAs are used to guide transfusion therapy in cardiac surgery, although for other clinical settings of major bleeding (e.g. trauma and PPH), hospitals should evaluate the costs and benefits of running these assays and ensure policies are in place to maintain these devices on a daily basis. (1B)

Recommendations—alternatives to transfusion

- Tranexamic acid is recommended for patients with presentations of major bleeding due to trauma and PPH, but not gastrointestinal bleeding. (1A)
- Current evidence does not support the universal policy of 24-h cell salvage for patients with major bleeding and hospitals should evaluate the costs and benefits of running the cell salvage service. (1B)
- The use of cell salvage should be considered for patients who refuse to have blood transfusion. (1B)
- The use of desmopressin, rVIIa or aprotinin is not recommended in the management of major haemorrhage unless as part of a clinical trial. (1B)

Recommendations—specific settings

Postpartum haemorrhage

- In patients with PPH, general recommendations for RBC and plasma transfusion should apply. (2A)
- Special attention should be paid to identifying women with PPH who develop a coagulopathy and/or low

fibrinogen levels. Use of fibrinogen supplementation is recommended in PPH, especially when there is ongoing bleeding and if fibrinogen levels are <2.0 g/l. (2B)
- We recommend that an initial dose of TXA (1 g intravenously) is given to women with PPH within 3 h of bleed onset. If bleeding continues after 30 min, or it stopped and restarted within 24 h of the first TXA dose, a second dose of 1 g should be given. (1A)

Gastrointestinal bleeding

- In patients with gastrointestinal haemorrhage, general recommendations for RBC transfusion should apply. (1A)
- Special attention should be paid to heightened risks of raising vascular pressures with excessive plasma transfusions and the limitations of standard coagulation tests to monitor coagulation status in patients with liver disease. (2B)
- Tranexamic acid is not recommended for patients with acute gastrointestinal bleeding. (1A)

Trauma

- There are insufficient clinical data to support a role for pre-hospital transfusion resuscitation with RBCs and plasma, but if considered, it should not unduly add to transport delays to hospital. (2C)
- We recommend plasma should be given early as part of initial resuscitation in major haemorrhage due to trauma, and in a 1:1 (not >1:2 ratio) with RBCs, until results from coagulation monitoring are available. (1B)
- Fibrinogen supplementation should be given to patients with traumatic injury if fibrinogen levels fall to <1.5 g/l. (1B)
- Patients with traumatic injury (including mild–moderate TBI) should be given TXA as soon as possible after injury (and no later than 3 h); a suitable regimen includes 1 g bolus dose intravenously over 10 min, followed by a maintenance infusion of 1 g over 8 h should be used. (1A)

Surgical bleeding

- In major bleeding during/after surgery, general recommendations should apply, for RBC transfusion and other blood components. (2C)
- Timely and repeated access to laboratory coagulation monitoring should be available and inform the need for blood components including plasma. (2C)
- It is recommended that all patients having in-patient surgery should receive 1 gram of tranexamic acid prior to skin incision to reduce major surgical bleeding and reduce the need for blood transfusion. (1A).

Recommendations—mass casualty events

- The laboratory should have systems in place to identify and prioritise the testing of group and screen samples from major haemorrhage cases, patients receiving pre-hospital transfusion and severely injured patients during MCEs). (2C)
- Hospital Transfusion Teams should be engaged with local MCEs planning, scenario training, skills and drills, which include effective policies for extended use of TXA. (2C)
- Effective systems should be in place for major haemorrhage management in the context of blood shortage and/or MCEs. Modified MHPs or tailored transfusion should be considered together with triage during blood shortage or MCEs to optimise the use of blood and support blood stocks management. (2C)
- Transfusion Teams should be aware of their hospital's predetermined casualty load and their regional incident response plan to aid with stock and staff planning. (2C)

GOOD PRACTICE STATEMENTS FOR LABORATORY/ ORGANISATIONAL SUPPORT

- Major haemorrhage protocols should be reviewed at least annually, or whenever there are changes in guidance, or new evidence becomes available to suggest change of practice. Where MHPs are not used frequently through 'live' events, they should be tested periodically, at least annually, with regular drills, especially in areas known to be at greatest risk due to location or clinical speciality. (2C)
- The most significant adverse transfusion-associated event in emergencies is ABO mismatched transfusion. Robust patient and sample identification systems for unknown patients are essential to avoid errors in emergency and multiple casualty situations. All patients receiving a blood transfusion must wear a patient identification wristband containing the unique identifier. (2C)
- Hospitals must have clear policies on changing patient's Unique Identifier from 'Emergency' or 'Major Incident' identifiers to 'Routine' hospital Identifiers. (2C)
- Group and screen samples should be taken wherever possible before administration of the first unit of RBCs and samples must be labelled correctly. For hospitals supporting pre-hospital care with blood components, there should be a clear policy for how pre-transfusion samples are collected and labelled. (2C)
- The use of pre-hospital transfusion should follow the regulatory framework with special attention to cold chain monitoring and traceability (2C)
- The laboratory should have a clear protocol for when it is appropriate to convert to group-specific blood, including consideration of potential mixed field reactions caused by group O RBC transfusion. (2C)
- If a patient's blood group is unknown or unsure, universal components or appropriate substitutes should be used to avoid delays in issuing blood during major bleeding. (2C)
- Hospital transfusion laboratories should have a formal training and competency process evaluation,

covering all aspects of blood component provision for major haemorrhage cases and emergency stock management. (2C)

AUTHOR CONTRIBUTION

Simon J. Stanworth chaired the Guidelines Group, with Kerry Dowling for the laboratory aspects. Laura Green was the BSH Blood Transfusion Taskforce representative. All authors were involved in formulation, writing, and all authors approved the final version of the manuscript.

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CONFLICT OF INTEREST

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DISCLAIMER

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

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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