Patient blood management guideline for adults with critical bleeding

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Abstract

Introduction: The management of patients with critical bleeding requires a multidisciplinary approach to achieve haemostasis, optimise physiology, and guide blood component use. The 2011 *Patient blood management guidelines: module 1 — critical bleeding/ massive transfusion* were updated and published. Systematic reviews were conducted for pre-specified research questions, and recommendations were based on meta-analyses of included studies.

Main recommendations: The critical bleeding/massive transfusion guideline includes seven recommendations and 11 good practice statements addressing:

- major haemorrhage protocols (MHPs) facilitating a multidisciplinary approach to haemorrhage control, correction of coagulopathy and normalisation of physiological derangement;
- measurement of physiological, biochemical and metabolic parameters in critical bleeding/massive transfusion;
- the optimal ratio of red blood cells to other blood components;
- the use of tranexamic acid;
- viscoelastic haemostatic assays; and
- cell salvage.

Changes in management as a result of the guideline: The new guideline recommends MHPs be established as standard of care in all institutions managing patients with critical bleeding. In addition to routine physiological markers, the new guideline recommends temperature, biochemistry and coagulation profiles be measured early and frequently, providing parameters that define critical derangements. Ratio-based MHPs should include no fewer than four units of fresh frozen plasma and one adult unit of platelets for every eight units of red blood cells. In the setting of trauma and obstetric haemorrhage, administration of tranexamic acid within three hours of bleeding onset is recommended. The use of recombinant activated factor VII (rFVIIa) is not recommended. There was insufficient evidence to make recommendations on the use of viscoelastic haemostatic assays or cell salvage as part of MHPs.

Critical, or life-threatening, bleeding results in decreased circulating blood volume, loss of oxygen-carrying capacity, organ dysfunction, and coagulopathy. Critical bleeding remains a leading cause of death and years lived with disability.[1,2] Data from the Australian and New Zealand Massive Transfusion Registry showed that, between 2011 and 2015, 19.4% of patients who received a massive transfusion due to critical bleeding died while in hospital.[3] Improved outcomes in patients with critical bleeding have been associated with early recognition, haemorrhage control, regular assessment of the efficacy of therapy using clinical assessment of bleeding and monitoring of coagulation parameters.[4]

In 2011, the Australian National Blood Authority (NBA) published the *Patient blood management guidelines: module 1 — critical bleeding massive transfusion*. In 2016, the NBA convened a Clinical/Consumer Reference Group to review and update the guidelines to ensure they remain current and relevant to the Australian population. For this guideline, critical bleeding refers to major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion (ie, five or more units of red blood cells [RBCs] in four hours).[5,6] The final guideline was published online by the NBA in 2023.[7]

Methods

The revision of the guidelines followed methods outlined by the National Health and Medical Research Council (NHMRC)[8] and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.[9] The reference group consisted of experts in critical care medicine, emergency medicine, trauma, haematology and transfusion medicine and included a consumer representative.

In a series of meetings between September 2016 and June 2018, the reference group reviewed all research questions from the 2011 guidelines and considered the need to develop new questions. The nine research questions included in this update of the guidance are outlined in Box 1. Systematic reviews for each question were conducted based on methods described in the *Cochrane handbook for systematic reviews of interventions*[10] and relevant sections in the Joanna Briggs Institute's manual for evidence synthesis.[11] A summary of study designs eligible for each question is provided in Box 2. Case series with post-test or pre-test/post-test outcomes, cross-sectional studies and case reports were not eligible for inclusion.

For all questions, the population included patients who were critically bleeding, which is defined as people with decreased circulating volume, loss of oxygen-carrying capacity, or coagulopathy due to major haemorrhage that was life threatening and likely to result in the need for massive transfusion. There were no limits to age or ethnicity. Specific interventions for each research question are listed in Box 2.

The critical outcome measure to inform decisions on benefits was all-cause mortality reported at 30 days or at the latest measured time point. Other measures related to mortality (eg, death due to bleeding) were also recorded. The critical outcome measures to inform decisions on harms were related to morbidity, specifically thromboembolic events, acute respiratory distress syndrome, duration of mechanical ventilation, transfusion-related acute

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1 The 2023 critical bleeding guideline research questions

Question 1: In patients with critical bleeding, which physiological, biochemical and metabolic (including temperature) parameters should be measured early and frequently, and what values of these parameters are indicative of critical physiological derangement?

Question 2: In patients with critical bleeding, what is the effectiveness of major haemorrhage protocols?

Question 3: In patients with critical bleeding, what is the optimal dose, timing and ratio of red blood cells (RBCs) to blood component therapy to reduce morbidity, mortality and transfusion?

Question 4: In patients at risk of critical bleeding, is the transfusion of higher volumes of RBCs associated with an increased risk of mortality or adverse effects?

Q5: In patients with critical bleeding, what is the effect of recombinant activated factor VII treatment on morbidity, mortality and transfusion rate?

Question 6: In patients with critical bleeding, what is the effect of fresh frozen plasma, cryoprecipitate, fibrinogen concentrate, prothrombin complex concentrates and/or platelet transfusion on RBC transfusion and patient outcomes?

Question 7: In patients with critical bleeding, what is the effect of antifibrinolytics on blood loss, RBC transfusion and patient outcomes?

Question 8: In patients with critical bleeding, does the use of viscoelastic haemostatic assays change patient outcomes?

Question 9: In patients with critical bleeding, what is the effect of cell salvage on patient outcomes?

lung injury, transfusion-associated circulatory overload, and multiple organ failure. Important or critical outcome measures related to resource use included volumes of blood components transfused, wastage of blood components, time to delivery of blood components, and length of hospital or intensive care unit stay.

Detailed search strategies are available with the complete guidelines.[7] Search strategies were developed in Ovid (for Embase and MEDLINE) based on key elements of the research questions (ie, patients, intervention, comparison, or prognostic factors). The search strategy was then adapted to suit the Cochrane Library and PubMed (limited to in-process citations and citations not indexed in MEDLINE).

Methodological filters for identifying different study designs were applied, with exclusions for added publication type. In addition to the primary databases listed above, searches of OpenGrey, clinical trial registries (ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform), health technology assessment/government websites (National Institute for Health and Care Excellence, Canadian Agency for Drugs and Technologies in Health, and Agency for Healthcare Research and Quality), and guideline databases (Guidelines International Network and National Guidelines Clearinghouse) were conducted.

Additional trials or studies recommended by reference group members, and potentially relevant trials or studies and systematic reviews identified in a scoping report were also included if they satisfied the eligibility criteria and were published within the specified search period (last performed on 28 September 2021). Pivotal new evidence could also be referenced and used to inform good practice statements.

Covidence was used for screening citations and recording decisions.[12] At the title/abstract stage, one systematic reviewer independently screened each citation and discarded ineligible studies. Full text articles for possible inclusion in the evidence synthesis were assessed independently by two reviewers. Where uncertainty existed, a decision was made after discussion with the lead reviewer (MJ), or advice sought from the reference group.

Judgements about the quality of included systematic reviews or risk of bias within primary studies were made using assessment tools appropriate to the study design.[13-16] Data synthesis was performed by two reviewers (MJ and AM). Using RevMan 5.4, studies with matched cohorts reporting pre-specified outcomes were included for meta-analysis.[17] Effect estimates were combined across studies for each outcome

2 Summary of study types, participants and interventions

Question No.	Participants	Interventions	Study design features
1	People with critical bleeding	Physiological, biochemical and metabolic parameters	SR, observational cohort or single arm analysis of an RCT
2	People with critical bleeding	Major haemorrhage protocol	SR, RCT or observational cohort
3	People who received a massive transfusion	RBC:FFP ratio, RBC:PLT ratio, RBC:CRYO ratio	SR, RCT or observational cohort
4	People who were at risk of critical bleeding	RBC volumes	SR, observational cohort or single arm analysis of an RCT
5	People who failed to achieve adequate haemostasis despite surgical management and appropriate blood component therapy	rFVIIa administered as treatment	SR, RCT or observational cohort
6	People with critical bleeding	FFP, CRYO, PLT, FgC, PCC	SR, RCT or observational cohort with at least 500 participants
7	People with critical bleeding including a subgroup of patients who received a massive transfusion	Antifibrinolytics (TXA)	SR, RCT or observational cohort with at least 500 participants
8	People with critical bleeding, including subgroups of patients with trauma, obstetrics, perioperative and other settings	Use of VHA to guide transfusion of blood component therapy	SR, RCT or observational cohort
9	People in the emergency setting (not elective)	Cell salvage	SR, RCT or observational cohort

CRYO = cryoprecipitate; FFP = fresh frozen plasma; FgC = fibrinogen concentrate; PCC = prothrombin complex concentrate; PLT = platelets; RBC = red blood cell; RCT = randomised controlled trial; rFVIIa = recombinant activated factor VII; SR = systematic review; TXA = tranexamic acid; VHA = viscoelastic haemostatic assay. ◆

using Mantel–Haenszel random effects models, with data from randomised controlled trials (RCTs) and observational studies considered separately.

As per the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidance, the body of evidence was rated across five key domains: risk of bias, inconsistency, imprecision, indirectness, and publication bias.[18,19] For each domain, a judgement was made about whether there were serious, very serious or no concerns, resulting in an overall certainty of evidence (high, moderate, low or very low) for each outcome.

Recommendations were developed according to the evidence to decision process outlined by the GRADE working group[18,20,21] within MAGICApp (https://magicevidence.org/magicapp). The recommendations considered the benefits and harms, certainty of evidence, values and preferences, resources, equity, acceptability and feasibility.

Based on systematic reviews, the recommendations were graded as either strong or weak and for or against an intervention. Good practice statements were developed based on indirect evidence and expert opinion from the reference group.[22] The recommendations and good practice statements were reviewed by the reference group between November 2021 and September 2022.

Public consultation and external review

The draft guideline was advertised and published online for a six-week public consultation in September 2022. There were 26 public consultation submissions, and all were considered. No errors of fact or significant omissions of evidence were identified but the phrasing of the guideline and accompanying resources was clarified. The draft guideline was sent to two Australian reviewers, independent to the guideline development process, who used the AGREE II tool to assess the quality and usability of the guideline against international quality standards.

Recommendations and good practice statements

The recommendations are outlined below with a summary of the evidence for benefits and harms, certainty of the evidence and, where relevant, values and preferences for consumers, impact on resources, equity, acceptability and feasibility.

Recommendation 1. In patients with critical bleeding, it is recommended that institutions use a major haemorrhage protocol (MHP) that includes a multidisciplinary approach to haemorrhage control, correction of coagulopathy and normalisation of physiological derangement (*Strong recommendation*).

In the meta-analysis of cohort studies, a large beneficial effect on mortality (latest time point or all-cause) associated with MHPs was demonstrated; however, the certainty of evidence is very low (Supporting Information 1, figure S1). The magnitude of any benefit, therefore, remains uncertain (Supporting Information 1, table S1). The available evidence did not demonstrate an increase or decrease in the transfusion volume of RBCs or fresh frozen plasma (FFP) associated with MHPs in any setting, and in the absence of high certainty evidence, the resource implications of MHPs are uncertain (Supporting Information 1, tables S1–S3).

Good practice statement 1. The reference group agreed that it is essential to identify the cause of bleeding and control it as soon as possible. This reinforces the importance of early identification of the cause of bleeding and haemorrhage control. Specific strategies for haemorrhage control were outside the scope of this guideline.

Recommendation 2. In patients with critical bleeding requiring activation of an MHP, it is recommended that the following parameters be measured early and frequently: temperature, acid-base status, ionised calcium, haemoglobin, platelet (PLT) count, prothrombin time, international normalised ratio, activated partial thromboplastin time (aPTT), and fibrinogen levels, in addition to standard physiological monitoring (*Strong recommendation*).

The identified cohort studies suggested an association between prognostic factors and an increased risk of mortality (Supporting Information 1, tables S4–S11). However, the overall certainty of the evidence was low or very low.

Good practice statement 2. The reference group agreed that it is good practice to monitor the parameters (Box 3) and include a full blood count on, or before, activation of an MHP and consider repeating after administration of every four units of RBCs. Acknowledging the overall certainty of evidence is very low, the reference group listed values indicative of critical physiological derangement of the assessed clinical and laboratory parameters.

Recommendation 3. In patients with critical bleeding managed with a ratio-based MHP, a high ratio of RBC:FFP:PLT may be beneficial, although there is insufficient evidence to support a 1:1:1 ratio over a 2:1:1 ratio (*Weak recommendation*).

A transfusion ratio of 2:1:1 of RBC:FFP:PLT is lower than a transfusion ratio of 1:1:1, as the number of units of RBCs increases without a proportionate increase in FFP or platelets. A transfusion ratio of 2:1:1 would equate to eight units of RBCs, four units of FFP and one adult unit of platelets. One adult unit of apheresis or pooled platelets in Australia is equivalent to platelets derived from four single whole blood donor units. Therefore, a transfusion ratio of 1:1:1 would equate to four units of RBCs, four units of FFP and one adult unit of platelets.

In the meta-analysis of RCTs comparing 1:1:1 with 2:1:1 ratios, no effect on mortality was demonstrated. In the meta-analysis of cohort studies, a large effect favouring ratio-based transfusion on mortality was demonstrated (Supporting Information 1, figure S2). However, the certainty of the evidence was very low and, based on the available evidence, the magnitude of

3 Critical clinical and laboratory derangements in patients with critical bleeding/massive transfusion

	Values
Temperature (°C)	< 35
pH	< 7.2
Base excess (mEq/L)	< -6
Lactate (mmol/L)	> 4
Ionised calcium (mmol/L)	< 1
PT (seconds)	> 1.5*
INR	> 1.5
aPTT (seconds)	> 1.5*
Fibrinogen level (g/L)	< 2.0

aPTT = activated partial thromboplastin time; INR = international normalised ratio; PT = prothrombin time. * × Upper limit of normal. ◆

any true benefit is unknown. In the meta-analysis of RCTs, thromboembolic events and multiple organ failure rates did not differ among populations that received higher ratios of blood components compared with those who received lower ratios (Supporting Information 1, tables S12–S14). Based on the available evidence, the harms are unknown.

Good practice statement 3. The reference group agreed that in a ratio-based MHP, it is good practice for the transfusion ratio of RBC:FFP:PLT to be no lower than 2:1:1. The direct evidence regarding the optimal dose of RBC:FFP:PLT is weak, but guidance is provided for patient care.

Good practice statement 4. The reference group agreed that in a ratio-based MHP, it is good practice that the ratio of RBC:FFP:PLT of at least 2:1:1 be achieved as soon as possible and be maintained until critical bleeding is controlled. In addition, fibrinogen should be assessed and replaced as required. Options to assess fibrinogen level and function include laboratory measures of fibrinogen or viscoelastic haemostatic assay (VHA).

Recommendation 4. In patients with critical bleeding, FFP at a minimum one unit per two units of RBC and platelets at a minimum dose of one adult unit with every eight units of RBC are suggested (*Weak recommendation*). This recommendation focuses on the quantity of blood components to achieve high ratios. One adult unit of apheresis or pooled platelets in Australia is equivalent to platelets derived from four single whole blood donor units. Substantial clinical heterogeneity between identified studies precluded a strong recommendation regarding administration and dose of FFP, platelets, prothrombin complex concentrate (PCC), cryoprecipitate or fibrinogen concentrate (FgC; Supporting Information 1, figures S3–S6 and tables S15–S19).

Good practice statement 5. For other blood components and products, the reference group agreed that the following doses are a guide:

- fibrinogen replacement — 3–4 g of fibrinogen which may be achieved using FgC or cryoprecipitate (ten units of whole-blood cryoprecipitate, or four units of apheresis cryoprecipitate in Australia, or one unit of cryoprecipitate per 30 kg body weight in New Zealand); and
- prothrombin complex concentrates for warfarin reversal — 25–50 IU/kg.

Good practice statement 6. The reference group agreed that it is good practice to administer RBCs through a blood warming device whenever possible and aim to maintain the patient's core temperature ≥ 35°C. Evidence regarding the warming of blood components was not evaluated, but guidance is provided for patient care.

Good practice statement 7. The reference group agreed that it is good practice to administer group-specific blood components as soon as possible. Transition to ABO-identical blood components as soon as possible is to ensure optimal stewardship of scarce blood components, especially group O negative RBCs.[23]

Good practice statement 8. When critical bleeding is controlled, the reference group agreed that it is good practice to cease the MHP and proceed to targeted optimisation of coagulation, physiological and biochemical parameters and continued patient assessment. After critical bleeding is controlled, recommendations on further management were outside the scope of this guideline.

Recommendation 5. In patients with critical bleeding, the reference group suggests against the routine use of recombinant activated factor VII (rFVIIa) (*Weak recommendation*). There was no statistically significant survival benefit observed in critically bleeding patients who received rFVIIa, and there is limited evidence of harm from thromboembolism (Supporting Information 1, tables S20–S23). In the meta-analysis of placebo-controlled trials, treatment with high doses of rFVIIa on an off-label basis significantly increased the risk of arterial but not venous thromboembolic events (Supporting Information 1, figure S7). The use of rFVIIa in patients with critical bleeding has been declining, and the urgency to address the off-label use of this product has waned. Use of rFVIIa should only be considered in exceptional circumstances where all other available measures to control bleeding have been exhausted.

Recommendation 6. In trauma patients with critical bleeding, the reference group suggests the early (within three hours of injury) use of tranexamic acid as part of an MHP (*Weak recommendation*). Evidence from RCTs showed a slight decrease in the risk of mortality (latest time point) among trauma patients who received tranexamic acid (Supporting Information 1, figure S8). The PATCH-Trauma trial was published after the census date of the systematic reviews, but the results on the outcome of mortality at hospital discharge were consistent with the evaluated evidence.[24] Among cohort studies, the risk of mortality was not different between groups. The certainty of evidence was low to very low (Supporting Information 1, tables S24–S25). The effects on harms were uncertain.

Good practice statement 9. The reference group agreed that there was insufficient evidence to provide a recommendation on the use of tranexamic acid in patients with critical gastrointestinal bleeding (Supporting Information 1, table S25). This statement is based on the results of a single RCT that concluded no effect of tranexamic acid on the primary outcome of death due to bleeding, but potential increase in the risk of thromboembolic events.[25]

Recommendation 7. In obstetric patients with critical bleeding, the early (within three hours of the onset of bleeding) use of tranexamic acid may be considered as part of an MHP (*Weak recommendation*). In obstetric patients, although no difference was observed for the primary outcome of overall hospital mortality, a large RCT demonstrated a reduction in the number of deaths attributable to bleeding (Supporting Information 1, table S26).[26] In 2018, there were 15 maternal deaths in Australia and only one was attributable to bleeding.[27] This makes assessment of the benefits and risks of tranexamic acid difficult in the Australian population. As a result of this uncertainty, a weak recommendation was made.

Good practice statement 10. The reference group agreed that the use of VHAs may be beneficial in patients with critical bleeding. There was insufficient evidence to provide a recommendation. If VHAs are used in the assessment of patients with critical bleeding, they must be used in conjunction with an MHP.

Among trauma patients, evidence from RCTs showed no difference in mortality when blood component therapy was guided by VHA compared with haemostatic management guided by standard laboratory tests (Supporting Information 1, figure S9). Evidence from cohort studies suggested that blood component therapy guided by VHA was associated with significantly lower mortality than treatment guided by standard laboratory tests. There were no differences with regards to morbidity or transfusion volumes. Based on this available

evidence, the true benefit is unknown (Supporting Information 1, tables S27–S29). There are significant additional resources associated with the implementation and use of VHAs as part of an MHP and substantial jurisdictional, geographical and institutional variability.

Good practice statement 11. Cell salvage is a technique that involves aspirating patient's own blood that is lost within a surgical field and processing of the blood for re-infusion to the patient. The reference group agreed that the use of cell salvage in patients with critical bleeding may be considered as part of an MHP. There was insufficient evidence to provide a recommendation. In the meta-analysis of observational cohort studies, little to no effect on mortality was demonstrated and evidence of harm was uncertain (Supporting Information 1, table S31 and figure S10). A subgroup of patients may decline cell salvage based on personal preference or beliefs.

Collating the recommendations, a template MHP is provided in the Supporting Information 2.[24] Adaptation of this template and guidance at a local level is required upon consideration of the resources available. The full guideline, including technical details of the evidence are available online.[7]

Limitations and challenges

A key feature of the guideline was the foundation of systematic reviews for the research questions. Therefore, the strength of recommendations was limited by the certainty of evidence. The weak strength of many recommendations highlights the challenges and paucity of high quality trials among patients with critical bleeding. The NBA manages the Australian national blood supply to ensure reliable and efficient access to blood components and products and its cost effectiveness. Collating the available evidence on the key interventions is therefore essential to inform standardised management.

There exists geographical and institutional variability in composition and delivery of MHPs throughout Australia. There are many contributing factors to this including variations in access to blood components, access to results from laboratory tests, point of care tests and/or VHAs. Facilities that can store and supply blood components/products are limited by requirements for storage conditions, financial costs, education, staff training and wastage implications. Implementation of this guideline requires adaptation to the local context. Health service organisations should have local policies and procedures outlining the structure, composition, and delivery of an MHP that is appropriate for their local inventory, supply logistics, resources requirements, local practice and system limitations.

4 Evidence gaps and potential research priorities

- Indications for initiation and cessation of a major haemorrhage protocol:
  - patient-specific physiological and biochemical endpoints to guide cessation of a major haemorrhage protocol
- The optimal strategy for storage, transport and use of blood components and products including, but not limited to:
  - whole blood
  - plasma
  - platelets
  - fibrinogen
  - coagulation factor concentrates
- Adjuvant interventions, for example:
  - viscoelastic haemostatic assay-guided major haemorrhage protocols
  - cell salvage
  - novel methods for assessment of oxygen delivery and tissue perfusion
  - alternatives to blood components and products
  - variations in assessment and management of critical bleeding for age-specific subgroups, such as paediatric and older patients

Future directions

The uptake of this guideline will be measured under a comprehensive evaluation of Australia's 2017–2024 National Patient Blood Management Implementation Strategy.[28] The ongoing review of the guideline will be necessary to reduce variation in practice patterns, support appropriate use of blood component therapy and reduce inappropriate exposure of patients to blood components. In addition, this review of evidence identified areas where best practice is uncertain or unknown. A summary of potential research priorities is provided in Box 4 and suggested to be topics for further research.

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Supporting Information

Additional Supporting Information is included with the online version of this article.