Critical Care Society of Southern Africa adult patient blood management guidelines: 2019 Round-table meeting, CCSSA Congress, Durban, 2018

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The CCSSA PBM Guidelines have been developed to improve patient blood management in critically ill patients in southern Africa. These consensus recommendations are based on a rigorous process by experts in the field of critical care who are also practicing in South Africa (SA). The process comprised a Delphi process, a round-table meeting (at the CCSSA National Congress, Durban, 2018), and a review of the best available evidence and international guidelines. The guidelines focus on the broader principles of patient blood management and incorporate transfusion medicine (transfusion guidelines), management of anaemia, optimisation of coagulopathy, and administrative and ethical considerations. There are a mix of low-middle and high-income healthcare structures within southern Africa. Blood products are, however, provided by the same not-for-profit non-governmental organisations to both private and public sectors. There are several challenges related to patient blood management in SA due most notably to a high incidence of anaemia, a frequent shortage of blood products, a small donor population, and a healthcare system under financial strain. The rational and equitable use of blood products is important to ensure best care for as many critically ill patients as possible. The summary of the recommendations provides key practice points for the day-to-day management of critically ill patients. A more detailed description of the evidence used to make these recommendations follows in the full clinical guidelines section.

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The Critical Care Society of Southern Africa (CCSSA) patient blood management (PBM) guidelines have been developed to improve patient blood management in critically ill patients in southern Africa. These consensus recommendations are based on a rigorous process by experts in the field of critical care who are also practising in South Africa (SA). The process comprised a Delphi technique, a round table meeting (at the CCSSA National Congress, Durban International Convention Centre (ICC), 2018), and a review of the best available evidence and international guidelines. The guidelines focus on the broader principles of PBM and incorporate transfusion medicine (transfusion guidelines), management of anaemia, optimisation of coagulopathy, and administrative and ethical considerations.

There is a mix of low-middle- and high-income healthcare structures within southern Africa. Blood products are, however, provided by the same not-for-profit non-governmental organisations to both private and public sectors. There are several challenges related to PBM in SA, owing most notably to a high incidence of anaemia, a frequent shortage of blood products, a small donor population, and a healthcare system under financial strain. The rational and equitable use of blood products is important to ensure best care for as many critically ill patients as possible.

The summary of the recommendations provides key practice points for the day-to-day management of critically ill patients. A more detailed description of the evidence used to make these recommendations follows in the full clinical guidelines section.

We acknowledge and thank the organisers of the CCSSA Congress 2018, all the authors who participated, the support of the CCSSA, as well as the Australian Critical Care Patient Blood Management Guidelines (Module 4) of 2012 and the British Committee for Standards in Haematology Guidelines of 2012. We also extend our thanks to Prof. Vernon Louw for his suggestions and advice.

Summary of recommendations

Grading of recommendations

Each recommendation has been given a grade, using the following definitions, set by the Australian National Health and Medical Research Council (NHMRC) (Boxes 1 and 2).

Scope and purpose

The aim of this guideline is to improve the practice of critical care in SA by providing clear blood management guidelines to be utilised in the care of critically ill patients in SA. The specific objectives of the guideline are:

- to provide current, evidence-based, context-specific blood management guidelines to be used in the treatment of critically ill patients in SA
- to improve clinical outcomes of critically ill patients by ensuring they receive blood products according to current, evidence-based guidelines
- to conserve resources in SA critical care by ensuring rational utilisation of blood and blood products.

Box 1. Grading of recommendations

Grade A	Body of evidence can be trusted to guide practice.
Grade B	Body of evidence can be trusted to guide practice in most situations.
Grade C	Body of evidence provides some support for recommendation(s), but care should be taken in its application.
Grade D	Body of evidence is weak and recommendations must be applied with caution.

The guidelines focus on providing practical answers to key patient-centred questions regarding indications for administration of blood, blood products and adjunctive agents; and also regarding coagulation testing, ethics and general principles of PBM.

Critically ill patients are those patients with, or at high risk of developing, acute organ dysfunction. While these patients may be treated in critical care units (high care units, intensive care units), many – if not most – in SA are not. These guidelines are therefore intended for use in all adult critically ill patients, whether or not they are in dedicated critical care units. While the guidelines have been developed from current international best evidence, the recommendations have considered the unique requirements of the SA context and are therefore specifically intended for use in SA. The guidelines are intended for adult patients (i.e. ≥18 years); however, practitioners may choose to apply them in patients deemed physiologically to be adults. These patients may be subject to certain legal and ethical considerations and, as such, these are dealt with specifically in the guidelines.

The guideline is intended for use by any medical professional who may be providing care for critically ill adult patients. The guideline may also be useful to hospital administrators in creating institutional PBM guidelines.

Guideline development

The development of the document involved a multi-step process (Fig. 1).

Guideline working group

Experts in the field of critical care and those with an interest in blood management were invited by the primary authors to participate after they had been tasked to co-ordinate a round table meeting at the CCSSA Congress of 2018. An effort was made to ensure representation from all major centres across SA, to include intensivists with different baseline specialities, and to have participants from both the public and private sectors. Owing to the nature of critical illness, specific input from the target population was not sought; however, the guideline will be made freely available for public comment.

Clinical research questions

A literature review was performed by the primary study authors to identify existing PBM guidelines. Relevant guidelines were selected from this, and the clinical research questions were derived following a review of the extensive Australian Critical Care Patient Blood Management Guidelines (Module 4) of 2012 and the British Committee for Standards in Haematology Guidelines of 2012. Additional questions were added, based on local clinical experience. All questions were compiled in a survey format that was tested among a group for ambiguity and clarity.

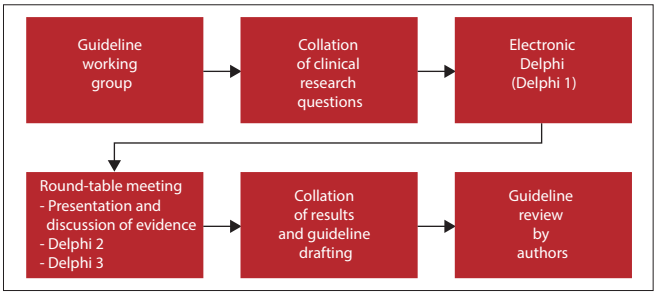

Fig. 1. Flow diagram depicting the multi-step process of the guideline development.

Box 2. Recommendations

		Consensus	Grade
General PBM measures			
1.1	Minimise blood sampling for diagnostic testing.		
1.2	Investigate and treat specific causes of anaemia when identified.		
1.3	Apply restrictive transfusion thresholds unless evidence exists to the contrary.		
1.4	A single-unit blood transfusion policy with reassessment of the ongoing need for transfusion after each unit should be used except when there is active bleeding.		
1.5	Non-transfusion methods to reduce the need for blood products should be utilised when possible.		
1.6	Coagulation should be optimised by correcting temperature and electrolyte (calcium) abnormalities to reduce the need for blood products.		
1.7	Point-of-care testing should be available with appropriate training.		
1.8	Elective surgery in patients requiring critical care should be postponed in the presence of untreated anaemia.		
1.9	Every effort should be made to minimise bleeding during procedures in the ICU.		
Red cells		**Consensus**	**Grade**
2.1	A restrictive transfusion strategy is recommended in critically ill patients.	Yes	B
2.2	The need for RCC transfusions should not be dictated solely by Hb concentration.	Yes	B
2.3	The need for RCC transfusions should include a clinical assessment of the patient's need for transfusion.	Yes	B
2.4	An individualised approach to the need for RCC transfusion should be followed, using Hb and clinical assessment.	Yes	B
2.5	An appropriate transfusion trigger in the general critically ill patient is Hb <7 g/dL.	Yes	B
2.6	In the general critically ill patient, transfusion is unlikely to be beneficial with Hb >7 g/dL.	Yes	B
2.7	In a patient with sepsis/septic shock, an appropriate transfusion trigger is Hb <7 g/dL.	Yes	B
2.8	In a patient with acute coronary syndrome, an appropriate transfusion trigger is Hb <8 - 9 g/dL.	Yes (R)*	C
2.9	In a patient with a traumatic brain injury, an appropriate transfusion trigger is Hb <7 - 9 g/dL.	Yes (R)*	C
2.10	In a patient with a subarachnoid haemorrhage, an appropriate transfusion trigger is Hb <8 - 9 g/dL.	Yes (R)*	C
2.11	In a patient with other acute cerebrovascular events, an appropriate transfusion trigger is Hb 7 - 8 g/dL.	Yes (R)*	C
2.12	In a resuscitated, non-bleeding trauma patient, an appropriate transfusion trigger is Hb <7 g/dL.	Yes (R)*	C
2.13	In a non-resuscitated trauma patient with significant active bleeding, transfusion triggers may be unreliable. In other scenarios, an appropriate transfusion trigger is Hb 7 - 10 g/dL. In both cases, transfusion must be individualised based on the patient's physiological status and access/availability of blood products.	Yes (R)*	D
2.14	Where feasible, RCCs should be transfused one unit at a time, with clinical assessment after each unit to determine if further units are required.	Yes	B
2.15	Target Hb levels need only be above the trigger.	Yes	C
2.16	Leucodepleted packed red blood cells should not be routinely used in the critically ill, in the SA context.	Yes	D
2.17	The are no other specific forms (whole blood, irradiated, specific donor) of RCC transfusion routinely indicated in critically ill patients.	Yes	D
Non-transfusion interventions to reduce RCC transfusions			
3.1	There is no role for erythropoietin in general critically ill anaemic patients as an alternative to RCC transfusion.	Yes	B
3.2	There is no role for routine use of IV Fe in general critically ill anaemic patients as an alternative to RCC transfusion.	Yes	B
3.3	The use of cell salvage should be considered in the critically ill where appropriate.	Yes	C
3.4	There is currently no role for the routine use of artificial oxygen carriers in the general critically ill patient in SA.	Yes	D
Platelets			
4.1	In critically ill patients without acute bleeding and who are not undergoing invasive procedures, platelets should be administered at a platelet count $\leq 10 \times 10^9$/L. Platelet transfusion should be considered if the level is $<20 \times 10^9$/L if active bleeding, or infection, or rate of platelet decline is such that platelet count is expected to drop below 10 in the next 24 hours.	Yes	B
4.2	A platelet count $\geq 50 \times 10^9$/L is generally acceptable for invasive procedures in the ICU.	Yes	C
4.3	A platelet count $\geq 20 \times 10^9$/L may be acceptable for CVC placement in the absence of any other bleeding risk.	Yes	D
4.4	A platelet count $\geq 50 \times 10^9$/L is generally acceptable for surgical procedures.	Yes	C
4.5	Neurosurgery and posterior ophthalmic surgery may require a higher platelet count $\geq 100 \times 10^9$/L.	Yes	C
4.6	A platelet count ≥ 20 - 30×10^9/L is generally acceptable for bronchoscopy with BAL.	ND†	C
4.7	A platelet count $\geq 10 \times 10^9$/L is generally acceptable for lumbar puncture in patients with haematologic malignancies and $>40 \times 10^9$/L in patients without haematologic malignancies, but lower in patients with ITP.	ND†	C
4.8	A platelet count $\geq 75 \times 10^9$/L is generally acceptable for epidural catheter placement.	ND†	C
4.9	A platelet count $\geq 20 \times 10^9$/L is generally acceptable for bone marrow aspiration/biopsy.	ND†	C
4.10	In a patient with clinically significant bleeding, platelets should be administered if the platelet count is $<50 \times 10^9$/L	Yes	D
4.11	Where available, point-of-care viscoelastic testing may be used to guide therapy with platelets instead of the platelet count.	Yes	C
4.12	In the setting of large volume blood transfusion, a ratio of 1 unit of platelets for each 1 unit of RCCs should be transfused (1 pooled unit of platelets = 5 units).	Yes	C
4.13	Platelets should be transfused 1 pooled unit at a time, followed by reassessment to determine if additional platelet transfusion is required.	Yes	D
Plasma			
5.1	FFPs and FDPs should be considered clinically interchangeable.	Yes	N/A
5.2	Invasive procedures can generally be performed safely with INR <2.	Yes	C
5.3	FDPs/FFPs are indicated prior to invasive procedures if INR >2.	Yes	C
5.4	In the bleeding patient, FFPs/FDPs should be administered if INR >2.	Yes	C
5.5	Where available, point-of-care viscoelastic testing, instead of the INR, may be used to guide therapy with FFPs/FDPs.	Yes	C
5.6	Empiric FFP/FDP therapy may be indicated in specific circumstances e.g. large volume haemorrhage, TTP.	Yes	B
5.7	A dose of 15 mL/kg of FFP/FDP should be utilised when indicated. This may need to be increased to 30 mL/kg in specific conditions.	Yes	C

...continued

Box 2. (continued) Recommendations

General PBM measures		Consensus	Grade
5.8	In the setting of large-volume haemorrhage, a ratio of 1 unit of FFPs/FDPs to 1 unit of packed RCC should be transfused.	Yes	C
Cryoprecipitate			
6.1	Cryoprecipitate should be given in patients with significant bleeding if fibrinogen <2.0 g/L.	Yes	B
6.2	Cryoprecipitate should not be given in the absence of significant bleeding even if fibrinogen levels are low.	Yes	C
6.3	Cryoprecipitate administration should be guided by point-of-care viscoelastic testing where available.	Yes	C
6.4	The recommended dose of cryoprecipitate for adults is 1 unit/10 kg (SANBS recommends administration of a fixed dose of 10 units, while WCBS recommends administering 1 pooled unit).	Yes	C
Tranexamic acid			
7.1	Tranexamic acid should be administered empirically in critically ill patients with severe trauma within 3 hours of the injury.	Yes	B
7.2	The dose of tranexamic acid in severe trauma is 1 g IV stat and then 1 g IV over 8 hours.	Yes	B
7.3	Tranexamic acid should be administered empirically in bleeding postpartum obstetric patients.	Yes	B
7.4	The dose of tranexamic acid in bleeding obstetric patients is 1 g stat, and 1 g after 30 minutes if bleeding persists.	Yes	B
7.5	Empiric use of tranexamic acid may be considered in patients with upper gastrointestinal bleeding.‡	No	D
7.6	The use of tranexamic acid may be considered in patients with TBI, if administered within 3 hours of injury.	ND†	C
7.7	Empiric tranexamic acid therapy is not indicated in other settings in ICU.	Yes	D
7.8	Where available, point-of-care viscoelastic testing should be used to guide therapy with tranexamic acid.	Yes	C
Coagulation testing and monitoring			
8.1	Point-of-care viscoelastic testing is the preferred test of coagulation function to direct therapy in critically ill patients.	Yes	C
8.2	The aPTT has a limited role in monitoring critically ill bleeding patients and is generally limited to monitoring the effect of heparin and screening for possible coagulopathies in the absence of viscoelastic testing.	Yes	C
8.3	The INR has a limited role in monitoring critically ill bleeding patients and is generally limited to monitoring the effect of warfarin and screening for possible coagulopathies in the absence of viscoelastic testing.	Yes	C
8.4	Fibrinogen levels are recommended in critically ill bleeding patients to guide the use of cryoprecipitate in the absence of viscoelastic testing.	Yes	C
Administration			
9.1	The use of blood and blood products should be directed by established protocols.	Yes	B
9.2	The use of blood and blood products should be subjected to gatekeeping controls.	Yes	B
Ethics			
10.1	Informed consent should be obtained from the patient or surrogate prior to the transfusion of blood products if time allows.	Yes	N/A
10.2	In the adult patient who is unable to provide informed consent, and where a clear advanced directive against the use of blood products does not exist, blood products may be transfused in the emergency setting if deemed potentially lifesaving.	Yes	N/A
10.3	In the paediatric patient, where the surrogate refuses consent for the use of blood products, legal advice should be sought prior to the administration of blood products unless there is an emergency life-threatening situation necessitating immediate transfusion.	Yes	N/A
10.4	The use of blood products should be triaged in a resource-limited environment.	Yes	N/A

PBM = patient blood management; ICU = intensive care unit; RCC = red cell concentrate; Hb = haemoglobin; Fe = iron; CVC = central venous catheter; N/A = not applicable; FFP = fresh frozen plasma; FDP = fibrin degradation products; INR = international normalised ratio; TTP = thrombotic thrombocytopenic purpura; SANBS = South African National Blood Services; WCBS = Western Cape Blood Services; IV = intravenous; TBI = traumatic brain injury; aPPT = activated partial thromboplastin time.
*(R) indicates that while consensus was not reached on a single value, consensus was reached on the range indicated.
†ND indicates that the recommendation was not subject to the Delphi process; this was due to the availability of new study data that were published after the Delphi process.
‡Review undertaken prior to the publication of the HALT-IT trial. Refer to section 7.1 Tranexanamic acid: Upper gastrointestinal tract bleeding.

Electronic Delphi process

An electronic Delphi process was conducted using the questions developed above. The threshold for consensus was set at 80%. Results were collated and, where consensus was not reached, the questions were selected for further review and research.

Review and research

Questions where consensus was not reached in the electronic Delphi process were divided among the working group. Each question was allocated to two members who were tasked with researching the question further, collating the available data on the topic and presenting a summary of the data at the round table meeting.

Round-table meeting (and Delphi 2 and 3)

The data on the questions where consensus was not reached were presented at a round table meeting held in Durban on 22 August 2018. Following this, a second Delphi process was completed. The questions where consensus was still not reached were discussed further, and a third and final Delphi process was completed. Where consensus was still not reached but there was consensus within a narrow range, this was noted. If no consensus was possible, this was also noted.

Formulation of recommendations

The results of the three Delphi rounds and data syntheses from the members of the working group were collated to form the backbone of the current guidelines. Each recommendation is derived directly from the responses to the clinical research questions from the expert working group. Consensus was achieved for all but one recommendation, and the recommendations thus represent a synthesis of the best available current research evidence and the practical experience of SA intensive care clinicians. The draft guideline was prepared by the first two authors and sent to all other members of the working group for review and comment, after which the draft was modified, and sent to all members for a second review process. The final version of the guideline was then adopted after this second review process.

Clinical guidelines

1. General PBM measures

Refer to Table 1.

2. Red cells

Refer to Table 2.

General critical care patients

The need for red blood cell transfusions in the critically ill patient is a balance between the potential for improved oxygen delivery and harm from the allogeneic blood transfusion.

Randomised controlled trials

The seminal Transfusion Requirements in Critical Care (TRICC) trial randomised 838 adult critically ill patients either to a restrictive (transfusion trigger <7 g/dL, target 7 - 9 g/dL) or liberal (trigger <10 g dL, target 10 - 12 g/dL) transfusion strategy.[1] All patients were deemed to be 'euvolaemic' and the cohort included a broad range of critically ill patients but excluded cardiac surgical patients. Thirty-day mortality was 18.7% in the restrictive group and 23.3% in the liberal group (p=0.11). The mortality rate was significantly lower in the restrictive group in younger patients (<55 years) and less severely ill patients (APACHE II score <20). Significantly fewer units of red cell concentrate (RCC) were transfused in the restrictive group (2.6 v. 5.6 units; p<0.01).

The Transfusion Requirements in Septic Shock trial[82] randomised 1 005 adult patients with septic shock to receive one unit of leucodepleted RCC with an Hb level <7 g/dL (lower threshold group) or <9 g dL (higher threshold group).[2] The 90-day mortality was 43% in the lower threshold group as opposed to 45% in the higher threshold group (p=0.44). The median number of transfusions was significantly lower in the lower-threshold group (1 v. 4 units; p<0.001).[3]

In the single-centre Transfusion Requirements in Surgical Oncology Patients (TRISOP) study, de Almeida *et al.*[4] randomised 198 patients with cancer who required ICU following major abdominal surgery to a restrictive (Hb trigger <7 g/dL) or liberal (Hb trigger <9 g dL) transfusion strategy. The 30-day mortality was 22.8% in the restrictive group and 8.2% in the liberal group (p=0.005). Major cardiac complications occurred in 13.9% of the restrictive group and 5.2% in the liberal group (p=0.038).

In a study from the same hospital as the de Almeida study, the Transfusion Strategy in Critically Ill Oncological Patients (TRICOP) trial randomised 300 adult cancer patients with septic shock to a restrictive (trigger of 7 g/dL) or liberal (trigger 9 g/dL) transfusion strategy. The 28-day mortality was 56% in the restrictive group v. 45% in the liberal group (p=0.08). Although not the primary outcome, this difference reached statistical significance for 90-day mortality (70% v. 59%; p=0.03). The difference in the median number of units of RCC transfused was statistically significant but clinically small (0 units in the restrictive group v. 1 unit in the liberal group; p<0.001). All patients received leucodepleted red cell units. There was a short period of overlap between the two studies carried out in the same ICU and it is not clear if duplicate patients were included in both studies.

Table 1. General PBM measures

1.1	Minimise blood sampling for diagnostic testing.
1.2	Investigate and treat specific causes of anaemia when identified.
1.3	Apply restrictive transfusion thresholds unless evidence exists to the contrary.
1.4	A single-unit blood transfusion policy with reassessment of the ongoing need for transfusion after each unit should be used except when there is active bleeding.
1.5	Non-transfusion methods to reduce the need for blood products should be utilised when possible.
1.6	Coagulation should be optimised by correcting temperature and electrolyte (calcium) abnormalities to reduce the need for blood products.
1.7	Point-of-care testing should be available with appropriate training.
1.8	Elective surgery in patients requiring critical care should be postponed in the presence of untreated anaemia.
1.9	Every effort should be made to minimise bleeding during procedures in the ICU.

PBM = patient blood management; ICU = intensive care unit.

Table 2. Red cells

		Consensus	Grade
2.1	A restrictive transfusion strategy is recommended in critically ill patients.	Yes	B
2.2	The need for RCC transfusions should not be dictated solely by a Hb concentration.	Yes	B
2.3	The need for RCC transfusions should include a clinical assessment of the patient's need for transfusion.	Yes	B
2.4	An individualised approach to the need for RCC transfusion should be followed, using Hb and clinical assessment.	Yes	B
2.5	An appropriate transfusion trigger in the general critically ill patient is Hb <7 g/dL.	Yes	B
2.6	In the general critically ill patient, transfusion is unlikely to be beneficial with Hb >7 g/dL.	Yes	B
2.7	In a patient with sepsis/septic shock, an appropriate transfusion trigger is Hb <7 g/dL.	Yes	B
2.8	In a patient with acute coronary syndrome, an appropriate transfusion trigger is Hb <8 - 9 g/dL.	Yes (R)	C
2.9	In a patient with a TBI, an appropriate transfusion trigger is a Hb <7 - 9 g/dL.	Yes (R)	C
2.10	In a patient with a SAH, an appropriate transfusion trigger is Hb <8 - 9 g/dL.	Yes (R)	C
2.11	In a patient with other acute cerebrovascular events, an appropriate transfusion trigger is Hb 7 - 8 g/dL.	Yes (R)	C
2.12	In a resuscitated, non-bleeding trauma patient, an appropriate transfusion trigger is Hb <7 g/dL.	Yes (R)	C
2.13	In a non-resuscitated trauma patient with significant active bleeding, transfusion triggers may be unreliable. In other scenarios, an appropriate transfusion trigger is Hb 7 - 10 g/dL. In both cases, transfusion must be individualised based on the patient's physiological status and access/availability of blood products.	Yes (R)	D
2.14	Where feasible, RCCs should be transfused one unit at a time, with clinical assessment after each unit to determine if further units are required.	Yes	B
2.15	Target Hb levels need only be above the trigger.	Yes	C
2.16	Leucodepleted packed red blood cells should not be routinely used in the critically ill, in the SA context.	Yes	D
2.17	The are no other specific forms (whole blood, irradiated, specific donor) of RCC transfusion routinely indicated in critically ill patients.	Yes	D

RCC = red cell concentrate; Hb = haemoglobin; TBI = traumatic brain injury; SAH = subarachnoid haemorrhage; SA = South Africa.

Walsh *et al.*[5] conducted a randomised pilot trial comparing a restrictive (Hb trigger 7 g/dL) with a liberal transfusion (Hb <10 g/dL) strategy in 100 mechanically ventilated patients ≥55 years old. Mortality at 180 days was 37% in the restrictive group and 55% in the liberal group (p=0.073).

Cohort studies

The 'Anemia and blood transfusion in the critically ill – current clinical practice in the United States' (CRIT) study was a prospective observational study of 4 892 heterogeneous, adult ICU patients. Red-cell transfusion was associated with a significantly greater odds of 30-day mortality (odds ratio (OR) 1.48 (1.07 - 2.05); p=0.018) for transfusion of 1 - 2 units, with OR 4.01 (2.74 - 5.87); p<0.001) if >4 units were transfused. This effect remained even after propensity score matching (adjusted mortality ratio, 1.65 (1.35 - 2.03); p<0.001).

A retrospective observational study of 5 925 surgical ICU patients reported a higher hospital mortality (18.3% v. 6.5%; p<0.001) in transfused patients.[6] This difference was no longer significant in propensity score matched groups (11.8% v. 12.2%; p=0.800) and, after multivariable analysis, blood transfusion was associated with a lower risk of death (relative risk (RR) 0.96 (0.92 - 0.99); p=0.031). Subgroup analyses showed a significantly lower risk of death in patients with severe sepsis, higher severity scores, non-cardiac surgery and those aged 66 - 80 years.

Related randomised controlled trials

The protocol-based care for early septic shock (ProCESS) trial randomised 1 341 patients with septic shock to one of three resuscitation strategies. This included an early goal-directed therapy (EGDT) group with an Hb trigger equivalent to 10 g/dL if resuscitation goals were not met, which was compared with a standard therapy protocol with an Hb trigger of 7.5 g/dL. The primary outcome of 60-day mortality did not differ between the treatment groups (RR 1.15 0.88 - 1.51; p=0.31). However, patients in the EGDT group received significantly more red cell transfusions (14.4% v. 8.3%; p=0.001).[7]

Meta-analyses

A meta-analysis by Holst *et al.*[8] evaluated all randomised controlled trials (RCTs) published up to October 2014 (31 studies and 9 813 patients) that compared outcomes in liberal v. restrictive transfusion strategies. This meta-analysis included a broad spectrum of patient populations, from paediatric to adult and from trauma to perioperative patients and the critically ill. There was no difference in overall all-cause mortality between the restrictive and liberal groups (RR 0.95 (0.81 - 1.11); p=0.52) and this result persisted in the critical care subgroup (RR 0.92 (0.80 - 1.06); p=0.24). There was also no difference in the risk of myocardial infarction between the restrictive and liberal groups (RR 1.05 (0.82 - 1.36); p=0.70).[8]

A meta-analysis by Fominskiy *et al.*[9] had significant overlap with the Holst *et al.*[8] meta-analysis. However, it included studies up to 27 March 2015 and only included adult perioperative or critically ill patients (17 trials and 7 552 patients).[9] The primary outcome was 90-day mortality. They reported an OR of 1.10 (0.99 - 1.23; p=0.07) for mortality in critically ill patients (10 studies and 3 469 patients) when comparing a liberal and restrictive transfusion strategy.

The most recent meta-analysis by Chong *et al.*[10] included 12 studies of 4 332 critically ill patients up to June 2016. They showed a significant reduction in 30-day mortality (OR 0.82 (0.70 - 0.97); p=0.019) with a restrictive transfusion strategy. The number needed to benefit from a restrictive strategy was calculated to be 33, meaning for every 33 patients treated with a restrictive transfusion strategy, one death (at 30 days) would be prevented. The majority of the studies in the restrictive group used a trigger of 7 g/dL, while the most common trigger in the liberal group was 10 g/dL. According to the authors, trial sequential analysis suggests that these findings are definitive evidence of the benefit of a restrictive strategy in critically ill patients.

Summary

The overwhelming body of evidence in the critically ill patient suggests that a restrictive red cell transfusion strategy (Hb trigger <7 g dL) is at least equivalent, and possibly superior, to a liberal strategy (Hb trigger <9 g/dL) in terms of mortality, and significantly reduces allogeneic red cell transfusion requirements. There is concern in the case of critically ill cancer patients as studies from a single centre suggest an improved outcome with a liberal transfusion strategy. These findings require confirmation from other sites before a clear recommendation can be reached for cancer patients.

Sepsis and septic shock

Although anaemia is both frequent and associated with increased morbidity and worse outcomes in critically ill patients, the need for red blood cell transfusion in septic patients remains debatable.[11] The physiological benefit of improved oxygen delivery to tissues following RCC transfusion has fuelled the drive for higher haemoglobin transfusion triggers. However, this approach has remained contentious owing to a lack of evidence of improved outcomes, which may be due to the inability of transfused stored RCC to perform the same functions at the same efficiency as normal circulating red blood cells.

Several negative effects of transfusion have been noted, including infectious complications associated with immunomodulatory effects, fluid overload, and the other risks associated with transfusions of human products.[12-14] Holst *et al.*[8] demonstrated that lowering the transfusion threshold for septic critically ill patients was safe, with no increased risk for these patients.

A recent systematic review of the available evidence has been published.[15] There is only one RCT on the subject, but many cohort studies (12 included in the systematic review). The systematic review looked at several outcomes: mortality, acute lung injury, acute kidney injury and nosocomial infections, and concluded that a restrictive transfusion strategy in septic patients was safe. Transfusions were associated with increased occurrence of nosocomial infections, acute lung injury and acute kidney injury.[16]

More problematic was the effect of transfusions in septic patients with underlying cardiac events. This was largely because of the exclusion of such patients from the studies evaluating early goal-directed therapy (ProCESS,[7] ARISE[17] and ProMISe.)[18] However, two studies showed that transfusion during the early resuscitative phases of sepsis was safe and beneficial.[19,20] Further research in the different phases of sepsis is required.

Another area where the evidence is still unclear, is in those patients with both sepsis and haematological oncological disorders. A more liberal transfusion strategy may be of benefit, but the available evidence is insufficient to recommend this routinely.

The effects of leucodepletion were not evaluated sufficiently in the septic ICU population owing to the heterogeneity of studies. However, transfusion-related immune modulation does require further research and leucodepleted RCC could contribute to reduced nosocomial infections.[21] Although a reduction in nosocomial infections is in line with a previous metanalysis,[22] contradictory evidence has been

published by Juffermans.[23] There is, in addition, early evidence to suggest that transfusions may potentially contribute to acute kidney injury.[24-27]

Summary

Restrictive RCC transfusion strategies were associated with neither benefit nor harm compared with liberal strategies and had no impact on mortality. Liberal strategies may, however, increase the occurrence of nosocomial infection and both lung injury and acute kidney injury. A precautionary approach that involves a restrictive transfusion strategy is therefore preferred. With regard to critically ill septic patients, currently available evidence supports a restrictive RCC transfusion strategy. Exceptions to this may include those with concurrent sepsis and acute coronary syndromes, or haematological oncology disease.

Acute coronary syndrome (ACS)

ACS has evolved as a useful operational term that refers to a spectrum of conditions compatible with acute myocardial ischaemia or infarction that are usually due to an abrupt reduction in coronary blood flow.[28]

From a pathophysiological point of view, there is an imbalance between myocardial oxygen delivery and demand. The determinants of oxygen delivery to the myocardium are governed mainly by coronary blood flow and oxygen content. The latter is mainly driven by the oxygen-carrying capacity of Hb. Controversy prevails as to the optimal Hb level for patients with myocardial ischaemia.

Anaemia in the setting of ACS has been shown to be an independent predictor of short- and long-term mortality.[29] Anaemia is also common among patients with ACS with prevalence varying between 10% and 43%.[30] Anaemia, however, may not be the causative factor, as it is often associated with a host of comorbidities.[31] Transfusion is not without risk in these patients. The ability of transfused RCC to increase oxygen delivery may be reduced because of rapid depletion of red cell nitric oxide during storage.[32] Furthermore, the increased haematocrit as a result of increased blood viscosity may further reduce oxygen delivery.[33] For these reasons the threshold level at which treatment needs to be implemented remains a matter of debate.

The debate has centred on two distinct transfusion strategies: a restrictive Hb threshold <7 - 8 g/dL or a more liberal Hb threshold <9 - 10 g/dL. Most of the evidence has focused on the perioperative setting and the results of large RCTs show non-inferiority of a restrictive strategy compared with a more liberal strategy. In the non-cardiac surgery setting, the evidence from a large systematic review shows a signal for harm associated with more liberal transfusion strategies. The summary of the evidence is as follows:[34-38]

- correction of anaemia if Hb <8 g/dL in patients with ACS
- target an Hb >8 - 9 g/dL in patients with ACS who are haemodynamically unstable.

Summary

Anaemia is common in the ACS setting and is associated with worse outcomes. Evidence is not clear whether anaemia is causative or merely an association with poor outcomes. The optimal Hb transfusion trigger has yet to be established. A clearer definition of significant anaemia, i.e. the precise Hb concentration at which a transfusion is beneficial, would potentially improve outcomes in anaemic cardiac patients.[39] Revision of current recommendations may be possible after the publication of the ongoing Myocardial Ischaemia and Transfusion[40] trial (ClinicalTrials.gov identifier: NCT02981407).

Traumatic brain injury (TBI)

The overarching goal in managing critically ill patients with TBI is the prevention of secondary neuronal injury.[41] Oxygen delivery is critical to achieving this goal, as ischaemic tissue damage is evident in most patients who die with TBI.[42] Hb is one of the most important determinants of oxygen delivery, and critically ill patients frequently have lower values for a variety of reasons.[43]

Cerebral function remains fairly well preserved in patients without TBI down to Hb levels of ~7 g/dL.[44] This tolerance is due to improved local organ blood flow secondary to the lower viscosity. In patients with anaemia, cerebral blood flow would normally be preserved due to an increase in cardiac output and autoregulatory phenomena, resulting in cerebral vasodilation.[45] In contrast, in patients with TBI the benefit of cerebral autoregulation is lost and higher Hb levels may be required to preserve local tissue perfusion.[46] Several retrospective and observational studies which support a lower transfusion trigger of 8 - 9 g/dL have demonstrated worse outcome in TBI patients with lower Hb levels.[47-50]

A low Hb could result in reduced oxygen delivery from reduced oxygen-carrying capacity, whereas a high Hb could potentially do the same by increasing viscosity and reducing blood flow.[51] A subgroup analysis of the TRICC trial, examining patients with TBI, demonstrated that there were no differences in outcome between liberal (Hb >9 g/dL) and restrictive (Hb >7 g/dL) transfusion strategies.[52] This restrictive strategy is supported by a retrospective study by Carlson *et al.*[53] showing that patients with an Hb level <10 g/dL had better outcomes. A recent small RCT by Robertson *et al.*[54] also found no benefit and an increased rate of adverse events in targeting an Hb level of >10 g/dL v. 7 g/dL. In the same study, erythropoietin (EPO) was investigated for its neurocytoprotective effects rather than its stimulatory effects on red cell production, but no benefit accrued. Finally, the deleterious effects of blood transfusion are well established, and there is evidence of worse neurological outcome and increased mortality in critically ill patients with TBI who receive transfusions during their ICU stay.[55-58]

The conflicting results reported by these studies should be interpreted with caution, as significant methodological flaws in each prohibit meaningful comparisons. The single meta-analysis to date on this topic, published by Boutin *et al.*,[59] reflects this paucity of quality data. The authors reported that although hospital length of stay was longer in transfused patients, they cannot provide guidance regarding transfusion triggers in TBI owing to the high heterogeneity and observational nature of the studies available.[59] A suggested conclusion from the above data is that Hb in critically ill patients with TBI should be kept between 7 g/dL and 9 g/dL, a recommendation voiced by several recent international guidelines.[60,61] A reasonable strategy would be to individualise this target in each patient: balancing the beneficial effects on viscosity, bloodflow and oxygen-carrying capacity against the adverse effects of transfusion. While the success of optimising oxygen delivery may be measured at the bedside using global variables such as lactate, superior vena caval oxygen saturation ($ScvO_2$) or arteriovenous carbon dioxide difference (CO_2 gap), these may not accurately reflect cerebral oxygen delivery. Cerebral oxygen delivery can be more accurately assessed by brain tissue oxygen pressure ($PbtO_2$), lactate to pyruvate ratio (LPR) and jugular venous oxygen saturation ($SvjO_2$). Small physiological studies have determined that the administration of blood may improve $PbtO_2$ in some but may also paradoxically reduce brain tissue oxygen levels in others. It is also unclear if cerebral metabolism is improved or if there is any meaningful impact on clinical outcomes.[46,62-64] In addition, although these local perfusion variables are more specific to the brain, they are costly and require neurosurgical expertise and specific equipment to be of practical

use, particularly as they seem to be associated with more liberal blood transfusion.[65] These variables hold promise for the future but, on the basis of current evidence, cannot be recommended for routine use until well-conducted RCTs show clinical benefits.

There is insufficient high-quality evidence to make a strong recommendation on a transfusion trigger in critically ill patients with TBI. Based on existing evidence, it seems prudent to keep the Hb between 7 and 9 g/dL in patients with TBI, tending toward the lower end of the range in mild TBI and the high end of the range in severe TBI, or if there are features of poor brain oxygenation or poor global oxygenation. The unproven benefit of a higher target Hb in patients with severe TBI needs to be balanced against the potential for inappropriate blood utilisation in patients with anticipated low rates of survival and/or poor neurological outcomes.

Cerebrovascular events

The term 'stroke' broadly defines the death of brain cells resulting from inadequate blood supply and oxygen delivery. In this guideline, the term refers to:

- aneurysmal subarachnoid haemorrhage (aSAH) complicated by vasospasm and delayed cerebral ischaemia (DCI)
- intracerebral haemorrhage
- cerebral infarction (including brain, retinal and spinal cord neural cells).

Both anaemia and RCC transfusion can be associated with adverse outcomes: anaemia through the potential for inadequate oxygen delivery in a compromised brain; and blood transfusions by transfusion-associated acute lung injury (TRALI), and other known complications of blood transfusions in patients already at risk of neurogenic pulmonary oedema. There is a dearth of literature providing clear guidance on the optimal haemoglobin to target in stroke pathologies in the neurocritical care unit. Randomised trials on transfusion triggers in critically ill patients have not addressed this question specifically, as they have included very few patients with stroke. Most published research on this subject is on aSAH. The present guideline addresses aSAH and the other stroke pathologies as separate entities.

Aneurysmal subarachnoid haemorrhage

Anaemia may have an effect on oxygen delivery, particularly during periods of cerebral ischaemia and specifically in relation to DCI, a complication of vasospasm. Historically, 'Triple H' therapy (haemodilution, hypervolaemia and hypertension) variably used to treat vasospasm, involved manipulation of Hb levels by haemodilution. However, the risks seemed to outweigh the benefit and this strategy is no longer followed.[66] The problem arises from determining the optimal Hb that balances improved cerebrovascular blood flow rheology and oxygen delivery to ischaemic brain cells. Moreover, there is concern that RCC may directly cause vasospasm through the action of mediators in blood products.[67,68]

Studies using physiological endpoints such as brain tissue oxygenation have demonstrated positive benefits of maintaining higher Hb levels.[69] Kurtz *et al*.,[69] in a prospective observational study of 15 patients with poor grade aSAH, at high risk of vasospasm, showed a significant improvement of brain tissue oxygenation with blood transfusions from a baseline Hb of 8.0 g/dL and with increments of about 2.2 g dL. The Kurtz study,[69] however, did not assess neurological function and complications arising from transfusion and, as such, the improvement in tissue oxygenation cannot be extrapolated to improved outcomes.

Research on transfusion triggers in this population is scanty. Naidech *et al*.,[68] in one of the few published RCTs on the subject, directly compared two haemoglobin targets, of 10.0 and 11.5 g/dL, with safety as an endpoint. This pilot study investigated the feasibility and safety of a larger trial of transfusion triggers in aSAH. Although the outcomes between the two groups were similar in terms of safety from transfusion-associated complications, vasospasm and neurological outcomes, the trial was not adequately powered beyond that of the safety outcome. English *et al*.[70] published a retrospective cohort study of 527 adults with aSAH of whom 100 were transfused and 66% had significant anaemia <8 g/dL.The authors concluded, after controlling for potential confounders, that the low Hb did not adversely influence patient outcome.

Guidance from surveys conducted among practicing neurointensivists around the world suggest a safe Hb trigger to be 9 g/dL, though triggers as low as 7.5 g/dL have been suggested in country-specific surveys.[71] The benefits of blood transfusion may vary with aSAH grade and presence of vasospasm.

In summary, as the evidence is poor, we suggest an Hb trigger of 8 - 9 g/dL in patients with aSAH, owing to the risk of delayed cerebral ischaemia. Individualised multimodal neuromonitoring, where feasible, may help to individualise transfusion triggers, although this approach is unproven.

Other stroke pathologies: intracerebral haemorrhage and cerebral infarction

The direct impact of anaemia on stroke outcomes is difficult to investigate, owing to confounding conditions such as severity of stroke, bleeding from thrombolytic therapy, advanced age and underlying pathology in the case of embolic stroke.

Both anaemia and elevated Hb have been implicated in the causation of cerebral infarction. Anaemia is thought to induce hyperkinetic blood flow that disrupts endothelial adhesion and leads to thrombus formation.[72] Anaemia has also been associated with poor long-term outcomes, although this relationship is not consistent.[73,74] A large database of 8 013 stroke patients in the UK showed increased mortality in the presence of anaemia on admission which persists up to a year after the event.[75] However, increased mortality was also observed in the same cohort, with elevated Hb in the first month after the stroke. World Health Organization definitions of anaemia (<12 g/dL in women and <13 g/dL in men) were used with no clear differentiation of outcome with more severe degrees of anaemia.

Summary

There are no comparative studies of transfusion triggers and targets in this population. Current guidelines are based on expert opinion and recommendations supporting higher triggers should be balanced against the potential for complications of RCC and availability of blood products in SA. In the absence of good-quality evidence, we suggest an Hb trigger of 7 - 8 g/dL in patients with cerebral infarction and intracerebral haemorrhage. Although unproven, individualised multimodal neuromonitoring, where feasible, may allow for individualised transfusion triggers.

Trauma

There is a paucity of good-quality data to provide information on when to transfuse packed red cells in the context of trauma. Trauma resuscitation is a dynamic scenario, so single physical parameters such as Hb may be unreliable. Various recommendations exist for initiation of a massive transfusion protocol and these continue to evolve as better evidence emerges.[76]

Trauma resuscitation practitioners must rely on a constellation of parameters, both physical and physiological, to decide on RCC transfusion. These include:

- anatomical injury pattern
- physiological instability
- estimated blood loss or anticipated blood loss in theatre
- ease of control of haemorrhage
- risk of ongoing bleeding from coagulopathy.

Access to blood products in SA hospitals (both the public and private sector) may be limited or delayed.[77] This potential delay in time from trauma to transfusion should be considered when deciding on blood product transfusions.[78,79]

The role of hypotensive resuscitation, use of crystalloid and synthetic colloid fluids, and blood product ratios in trauma resuscitation are outside the scope of this consensus document.

In non-bleeding, stable, non-TBI trauma patients, the transfusion trigger should remain at <7 g/dL as per current ICU guidelines found elsewhere in this document.

Summary

Hb concentration may not accurately reflect the degree of blood loss in the non-resuscitated trauma patient. Transfusion in these situations may be more appropriately based on the estimated blood loss or on ongoing blood losses. There is no current evidence to suggest that these patients require normal or supranormal haemoglobin concentrations. In a non-resuscitated trauma patient with significant active bleeding, transfusion triggers may be unreliable. In other scenarios, an appropriate transfusion trigger is an Hb of 7 - 10 g/dL. In both cases, transfusion must be individualised, based on the patient's physiological status and access/availability of blood products. In a resuscitated non-bleeding trauma patient, an appropriate transfusion trigger is Hb <7 g/dL.

Use of specific types of RCCs

Several high-income countries have switched their transfusion practice to use only leucodepleted blood.[21,80] Benefits of leucodepleted over non-leucodepleted blood include decreased infection transmission risk and reduced allergic reactions.[81] The evidence for improved patient outcome and cost-effectiveness of leucodepleted, irradiated and washed blood is, however, still lacking.

We could not find any RCTs that compared either leucodepleted, irradiated or washed RCC with a control with regard to patient outcomes. Some RCTs and observational studies have assessed the outcome of liberal v. restrictive transfusion triggers when using leucodepleted RCC but there was no direct comparison with a non-leucodepleted product.[4,82-84]

Summary

RCTs do not support the routine use of leucodepleted, irradiated or washed blood in critically ill patients. This emphasises the need for adequately powered RCTs to evaluate the efficacy, cost and safety of leucodepleted RCC in the critical care setting.

3. Non-transfusion interventions to reduce RCC transfusions

Erythropoietin (EPO) and iron (Fe)

Erythropoietin

Anaemia develops in the majority of critically ill patients, many of whom have a relative deficiency of EPO and, therefore, EPO receptor agonists[85] have been used in critically ill patients with the aim of stimulating erythropoiesis and mitigating the effects of anaemia.[79] Twelve relevant studies[85] evaluating the benefits and harms of EPO use in critically ill patients were evaluated.

Table 3. Non-transfusion interventions to reduce RCC transfusions

		Consensus	Grade
3.1	There is no role for erythropoietin in general critically ill anaemic patients as an alternative to RCC transfusion.	Yes	B
3.2	There is no role for routine use of IV Fe in general critically ill anaemic patients as an alternative to RCC transfusion.	Yes	B
3.3	The use of cell salvage should be considered in the critically ill where appropriate.	Yes	C
3.4	There is currently no role for the routine use of artificial oxygen carriers in the general critically ill patient in SA.	Yes	D

RCC = red cell count; IV = intravenous; Fe = iron; SA = South Africa.

Nine studies were included in a meta-analysis of RCTs evaluating the effect on mortality.[86] The inclusion criteria were random assignment, EPO v. placebo or none, ICU admission and age >1 year, and the primary outcome was mortality. Secondary outcomes included length of stay (LOS) in ICU and hospital, duration of ventilation and adverse events (thrombosis and hypertension). Three further trials of relevance were evaluated, one in trauma patients,[87] one in burn patients[88] and one in moderate to severe TBI.[89]

The meta-analysis described above included 3 326 patients, 2 762 (83%) of whom came from 2 large trials. With the exception of 1 study, a transfusion threshold of between 9 and 10 g/dL was used. The duration of the intervention ranged from 2 to 6 weeks with follow-up of between 21 and 140 days. All but one study used iron (Fe) with EPO. No heterogeneity was noted in any of the findings.

Overall no mortality benefit accrued from EPO (OR 0.86, confidence interval (CI) 0.71 - 1.05; p=0.14; n=3 314) and, among patients who received more than 40 000 U/week, there was a trend to harm. Adverse events were evaluated in 6 studies; however, LOS and duration of ventilation were not suitable to be included in the pooled analysis. Although no study actively screened for common EPO-associated adverse events such as thrombosis, the overall OR for thrombosis with EPO was 1.32 (CI 0.95 - 1.84). The largest trial found a significant increase in thrombosis and a trend to increased myocardial infarction.[90]

Transfusion requirements were evaluated in 7 studies. Although EPO reduced the odds of a patient receiving at least one transfusion (OR 0.73; CI 0.64 - 0.84), given the transfusion thresholds of 9 - 10 g/dL, the value of this is questionable and a reduction in transfusion was not found in the one study with a restrictive transfusion threshold ≤8 g/dL.[90]

Luchette *et al.*[89] randomised 192 trauma patients to EPO or placebo. They assessed functional outcomes at 12 weeks, transfusion requirements, discharge Hb and thromboembolic events. Aside from a 0.3 g/dL higher discharge Hb in the EPO group, no differences were found.[87] Lundy *et al.*[88] performed a retrospective review of a previous burns study looking at the subgroup with severe burns >30% (n=25). Two control groups, historical (n=52) and a contemporary group (n=29), were used for comparison and no significant differences in mortality or transfusion needs were found. Finally, Nichol *et al.*[89] randomised 606 patients with moderate to severe TBI to weekly EPO or placebo. They found no difference in the proportion of patients with a

Glasgow outcome score extended (GOSE) of 1 to 4. There was also no difference in mortality.[89]

In summary, given the lack of a clear mortality benefit and the risk of adverse events, the use of EPO does not justify the small decrease in transfusion requirements. Routine EPO cannot be recommended for anaemia in critically ill patients, given the current data.

Fe therapy

Under physiological conditions, there is a balance between Fe absorption, Fe transport and iron storage in the human body. However, Fe deficiency and Fe-deficiency anaemia (IDA) are common conditions among medical, surgical and critically ill patients. Fe deficiency can be either absolute or functional. In absolute Fe deficiency, iron stores are depleted; in functional Fe deficiency,[58] Fe stores, although replete, cannot be mobilised as fast as necessary from the macrophages of the reticuloendothelial system (RES) to the bone marrow. Increased secretion of hepcidin, a hormone that controls ferroportin activity in releasing Fe from cells, may play a role.

The majority of data evaluating the use of iron in critically ill patients comes from a recent systematic review and meta-analysis.[92] The goal of this review was to evaluate the effects of Fe supplementation on RCC transfusion and clinical outcomes. The systematic review included published data to 14 March 2016 and included 5 studies. One additional study published after 2016, the Ironman study by Litton *et al.*,[93] was included for review in these guidelines.[93]

The systematic review included critically ill patients randomised to Fe (whether oral, intravenous or intramuscular) v. placebo or no therapy. Pregnant patients, those with chronic kidney disease and paediatric patients were excluded. Five trials included 665 patients of whom 368 received Fe therapy and 297 placebo. Four of these trials were in a surgical ICU, one each in a combined medical and surgical unit, and one in a trauma ICU. Two trials included vitamin B_{12}, folate and vitamin C as co-interventions. There was no effect on mortality (relative risk of death 1.04 (0.43 - 2.52)). There was also no effect on red cell transfusion requirements (5 trials) or adverse events (1 trial). Complete data on ferritin levels were available in 3 out of the 5 studies and there was a significant increase in the Fe therapy group in both the short and medium term. All outcomes showed heterogeneity reflecting differences in critically ill populations, interventions and dose.

The Ironman study randomised 140 patients equally into 2 groups receiving intravenous Fe or placebo. Patients with 'severe sepsis' were excluded from the study. There was no significant difference in mortality, LOS (both ICU and hospital) and there was no difference in the number of RCC transfusions between the groups. The discharge Hb was significantly higher in the Fe treatment group (10.7 v. 10 g/dL; p=0.02). Infections or bacteraemia were not different between the groups.

In summary, given the lack of a meaningful outcome benefit and the burden of infection in the SA context, we cannot recommend IV Fe as a general strategy for the management of anaemia in the critically ill. The risk of infection is, however, likely to be low in the non-septic critically ill patient.

Cell salvage

Cell salvage, the three-step process of collecting blood from the surgical field, washing and storage of the cells and re-infusion, has been practised since 1818.[94,95] Growing interest in this method of autologous transfusion is due to increased reports of complications with allogenic blood transfusion as well as diminished supplies from national blood bank services.[94,96]

Generic indications for the use of cell salvage include anticipated intra-operative blood loss of more than a litre or more than 20% blood volume, pre-operative anaemia, increased risk of bleeding, rare blood groups or antibodies and patient refusal of allogenic blood transfusion.[94] Benefits of cell salvage have been demonstrated in cardiac, vascular, obstetric and orthopaedic surgery.[95]

Postoperative cell salvage has in particular gained acceptance in orthopaedic surgery. Blood is collected from surgical drain sites and should be completed within 12 hours of surgery to minimise microbiological contamination. Re-infusion of blood needs to be started within 6 hours of collection commencement.[94]

Complications of cell salvage are uncommon. Coagulation defects may occur when large volumes of blood are re-infused as, during the washing process, red cells become suspended in saline solution and platelets and clotting factors are removed. With regard to washed v. unwashed cells, a Cochrane review revealed no additional risk or complication in using the latter.[94,95]

Cell salvage has proven to be economical (cost for 1 - 2 units RCC is equivalent to the cost of the disposables utilised for the procedure) and is well suited to resource-constrained environments where access to blood is often limited.[96,97] It is recommended that, given the relative lack of blood product availability and the neutral cost difference, cell salvage be used in SA where feasible.[96]

Artificial oxygen carriers

Hb glutamer-250 (bovine: HBOC-201) (Hemopure) is an Hb-based oxygen carrier (HBOC) registered with the South African Health Products Regulatory Authority (SAHPRA). It is indicated for the purpose of maintaining oxygen delivery in adult patients who are acutely anaemic, and where RCC are not available, there is a delay in access to RCCs, or where ABO incompatibility exists.[98-102] The product is not as effective as RCC for restoring Hb content and concentration, but it may provide an immediate alternative for improving oxygen transport in the circumstances described above. The product is temperature stable for up to 3 years, and may be administered via a central or peripheral vein, using a standard infusion set. The product may interfere with a number of laboratory tests and its use should be noted on any laboratory request form. The product is not readily available, and the reader is referred to a recently published consensus guideline for further information.[98]

In summary, there are no RCTs demonstrating benefit of this product but it is an option where administration of RCC is not possible.

4. Platelets

Refer to Table 4.

Platelet transfusions

Platelets are the second most numerous circulating cells in blood and are essential for coagulation, maintenance of vascular integrity and control of haemostasis. Abnormalities of platelet number and function are the most common coagulation disorder seen among ICU patients, and deficiencies can result in bleeding.[103]

Thrombocytopaenia or platelet dysfunction may result from congenital diseases, medications, liver or kidney diseases, sepsis, disseminated intravascular coagulopathy (DIC), massive transfusion, immune mechanisms, sequestration, nutritional deficiencies, the use of extracorporeal circuits, including cardiac bypass and extracorporeal membrane oxygenation (ECMO), as well as bone marrow infiltration and various haematologic diseases and associated therapies. Platelet transfusions are used for prophylaxis to prevent bleeding, or for treatment

Table 4. Platelets

4.1	In critically ill patients without acute bleeding and who are not undergoing invasive procedures, platelets should be administered at a platelet count ≤10 × 10^9/L. Platelet transfusion should be considered if the level is <20 × 10^9/L if active bleeding, or infection, or rate of platelet decline is such that platelet count is expected to drop below 10 in the next 24 hours.	Yes	B
4.2	A platelet count ≥50 × 10^9/L is generally acceptable for invasive procedures in the ICU.	Yes	C
4.3	A platelet count ≥20 × 10^9/L may be acceptable for CVC placement in the absence of any other bleeding risk.	Yes	D
4.4	A platelet count ≥50 × 10^9/L is generally acceptable for surgical procedures.	Yes	C
4.5	Neurosurgery and posterior ophthalmic surgery may require a higher platelet count ≥100 × 10^9/L.	Yes	C
4.6	A platelet count ≥20 - 30 × 10^9/L is generally acceptable for bronchoscopy with BAL.	ND	C
4.7	A platelet count ≥10 × 10^9/L is generally acceptable for lumbar puncture in patients with haematologic malignancies and >40 × 10^9/L in patients without haematologic malignancies, but lower in patients with ITP.	ND	C
4.8	A platelet count ≥75 × 10^9/L is generally acceptable for epidural catheter placement.	ND	C
4.9	A platelet count ≥20 × 10^9/L is generally acceptable for bone marrow aspiration/biopsy.	ND	C
4.10	In a patient with clinically significant bleeding, platelets should be administered if the platelet count is <50 × 10^9/L.	Yes	D
4.11	Where available, point-of-care viscoelastic testing may be used to guide therapy with platelets instead of the platelet count.	Yes	C
4.12	In the setting of large volume blood transfusion, a ratio of 1 unit of platelets for each 1 unit of RCCs should be transfused (1 pooled unit of platelets = 5 units).	Yes	C
4.13	Platelets should be transfused 1 pooled unit at a time, followed by reassessment to determine if additional platelet transfusion is required.	Yes	D

ICU = intensive care unit; CVC = central venous catheter; BAL = bronchoalveolar lavage; ITP = immune thrombocytopaenia; RCC = red cell concentrate.

of bleeding in patients who have inherited or acquired thrombocytopaenia or qualitative defects in platelet function.

Thrombocytopaenia is the most common disorder that causes bleeding, with the bleeding tendency in general being inversely proportional to the level of platelet count. A normal platelet count is 150 - 400 × 10^9/L and clinical thrombocytopaenia is usually regarded as a platelet count <100 × 10^9/L. Various grading systems for thrombocytopaenia have been proposed, with most clinicians regarding mild thrombocytopaenia as a count >50 - 100 × 10^9/L, moderate as >20 - 50 × 10^9/L, and severe as <20 × 10^9/L.

Platelet products include those manufactured from whole blood and those manufactured from apheresis. Platelets derived from whole blood are referred to as whole blood derived platelets, random donor platelets, or platelet concentrates. Those derived from apheresis are referred to as single donor platelets or apheresis platelets. In an average adult, platelet concentrates are usually administered in pools of 5 units. A single platelet concentrate unit (volume 30 - 60 mL), should increase the platelet count by 5 - 10 × 10^9/L. A pooled unit (volume 180 - 300 mL), should increase the platelet count by 30 - 60 × 10^9/L. In an infant, 10 - 15 mL/kg should achieve an increment of 50 - 100 × 10^9/L. An adequate response and/or need for further therapy should be guided by comparing the pre-transfusion count with that measured within 1 hour of completion of the transfusion. Platelets should be stored at room temperature with continuous gentle agitation and should be administered through a platelet giving set. Platelets have a shelf life of up to 5 days after collection.

In a recent systematic review, thrombocytopaenia (defined as a platelet count <150 × 10^9/L) was present in 8.3 - 67.6% of adult patients on admission to the ICU and acquired by 13 - 44% of patients during their ICU stay.[104-106] Thrombocytopaenia in ICU has been shown to be an independent predictor of mortality in adults,[104] is associated with bleeding,[105] and may deter clinicians from performing essential invasive procedures. The first principle of treatment of ICU-associated thrombocytopaenia is to treat the underlying cause. Data indicate that 9 - 30% of critically ill patients receive platelet transfusions, the majority of which are used to prevent rather than treat bleeding.[106,107] The use of platelet transfusions in patients with sepsis has been addressed previously in the Surviving Sepsis Campaign guidelines, in which platelet transfusions were recommended for adults with platelet counts <20 × 10^9/L who were considered to be at significant risk for bleeding. This was a weak recommendation reflecting consensus opinion and informed by data derived from other patient groups.[108] Despite the high utilisation of platelet products, platelet transfusion practices in the ICU are variable, and there is a paucity of evidence to underpin a very common medical intervention in this setting.[109] Various national and international guidelines and recommendations for platelet administration in critically ill patients exist but vary and are largely based on expert opinion. Two recently published guidelines from the USA and Britain are consistent with current standard of practice and similar to those from the Netherlands, France, Italy and the American Society of Oncology.[40,110]

Summary

The recommendations put forward in this guideline are based on a contemporary understanding of current best practice and evidence available.

5. Plasma

Refer to Table 5.

Table 5. Plasma

		Consensus	Grade
5.1	FFPs and FDPs should be considered clinically interchangeable.	Yes	N/A
5.2	Invasive procedures can generally be performed safely with an INR <2.	Yes	C
5.3	FDPs/FFPs are indicated prior to invasive procedures if the INR is >2.	Yes	C
5.4	In the bleeding patient, FFPs/FDPs should be administered if the INR is >2.	Yes	C
5.5	Where available, point-of-care viscoelastic testing, instead of the INR, may be used to guide therapy with FFPs/FDPs.	Yes	C
5.6	Empirical FFP/FDP therapy may be indicated in specific circumstances, e.g. large-volume haemorrhage, TTP.	Yes	B
5.7	A dose of 15 mL/kg of FFP/FDP should be utilised when indicated; this may need to be increased to 30 mL/kg in specific conditions.	Yes	C
5.8	In the setting of large-volume haemorrhage, a ratio of 1 unit of FFPs/FDPs to 1 unit of packed RCC should be transfused.	Yes	C

FFP = fresh frozen plasma; FDP = fibrin degradation products; INR = international normalised ratio; RCC = red cell concentrate.

Plasma products

Plasma products are available in various forms in SA:

- Fresh-frozen plasma (FFP) – prepared from whole blood and frozen within 8 hours of collection. The SA National Blood Service (SANBS) and the Western Cape Blood Transfusion Service provide this product.
- Freeze-dried plasma (FDP) – the liquid component has been removed, allowing storage at room temperature with reconstitution on site. It is useful if freezing, refrigerating and thawing facilities are not available. It is supplied by the National Bioproducts Institute.
- Cryoprecipitate-reduced plasma – here the cryoprecipitate has been removed. It is referred to as cryo-poor plasma.

The SANBS tests for both anti-A and anti-B antibodies. If above a certain threshold, the plasma is discarded. The FFP or FDP that is available is in a universal donor form.

Other products available internationally but not in SA include:

- plasma frozen within 24 hours after phlebotomy (PF24)
- thawed plasma – plasma that was frozen (i.e. FFP), that has been thawed (can be kept at refrigerator temperature (1 - 6 degrees) ≤5 days). This product may be useful in busy trauma centres where large volumes of plasma are used.
- liquid plasma – plasma that has never been frozen.

Each unit of FFP is prepared from a unit of whole blood and FDP is made from pooled plasma from many donors. FFP contains all coagulation factors and proteins present in the original unit of blood and is stored in a citrate anticoagulant solution.

FFP/FDP is used in the following situations:

- major bleeding in the setting of warfarin anticoagulation, vitamin K deficiency, liver disease, and as part of a massive transfusion protocol[85,111]
- to correct an INR >2 preceding an urgent invasive procedure[112,113]
- potential replacement during plasmapheresis for certain conditions (e.g. thrombotic thrombocytopaenic purpura (TTP))
- DIC if significantly prolonged prothrombin time (PT) or partial thromboplastin time (PTT), fibrinogen <0.5 g/L and serious bleeding
- afibrinogenaemia or hypofibrinogenaemia-related serious bleeding if cryoprecipitate is not readily available.

FFP/FDP should not be used primarily as a volume expander as crystalloids are as effective and have fewer potential side-effects.[114] The dose of plasma is based on the need to elevate the clotting factors to ~30% of normal. To do this, 15 mL/kg (3 - 5 units given that total plasma volume is ~2.8 L for a 70 kg patient) is generally required. Optimal effects are seen in the absence of heparin and with a fibrinogen level of at least 0.75 - 1.0 g/L.[115,116] The dose of 15 mL/kg of FFP/FDP may need to be increased to 30 mL/kg if clinically needed in specific conditions (e.g., needed in TTP to avoid need for plasma exchange). If volume overload is a problem, the plasma can be substituted by prothrombin complex concentrate (PCC) which also decreases risk of TRALI and rare instances of anaphylaxis.

6. Cryoprecipitate

Refer to Table 6.

Table 6. Cryoprecipitate

		Consensus	Grade
6.1	Cryoprecipitate should be given in patients with significant bleeding if fibrinogen <2.0 g/L.	Yes	B
6.2	Cryoprecipitate should not be given in the absence of significant bleeding even if fibrinogen levels are low.	Yes	C
6.3	Cryoprecipitate administration should be guided by point-of-care viscoelastic testing where available.	Yes	C
6.4	The recommended dose of cryoprecipitate for adults is 1 unit/10 kg (SANBS 10 units), or 1 pooled unit from WCBS.	Yes	C

SANBS = South African National Blood Services; WCBS = Western Cape Blood Services.

Use of cryoprecipitate

The final product of the coagulation cascade is fibrin, which binds platelets together and forms the matrix of a stable clot. The precursor molecule of fibrin is fibrinogen, in the absence of which a stable clot cannot be formed, even if all other components of the haemostatic system are available.

With major haemorrhage (especially when caused by major trauma or postpartum haemorrhage), and in bleeding disorders involving consumption or degradation of haemostatic components (as may be seen in sepsis, and after cardiopulmonary bypass), multiple pathways that specifically cause the loss or degradation of fibrinogen are activated. As a result, it is common for fibrinogen to become depleted more quickly than other components of the coagulation cascade. When this happens, the fibrinogen concentration in plasma can fall below minimum functional levels and critically impair coagulation, even though adequate concentrations of other components of the coagulation system are still present. Under these circumstances, clinically acceptable volumes of FFP/FDP may not contain sufficient fibrinogen to replace this disproportionate deficit, which may be worsened by the further administration of fluids or blood products that do not have high concentrations of fibrinogen.

To identify and treat this situation appropriately, a formal measurement of fibrinogen concentration or activity should be done. In the setting of ongoing significant bleeding, fibrinogen levels <2.0 g/L, as measured by the laboratory-based Clauss test, probably signify that fibrinogen deficiency is contributing to bleeding. Unfortunately, the Clauss test requires several hours to complete, and numerous pre-analytical factors can affect the result. Fibrinogen-specific viscoelastic tests can provide guidance in a more clinically useful timeframe, and these should be used when possible. Fibrinogen levels are normally elevated in pregnancy (4.0 - 6.0 g/L in the third trimester). Clinicians should be alert to early changes in fibrinogen levels in bleeding parturients, particularly if the level is <2.0 g/L, because of the association with postpartum haemorrhage. If both laboratory and viscoelastic test results are unavailable, it may be reasonable to infer a fibrinogen deficit in patients who have a history of rapid major blood loss or a prolonged consumptive process **and** have ongoing bleeding despite normalisation of temperature, correction of platelet deficit, and administration of recommended volumes of FFP/FDP.

To correct a fibrinogen deficiency that is causing ongoing bleeding, a concentrated (volume-restricted) dosage form of fibrinogen is desirable. Fibrinogen concentrate is not yet available in SA and cryoprecipitate, presented as non-pooled, individual units of ~15 mL volume by SANBS (WCBS use pooled cryoprecipitate consisting of an equivalent 10 individual units), processed from an individual donor unit of plasma, is the most concentrated source of fibrinogen available. Cryoprecipitate must be thawed in a prescribed manner over 30 - 60 minutes prior to issue as failure to follow the correct thawing procedure may result in inactivation of the contents. Owing to the single-donor source of each unit, there is an

unavoidable variation in the fibrinogen content of each unit, thus attempts at extreme precision in dosing are not possible. For adult patients with ongoing bleeding due to a measured or inferred deficiency of fibrinogen, a dose of 1 unit/10 kg of cryoprecipitate to functionally correct bleeding appears reasonable.

It may be logical to include cryoprecipitate as a component of ratio-based combined blood product bundles for emergency management of massive exsanguinating haemorrhage, but strong evidence as to the best ratio of cryoprecipitate to other products in such bundles is not yet available.

Summary

Cryoprecipitate is relatively expensive, is in limited supply, contains platelet fragments and other plasma proteins that may cause complications in recipients, and carries a risk of pathogen transmission. There is no evidence of benefit in patients who are not currently bleeding, even if measured fibrinogen concentrations are low. Cryoprecipitate should therefore not be given in the absence of significant bleeding. In patients with significant bleeding, 1 unit/10 kg of cryoprecipitate should be given if the fibrinogen level is <2.0 g/L (in the absence of viscoelastic testing) or viscoelastic testing indicates fibrinogen deficiency.

7. Tranexamic acid

Refer to Table 7.

Table 7. Tranexamic acid

		Consensus	Grade
7.1	Tranexamic acid should be administered empirically in critically ill patients with severe trauma within 3 hours of the injury.	Yes	B
7.2	The dose of tranexamic acid in severe trauma is 1 g IV stat and then 1 g IV over 8 hours.	Yes	B
7.3	Tranexamic acid should be administered empirically in bleeding postpartum obstetric patients.	Yes	B
7.4	The dose of tranexamic acid in bleeding obstetric patients is 1 g stat, and 1 g after 30 minutes if bleeding persists.	Yes	B
7.5	Empirical use of tranexamic acid may be considered in patients with upper gastrointestinal bleeding.*	No	D
7.6	The use of tranexamic acid may be considered in patients with TBI, if administered within 3 hours of injury.	ND	C
7.7	Empirical tranexamic acid therapy is not indicated in other settings in ICU.	Yes	D
7.8	Where available, point-of-care viscoelastic testing should be used to guide therapy with tranexamic acid	Yes	C

IV = intravenous; TBI = traumatic brain injury; ICU = intensive care unit.
*Review undertaken prior to the publication of the HALT-IT trial. Refer to section 7 (Tranexanamic acid: Upper gastrointestinal tract bleeding).

Tranexamic acid (TXA)

TXA is a synthetic derivative of the amino acid lysine and exerts its effects by binding tolysine binding sites on plasminogen, thereby inhibiting plasmin formation and displacing plasminogen from the fibrin surface. At higher concentrations, it can directly inhibit plasmin and partially inhibit fibrinolysis.[117]

Fibrinolysis is a key component of the haemostatic process that maintains vascular patency. Hyperfibrinolysis can occur as a result of severe tissue damage or trauma and is implicated in the pathogenesis of the coagulopathy that occurs after these events through upregulation of tissue plasminogen activator (tPA). Coagulation and inflammation are intimately interrelated and, along with damage-associated molecular patterns, plasmin promotes inflammation by activating monocytes, neutrophils and the complement cascade.[117]

The safety of TXA in the perioperative period in knee and hip arthroplasty surgery has been established over decades, with a few small studies indicating some benefit in the critically ill patient. This prompted the generation of four recent multicentre randomised trials looking at the use of TXA in the critically ill with postpartum haemorrhage (WOMAN), severe trauma (CRASH-2 and MATTERs), cardiac surgery (ATACAS) and post-upper gastrointestinal tract bleeding (HALT-IT). At the time of review, TXA was registered in SA for the following indications:

- heavy menstrual bleeding
- coagulopathies
- severe bleeding.

Severe trauma – in-hospital (CRASH-2)[118] and military (MATTERs)[119] trials

CRASH-2 was a multinational trial of 20 211 patients set in a civilian population in mostly low-to middle-income countries and is therefore of relevance to SA. The use of TXA at a loading dose of 10 mg/kg over 10 minutes within 3 hours of injury followed by infusion of 1 mg/kg/hour or placebo for 8 hours showed a reduction in mortality. This strategy did not have an effect on RCC transfusion incidence or volume but was safe and did not result in an increase in either venous or arterial thrombotic complications. The MATTERs trial sought to answer the same question in a non-civilian population with mainly penetrating injuries on the combat field. The results from MATTERs also showed reduced mortality from severe haemorrhage (transfusion >10 units RCC) in patients treated with TXA 1 g stat followed by subsequent doses as per prescribing physician (2.3 g per patient) compared with placebo. These trials provide evidence for the use of TXA in trauma.

In summary, in critically ill trauma patients, TXA should be administered within 3 hours of injury. The late administration of TXA is less effective and may be harmful. The suggested dose of TXA is 1 g bolus followed by 1 g infusion over 8 hours which was derived from the CRASH-2 trial.

Tranexamic acid for significant TBI (CRASH-3) trial[120]

CRASH-3 was a randomised, multinational, placebo-controlled trial of TXA in patients with TBI. The primary outcome was head injury-associated hospital mortality within 28 days. Patients with a Glasgow Coma Scale (GCS) ≤12 or with intracranial bleeding on computerised tomography (CT) scan, were initially randomised within 8 hours of injury, but this was subsequently reduced to 3 hours. The treatment group received 1 g of TXA over 10 minutes, with a subsequent infusion of 1 g over 8 hours. There was no significant difference in the primary outcome; however, subgroup analysis of patients with a GCS of 9 - 15 (mild to moderate TBI) showed a reduction in the primary outcome (RR 0.78 (95% confidence interval (CI) 0.64 - 0.95). Owing to the negative primary outcome, methodological controversies, and because the study results were released following the Delphi process required for these guidelines, the guidelines cannot recommend the use of TXA in patients with TBI; however, it does appear that the use of TXA is at least safe in these patients.

Postpartum haemorrhage patients – WOMAN[121] trial

The WOMAN trial was an international study that examined the impact of TXA on mortality after postpartum haemorrhage with a sample size of 20 060 patients. A dose of 1 g stat followed by another 1 g after 30 minutes if bleeding persisted (or stopped and restarted within 24 hours) was used. If TXA was given within 3 hours of bleeding, the mortality risk from bleeding was reduced significantly v. placebo with no alteration of the risk for hysterectomy and no increase in thrombotic risk. The WOMAN trial therefore supports the use of TXA in patients with severe postpartum haemorrhage.

In summary, critically ill patients with severe postpartum bleeding (>500 mL after vaginal delivery and 1 000 mL after caesarean delivery), should receive TXA once the bleeding threshold is reached. TXA should be given at a dose of 1 g at threshold followed by a dose of 1 g after 30 minutes if bleeding persists or recurs after 24 hours.

Cardiac surgery – ATACAS[122] trial

The Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial was a multicentre study of 4 331 cardiac patients undergoing coronary artery bypass surgery (CABG) who were randomised to preoperative aspirin 100 mg daily (n=1 059) 1 - 2 hours before surgery v. placebo (n=1 068). Patients were also randomised to TXA (n=2 311) v. placebo (n=2 320) dosed initially at 100 mg/kg within 30 minutes of induction, but halved to 50 mg/kg after 1 526 patients were enrolled. TXA was associated with a statistically non-significant reduction in mortality, but significantly reduced transfusion (46% less RCC) and re-operation for bleeding and tamponade compared with placebo (1.4% v. 2.8%). There was a significant increase in seizures in patients receiving TXA (0.7% v. 0.1%). The initial higher doses may have contributed to the high seizure rate, and the terminal dose of 50 mg/kg may have still been too high. Unfortunately, this study was underpowered to test for a dose effect. Preoperative aspirin neither reduced thrombotic nor increased bleeding complications.

In summary, no recommendations can be made with regard to the use of TXA in the post-CABG patient in ICU despite these positive intra-operative results.

Upper gastrointestinal tract bleeding – Cochrane review[123] of 7 randomised trials

The evidence for the use of TXA in upper gastrointestinal (GI) bleeding has been evaluated in a Cochrane review. The analysis of the 7 heterogeneous trials in the Cochrane database could not reach meaningful conclusions with regard to the impact of TXA on mortality, thrombotic complications and blood transfusion owing to various problems with the studies (high dropout, poor randomisation, poorly defined outcomes and extent of bleeding).[123] These small studies consistently showed marginal improvements in mortality and reduction in rebleeding rates with no increase in thrombotic complications.

In summary, it is reasonable for the clinician caring for the critically ill patient with an upper GI haemorrhage to consider the use of TXA. The dosing, safety and efficacy of TXA in this context need to be established through well-designed RCTs. At the time of review, the HALT-IT trial was in the recruitment phase. (Results of this large randomised, placebo-controlled, double blind trial was published in 2020. It was found that tranexamic acid does not reduce death from upper GI bleeding, and concluded that it should not form part of a uniform approach to the management of upper GI bleeding.[124])

8. Coagulation testing and monitoring

Refer to Table 8.

Table 8. Coagulation testing and monitoring

		Consensus	Grade
8.1	Point-of-care viscoelastic testing is the preferred test of coagulation function to direct therapy in critically ill patients.	Yes	C
8.2	The aPTT has a limited role in monitoring critically ill bleeding patients and is generally limited to monitoring the effect of heparin and screening for possible coagulopathies in the absence of viscoelastic testing.	Yes	C
8.3	The INR has a limited role in monitoring critically ill bleeding patients and is generally limited to monitoring the effect of warfarin and screening for possible coagulopathies in the absence of viscoelastic testing.	Yes	C
8.4	Fibrinogen levels are recommended in critically ill bleeding patients to guide the use of cryoprecipitate in the absence of viscoelastic testing.	Yes	C

aPPT = activated partial thromboplastin time; INR = international normalised ratio .

Conventional tests of coagulation

Conventional tests of coagulation (INR, aPTT, fibrinogen, and platelet count) have been used extensively in the clinical setting to diagnose and guide the treatment of coagulopathies. The INR and aPPT were, however, designed to assist with the diagnosis of inherited coagulation disorders and to guide therapy with warfarin and heparin respectively. There is little evidence to support their use in the critically ill patient who is bleeding or who is at risk of bleeding. Standard coagulation tests, in addition, only test a limited component of the physiological process of clot formation and not a functional assessment of clotting ability.

Viscoelastic testing

Viscoelastic testing (TEG or ROTEM) provides an integrated functional assessment of coagulation, theoretically allowing diagnosis and treatment of clinically relevant coagulation abnormalities. As viscoelastic testing is point-of-care, the test results are also generally available more rapidly than with standard coagulation testing.

Evidence

A review of the role of viscoelastic testing in cardiac surgery analysed data from 12 trials that included 6 835 patients, 749 of them in 7 RCTs, and showed significantly lower odds for transfusion of RCC, FFP and platelets with the use of viscoelastic testing. There was an increase in the odds of receiving fibrinogen and PCC in the viscoelastic testing group. Massive bleeding, transfusion and the need for surgical re-exploration were lower in the viscoelastic group.[125]

A Cochrane review from 2011 on the use of viscoelastic testing in surgical patients undergoing massive transfusion found no reduction in mortality as compared with standard practice, but did show reduced blood loss in the viscoelastic group.[126] An updated review from 2016, however, that included 8 new studies, did show a reduced mortality and reduced RCC, FFP and platelet transfusion in the viscoelastic testing patients.[127] The majority of the studies included in the systematic review were cardiac surgical studies.

Summary

While viscoelastic testing has been used extensively in the trauma setting, there is a paucity of good-quality outcome-based evidence to support its use. The available evidence does, however, support its role in the rapid diagnosis of specific coagulation abnormalities in these patients, which would allow rapid, specific therapy.[128-130] Viscoelastic elastic testing has also been utilised in obstetrics but, again, good-quality outcome-based evidence is awaited.[131,132]

9. Administration

Table 9. Administration

		Consensus	Grade
9.1	The use of blood and blood products should be directed by established protocols.	Yes	B
9.2	The use of blood and blood products should be subjected to gatekeeping controls.	Yes	B

10. Ethics

Refer to Table 10.

Table 10. Ethics

		Consensus	Grade
10.1	Informed consent should be obtained from the patient or surrogate prior to the transfusion of blood products if time allows.	Yes	N/A
10.2	In the adult patient who is unable to provide informed consent, and where a clear advanced directive against the use of blood products does not exist, blood products may be transfused in the emergency setting if deemed potentially lifesaving.	Yes	N/A
10.3	In the paediatric patient, where the surrogate refuses consent for the use of blood products, legal advice should be sought prior to the administration of blood products unless there is an emergency life-threatening situation necessitating immediate transfusion.	Yes	N/A
10.4	The use of blood products should be triaged in a resource-limited environment.	Yes	N/A

Blood product transfusions, like most other medical therapies, are not without risk and, as such, the issue of informed consent becomes vital. In the critical care setting, a number of ethical concerns may arise as patients may be incapacitated and unable to consent, minors may require blood product transfusions (where one or both parents may disagree with the healthcare practitioner), resources are often limited and, not uncommonly, blood product transfusions may be required as an emergency. It is essential that the decision-making process considers not only patient autonomy but also the legal framework that informs our clinical practice as well as the rules and regulations of our regulatory body.[133]

In SA, the actions of clinical practitioners are governed and guided by the following:[133-138]

- National Health Act No. 61 of 2003
- South African Constitution Act No. 108 of 1996
- Health Professions Act No. 56 of 1974
- HPCSA Ethical Guidelines for Good Practice in the Healthcare Professions (Booklet 4)
- Children's Act No. 38 of 2005 (Section 129)
- Common Law
- Mental Health Care Act No. 17 of 2002.

Informed consent should be obtained from the patient or surrogate prior to the transfusion of blood products if time allows

The National Health Act No. 61 of 2003 mandates that healthcare practitioners obtain informed consent following an explanation of the risks and benefits involved prior to the administration of transfusions as it constitutes a medical intervention.[108] Taking into account the risks posed by blood transfusions, written informed consent should be obtained.

Where the adult patient (18 years and older) is temporarily or permanently unable to participate fully in the informed consent/decision-making process (inability to decide owing to incapacity to either clearly understand the therapy, or the rationale for it, or the risks associated with blood product transfusions), the following process, which is listed in order of priority, needs to be followed:

(i) Known patient

If an advance directive or a living will is available or if there is a previous clear refusal that was voiced by the patient that s/he does not want to receive blood or blood products under any circumstances when s/he was capable of decision-making, the patient's autonomy needs to be respected.

If a legal court order has been issued, this should be respected and adhered to.

A surrogate decision-maker needs to be consulted for the process in the absence of 1 and 2 above. The order of consultation is as follows:

- spouse/partner
- parent
- grandparent
- adult child
- adult sibling.

(ii) Unknown patient or uncontactable surrogate decision-maker

It is recommended that in such situations (until the identity of the patient is established or the surrogate decision-maker is traced, the practitioner should do what is in the best interest of the patient and that the hospital manager be consulted.

(iii) Mentally ill patient

If the patient is capable of consenting, then s/he may do so. In situations where the patient is deemed to be incapable of consenting, then a court-appointed curator or a surrogate decisionmaker (as per above) would need to be consulted for informed consent.

In the adult patient who is unable to provide informed consent, and where a clear advanced directive against the use of blood products does not exist, blood products may be transfused in the emergency setting if deemed potentially lifesaving

In emergency situations where the patient is unable to provide informed consent, or the surrogate decision-maker is not immediately available/contactable and blood products are required immediately as a lifesaving measure or to prevent significant health deterioration, then a practitioner may transfuse blood products if deemed to be in the best interest of the patient. Once the patient improves clinically or the

surrogate decision-maker becomes available, they need to be informed of the therapy that was implemented and the rationale for it.

In the paediatric patient, where the surrogate decision-maker refuses consent for the use of blood products, legal advice should be sought prior to the administration of blood products. In an emergency life-threatening situation that necessitates an immediate transfusion of blood products, consent from the hospital superintendent (or the person in charge of the hospital if the superintendent is not available) should be sought

According to the Children's Act 38 of 2005, children who are 12 - 18 years old and are deemed mature and able to understand the need, risks and benefits of blood transfusions, are in a position to legally consent to the receipt of blood products.

In the following situations, informed consent needs to be obtained as follows:

(*i*) From the parent, guardian or caregiver in:

- children under 12 years of age
- any older child (12 to 18 years old) who
  - lacks sufficient maturity to participate in the informed consent decision-making process
  - is incapacitated and unable to participate in the informed consent decision-making process.

(*ii*) From the Minister of Health if:

- the parent, guardian or caregiver is unreasonable in their refusal (it is considered to be irrational or not in the interests of the child), or if they cannot be traced or are incapable of providing consent
- the child (<18 years old) refuses unreasonably.

Generally, both biological parents have parental rights and parental responsibilities and it is regarded as adequate to have one of them to provide informed consent for blood product transfusions. There may, however, be situations where a court order stipulates the need for dual consent and this needs to be adhered to. Further, there may be situations where only one parent has parental rights and parental responsibilities (custody/guardianship awarded to a single parent). In such cases, the informed consent must be obtained from the appropriate legally appointed individual. Parents with only visitation rights are not in a position to consent. If a parent with only visitation rights refuses to consent, then although the parent who has custody needs to consider the other's input, s/he is not obliged to comply with those views.

In a lifesaving emergency, where the transfusion cannot be deferred, and the parent or guardian is not contactable, the hospital superintendent (or the person in charge of the hospital if the superintendent is not available) may consent to the administration of the blood products.

The above process poses a problem in an emergency where blood products are required immediately, as a lifesaving measure, or to prevent significant health deterioration, and the parent or guardian refuses to provide consent. In such a situation, a practitioner may go ahead and transfuse blood products provided it is in the interest of the patient by obtaining consent from the hospital manager (or the person in charge of the hospital if the superintendent is not available).

Religious beliefs cannot be used as a sole reason (by parents or guardians) to withhold blood products for minors less than 12 years old or for incompetent children under 18 years of age.[139] In such situations, the 'child's right to life' supersedes the parents' right to dignity.

The use of blood products should be triaged in a resource-limited environment

Blood shortages constitute a global reality; this may be attributed to donor shortages, the sudden need for an increased supply (disaster), outbreaks of communicable diseases, transport problems, communication issues or labour strikes, among others. In SA, shortages are not uncommon, largely owing to an insufficient pool of donors. It is imperative that a process be in place to address such shortages. Many institutions have developed a framework to deal with variable levels of blood product shortages.[140,141] The purpose of these is to guide use and ensure that in such situations there is efficient, transparent and appropriate use of blood, and that key stakeholders work as a harmonised team to ensure that blood products are administered appropriately and in a transparent and equitable manner that also takes into account the clinical condition of the potential recipients.

The tasks of such a team should include:

- assessment and maintenance of blood product stocks
- development of transfusion guidelines
- developing proposals to manage variable levels of blood product shortages including:
  - blood conservation strategies
  - protocols to reduce inappropriate use (e.g. halting major elective surgery and avoiding transfusions where therapy is considered futile)
- ethical considerations that guide such decision-making (the process needs to be transparent, fair and defensible)
- review of appeals to the team
- audit of practice.

Implementation, monitoring and review of guidelines

Implementation of the guidelines may take place at:

- the level of the individual practitioner
- critical care unit level
- institutional level
- regional level (district/provincial/national).

For maximum impact, it is recommended that these guidelines be incorporated into comprehensive institutional or regional blood management guidelines and that they are implemented under the auspices of a dedicated institutional or regional blood management committee. The committee operationalises and reviews adherence to, and efficacy of, the guidelines.

It is recommended that frequent monitoring of adherence to the guidelines is conducted and that their effect on blood product utilisation is assessed.

It is intended that these guidelines should be reviewed every 5 years. In the event of practice-changing research emerging prior to the 5-year review, a focused update should be provided.

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