Provincial Health Services Authority

Trauma Services BC
Specialist Trauma Advisory Network

Clinical Practice Guideline

for the management of

TRAUMA-BASED MASSIVE HEMORRHAGE

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TRAUMA SERVICES BC
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UBC

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Guideline development group

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Trauma-based massive hemorrhage Algorithm

Pre-hospital notification suggestive of massive hemorrhage

Trauma Bay Preparation

Equipment
- Rapid transfusion device
- Auto-transfusion chest tube
- Warming device
- Compression; tourniquet; pelvic binder

Personnel
- Notify Trauma Team of potential MHP (assemble team in trauma bay) & pre-register patient
- Ensure dedicated phone line with blood bank and clinical
- Notify consult services prior to patient arrival if pre-hospital information warrants

Blood
- Initiate Massive Hemorrhage Protocol/ "Code Transfusion"
- Blood products
- Group & Screen
- Test every 30–60 minutes:
  - CBC
  - INR, PTT, Fibrinogen
  - Ca, Lytes, lactate
  - serum Cr
  - ABG
  - ROTEM/TEG if available
- Contact transfusion medicine for laboratory guided transfusion if available

Trauma Bay Management
- Ensure appropriate consulting services and the OR have been notified
- Minimize crystalloids to <1L
- Temperature: Avoid hypothermia, maintain target T >35C
- TXA: 2G bolus ASAP; if not given pre-hospital
- Start >2:1 transfusion [pRBCs, plasma] with platelets as needed then goal directed transfusion (Table 1)
- Targets:
  - Hb 70–90, INR <1.8
  - Plts >50
  - Fibrinogen >1.5
  - iCa >1.15
- Reverse/treat anticoagulants (Table 2)
- Monitor for complications: TRALI/TACO
- Monitor Ca++, K+

Resuscitation targets achieved
- Hemorrhage control
- Hb >70–90
- INR <1.8
- plt >50
- Fibrinogen >1.5
- iCa >1.15 targeted

Yes → **Terminate Massive Hemorrhage Protocol**

No → **Continue Massive Hemorrhage Protocol**

Goal Directed Transfusion — Table 1

Value	Transfuse
Hb <80	pRBC 2 units
INR >1.8	Plasma 4 units
Fibrinogen <1.5* (or <2 for post-partum)	Fibrinogen concentrate 4g
Platelets <50	1 unit platelets
Ionized CA <1.15	CaCl 1g

Anticoagulation Reversal — Table 2

Drug	Reversal
Warfarin	PCC 2000U IV over 10 min Vit K 10mg IV over 10min
Apixaban (Eliquis) Rivaroxaban (Xarelto) Edoxaban (Lixiana)	PCC 2000U IV over 10min Repeat in 1 hour if bleeding continues
Heparin / LMWH	Protamine — contact Pharmacy for dosing

Purpose

Hemorrhage is the most common cause of death in the first hour of arrival to a trauma facility [1]. The utilization of massive hemorrhage protocols improves appropriate blood use, mobilizes necessary teams in a more organized fashion, and facilitates standardized communication between the various teams involved [2].

These protocols, combined with educational programs (on the protocol and simulations), improve patient outcomes in hemorrhage associated with trauma. They also assist in judicious use of blood components and products, which is particularly helpful in locations with limited blood supply or intermittent blood shortages.

Summary of recommendations

PREHOSPITAL

1. Communicate with a trauma center and arrange transportation as early as possible after EHS recognition of a massive hemorrhage situation.
2. Pre-register patients to streamline the laboratory identification process.
3. Use ATLS approach with initial stabilizing measures such as compression, staples, tourniquets and pelvic binders.
4. Give 2 g TXA as early as possible in a massive hemorrhage.
5. Regularly assess temperature and keep patient above 36 degrees Celsius.
6. Prehospital transfusion can include pRBC and other therapies to improve coagulopathy, such as plasma and clotting factor concentrates.

IN HOSPITAL

7. Assign team designations prior to patient arrival, including a team leader, trauma surgeon, anesthesiologist, nurses, laboratory personnel and a dedicated blood runner.
8. Prime rapid transfusion devices prior to patient arrival.
9. Emergency blood products should be hanging and ready to infuse.
10. Use an ATLS approach with primary, secondary survey, c-spine precautions, and SAMPLE history for the initial assessment.
11. Predict massive hemorrhage with ABC and shock index scores.
12. Communicate a hospital wide notification of massive hemorrhage for mobilization of resources.

IN HOSPITAL *(continued)*

13. Achieve early large bore IV access (18g or larger) and arterial line monitoring.
14. First pRBC should be given within 10 minutes of arrival.
15. Send group and screen early so that crossmatched blood can be given within 1 hour.
16. Laboratories should have a pre-set 'massive hemorrhage protocol' panel including CBC, INR, PTT, Fibrinogen, calcium, electrolytes, lactate, base deficit and ABG, and repeat this at least every hour during active resuscitation.
17. ROTEM or TEG may be used as a point of care device to guide resuscitation.
18. 2:1 or 1:1 (pRBC: plasma) should be used until lab results can guide resuscitation (including transfusion of platelets based on thrombocytopenia).
19. Plasma should be given with 30 minutes of initiation of the protocol.
20. Blood and vasopressor treatment should take priority over crystalloid resuscitation. Limit crystalloids to 1L if possible.
21. Early fibrinogen administration should be considered in severe trauma patients.
22. Transfusion targets include a Hb of >70–90, INR <1.8, Platelets >50, Fibrinogen >1.5.
23. Complications to be monitored for during transfusion include hemolysis, TRALI, TACO, alloimmunization, hypothermia, acidosis, hyperkalemia and hypocalcemia.

FURTHER MANAGEMENT IN HOSPITAL

24. A key early decision point includes whether the patient needs surgical intervention or angioembolization for hemostasis.
25. Investigations that may aid decision making include a FAST scan and whole body CT.
26. Involving hematopathology can be important with reversal of anticoagulants. PCC/Vitamin K can be used for warfarin, and TXA/PCC can be used for anti-Xa DOACs if no specific reversal agents available.
27. Appropriate termination of massive hemorrhage protocol including informing the blood bank can prevent wastage of blood products.
28. Patients will need ICU or alternate higher level of care, and due to elevated thromboembolic risk will require chemical DVT prophylaxis when feasible.

Disclaimer for special populations

Although outside the scope of this document, massive hemorrhage protocols are often used outside of adult trauma, though largely derived from trauma literature. There are specific considerations for pediatric and obstetric populations in the above algorithm. Early consultation of obstetrics, pediatrics and neonatology is essential. These patients should be cared for in the appropriate hospital/setting, and in centres with experience with these populations.

PEDIATRICS

Pediatric populations need weight specific dosing of medications and blood products and strict fluid balances. Shock may not be as easily discerned as in adults, as children tend to compensate in the early stages better than adults do.

OBSTETRICS

In obstetrics, fibrinogen thresholds are higher due to higher fibrinogen levels in pregnancy. Consider surgical maneuvers to stop blood loss, including B-lynch sutures, Bakri balloon inflation, internal iliac artery ligation, interventional radiology embolization, and hysterectomy. Uterotonics should be administered if no contraindications are present.

When giving blood products, it is important to have a discussion regarding risk of alloimmunization and consider giving Rh immunoglobulin in consultation with a transfusion medicine physician/ hematopathologist when an Rh negative person of child bearing potential has received an Rh positive blood component.

Key management questions

PREHOSPITAL

1. What are the key steps at the prehospital stage in an expected massive hemorrhage protocol (MHP)?
2. What is the definition of a massive hemorrhage/transfusion situation?

IN HOSPITAL

3. Which scores and/or transfusion needs should be used to activate the massive hemorrhage protocol?
4. What are signs a patient should be transferred to a higher level of care centre?
5. What initial strategy should be used in a massively bleeding patient?
6. What clinical specialties and/or care providers should be involved in a massive transfusion protocol?
7. How can communication between clinical teams and the laboratory be optimized?
8. How can we minimize time to blood administration?
9. What laboratory work should be ordered at the beginning of the MHP, during the MHP, and how often?
10. What are the specific laboratory values that should guide resuscitation?
11. What role do point of care coagulation function tests (ROTEM or TEG) play in massive transfusion?
12. What complications should be assessed for in ongoing resuscitation?
13. What ratio of conventional blood products (red blood cells, plasma, and platelets) should be given?

FURTHER MANAGEMENT IN HOSPITAL

14. What role do clotting factor concentrates and other blood products play as adjuncts in MHP resuscitation?
15. What other non-blood product therapies can be used as adjuncts in MHP resuscitation?
16. If the patient is on anticoagulants, what should be done and/or who should be contacted?
17. What signals that the massive transfusion can be terminated?
18. What are actions that should be taken after MHP discontinuation?
19. When should a formal debrief process take place, and how can quality improvement be integrated into this process?
20. How often should MHP simulations and/or training occur for hospital staff to maintain competency?
21. Are there any special considerations non-tertiary care sites should keep in mind that may be different from larger centres?
22. What are some special considerations for obstetric and pediatric patients?
23. How often should this protocol be reviewed?

Answers to key management questions

PREHOSPITAL

KMQ-1. What are the key steps at the pre-hospital stage in an expected massive hemorrhage protocol (MHP)?

i. Communicate with an appropriate trauma center and transport patients with massive hemorrhage needs as early as possible

ii. Hospitals need to have a process for pre-registering a patient before arriving to the hospital

iii. Use an ATLS approach, along with critical initial stabilizing measures such as compression, staples, tourniquets and pelvic binders

iv. Give 2g of TXA as early as possible, ideally at the pre-hospital stage

v. Ensure the patient's temperature is monitored and stays above 36 degrees Celsius

vi. Pre-hospital transfusion can include pRBC and other therapies to improve coagulopathy, including plasma and clotting factor concentrates (such as prothrombin complex concentrates and fibrinogen concentrate)

RATIONALE

The most important first step when patients with massive hemorrhage are encountered is to get them to an appropriate trauma facility. In order to identify the patient early in the healthcare pathway, hospitals must have a process for pre-registration. Pre-registration will allow the blood bank to issue blood more efficiently using the electronic system. Along with initial stabilization efforts at the pre-hospital stage, the trauma facility needs to be contacted so that the trauma team can assemble, the blood bank can be aware of a possible massive transfusion, and so that the emergency department can mobilize resources.

After ensuring adequate oxygenation and ventilation, initial stabilizing measures for bleeding include local compression, dressings, staples, tourniquets, pelvic binders and early administration of blood products [3]. On recognition of a possible massive transfusion situation, TXA (2g) should be given as early as possible. No literature currently supports the superiority of one dosing strategy over another, where 1g bolus + 1g infusion and 2g bolus strategies have both been observed in the literature. Prehospital TXA appears to reduce mortality in trauma patients, and one meta-analysis found a trend toward lower 30-day mortality and reduced risk of thromboembolic events [4]. TXA must be given within 3 hours of injury to provide benefit, and earlier TXA leads to better outcomes in massively hemorrhaging patients.

Efforts to keep the patient warm from initial presentation throughout resuscitation are critical. This is to avoid the triad of hypothermia, acidosis, and coagulopathy, which tend to beget each other. To achieve this goal, wet clothing at the scene needs to be removed and the patient should be covered with warm blankets/forced air warmer, warm fluids should be used, and the ambient temperature of the environment needs to be reflective of this.

With respect to prehospital blood transfusion, although systematic reviews have showed observational studies suggesting improved survival after prehospital RBC transfusion, consistent evidence of beneficial effects have not been found [5]. That being said, it may improve initial hemodynamic parameters, and early pRBC transfusion seems pragmatic in the appropriate scenario. Interestingly, in a meta-analysis by Coccolini et. al in 2019, they found that prehospital plasma transfusion may reduce 24-hour mortality in patients with hemorrhagic shock [6]. This was based on both the PAMPer and COMBAT trials [7, 8]. It did not, however, influence 1 month mortality, acute lung injury or multi organ failure rates.

Thus, we suggest that prehospital resuscitation include TXA, and that prehospital transfusion with pRBC and/or plasma be used pragmatically.

KMQ-2. What is the definition of a massive hemorrhage/transfusion situation?

i. In adults, massive hemorrhage is defined by losing a total blood volume within 24 hours, 50% of total blood volume (40 ml/kg) replaced within 3 hours, or by subjective assessment of rapid bleeding [9, 10]

ii. Rapid bleeding has been proposed as 4 units of pRBC within 4 hours, or 150 mL/min

iii. In pediatrics, massive hemorrhage may be defined as 50% blood volume lost in 3 hours, 100% blood volume in 24 hours, or >10% TBV in one minute [11]

iv. Patients at risk of massive hemorrhage are those in with hemodynamic instability or clinical signs of end organ dysfunction, or have had a severe penetrating injury

IN HOSPITAL

KMQ-3. Which scores and/or transfusion needs should be used to trigger the need for activating the massive hemorrhage protocol?

i. Use of both clinical gestalt and an objective trigger for activating the massive hemorrhage protocol are recommended, with clinical audits to assess appropriateness.

   The ABC Score is recommended if point-of-care ultrasound is available, otherwise Shock Index is an appropriate alternative.

   a. **ABC Score:** >2 of the following present, massive transfusion likely required:

      - Penetrating mechanism, systolic blood pressure ≤90 mmHg, heart rate ≥120 beats per minute, positive FAST ultrasound

   b. **Shock Index:** Heart Rate/Systolic Blood Pressure — if >1, then likely to require massive transfusion

ii. Other non-score ways to predict massive hemorrhage include persistent hemodynamic instability despite blood/fluid resuscitation, and clinical indications suggesting further intervention will be required (i.e., surgery or angioembolization)

RATIONALE

There are several algorithms that exist that predict the need for massive transfusion. Some scores may not be as practical to use since they depend on laboratory data. Before laboratory data is back to guide transfusion, the Assessment of Blood Consumption score (ABC) and Shock Index (heart rate over systolic blood pressure) can be used. The ABC score has been shown to be accurate and easy to use [12]. If ultrasound is not available, the Shock Index (heart rate over systolic blood pressure), is a simple score that only requires the vitals of the patient but has just fair performance [12]. These two scores are probably the most common scores used today in the setting of massive hemorrhage [13].

We propose the ABC score as a simple, effective score, that may overpredict massive transfusion at times in its efforts to avoid missing massive transfusion situations [1, 9]. The four predictors are penetrating mechanism, systolic blood pressures less than 90, HR >120, or positive fast; 2/4 is a positive result. The sensitivity and specificity for a massive hemorrhage situation range from 75–90%, and 67–88%, respectively [14].

Most importantly, the ABC score has a negative predictive value of less than 5%, meaning it identifies more than 95% of patients who will need a massive transfusion. Its positive predictive value is estimated between 50–55%, meaning it may overpredict the need for transfusion in 45–50% of people [12].

Other ways to predict the need for massive transfusion apart from predictive scores include persisting hemodynamic instability with fluid/blood resuscitation, and indications that bleeding will require further intervention such as surgery or angioembolization.

KMQ-4. What are signs a patient should be transferred to a higher level of care centre?

i. Early communication between the sending and receiving site clinical teams is needed to ensure an appropriate care plan is made

ii. Interventions for bleeding control including surgical intervention should be considered before transfer

iii. Predicting that local resources will be exhausted (blood products) or that resources are not available

iv. Predicting the need for surgical services or interventional radiology that is not available locally

v. Noncompressible and amputation injuries generally need evacuation within 60 minutes

RATIONALE

More obvious reasons to transfer to a higher level of care include need for further blood products that some sites may not have available [13]. Surgical/interventional radiology services are other reasons for transfer.

The number of surgical scenarios that would necessitate transfer are extensive. Generally, those with noncompressible abdominal/torso injuries and amputation injuries will need immediate evacuation within 60 minutes.

KMQ-5. What in hospital strategies should be used in a massively bleeding patient?

i. Clinical staff must be trained to recognize major blood loss early, and be familiar with contents of MHP and when to activate and deactivate local MHP

ii. Team designation should take place prior to the arrival of the patient including a team leader, with the active and early presence of a surgeon

iii. Rapid transfusion devices should be easily accessible in the trauma bay

iv. All bleeding patients require an ATLS approach with a primary and secondary survey, consideration of C-spine precautions, SAMPLE history and appropriate investigations

v. Patients need to be in a continuously monitored setting, oxygen applied, and have appropriate access for blood administration (large bore IV, i.e., 14–18 G and/or central access) if possible

vi. Each centre should have a clear method of communicating a 'code transfusion' or MHP activation

vii. Temperature should be monitored at two places and adjusted to prevent hypothermia. Fluids should be transfused through a warming device (except cryoprecipitate and platelets)

viii. Permissive hypotension (systolic blood pressure 80–100 mmHg or mean arterial pressure of ~50–60 mmHg) should be considered in specific patient cohorts (such as young patients without ischemic disease or neurological damage)

RATIONALE

It is very important that staff are familiar with their local MHP, and when to activate and deactivate it [36].

Initial strategies, as with any trauma patient, should include an ATLS approach with a primary and secondary survey with C-spine precautions, a focused history (such as SAMPLE: Signs & Symptoms, Allergies, Medications, Past medical history, Last oral intake, and Events), and appropriate investigations. However, severe hemorrhage may preclude finishing the primary survey.

As soon as the patient rolls into the trauma bay, efforts should be made to apply monitors, achieve large bore IV access (18 G or larger), oxygen, and get a full set of vitals. The trauma team ideally should be awaiting the patient and team designation should have already taken place. There needs to be a leader present who will delegate other positions. Each centre should have a clear method of communicating activation of the MHP, often by starting communication with the blood bank. Temperature needs to be always monitored during a massive hemorrhage protocol and kept above 36 degrees Celsius. Rapid transfusion devices should be available and primed prior to patient arrival, as should methods of keeping the patient warm, such as a forced air warmer and warm fluids. Emergency blood products should be available promptly, where strategies to decrease turnaround time are to be optimized before MHP activation.

If adequate prehospital hemorrhage temporization has not occurred, efforts should be made to have local compression, tourniquets, staples, and pelvic binders in place.

If it is discovered based on the patient's medication history or bloodwork that anticoagulants are contributing to massive blood loss, they should be immediately reversed. Please refer to key management question 16 for further detail.

KMQ-5. What in hospital strategies should be used in a massively bleeding patient? *(continued)*

ix. Obtain consent for blood wherever possible

x. Transfuse pRBC within 10 minutes of arrival to the hospital should be a key goal metric for best resuscitation practice

xi. Send a group and screen as soon as possible to facilitate use of group-specific blood components; with a request for 2–4 units of red blood cells

xii. Send a rapid testing laboratory panel with expedited turnaround times such as a "massive hemorrhage protocol" lab set for completeness of investigations and for efficiency

xiii. Massive hemorrhage bloodwork includes CBC, INR, PTT, Fibrinogen, calcium, electrolytes, lactate, base deficit and ABG

xiv. ROTEM or TEG can also be used in addition to the above bloodwork

xv. Determine early if patient has taken anticoagulants or antiplatelets. If they are contributing to blood loss, reverse, unless specific contraindications exist

RATIONALE

If possible, consent should be obtained by either the patient or substitute decision maker, and an appropriate risk discussion of blood transfusion should be had. We realize that given the time-critical nature of a massive hemorrhage situation, this may not always be possible. The first pRBC should be started as soon as possible, ideally within 10 minutes. This is the first critical timepoint. Secondly, the group and screen is to be sent as soon as possible (ideally before the first unit of blood) to facilitate the use of group specific units, with a request for 2–4 units of red blood cells (uncrossmatched until the group is determined). This hemorrhage blood work should be sent every hour at the least, and should include CBC, INR, PTT, Fibrinogen, calcium (ideally ionized), electrolytes, lactate, base deficit and an ABG. Initial response including transfusion and resuscitation should not be delayed for laboratory information to come back. For assessment of coagulation, repeat point of care tests such as TEG or ROTEM can also be used.

KMQ-5. What in hospital strategies should be used in a massively bleeding patient? *(continued)*

xvi. Serial testing of bloodwork including coagulation testing should be sent every 30–60 minutes, based on bleeding severity, during a massive hemorrhage situation

xvii. A >2:1 (pRBC:plasma) ratio can be used with platelets if needed, until lab parameters are available to guide further transfusion needs

xviii. As soon as the blood group is known, it should be switched from the emergency blood supply, ideally within 1 hr (pRBC/plasma)

xix. A dedicated blood runner needs to be appointed

xx. For RBC transfusion, threshold is Hb 70g/L, target range for post-transfusion of 70–90g/L

RATIONALE

An initial >2:1 (pRBC:plasma) ratio should be used with platelet transfusions, which is also recommended by the European and Ontario guidelines (3). Plasma should be given within the first 30 minutes of initiation of the protocol. A >2:1 (pRBC:plasma) approach with platelet transfusions when needed is appropriate in most MHP scenarios (many trauma patients do not have thrombocytopenia). The British guidelines suggest 1:1 (pRBC:plasma) ratio in trauma, based on the PROPPR study's secondary outcomes [36]. Increased plasma in other types of medical and surgical bleeding may lead to worse outcomes.

Once group specific blood is available, it should be immediately switched to from the emergency blood supply. To aid in the efficiency of delivery of blood products, there needs to be a dedicated blood runner. The switch to group specific and crossmatched units should be achieved ideally within 1 hour, however, there will be exceptions such as if patient has unexpected red cell antibodies identified or rare blood type, in which case the crossmatch may take up to several hours or even days.

The British guidelines recommend serial testing every 30 to 60 minutes, depending on the severity of the bleeding.

KMQ-5. What in hospital strategies should be used in a massively bleeding patient? *(continued)*

xxi. Crystalloid use for fluid resuscitation should be given at a maximum of 2 litres, ideally less than 1 litre before blood transfusion, to avoid dilutional coagulopathy

xxii. Vasopressors should be prioritized to support blood pressure before excessive fluid resuscitation

xxiii. A bedside transthoracic echocardiogram can guide inotrope use

xxiv. Transfusion medicine services determine the Rh status of emergency supply pRBCs, where Rh negative and Kell negative pRBCs are ideally used for patients with childbearing potential (primarily women aged <45)

xxv. Baseline blood samples for ABO group and antibody screen taken as early as possible (ideally prior to start of 1st transfusion)

xxvi. Group AB plasma can be used as emergency supply, with group A plasma as an alternative

RATIONALE

Blood transfusion takes priority over fluid resuscitation, as over resuscitation with fluids may lead to a dilutional coagulopathy. Fluids that are appropriate to use include balanced solutions such as Ringer's lactate or Plasmalyte. Normal saline should not be used to avoid hyperchloremic metabolic acidosis, which could further exacerbate the triad of hypothermia, acidosis and coagulopathy. Lactated Ringer's should be avoided in head injury, as it is relatively hypotonic and may worsen edema and increased intracranial pressure, when compared to Plasmalyte and Normal saline. Albumin use in traumatic brain injury has been shown to worsen outcomes. Colloids are also not recommended in the setting of acute trauma resuscitation.

Vasopressors can be prioritized to support blood pressure in the interim. A bedside transthoracic echocardiogram can assist in assessing systolic function to determine whether inotropes are needed.

O-negative pRBCs should be reserved for persons of childbearing potential (often women aged <45 years old), with O-positive pRBCs for other populations until the group is determined, where group-specific blood should be used as soon as possible [36]. This mirrors the British MHP guidelines and Canadian transfusion medicine standards.

Traditionally AB plasma has been given as emergency supply, however, AB blood type is relatively rare, and A plasma with low titre anti-B agglutinin is now commonly being used [9]. The STAT study found that the use of group A plasma during initial resuscitation of traumatically injured patients was not associated with in hospital mortality, early mortality or increased length of stay [15]. Seheult et. al in 2020 looked retrospectively on civilian trauma patients and found that incompatible plasma did not lead to higher 30-day mortality [16]. Lastly, Chhibber et. al examined the outcomes associated with group A plasma versus group AB plasma for patients with Group B or AB blood type, and they found no hemolytic or other adverse reactions [17].

KMQ-5. What in hospital strategies should be used in a massively bleeding patient? *(continued)*

xxvii. Early fibrinogen administration with the first units of blood administered should be considered in severe trauma patients, with a recommendation to target levels of at least > 1.5 g/L

xxviii. Blood coolers should be organized according to blood administration priority

xxix. Smaller institutions may need to use factor concentrates and fibrinogen in place of stored plasma

xxx. Key clinical decisions in early hemorrhage include whether or not the patient needs surgical intervention or angioembolization for hemostasis

RATIONALE

If fresh frozen plasma is thawed, it only retains a shelf life of 5 days post-thaw in a controlled refrigerated setting. Thawed plasma minimizes delay for plasma administration for massive hemorrhage use, but may have degradations of factor levels [9] and does contribute to significant plasma wastage.

Low fibrinogen levels are associated with impairment of hemostasis, bleeding, and poor outcomes in patients with trauma [18]. Early fibrinogen administration should be considered in severe trauma patients, aiming for a level of at least 1.5g/L [30, 36]. A single-centre propensity score matched analysis by Itagaki et. al found that patients with an injury severity score greater or equal to 16 who were given Fibrinogen within 1 hour after arrival to the emergency department compared to no fibrinogen, or after the 1 hour mark, had a higher in-hospital survival rate compared to the control group.

When a massive hemorrhage protocol is triggered, it's important to have an organized way to deliver blood products. Various 'packages' or coolers have been proposed, with some organizations advocating giving equal proportions of blood/plasma/platelets in the first set of blood components, to reflect a 1:1:1 transfusion (pRBC:plasma:platelets) [9]. However, the European Trauma Guidelines and the Ontario Regional Massive Hemorrhage Protocol, have packages that reflect more of a 2:1 (pRBC:plasma) ratio, with platelet transfusion as needed given trauma patients are often not thrombocytopenic [3, 13]. Early fibrinogen replacement is also recommended through fibrinogen concentrate (4g) or cryoprecipitate (10 IU), with fibrinogen concentrate now largely considered standard of care.

For smaller institutions that may not have plasma stocked, recommendations include having 4 pRBC, 2000 IU PCC and 4 g fibrinogen, with platelets being ordered if needed immediately upon hearing of a massive hemorrhage situation, or prompt decision making to transfer to a higher-level centre [13].

Along with initial resuscitation, key decisions need to be made including whether to go to the operating room, for further imaging, or to interventional radiology for angioembolization. The decision to move to the operating room needs to be made early, so operating room personnel can mobilize, and equipment can be organized. Patients that damage control surgery should be considered for are those with deep hemorrhagic shock, coagulopathy, hypothermia, ongoing bleeding, hypothermia, acidosis or inaccessible major anatomic injury [3].

KMQ-5. What in hospital strategies should be used in a massively bleeding patient? *(continued)*

- **xxxi.** Decision to move to operating room needs to be made early (within an hour), so that the operating room personnel can mobilize, and equipment can be organized
- **xxxii.** Surgical techniques for hemostasis include packing, fibrin and synthetic glues
- **xxxiii.** Hypotensive resuscitation may reduce blood transfusion, ARDS and multiple organ dysfunction but increase acute kidney injury (AKI)
- **xxxiv.** Investigations that aid decision making include a FAST scan, and whole body CT
- **xxxv.** A hospital wide notification of massive hemorrhage may help to mobilize resources

RATIONALE

Those that are more stable, or with an unidentified source of bleeding may need further investigation in the emergency room. The initial assessment of a trauma patient should include a Focused Assessment with Sonography in Trauma (FAST) ultrasound exam, and a whole body CT scan [3].

Surgical techniques to aid hemostasis include packing for venous or moderate arterial bleeding, using collagen, gelatine, cellulose based products, fibrin and synthetic glues or other adhesives [3].

Regarding permissive hypotension, a meta-analysis in 2018 found that aiming for a low normal blood pressure in resuscitation reduced the need for blood transfusion, and incidence of ARDS, and multiple organ dysfunction [19]. However, it increased the incidence of AKI. It is contraindicated in patients with organ function compromised by ischemia, such as ischemic heart disease or concomitant brain injuries, where cerebral perfusion pressure needs to be maintained by keeping MAP >80 in elevated intracranial pressure (ICP) [3].

The Ontario Regional Massive Hemorrhage Protocol has suggested that in order to quickly utilize resources, and to mobilize teams and services, that a hospital wide notification of massive hemorrhage or 'code transfusion' announcement is made in the setting of a massive hemorrhage situation [13]. This sort of announcement alerts the hospital simultaneously to mobilize resources, reducing unnecessary calls and notifies other services that non-urgent transfusions may be delayed. Our group agreed with this recommendation.

KMQ-6. What clinical specialties and/or care providers should be involved in a massive transfusion protocol?

i. Trauma teams ideally should have a trauma surgeon, an anesthesiologist, and a clearly designated trauma leader

ii. Other team members may include the emergency team, nursing, critical care, blood transport personnel, a dedicated blood runner, communication services and the blood bank/laboratory

RATIONALE

It is critical to involve surgery on the trauma team as early as possible, as surgical control is often needed for definitive management.

Of course, the clinical specialties involved in a massive hemorrhage protocol will depend on the level of care the facility provides and available services. According to the World Federation of Societies of Anesthesiologists (WFSA), at a minimum, the trauma team should have a trauma surgeon (general surgeon) and an anesthesiologist, with a clearly designated trauma leader [3]. Other team members will include the emergency team, nursing, critical care, blood transport personnel with a dedicated blood runner, communication services and the laboratory/blood bank [13].

One of the most important team members is the transfusion medicine laboratory including the transfusion medicine physician on-call. They need to be alerted as soon as possible, ideally at the prehospital stage, so that they can get ready to mobilize blood products, and minimize time to first blood product, and time to type specific blood. One way to speed up this process up as outlined above is to have patients pre-registered at the prehospital stage.

KMQ-7. How can communication between clinical teams and the laboratory be optimized?

i. A 'Code Transfusion' announcement in the hospital may efficiently communicate to the blood bank as well as the rest of the hospital that resources need to be mobilized

ii. 1:1 communication between the lab and the clinical team during massive hemorrhage may avoid communication gaps, notably moving from one environment to the next

iii. The laboratory must have a system of communicating critical lab results

RATIONALE

As stated previously, the optimal way to communicate hospital wide is with a code transfusion announcement [13]. Coordinating the trauma team and massive transfusion is important. Otherwise, efforts must be made to contact the blood bank as soon as a massive hemorrhage situation is recognized, ideally at the prehospital stage. Teams must be assembled, and a dedicated blood runner as well as a designated role to have one-to-one communication with the blood bank should be assigned. Some hospitals advocate for dedicated phone lines or cell phones for communication between the blood bank and the resuscitation team.

The lab is responsible for communicating lab results including CBC and coagulation abnormalities, as well as complications related to transfusion such as hyperkalemia, hypocalcaemia and acidosis.

KMQ-8. How can we minimize time to blood administration?

i. Local laboratories must streamline communication, blood transport and testing

ii. Communication with the laboratory regarding need for massive transfusion should be made prehospital, but if in hospital, a "code transfusion" may convey the message quickly

iii. Dedicated contact persons between the blood bank and the clinical area should be established to communicate transfusion needs and laboratory results

RATIONALE

Every minute in a massive hemorrhage protocol is critical. A retrospective study by Meyer et. al found that for 680 patients, the median time from patient arrival to massive hemorrhage protocol initiation was 9 minutes with a median time from call to delivery of first cooler in 8 minutes [20]. In this study, every minute of time from massive hemorrhage protocol initiation to first cooler arrival delayed hemostasis and increased odds of mortality by 5%. As previously discussed, the Ontario Regional Massive Hemorrhage Protocol has suggested the same, with the expectation that the first unit of uncrossmatched pRBC be given within 10 minutes of activation of a massive hemorrhage situations [13].

The following critical time points will determine how fast blood can be administered:

1. Communication with blood bank regarding need for massive hemorrhage protocol
2. Time to first blood product after the massive hemorrhage protocol is initiated (goal <10 minutes)
3. Time to first plasma administration (goal <30 minutes)

Local laboratory departments must make concerted efforts to streamline communication, transport and testing to optimize this process. Identifying roles in the transport of blood from the laboratory to the bedside is also important to reduce turnaround time of the arrival of blood.

KMQ-9. What laboratory work should be ordered at the beginning of the MHP, during the MHP, and how often?

i. At a minimum, laboratory testing should be done every 30–60 minutes, depending on bleeding severity, during a massive hemorrhage protocol

ii. Blood work should include a CBC, INR, PTT, fibrinogen, electrolytes, ionized calcium, ABG, lactate +/- base deficit

iii. Point of care coagulation testing is an effective alternative

RATIONALE

At a minimum, laboratory testing should be ordered every 30 min to 1 hour during a massive hemorrhage protocol [3, 13, 36]. Blood work should include a CBC, INR, PTT, fibrinogen, electrolytes, ionized calcium, ABG, lactate and a base deficit. If point of care coagulation testing is available, it may be used as an alternative to repeat conventional coagulation testing. To streamline ordering laboratory tests in this scenario, a "massive hemorrhage" panel should be organized with the local laboratory. Shock can be monitored with repeated lactates or base deficits.

KMQ-10. What are the specific laboratory values that should guide resuscitation?

i. Transfusion should be goal directed as soon as possible.

ii. Hb in the range of 70–90, depending on the speed of blood loss.

iii. INR < 1.8 for plasma administration, as INR corrections to <1.5 are unrealistic

iv. Platelets >50, or >100 if torrential blood loss/concomitant head injury

v. Fibrinogen > 1.5, greater than 2 in obstetrics

vi. Calcium should be replaced if < 1.15

RATIONALE

Various organizations suggest different laboratory values to guide resuscitation in the setting of massive hemorrhage.

The European guidelines suggest the follow lab values [3]:

- Target Hb 70–90 for pRBC administration
- INR or PTT < 1.5 x normal for administration of plasma
- Platelets > 50, or >100 if ongoing, concomitant head injury
- Fibrinogen > 1.5 supplemented by 4 g at a time (which will raise fibrinogen by ~1 g/L; equivalent to 10 units of cryoprecipitate)

The Ontario Regional Massive Hemorrhage Protocol suggests the following lab values [13]:

- Hb > 80 g/L
- INR < 1.8
- Fibrinogen > 1.5
- Platelets > 50
- Ionized Calcium > 1.15

For replacement, fibrinogen concentrate can be used for fibrinogen <1.5g/L. Cryoprecipitate can be used to replace fibrinogen, however, longer time to prepare, limited shelf life (6 hours generally), and lack of pathogen reduction make it a less desirable product [3, 9].

Although an initial PTT is useful for determining if the patient has a pre-existing coagulopathy or has anticoagulants on board, as long as the PTT and INR are concordant, it may not be necessary in repeat laboratory work [13].

The threshold for platelet transfusion should be higher in patients with intracranial or spinal bleeding, or in actively falling platelet counts [36].

KMQ-11. What role do point of care coagulation function tests (ROTEM or TEG) play in massive transfusion?

i. Thromboelastography and ROTEM offer rapid turnaround time and can eliminate lag times and potential miscommunication of third parties

ii. If using point of care coagulation testing, we suggest an immediate ROTEM on arrival of the patient, and then a repeat ROTEM after each cooler until bleeding has been controlled

RATIONALE

Point of care testing such as thromboelastography and ROTEM are playing an increasing role in the functional assessment of acute bleeding, outside of their typical use in cardiac operating rooms. Their main benefits are rapid turnaround time and elimination of the lag time as well as potential miscommunication of third parties. According to the European guidelines, the turnaround times for TEG and ROTEM are substantially faster than conventional coagulation testing, and some studies have saved as much as 30–60 minutes in massive hemorrhage situations[3]. PT/PTT may overestimate coagulopathy treatment and point of care tests offer a more functional assessment of clot formation[21, 22].

FIBTEM via ROTEM is a measure of hyperfibrinolysis and FIBTEM A5 < 10 mm has been associated with prolonged bleeds[9, 23].

KMQ-12. What complications should be assessed for in ongoing resuscitation?

i. Constant vigilance is necessary to pick up the following complications of transfusion: hemolysis, TRALI, TACO, hypothermia, acidosis, hyperkalemia and hypocalcaemia

ii. Repeated lab work every hour and consistent temperature monitoring can prevent these complications

iii. The most significant adverse transfusion-associated event in emergencies is ABO mismatched transfusion, which can lead to hemolytic transfusion reactions and is a life-threatening emergency

iv. Pretransfusion bed side checks and identification checks are critical to prevent morbidity and mortality from transfusing wrong blood to patients

RATIONALE

The following complications need to be looked out for during massive transfusion: hemolysis, TRALI, TACO, hypothermia, acidosis, hyperkalemia and hypocalcaemia. The most significant adverse transfusion-associated event in emergencies is ABO mismatched transfusion.

Pretransfusion bed side checks and identification checks are critical in order to prevent iatrogenic transfusion complications including ABO incompatibility.

Hypocalcaemia occurs from binding of citrate and needs to be monitored for. We recommend replacing with 1 g of calcium chloride or 3 g of calcium gluconate for calcium less than 1.15 mmol/L.

Hypothermia is a major cause of morbidity and mortality in trauma and massive hemorrhage and the patient's temperature must be monitored as soon as possible. A systematic review compared blood loss and transfusion requirements in normothermic versus mildly hypothermic patients (34–36 degree) and found that even a 1-degree Celsius difference dramatically increased blood loss by approximately 16%, and increased relative risk for transfusion by approximately 22%[24]. Temperature needs to be continually assessed and monitored from the prehospital stage until bleeding is controlled. At a minimum it should be checked at least every 30 minutes, or ideally, should be continually monitored. The temperature should be kept above 36 degrees. Hypothermia is mitigated by warm blankets, forced air warmers, warm fluids, warm environments, and potentially by extracorporeal membrane oxygenation (ECMO).

KMQ-13. What ratio of conventional blood products (red blood cells, plasma, and platelets) should be given?

i. A >2:1 (pRBC:plasma) is appropriate in most MHP scenarios

ii. Regardless of the ratio chosen, it's important not to over resuscitate with plasma or platelets. Thus, pRBC are prioritized in initial blood coolers

iii. Further blood transfusions are targeted for patient's needs. This avoids unnecessary patient exposure, risk of adverse events, and helps preserve local blood inventories

RATIONALE

The PROPPR trial showed that a ratio of 1:1:1 (red blood cell:plasma:platelets) versus 2:1:1 had no statistically significant difference in mortality at 24 hours or at 30 days [25]. However, exsanguination in the first 24 hours was decreased in the 1:1:1 group, and hemostasis was also improved in the 1:1:1 group.

The Ontario Regional Massive Hemorrhage Protocol uses a 2:1 strategy [12]. The European guidelines recommend at least a 2:1 ratio of pRBC to plasma, citing over resuscitation with plasma and platelets as being dilutional and potentially detrimental [12]. With respect to which ratio to use, we currently do not have a formal recommendation and think there are pros and cons to both approaches. We believe a >2:1 approach with consideration of platelet transfusion depending on clinical setting is appropriate in most MHP scenarios, but that a 1:1 strategy may better suit the pathophysiology of a trauma based bleed. This is, of course, until laboratory data or point of care coagulation testing can guide resuscitation, which is a more targeted approach.

FURTHER MANAGEMENT IN HOSPITAL

KMQ-14. What role do clotting factor concentrates and other blood products play as adjuncts in MHP resuscitation?

i. Recombinant Factor VII a is not recommended unless in exceptional circumstances where all other hemostatic efforts have been exhausted. It is associated with an increased thromboembolic risk

ii. PCC can be used to reverse warfarin and treat anti-Xa anticoagulant associated bleeding but is not recommended to correct INR/PTT abnormalities alone

RATIONALE

We do not recommend the use of Recombinant Factor VIIa, unless in exceptional circumstances where all other hemostatic efforts have been exhausted to correct significant bleeding, and with expert consultation. A Cochrane review has found that there is limited evidence to support its use, and there is an unacceptable risk of thromboembolic events [26]. The American College of Surgeons also do not recommend the use of factor VII in the management of refractory hemorrhage in trauma [1].

With respect to prothrombin complex concentrates, the European guidelines do not endorse their use in massive transfusion resuscitation, but do recommend their use in the reversal of anticoagulants such as warfarin or direct-acting anticoagulants in the absence of their respective antidotes [3]. PCCs should not replace plasma in the setting of massive hemorrhage. One downside to the use of PCCs in massive hemorrhage is that there is a subset of patients that may have an enhanced risk of thrombosis [9]. Plasma is the preferred agent for factor replacement in massive transfusion.

Vitamin K should usually accompany PCC administration for warfarin reversal. See key management question 16 for further explanation.

KMQ-15. What other non-blood product therapies can be used as adjuncts in MHP resuscitation?

i. Tranexamic acid (TXA) administration should be prioritized and be given at the prehospital stage if possible

ii. The timing of TXA is critical and must be given within 3 hours of the injury for beneficial effect

iii. 2g bolus of TXA should be given. A 2g bolus is accepted practice; along with the traditional dosing strategy of 1g bolus over 10 minutes with a maintenance infusion of 1g over 8 hours

RATIONALE

Tranexamic acid is a cornerstone in massive hemorrhage management. It significantly increases overall survival (up to 70%) in situations involving bleeding associated with trauma and in post-partum hemorrhage patients, with no increase in vaso-occlusive events [27].

Numerous trials support its use, some of the most significant being the CRASH 2 and CRASH 3 trials. These trials demonstrated the critical nature of the timing of their use. When TXA is given within 3 hours of the time of injury, it is associated with a reduction in overall and bleeding related mortalities in patients with bleeding associated with trauma. Gayet-agero found that the survival benefit of TXA decreased by 10% for every 15-minute treatment delay until 3 hours, with no benefit after 3 hours [27]. Importantly, the use of TXA was not associated with an increase in vaso-occlusive events or seizures.

It is crucial to give it as soon as massive hemorrhage is recognized, and must be given within 3 hours of injury, optimally at the prehospital stage. A meta-analysis looking at giving TXA at the prehospital stage has shown a trend toward lower 30-day mortality and reduced risk of thromboembolic events in patients with bleeding associated with trauma [4]. With respect to dosing, 2 g of TXA should be given [13]. Whether it is more beneficial to give 1 g bolus, and then infusion, or 2 g bolus, is not clear. If given by infusion, the first dose is 1 g infused over 10 minutes, and a second dose of 1 g should be given over the subsequent 8 hours. We endorse the use of TXA at the prehospital stage on route to hospital. Every minute counts after the onset of bleeding, with a short delay in the treatment of TXA dramatically reducing its benefit.

Obstetrics have similarly had great success with the use of TXA, with numerous studies demonstrating its benefit. Ducloy-Bouthors et al. found that high dose TXA can reduce blood loss and maternal morbidity in post-partum hemorrhage [28].

KMQ-16. If the patient is on anticoagulants, what should be done and/or who should be contacted?

i. Hematopathology or alternate expert consultation is recommended when reversing anticoagulants, or in the setting of unexpected hematologic derangements

ii. An elevated INR may identify a patient on Warfarin, which can be reversed with PCC and Vitamin K

iii. Patients on direct thrombin inhibitors such as Dabigatran can have a thrombin level evaluated

iv. An anti-Xa level may be ordered for patients potentially on direct Xa inhibitor anticoagulants

v. Various reversal agents exist, with alternative treatments for bleeding patients on anticoagulants including TXA and PCC. Approaches should be protocolized

RATIONALE

The patient's unknown identification status may preclude accurate history taking regarding medication use. Consultation with hematology or alternate expert consultation is recommended. Access to transfusion medicine consultation (hematopathology, clinical pathology, and/or hematology) should be available 24/7 in every regional health authority. If this service is not available at your centre, consider contacting a higher-level centre for expertise.

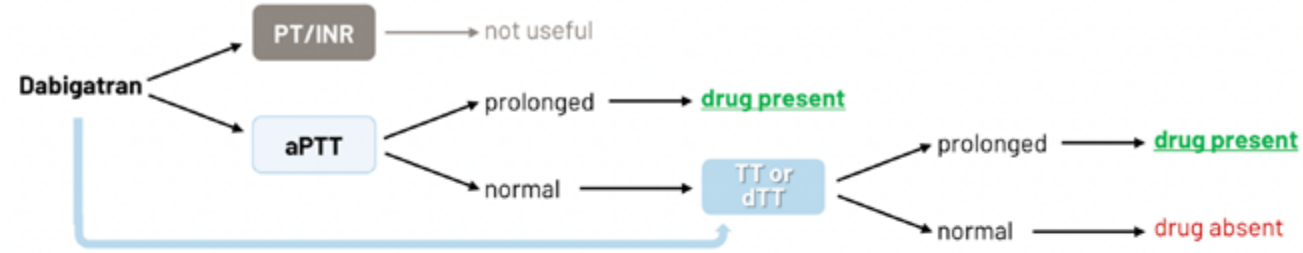
Laboratory tests vary in their availability across centres. They can be used to identify patients on potential anticoagulants, and to rule them out. Patients on warfarin may have an elevated INR. Warfarin can be reversed with PCC and vitamin K. If dabigatran is expected to be contributing to massive blood loss, dabigatran can be reversed with Idarucizumab.

Similarly, for direct acting oral anticoagulants, an anti-Xa level may be ordered, however, the test may take time to come back, and should not delay resuscitation.

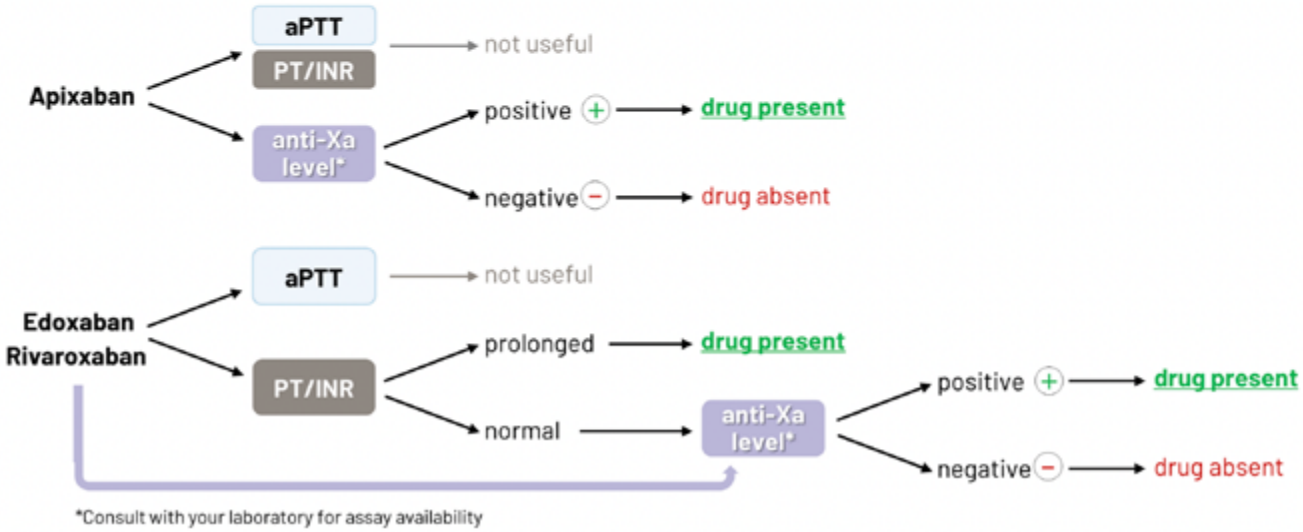
The following diagrams (https://treatthebleed.org/topics/doac-reversal.html) are an example of approaches to help categorize reversal agents and laboratory tests to determine whether anticoagulants have a clinically important effect [29].

With respect to reversal of anticoagulants, protamine may be used for unfractionated heparin and low molecular weight heparins, however, it may only be partially effective for the latter. Vitamin K antagonists such as warfarin can be reversed with PCCs and vitamin K (10 mg IV). The effective half-life of PCCs is approximately 6 hours, whereas Vitamin K has more of a prolonged effect, so both must be given. The amount of PCC to be given is based on guidelines (such as those recommended by the National Advisory Committee for Blood and Blood Products) and is often determined by the INR and/or weight [30]. Otherwise, a flat dose of 2000 IU is also appropriate. Antiplatelet agents can be partially reversed with platelets, however, patients with concomitant head injuries should not receive platelets unless indicated for other reasons, as the PATCH trial showed an increase in mortality and poor functional outcome in this patient population [31]. TXA is an adjunct in both Factor Xa inhibitors and dabigatran bleeding; it is not a reversal agent. The anticoagulant effects of factor Xa inhibitors can be treated with 2000 IU of PCCs as off label use if specific antidotes are not available. Dabigatran can be reversed specifically by Idarucizumab. TXA may also be used as an adjunct in anticoagulant associated blood loss, though there is no specific evidence to support this practice.

Direct Thrombin Inhibitor



Factor Xa Inhibitors



	Direct Thrombin Inhibitors	Factor Xa Inhibitors		
Assay	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
PT/INR	+/-	+/-	+/-	++
aPTT	++	-	-	-
TT or dTT	+++	-	-	-
Anti-Xa Level	-	+++	+++	+++

https://treatthebleed.org/topics/doac-reversal.html

KMQ-17. What signals that the massive transfusion can be terminated?

i. Terminating a massive hemorrhage protocol including informing the blood bank at the appropriate time and immediately returning all unused blood products/components to the blood bank eliminates unnecessary wastage of blood products and improves availability of blood products and transfusion services for the rest of the hospital

ii. Hemodynamic stability, identifying the bleeding source and controlling it, vasopressor requirements decreasing, transfusion rates sufficiently slowing, and/or patient death are all indicators that a massive hemorrhage protocol may be discontinued by contacting the blood bank

iii. In settings of limited blood supply, the utility of transfusion needs to be regularly reassessed with communication with stakeholders regarding care plans

iv. Surgical indicators may include direct visualization of control of bleeding, or resolution of blush on angioembolization

RATIONALE

Determining when a massive hemorrhage protocol should be terminated can be difficult. Two scenarios generally dictate that it is time to call the massive hemorrhage protocol off: when it is deemed that massive transfusion is futile, and when bleeding is controlled.

Determining futility in a massive transfusion has not been well studied. For trauma patients receiving greater than 60 pRBCs over 2 days, the 5-days survival in trauma patients was only 17%[41]. There are also NAC guidelines on triaging during blood shortages that can be found at www.nacblood.ca.

Terminating a massive hemorrhage protocol at the appropriate time can eliminate unnecessary wastage of blood products and improve the availability of both blood products and transfusion services for the rest of the hospital[9]. Signs that bleeding has been controlled include achieving hemodynamic stability, when the bleeding source has been identified and stopped, vasopressor requirements decrease, or transfusion rate has sufficiently slowed[13]. Surgical control of bleeding may be deemed in the surgical field, or it may be represented by resolution of blush after angioembolization[1].

Once bleeding has stabilized, the patient should be transferred to the ICU in most circumstances. If higher acuity is not available at a given centre, consideration should be given to transfer to a higher level of care. Importantly, once the patient is outside a zone of risk of rebleeding, the patient needs to be started on standard chemical venous thromboprophylaxis as they are at high risk of developing a prothrombotic state after massive blood loss[10].

KMQ-18. What are actions that should be taken after MHP discontinuation?

i. Transfer to an appropriate level of care, such as ICU, or trauma center, if appropriate

ii. Once patient is stabilized, blood products should be returned, and wastage minimized

iii. If imaging has not already been performed, ultrasound +/- head CT should be performed

iv. DVT prophylaxis should be started when safe after injury stability, usually within 24–72 hours, as these patients have a higher risk of venous thromboembolism

v. Resuming anticoagulation is a patient specific decision, based on their initial bleed, underlying thromboembolic risk, and comorbid conditions

RATIONALE

Prophylactic anticoagulation for deep venous thrombosis prevention after a massive hemorrhage has been shown to be safe. The highest incidence of venous thromboembolism (VTE) in trauma patients is in the first few days of hospitalization [37]. Traumatic brain injury (TBI) is also associated with increased rates of VTE [37].

The exact timing of VTE prophylaxis currently is still unclear. DVT prophylaxis should be initiated after injury stability, within 24–72 hours following admission, and in conjunction with surgery and hematology consultation as needed [37].

When resuming anticoagulation therapy after a life-threatening bleed, one must consider factors related to the index bleeding event, underlying thromboembolic risk, comorbid conditions, and collaborate with the patient/caregivers and other team members [38]. It should be an individualized decision. There is some evidence that in a gastrointestinal bleed, it is ideal to wait approximately 14 days prior to restarting anticoagulation (this time period balances the risk of recurrent bleeding, thromboembolism and mortality). The timing after an intra-cranial bleed, or other types of major bleeding is currently unclear [38].

KMQ-19. When should a formal debrief process take place, and how can quality improvement be integrated into this process?

i. Ideally, all massive hemorrhage protocol activations should be reviewed

ii. Cases with major complications secondary to transfusion or if a transfusion error occurred should be reviewed in detail, with adverse events captured in reporting systems (PSLS, hemovigilance systems through blood bank, BC trauma mortality module)

iii. Thus, we recommend a reconciliation process for blood components and products to ensure right blood went to the right patient

iv. Metrics that may define quality of transfusion include the following – where a defined time cut-off for some assessment may be appropriate (ie actions done within 1 hour):

   a. Time from injury to arrival and use of pre-hospital transfusion when BCEHS criteria are met

   b. Time to initiate massive transfusion and notification of blood bank

   c. Time to first pRBC from arrival to ED and/or activation of MHP (issue and/or transfusion)

   d. Time to first unit of plasma

   e. Time to crossmatched blood

   f. Wastage of blood products

   g. Whether balanced resuscitation is followed until lab parameters are available to guide transfusion (RBCs:plasma ratio within an hour)

   h. Time to receipt of group and screen specimen, time to completion of group and screen, and time to first coagulation lab results

   i. Frequency of coagulation specimens

   j. Time to/and or appropriateness of termination

RATIONALE

Ideally, all massive hemorrhage transfusion cases should be reviewed. There is always information that can be gained to improve upon the process of massive transfusion that is gleaned from these cases. Having multidisciplinary involvement is critical for different perspectives. Debriefing is beneficial not only to improve the quality of massive transfusion but also for the morale of the team involved. Below are some metrics that may be useful to guide feedback on how effective transfusion is, and ways of tracking common adverse effects and complications of massive transfusion.

There are certain cases that have been recommended by the American College of Surgeons to be reviewed; these cases include those with coagulopathy, thrombotic complications, development of ARDS, transfusion reactions including TACO, TRALI, hemolytic transfusion reactions, over transfusion of blood products, and death [1].

KMQ-20. How often should MHP simulations and/or training occur for hospital staff to maintain competency?

i. Simulations of MHP improve outcomes

ii. Simulations should take place at least yearly in settings that will encounter massive hemorrhage (emergency, ICU, OR, etc.)

RATIONALE

Multiple studies have demonstrated a correlation with simulation to likely improved clinical outcomes [13, 32, 33]. Improvements may come from improved provider behaviour and more efficient processes leading to defined end points such as reduction in time to critical operation for trauma patients. Additionally, these simulations may give a more realistic representation of how long these processes take, and some of the difficulties in communication that may arise.

We recommend that simulations take place at least yearly to parallel changes to this protocol and to ensure up to date knowledge translation. If possible, more frequent simulation training twice a year should take place with various teams (emergency, trauma, surgery, anesthesiology, nursing, blood bank) involved to improve fluidity and efficiency.

KMQ-21. Are there any special considerations non-tertiary care sites should keep in mind that may be different from larger centres?

i. Uncrossmatched RBC units should be prepared

ii. Platelets are often unavailable in inventory

iii. Methods of cell salvage and/or autotransfusion can be considered in settings with limited or no blood availability

iv. Prepared laboratory sample collection kits can expedite collection

v. TXA should be easily available

vi. Fibrinogen can be given, and PCCs can substitute plasma in the short term

vii. Depending on the clinical context, simple mechanical maneuvers and adjunct medications can be effective temporizing measures

viii. Early communication regarding transfer plans should be made to all stakeholders, including the transfusion service

RATIONALE

Remote sites will not have the same transfusion support and intervention related (surgery and interventional radiology) services. As an example, platelet doses are often not available in remote sites due to their short expiry dates. Priority must be to decide whether the patient needs to be transported and what substitutes for needed blood products can be given to temporize.

Uncrossmatched RBC units should be prepared, prepared laboratory sample collection kits should be available, and TXA should be given as soon as possible. Red cell salvage may lead to effective blood conservation. Although dosing regimens may vary, the ideal strategy is not determined, and so TXA may be dosed in the way of 2 g by bolus [13]. Alternatively, 1 g can be given in bolus, with the 2nd gram given over 8 hours. Substitutes for plasma and cryoprecipitate could include PCCs and fibrinogen concentrate in the short term. Other suggestions to improve temporization and efficiency of team processes include cross-training hospital personnel from other patient care areas [13].

In settings where there is limited blood availability, cell salvage should be considered. Cell salvage has been shown to significantly decrease the need for donor blood within the first 24 hours post-injury, in trauma surgery patients [39, 40]. One meta-analysis showed that use of cell salvage reduced rate of exposure to allogeneic RBC transfusion by 39% in surgical patients and was also associated with a lower risk of infection by 28% [40]. Another option is hemothorax or autotransfused blood, however, it typically contains higher levels of cytokines and lower coagulation factors and is less preferable to allogeneic blood.

Considering the clinical context is important when trying to slow down blood loss. Simple maneuvers can drastically curtail the speed of blood loss, aid in blood conservation, and buy time to transfer to a higher level of care. In trauma, this may mean binding, splinting, packing, compression and tourniquets. In obstetrics, this could be uterotonics, B-lynch sutures, Bakri balloon, internal iliac artery ligation, interventional radiology embolization and hysterectomy. In gastrointestinal bleeds, interventions to consider would depend on site of bleed and ideally in consultation with gastroenterology, and would include a PPI (pantoprazole 80 mg IV, followed by 40 mg q 12 hr or infusion at 8 mg/h, antibiotics (Ceftriaxone 1 g), Octreotide (50 mcg bolus and 50 mcg/hr infusion), balloon tamponade (Blakemore or Minnesota tube).

KMQ-22. What are some special considerations for obstetric and pediatric patients?

i. Target fibrinogen of >2g/L in the obstetric population

ii. Persons of childbearing potential need to be informed on the risk of red blood cell alloimmunization that could result in hemolytic disease of the newborn

iii. Relevant teams (obstetrics, pediatrics, neonatology) should be consulted as soon as it is feasible

iv. Transfer to centres that routinely take care of these populations should be arranged as soon as it is safe to do so

v. Use a weight-based approach for pediatrics to avoid over resuscitation

RATIONALE

Although this topic is outside the scope of this document, there are subtleties that need to be followed in these patient populations, so we offer a few key pieces of information regarding massive hemorrhage in pediatric and obstetric populations.

First of all, the relevant teams such as pediatrics, obstetrics, or neonatalogy, should be involved as early as possible. Their expert consultation will be required for resuscitation of these unique populations. Once temporized, these populations should ideally be cared for in centres that routinely deal with these populations.

In the obstetric population, fibrinogen should be replaced at a higher level, given their inherently higher fibrinogen levels. It should be replaced for a fibrinogen level less than 2g/L [13]. To temporize bleeding, uterotonics should be used, Bakri balloons can be deployed, and other maneuvers (B-Lynch suture, internal iliac artery ligation, interventional radiology embolization, and hysterectomy) may be considered prior to transport. Women of childbearing age need to be informed of the risk of red blood cell alloimmunization that could result in hemolytic disease of the newborn [13]. Callum's group from Toronto recommends red blood cell antibody screening at 6 weeks and 6 months after transfusion [13]. Neonatal and pediatric teams should be available in the setting of a potential post-mortem c-section.

Maternal-fetal hemorrhage occurs commonly in pregnant trauma patients. Rh Immune Immunoglobulin (RhIg) should be given to all obstetric trauma patients who are Rhesus D-negative, where there is risk of maternal-fetal hemorrhage [34] according to the SOGC. This is in order to prevent Rh alloimmunization. 300 mcg is the standard initial dose to be administered within 72 hours of injury, which provides protection for up to 30 mL of fetal blood in maternal circulation. In patients who are Rh-negative, a Kleihauer-Betke test should be done to determine the need for additional doses of RhIg. Hematopathology or transfusion medicine consultation is available to provide guidance on RhIg dosing.

In pediatrics, specific considerations include using weight-based dosing for blood products and an increased risk of hyperkalemia and hypothermia. The vastly different patient characteristics in those of a premature neonate compared to a teenager make it difficult to summarize these patients' considerations in the setting of a massive hemorrhage. However, there are patients such as neonates with congenital heart disease, those on extracorporeal life support, and ones in severe respiratory distress that may need a higher transfusion threshold for RBC [13].

KMQ-23. How often should this protocol be reviewed?

i. The protocol should be reviewed at a minimum of once every 3 years to stay up to date with the latest transfusion evidence

RATIONALE

We recommend that the protocol be reviewed a minimum of every 3 years to ensure that the protocol stays up to date with the latest evidence. Some groups have advocated updating their protocol every year, whereas others have decided on every few years, and there are pros and cons to each [13, 35]. We feel that 3 years strikes a balance between staying up to date and not having overly burdensome administrative work that may not lead to substantively new information.

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