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Introduction

Hemorrhage is the most common cause of death within the first hour of arrival to a trauma center. More than 80 percent of deaths in the operating room (OR) and nearly 50 percent of deaths in the first 24 hours after injury are due to exsanguination and coagulopathy. While only 3 percent of civilian trauma patients will receive a massive transfusion (>10 units red blood cells [RBC] in 24 hours), these patients consume 70 percent of all blood transfused at a trauma center. Because massive transfusions are unplanned and require the processing and delivery of large amounts of blood products rapidly for a sustained period of time, significant preplanning and coordination between the blood bank, the emergency department, the OR, and delivery personnel is required. The development and implementation of massive transfusion protocols (MTPs) have been associated with a reduction in mortality and overall blood product use in trauma centers. The purpose of the following guidelines is to identify the necessary components of an MTP and address key issues involved in developing an MTP for trauma.

Development of a Massive Transfusion Protocol: Engagement and Scope

An MTP should be a written document, accessible to all, and adopted by the center. All staff should be familiar with the procedures. Initial training and subsequent regular drills are recommended to maintain competency. This process is especially important in trauma centers where MTP initiations are rare, for example, smaller centers. The content of MT protocols should be based on the principles of damage control resuscitation. As such, they should provide for ratio-based blood products that are empirically delivered (hemostatic resuscitation) and have a process for the immediate availability of RBC, plasma, and platelets. Protocols should also include standardization of the assessment of coagulopathy and include assessment and treatment of acidosis, hypothermia, and hypocalcemia.

Massive transfusion protocols should be developed by a multidisciplinary committee that includes, at a minimum, representatives from:

- Transfusion service/blood bank
- Emergency department
- Anesthesia
- Trauma service
The massive transfusion protocol should address:

- Triggers for initiating massive transfusion in trauma
- Resuscitation in the trauma bay, including:
  - MTP product availability
  - MTP product delivery
  - MTP blood product transfusion
- Continuing MTP in the OR, angiography suite, and intensive care unit
- Transfusion service processes for delivery of blood products
- Transfusion targets
- The use of adjuncts for massive transfusion patients
- Termination of the MTP
- Performance improvement monitoring

Triggers for Initiating Massive Transfusion

Predicting the need for MT is difficult. Mortality is improved with rapid activation of a massive transfusion protocol, but complications are increased if patients have unnecessary exposure to blood products. Prediction tools for MT in adult trauma patients have been developed for both military and civilian trauma patients with injuries from penetrating or blunt trauma, respectively, with specificities that range between 80 percent and 90 percent. One well-validated scoring system is the Assessment of Blood Consumption (ABC) score. The ABC score consists of four variables (pulse >120, SBP<90, + FAST, and penetrating torso injury), each assigned one point. A score of two or more warrants MTP activation. The ABC score overestimates the need for transfusion, with a positive predictive value of 50 percent to 55 percent, meaning that 45 percent to 50 percent of patients in whom MTP is activated will not need a massive transfusion. However, the ABC score is excellent at identifying who will not need massive transfusion, with a negative predictive value of less than 5 percent, meaning it identifies more than 95 percent of all patients who will need a massive transfusion. Other prediction scores have been developed and all include the presence of severe tissue injury and hemorrhagic shock as important risk factors.

Criteria to trigger the activation of an MTP should include one or more of the following:

- ABC score of two or more
- Persistent hemodynamic instability
- Active bleeding requiring operation or angioembolization
- Blood transfusion in the trauma bay
Blood Product Resuscitation in the Trauma Bay, Operating Room, and Angiography Suite

Universally compatible RBC (O Rh-negative and O Rh-positive) and thawed plasma should be immediately available and ideally stored in the emergency department (ED). Centers that have used thawed plasma early in resuscitation have seen reductions in blood product utilization and product wastage. In areas where the transfusion service is unable to provide adequate stores of AB plasma, low (anti-B) titer A plasma may be utilized. For maximum effectiveness, damage control resuscitation (DCR) principles suggest that RBC and plasma should be delivered by a rapid transfuser and through a blood warmer. Initial rate of transfusion should restore perfusion but allow for permissive hypotension until the operation or angioembolization to stop the bleeding has begun. Platelets and cryoprecipitate should not be administered through a blood warmer.

- Universal blood products should be immediately available on patient arrival to support ratio-based transfusion.

If MTP triggers are met:

- Begin universal blood product infusion rather than crystalloid or colloid solutions.
- Transfuse universal RBC and plasma in a ratio between 1:1 and 1:2 (plasma to RBC).
- Transfuse one single donor apheresis or random donor platelet pool for each six units of RBC.
- Blood products should be automatically sent by the transfusion service in established ratios.
- Subsequent coolers should be delivered at 15-minute intervals until the MTP has been terminated.
- The goal is to keep at least one MTP cooler ahead for the duration of the MTP activation.

When the patient is moved from the resuscitation suite to the operating room or the angiography suite it is important that this is communicated to the Transfusion Service so that blood product delivery can continue to the site of patient care. During the procedure rapid delivery and transfusion of products should continue in appropriate ratios and at a rate to keep maintain adequate blood volume while the patient is actively bleeding. Once major bleeding has been controlled and the rate of transfusion has slowed it is appropriate to switch to a laboratory- or point of care (POCT)-based transfusion. For performance improvement purposes the ratio of blood product transfusion should be assessed at the time of bleeding cessation and not necessarily at a specific time point or at the end of an operation or angioembolization.
Massive Transfusion in the Intensive Care Unit

Trauma patients for whom a massive transfusion protocol is activated most frequently require intensive care. Arrival of these patients to the intensive care unit (ICU) marks an important checkpoint, including a systematic review of the patient’s prior resuscitative efforts. The ICU accepting team should anticipate arrival of these patients with the necessary equipment to continue rapidly infusing blood products. Attention should be paid to correcting factors that exacerbate coagulopathy, including hypothermia, acidosis, and hypocalcemia. If massive ongoing bleeding persists, the patient may require prompt return to the operating room, particularly if the coagulation status has been normalized.

An appropriate ICU-driven algorithm should be optimized to use blood components for goal-directed therapy.

- Upon arrival in the ICU, baseline laboratory measures should be obtained and then repeated as needed or at least hourly:
  - INR
  - aPTT
  - Fibrinogen level
  - Hemoglobin or hematocrit
  - Platelet count
  - Point-of-care testing/thromboelastometry and rotational thromboelastography, if available
  - Ionized calcium
  - Blood gas analysis, including base deficit

- Use of empiric fixed ratios of blood products should be followed in the ICU until bleeding is controlled and/or specific laboratory and POCT data are available. These products should be delivered in a ratio between 1:1 and 1:2 (plasma:RBC).

- Once laboratory data are available, resuscitation should be goal directed based on the laboratory findings and clinical evidence of ongoing bleeding.

Operational Aspects of the Transfusion Service/Blood Bank

A designated trauma center should have an on-site transfusion service that operates 24 hours a day, seven days a week and has specific operating procedures for the rapid early and continued delivery of blood components as dictated by an MTP. The MTP must allow adherence to current, standard safe practices for transfusion. During massive transfusion, timely and precise communication between the trauma team, the ED, the operating room, anesthesia, and the transfusion service regarding availability and need for transfusion products is imperative.
The most efficient way to immediately initiate an MTP is to have a blood refrigerator containing universal donor products in the resuscitation bay. Rapid delivery of subsequent blood coolers from the transfusion service to the resuscitation bay is best accomplished by the assignment of a dedicated runner. A process must be in place to rapidly deliver a group and screen to the transfusion service laboratory to facilitate the availability of crossmatched RBC. Uncrossmatched (O Rh negative or O Rh positive RBC) should be available immediately. Group O Rh negative RBC should be reserved for women of child-bearing potential (younger than 45 to 50 years old). Patients should be switched to crossmatched RBC as soon as it is available, which should be achievable within one hour for most patients (about 97 percent). For a small number of patients who have a positive antibody screen, obtaining crossmatched RBC may take hours. Staffing the transfusion service with technologists trained in antibody investigations is instrumental for providing these patients with compatible RBC. A transfusion medicine specialist should be available to consult with the trauma team regarding compatibility and other issues related to massive transfusion.

Currently RBC can be safely stored for up to six weeks and are released using a first-in, first-out system to minimize wastage. While there is concern that transfusion of RBC with longer storage times in trauma may increase complications, there is no current justification to prioritize the use of RBC with short storage times to the trauma patient at the expense of other patients. The RECESS and ABLE studies that are underway in the U.S. and Canada may give further guidance in the future.

For an MTP to be effective, universal thawed plasma should be immediately available. This step can be accomplished by storing thawed or liquid (never frozen) plasma. The ideal universal plasma is AB plasma, but unfortunately it is in short supply, as only 4 percent of donors have this blood type. As a result of increased use of AB plasma in resuscitation, shortages of plasma may occur for patients with AB blood type. However, 40 percent of donors are type A and many of them have low titers of anti-B; this low titer plasma can be safely given to almost everyone. In order to avoid overuse or wastage of AB plasma, transfusion services may utilize group A plasma with low anti-B titers. This process requires determining anti-B titer at the time of donation. Patients should be switched to group-specific plasma as soon as the blood group has been determined, which usually takes about 10 minutes. The transfusion service should maintain a sufficient quantity of platelets to support ratio-based massive transfusion. Additional platelets may be needed to support patients with bleeding disorders or those on antiplatelet therapy. Blood products should be transported and stored appropriately. RBC and plasma should be delivered and kept in temperature-controlled coolers. Platelets and cryoprecipitate should not be placed in coolers. Upon termination of MTP, all remaining blood products and coolers should be returned to the transfusion service promptly.
In multicasualty situations, especially when patients are poorly identified, the transfusion service should be notified immediately, and consideration should be given to exclusive use of universal donor blood products until stable identities or aliases can be established.

**A designated trauma center or its supporting transfusion service should have on hand and available for immediate release the following:**

- At least eight units of universal donor, uncrossmatched RBC (for example, four units of O Rh negative RBC and four units of O Rh positive RBC)
- At least eight units of thawed group AB or low titer anti-B group A plasma. Additional plasma should be obtainable from the transfusion service within 15 minutes of MTP activation.

**Uncrossmatched blood products should be delivered until group-matched products are available.**

- Once the transfusion service has received a blood specimen for group matching, group-matched products should be available within 10 minutes.
- Crossmatched RBC should be available within one hour for most patients. Notable rare exceptions include RBC alloantibody, rare blood group, and so on.

**Special consideration for universal product use should be given only in multicasualty situations**

**Endpoints of Transfusion**

To ensure that the MTP protocol does not needlessly waste scarce resources, it is important to determine the criteria and process for termination of the protocol. Based on guidelines for enrollment in the current Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) study, criteria for stopping the MTP should include both anatomic (control of bleeding) and physiologic criteria (normalizing hemodynamic status). The decision to stop should be made by the trauma surgeon in conjunction with the anesthesiologist, if the patient is still in the operating room, or the intensivist/trauma surgeon if in the ICU.

In addition, the exact laboratory value endpoints that should be used to guide further blood product use should be based on published data and the extensive clinical experience of those who are caring for the patient.

**The ratio-driven massive transfusion may be discontinued or downgraded to goal-directed transfusion based on the laboratory findings if surgical bleeding has been controlled by the surgeon in the operating room OR there is radiographic and physiologic evidence of bleeding control after angioembolization.**
● The MTP should be discontinued when there is recognition that further resuscitation is futile.

● The following should be used as guides to cease therapy with blood and blood components in a patient who is (1) not actively bleeding and (2) still in the acute resuscitation phase:

● RBC transfusions for hemoglobin ≥10 g/dL

● Plasma transfusion for prothrombin time (PT) <18 seconds

● Plasma transfusion for activated partial thromboplastin time (aPTT) <35 seconds

● Platelet transfusions for platelet count >150 x10^9

● Cryoprecipitate or fibrinogen concentrate for fibrinogen level >180 g/L

If standard thrombelastography (TEG®) is available, the following cut-points for transfusion triggers may also be used:

● Plasma for r-value >9 minutes

● Plasma and/or cryoprecipitate (fibrinogen concentrate) for k-time >4 minutes

● Cryoprecipitate (or fibrinogen concentrate) and/or plasma for a-angle <60°

● Platelets for mA <55 mm

● Anti-fibrinolytics for LY30 >7.5 percent

If rapid TEG is available, the following cut-points for transfusion triggers may also be used:

● Plasma for ACT >128 seconds

● Plasma and/or cryoprecipitate (fibrinogen concentrate) for k-time >2.5 minutes

● Cryoprecipitate (fibrinogen concentrate) and/or plasma for a-angle <60°

● Platelets for mA <55 mm

● Anti-fibrinolytics for LY30 >3 percent

If rotational thromboelastometry (ROTEM®) is available, the following cut-points for transfusion triggers may also be used:

● Plasma for CT exTEM>100 seconds and/or CT inTEM>230 seconds

● Cryoprecipitate (fibrinogen concentrate) and/or plasma for MCF fibTEM<8mm

● Platelets for MCF exTEM<45mm and MCF fibTEM>10mm

● Anti-fibrinolytics for ML exTEM>15 percent
For the purposes of reporting and documentation in registry and databases, hemorrhage control/hemostasis can be declared when both of the following have been met:

- The surgeon declares hemostasis based on the absence of bleeding requiring intervention in the surgical field or resolution of blush after angioembolization.
- The surgeon and/or anesthesiologists agree that the patient is adequately resuscitated based on the following criteria, if available:
  - Stable or increasing blood pressure, or
  - Stable or decreasing heart rate, or
  - Stable or increasing urine output, or
  - Decreasing requirement for vasopressors to maintain a stable blood pressure

Frequent communication between the members of the resuscitation and surgical teams cannot be overemphasized to guide the resuscitation, plan for continued need for blood products and adjuncts, and determination of when to move toward data-based resuscitation and when to end active resuscitation.

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**Therapeutic Adjuncts in Massive Transfusion**

There are several adjuncts available for massive transfusion. Antifibrinolytic medications, such as tranexamic acid (TXA) or aminocaproic acid, inhibit plasminogen activation and plasmin activity thus stabilizing the clot. Although available and widely used for many years, it was not until the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2 (CRASH-2) trial that the use of TXA in trauma was examined. Tranexamic acid has been shown to be effective in a variety of surgical settings, including cardiovascular surgery, orthopaedic surgery, postpartum hemorrhage, and trauma. In trauma, antifibrinolytic agents can be used empirically or in response to findings of increased fibrinolytic activity on POCT.

Recombinant activated factor VIIa was initially developed for the treatment of hemophilia with inhibitors and is only licensed by the U.S. Food and Drug Administration (FDA) for this indication. However, over the last decade, it has been studied and has been used in the setting of traumatic coagulopathy as well as reversal of warfarin-induced anticoagulation in serious bleeding. At this time, the role of factor VIIa is unclear. It certainly appears to reduce transfusion requirement, but lack of long-term mortality benefit and potential increases in morbidity have placed its position in the MTP in doubt.
A variety of prothrombin complex concentrates are currently available. These concentrates contain either three (II, IX and X) or four (II, VII, IX and X) clotting factors. Although widely available in Europe and elsewhere for years, the first FDA-approved four-factor PCC has just been released in the United States. This product is licensed for urgent reversal of warfarin but is sometimes used off-label for management of trauma-induced coagulopathy in Europe.

- TXA 1 gram intravenous over 10 minutes followed by infusion of 1 gram over eight hours is recommended in all injured patients who are actively bleeding and are within three hours of injury.

- PCC is currently only approved for correction of warfarin-induced coagulopathy in bleeding patients. As such, the American College of Chest Physicians Guidelines, 9th Edition, recommends use of PCC over FFP for warfarin reversal in the setting of major bleeding.

- Recombinant VIIa is generally not recommended for management of refractory hemorrhage in trauma.

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**Monitoring System Performance in Massive Transfusion**

Acute hemorrhage associated with traumatic injury places the patient at risk for a myriad of complications. Review of hemorrhage- and transfusion-related complications, along with monitoring of the availability and management of blood products during massive transfusion, can help identify opportunities for improvement in the MT process.

**The trauma center should review cases of massive transfusion with the following complications:**

- Coagulopathy
- Thrombotic complications
- ARDS
- Other transfusion reactions, including TACO (transfusion-associated volume overload), TRALI (transfusion-related acute lung injury), and hemolytic transfusion reaction
- Over-transfusion of RBC
- Death
Performance indicators for the process of massive transfusion should include:

- Time from calling MTP to infusion of first unit RBC
- Time from calling MTP to infusion of first unit plasma
- Adherence to a predetermined ratio or goal between one to two hours after initiation of the MTP
- Informing the transfusion service that MTP has been terminated within one hour of termination
- Wastage rates for blood products
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