Massive Transfusion Protocol (MTP)

December 7, 2020 by Josh Farkas

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introduction to massive transfusion protocol (MTP)
Patients with severe hemorrhage may develop refractory hemorrhage due to a collection of factors:

- Dilution of clotting factors (including platelets and fibrinogen).
- Hypothermia from transfusion of cold products.
- Hypocalcemia-induced coagulopathy (due to citrate in blood products).
- Acidosis.

Massive transfusion protocols involve the use of balanced transfusion (including PRBCs and clotting factors), in efforts to avoid dilutional coagulopathy. Traditional labs generally won't return fast enough to guide the use of clotting factors, so this is protocoted (example below).

Massive transfusion protocol in obstetrics

<table>
<thead>
<tr>
<th>Round</th>
<th>PRBCs</th>
<th>FFP</th>
<th>Platelets</th>
<th>Cryoprecipitate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 U</td>
<td>6 U</td>
<td>6 U</td>
<td>10 U</td>
</tr>
<tr>
<td>2</td>
<td>6 U</td>
<td>6 U</td>
<td>6 U</td>
<td>10 U</td>
</tr>
<tr>
<td>3</td>
<td>6 U</td>
<td>6 U</td>
<td>6 U</td>
<td>10 U</td>
</tr>
<tr>
<td>4</td>
<td>6 U</td>
<td>6 U</td>
<td>6 U</td>
<td>10 U</td>
</tr>
</tbody>
</table>

Consider activating the protocol when hemorrhage is expected to be massive (anticipated need to replace 50% or more of blood volume within 2 hours), bleeding continues after the transfusion of 4 U of packed red blood cells within a short period of time (1–2 hours), or systolic blood pressure is below 90 mm Hg and heart rate is above 120 beats per minute in the presence of uncontrolled bleeding. Once activated, blood bank personnel will continue preparing blood products until the surgical team inactivates the protocol. If this protocol involves rounds 4, it will start again from round 1.

FPP, fresh frozen plasma; PRBC, packed red blood cell. Adapted from Fuchecio et al.


When should the massive transfusion protocol be initiated?

- There are no simple criteria for this. Ultimately, initiation of a massive transfusion protocol is based on clinical judgement, considering the following factors:
  - How unstable is the patient?
  - How rapidly is the patient bleeding?
  - What is the expected trajectory of this type of bleeding?
  - Is the patient definitely in hemorrhagic shock? (If doubt exists about whether the patient is in hemorrhagic shock, echocardiography may be useful to confirm the presence of hypovolemia.)
- The hemoglobin level takes hours to fall after bleeding. Consequently, checking the hemoglobin has little role in determining need for MTP.
- Hypotension is usually a late manifestation of hemorrhage. Worsening hypotension and vasopressor requirement should prompt consideration for MTP.

Development versus reality of the MTP

- MTP was designed and validated primarily for the management of traumatic hemorrhage.
- Most hospitals seem to have a single MTP protocol which is used across various different contexts.
- In practice, the most common uses of MTP are for non-trauma applications (e.g., obstetric hemorrhage, operative bleeding, gastrointestinal hemorrhage). (29607593) These diverse problems are more heterogeneous and therefore harder to study.
  - It remains unclear whether MTPs are perfectly designed to deal with these situations.

Coagulation labs & MTP

- During an MTP, blood products are being given so rapidly that it's practically impossible to use standard coagulation labs to guide product administration. By the time a set of labs has returned, it is already obsolete. Therefore, blood products are administered empirically in a 1:1:1 ratio of PRBC:FFP:Platelets, with an aim to prevent the generation of dilutional coagulopathy.
  - One potential exception to this is that some institutions may have the capacity to run real-time viscoelastic testing at the bedside during a massive transfusion protocol (e.g., an operating room with the capacity for immediate intraoperative thromboelastography). Evidence does seem to support this, but it won't be discussed further here because the vast majority of MTPs must be performed in the absence of this technology. (29607593)
- However, known coagulation abnormalities may indicate specific management. For example, if the patient has a low fibrinogen or if the patient is on warfarin before initiation of the MTP, then additional blood products may be indicated to manage this.
clarifying some terminology: “massive transfusion” and “massive transfusion protocol”

- “Massive Transfusion” refers to any situation where a patient is getting a lot of blood transfusions. Different definitions exist, with a common one being >10 units in 24 hours. Definitions involving shorter time increments (e.g., >5 units within four hours), could be more useful for identifying massive transfusion early.
- Due to varying definitions and lack of crystal-clear clinical implications, the term “massive transfusion” may not be incredibly useful for everyday clinical use. It’s a bit like the omnipresent and ever-elusive term “massive hemoptysis.”
- “Massive Transfusion Protocol” (MTP) refers to rapid administration of large amounts of blood products (at least 6 units of PRBC) in fixed ratios (usually 1:1:1) for the management of hemorrhagic shock.
- Only a subset of patients with “massive transfusion” will receive a massive transfusion protocol.
- This chapter is specifically about massive transfusion protocols. However, the same general principles may apply to any patients who are receiving large quantities of blood products.
- “Ultramassive transfusion” has been defined as the administration of >20 units PRBC within a 48-hour time span.

procedural concerns

intravenous access

Although it is possible to perform MTP via a peripheral IV catheter, central access is preferable because this is more secure. Options include the following:

- **Hemodialysis catheter**
  - This is an excellent option which provides secure access with essentially infinite flow rates.
  - A trialysis catheter (a dialysis catheter with a third lumen) is perfect for this, as it also provides a third lumen.

- **Multilumen Access Catheter (MAC catheter)**
  - If you can find one, this is another excellent option.
  - When paired with a specialized triple-lumen catheter insert, this provides five lumens.
  - Don’t make the mistake of placing a standard triple-lumen catheter into the MAC catheter – the inserted catheter should be specially designed for this purpose. Insertion of a standard catheter may lead to bleeding or air embolization, as the seal may not be perfect.

- **Standard central line**
  - This is generally frowned upon, because the length of the central line reduces flow rates. However, a central line can often achieve respectable flow rates, when combined with a Level-1 pressure infuser.
  - Two points are especially important when using a central line (figure below). First, remove the line cap before attaching the central line to the pressure infuser (the line cap adds a lot of resistance to flow). Second, be sure to use the largest lumen of the central line (there may be huge variation between the different lumens!).

- **Introducer sheaths are potentially problematic**
Theoretically these are very large, which allows a large flow rate. However, in practice these have a high failure rate.

- **Without** a catheter passing through the sheath, the sheath may become kinked (thereby causing loss of IV access).
- **With** a catheter passing through the sheath, the sheath won’t become kinked. However, the flow rate is reduced (which defeats the purpose of the sheath).

![Image of catheter and IV access](https://emcrit.org/ibcc/mtp/attachment/highratecvc/)

**arterial catheter**

- Immediate, accurate knowledge of the blood pressure can be extremely useful in these patients.
- A fast way to establish arterial and venous access is to place a femoral central line and arterial line immediately adjacent to each other on the same side (the “dirty double” described [here](https://emcrit.org/pulmcrit/hemodynamic-access-for-the-crashing-patient-the-dirty-double/)).

**procedural sterility**

- It is usually impossible to place arterial and central lines in an exsanguinating patient in a 100% sterile fashion.
- A good approach is to place semi-sterile lines immediately (e.g., in a femoral position), with the understanding that these should be removed within 24 hours.
  - In most cases, the bleeding will be controlled, and ongoing access won’t be required for >24 hours anyway. If ongoing access is needed, a new pristine line may be placed in a 100% sterile fashion.
- More on crash femoral access [here](https://emcrit.org/pulmcrit/hemodynamic-access-for-the-crashing-patient-the-dirty-double/).

**intubation**

- Patients with exsanguinating hemorrhage will often need to be intubated (e.g., to facilitate endoscopic control of bleeding).
- Intubating a patient who is extremely under-resuscitated may precipitate hemodynamic collapse.
- It is often best to obtain access, give one round of massive transfusion (e.g., 6 units PRBCs, 6 units of platelets, and 6 units of FFP), and establish a reasonable blood pressure *prior* to intubation (“resuscitate before you intubate”).

**1) blood products in 1:1:1 ratio**

- The cornerstone of MTP is balanced transfusion with PRBCs, platelets, and fresh frozen plasma (FFP).
- Most hospitals should have a protocol in place to deliver these products rapidly and in the appropriate ratio.
- Current evidence generally supports a 1:1:1 ratio, which is used in most massive transfusion protocols.

**avoid crystalloid resuscitation**
For hemorrhagic shock with ongoing bleeding, crystalloid administration may dilute out coagulation factors and erythrocyte concentration. Ultimately blood products will be needed (to achieve target hemoglobin concentrations and coagulation factor levels), so front-loading your resuscitation with crystalloid may eventually serve to promote volume overload.

Whenever feasible, hemorrhagic shock resuscitation should be performed with blood products.

### 2) Fibrinogen supplementation?

- Fibrinogen may become depleted in massive transfusion, due to dilution. There is some fibrinogen in fresh frozen plasma, but not necessarily enough. Fibrinogen can be supplemented via the administration of fibrinogen concentrates or cryoprecipitate. In the United States, cryoprecipitate is most commonly used (10 units should increase the fibrinogen by ~75 mg/dL).
- Recent guidelines for trauma-induced bleeding suggest targeting a fibrinogen level >150-200 mg/dL. It may be best to replete this early, rather than waiting for levels to drop. ([25519751](https://pubmed.ncbi.nlm.nih.gov/25519751/)) Obstetric hemorrhage may also benefit more from fibrinogen supplementation.
- High-level evidence doesn't exist regarding exactly how aggressive to be with fibrinogen supplementation. Different hospitals may have varying protocols. This may also bear individualization depending on the type of hemorrhage and any available laboratory data (if the patient’s fibrinogen is known).

### 3) Tranexamic acid?

- Tranexamic acid has a proven benefit in obstetric hemorrhage and early traumatic bleeding. Its use in other contexts is under investigation, but tranexamic acid generally appears safe (although there was a signal for causing a slight increase in thromboembolic events when given for non-massive gastrointestinal hemorrhage in the HALT-IT trial). ([32563378](https://pubmed.ncbi.nlm.nih.gov/32563378/))
- Surveys find that ~50-60% of institutions include tranexamic acid in their MTP protocols. ([30124475](https://pubmed.ncbi.nlm.nih.gov/30124475/))
- Typical dosing is one gram IV given immediately, which may be followed by infusions of 1 gram over 8 hours repeatedly for 24 hours (the protocol used in the CRASH trials).

### 4) Reversal of other coagulopathies

- The MTP protocol is designed to avoid causing dilution coagulopathy, but it won't correct a pre-existing coagulopathy. So, consideration is warranted regarding any underlying coagulopathies that the patient may have. There should be a low threshold to call the blood bank (pathology) to optimize the management of these patients.
- **Warfarin or oral anticoagulation** require immediate reversal, for example with PCC (prothrombin complex concentrate)(described [here](https://emcrit.org/ibcc/anticoagulant-reversal/#warfarin:_urgent_reversal)).
- **Platelet dysfunction**
  - This is commonly caused by antiplatelet agents or uremia.
  - The most common emergency treatment is [desmopressin](https://reference.medscape.com/drug/ddavp-stimate-noctiva-desmopressin-342819) (DDAVP, 0.3 mcg/kg IV to a maximum dose of 21 micrograms).
- More on anticoagulation reversal in [this chapter](https://emcrit.org/ibcc/anticoagulant-reversal/#top).

### 5) Calcium

**Underlying physiology**

- Hypocalcemia may occur for several reasons:
  - Critically ill patients are often mildly hypocalcemic to begin with (for numerous reasons, more on this [here](https://emcrit.org/ibcc/hypocalcemia/#etiology)).
- Citrate in blood products chelates calcium, leading to hypocalcemia. When blood is given gradually, citrate is metabolized by the liver – so this isn’t an issue. However, when blood is infused rapidly, citrate may temporarily accumulate and promote hypocalcemia.
- Hypocalcemia is problematic because it causes coagulopathy.
- Moderate hypercalcemia is well tolerated (for example, see table below). Therefore, the therapeutic target is a high-normal level of calcium (in a massively hemorrhaging patient, it’s probably better to err on the hypercalcemic side).

<table>
<thead>
<tr>
<th>Total calcium (mg/dL)</th>
<th>Ionized calcium (mM)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal 8.5-10.5</td>
<td>1.12-1.32</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Mild hypercalcemia 10.5-11.9</td>
<td>1.32-3</td>
<td>Asymptomatic or mild symptoms</td>
</tr>
<tr>
<td>Moderate hypercalcemia 12-13.9</td>
<td>3.3-5.5</td>
<td>Symptoms more evident</td>
</tr>
<tr>
<td>Severe hypercalcemia &gt;14</td>
<td>&gt;3.5</td>
<td>Coma, bradycardia due to AV block can occur</td>
</tr>
</tbody>
</table>

(https://emcrit.org/ibcc/hypercalcemia/attachment/calevel45/)

### calcium dosing

- When administering one round of MTP (containing 6 units PRBCs), it’s probably reasonable to add either 1 gram of IV calcium chloride or 3 grams of IV calcium gluconate.
  - Calcium gluconate causes less tissue damage with extravasation, so this is preferred for peripheral administration.
  - If possible, bedside measurement of ionized calcium with a point-of-care monitor may help guide calcium administration in real-time.
  - An EKG or bedside telemetry may serve as a very rough guide to the calcium:
    - Hypocalcemia causes a shortening of the ST segment.
    - Hypocalcemia causes a prolongation of the ST segment.

#### 6) avoid acidosis

(https://emcrit.org/ibcc/mtp/attachment/acidosiscap/)

### physiological rationale

- Acidosis impairs the interaction between calcium and negatively charged phospholipids, blocking the initial steps in the coagulation cascade.
- Even mild acidosis (e.g., pH 7.20) may reduce coagulation considerably (figure below). (14608161 (https://pubmed.ncbi.nlm.nih.gov/14608161/))

(https://emcrit.org/ibcc/mtp/attachment/acidosiscap/)

#### clinical approach

- Acidosis should be treated using standard approaches. The only difference here is that a bit more attention may be warranted (compared, for example, to a stable medical patient – in whom a pH of 7.20 would generally not cause harm).
Examples of how acidemia might be treated would include:

1. For intubated patients, higher minute ventilation may be used to compensate for metabolic acidosis (thereby mimicking the normal physiology of respiratory compensation for a metabolic acidosis).
2. Non-anion-gap metabolic acidosis (NAGMA) or uremic acidosis may improve following administration of citrated blood products (which are alkalemic). In severe cases, additional sodium bicarbonate administration may be appropriate.
3. Lactic acidosis or ketoacidosis requires aggressive therapy of the underlying cause.

7) avoid hypothermia

Patients undergoing massive transfusion tend to develop hypothermia, which will impair blood clotting. This is promoted by rapid administration of cooled or room-temperature blood products and fluids.

Hypothermia may be avoided or treated by:

- Providing warmed blood products (e.g., via a Level-1 or Belmont Infusers with in-line warming).
- Preemptive use of warming blankets, in response to any evidence of hypothermia or shivering.
- With intubated patients, warming the inhaled gas as much as possible (some ventilators may allow control of the degree of warming).
- Monitoring the patient's temperature.

8) hemodynamic management

This is extremely tricky:

- Adequate resuscitation is required to perfuse vital organs.
- Over-resuscitation may promote bleeding. This is especially true of bleeding from any vein (e.g., variceal bleeding), because increasing the central venous pressure directly increases the pressure behind the bleed. However, increasing arterial pressure may also dislodge clots and encourage arterial bleeding sources (“pop the clot”).
- It is probably ideal to target a low-normal blood pressure (e.g., MAP ~60 mmHg) until hemostasis is achieved. This should provide adequate perfusion. However, for patients with traumatic brain injury, a somewhat higher MAP goal may be appropriate.

9) source control

Control of the bleeding source is obviously critical.

- Emphasis may be placed on the fastest strategy (e.g., surgical packing or interventional radiology, rather than definitive surgical repair).
- Close coordination with many consultants will usually be required (e.g., gastroenterology, interventional radiology, surgery).

post-MTP laboratory-based correction of coagulation factors

During the MTP, blood products are being given so rapidly that it's impossible to adjust product administration according to laboratory values (usually by the time a laboratory test results are available, they are already obsolete). However, once the MTP is stopped, there will be time to check labs and make adjustments accordingly.

post-MTP lab evaluation:

- Labs
  - Electrolytes, including ionized calcium
  - Complete blood count
  - INR, PTT, fibrinogen
- Examination
  - Check patient's temperature
- Echocardiography to evaluate volume status

**correction of abnormalities:**

- Platelets are generally transfused for a target >50,000 billion/uL.
- Fibrinogen is generally transfused to target >100-200 mg/dL. Sources vary regarding which target to choose, so this may be individualized, based on each patient and how definitively the bleeding source was controlled.
- Coagulation factors (e.g., fresh frozen plasma) may be transfused to target an INR below ~<2.
  - Note that an INR is unhelpful in patients with cirrhosis, in whom the INR may be elevated chronically (without correlation to the true state of coagulation).
  - If thromboelastography is available, this is often a more accurate assay of true enzymatic coagulation (especially in cirrhosis or disseminated intravascular coagulation).
- Aggressively treat hypothermia (if this has developed).
- Manage any electrolyte abnormalities which may have evolved (e.g., hypocalcemia, hyperkalemia).

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**summary**

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This doesn't include everything, but rather it focuses on less obvious items which have a tendency to get overlooked.
Excessive administration of crystalloids can interfere with coagulation (especially normal saline).

Delayed management of temperature. The best approach to hypothermia is to anticipate this and prevent it by using warmed fluids and blankets.

Inadequate calcium administration, which may promote coagulopathy.

**Going further:**

related

- EMCrit Podcasts on massive transfusion (Scott Weingart)
  - EMCrit Podcast 197: The logistics of massive transfusion
  - EMCrit Podcast 13: Trauma Resus II: Massive Transfusion
  - Podcast 71: Critical Questions on Massive Transfusion Protocols with Kenji Inaba
  - Podcast 144: The PROPPR trial with John Holcomb
  - Podcast 081 – An Interview on Severe Trauma with Karim Brohi
  - Hemorrhagic Shock Resus with Rick Dutton
  - The PROPPR RCT
  - The PROPPR trial (The Bottom Line, by Adrian Wong)

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**The Internet Book of Critical Care** is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.