



Massive Hemorrhage Protocol

Understanding what is needed to deliver high-quality, evidencebased care during a massive hemorrhage protocol activation

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Disclosures

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Outline

- Case
- Definitions and Goals of the MHP
- Core requirements and evidence
- Summary



Case

- 15 year old female child struck by pick-up truck while crossing the street at high speed
- Transported by land injury to arrival time 23 minutes
- Patient receives 500 mL crystalloid in transport
- Team assembled prior to arrival in the emergency department and tasks assigned to each person by the physician lead
- Blood transfusion laboratory notified of incoming young female trauma and 4 units of unmatched O-negative, Kell-negative blood requested in a cooler

Case

- On arrival: obtunded, GCS 12, intubated immediately, HR 125, sBP 70 mmHg, temp 35.5°C
- Pupils unequal, serious laceration to the back of the head
- Examination finds abdominal +FAST and concern for unstable pelvis
- Massive hemorrhage protocol activated
- Two large bore catheters inserted and surgery resident assigned to insert central line
- Two RBC units started via rapid infuser blood warmer
- TXA 1 gram bolus given



- Labs drawn for group and screen, CBC, INR, PTT, fibrinogen, lytes, iCa, lactate
- Forced air blanket applied
- Persistent marked bleeding and hematoma from scalp injury despite pressure and staples
- Bleeding from central line puncture site
- Persistent hypotension despite 1 L Ringers and 2 RBC so 2 more RBC and 2 plasma being infused while awaiting lab testing
- Patient being prepared to go to CT scan

Case

- While patient in CT the following labs come back: Hb 115 g/L, platelet count 56 x 10⁹/L, INR 5.4, fibrinogen 0.3 g/L
- You diagnose acute traumatic coagulopathy from shock and traumatic brain injury and transfuse 1 pool and platelets, 4 grams of fibrinogen, and 2 more plasma
- Second 1 gram bolus of TXA given
- CT shows severe TBI with moderate subdural, splenic rupture and pelvic fracture
- Operating room is preparing for patient arrival
- Second set of labs drawn to determine if additional fibrinogen is required



Massive Hemorrhage Protocol

A protocolized, multidisciplinary, and evidence-based approach to the management of the massively bleeding patient

Goals

- Activated promptly
- Right patient not all bleeding patients need an MHP activation
- Activated through standardized communication process with distinct terminology
- Team promptly assembled and a team lead is designated
- First RBC spiked within 15 minutes
- Tranexamic acid given within 60 minutes (excluding gastrointestinal bleeds)
- Blood work at activation and every 60 minutes or every 4 RBCs
- Transfusion to target values
- Avoid hypothermia
- Terminate when patient meets termination criteria
- Don't waste blood

Definitions

- Massive Transfusion = a retrospective definition used in clinical trials or observational studies to describe patients who were transfused a certain number (usually 10 U of RBC) in a 24 hour period
- Massive Hemorrhage Protocol (MHP) = a protocolized response to a massively bleeding patient (not all patients will end up receiving a massive transfusion)

Pathophysiology of trauma-associated coagulopathy

- Autoheparinization
- Upregulated thrombomodulin
- Activated protein C
- Depletion of factor V
- Uncontrolled tPA release
- Hyperfibrinolysis
- Activated endothelial cells
- Platelet dysfunction
- Hypofibrinogenemia



Other coagulation factors maintained

Duque P, Calvo A, Lockie C, Schöchl H. Pathophysiology of Trauma-Induced Coagulopathy. Transfus Med Rev. 2021 Oct;35(4):80-86.





 Every 1 minute delay from activation to first RBC is associated with a 5% increase in mortality

	Odds ratio	95% C.I.	p-value
Time to receipt of first cooler (min)	1.05	1.01-1.09	0.016
Anatomic injury severity (ISS)	1.05	1.03-1.06	< 0.001
Disturbed arrival physiology (w-RTS)	0.61	0.53-0.69	< 0.001
Randomization group (1:1:2)	1.46	0.92-2.29	0.102
Resuscitation Intensity (units)	1.03	0.60-1.44	0.184

Multivariate regression predicting 30-day mortality

680 patients from PROPPR study

Meyer DE, et al. Every minute counts: Time to delivery of initial massive transfusion cooler and its impact on mortality. J Trauma Acute Care Surg. 2017 Jul;83(1):19-24

Preventable delays in transfusion

- The UK Serious Hazards of Transfusion program put out an alert regarding delays in transfusion leading to preventable deaths:
 - 2010-2020: 809 reports to the haemovigilance system
 - There were 54 preventable deaths reported; accounting for 25% of all transfusion-related deaths

Shop Serious Hazards of Transfusion Preventing transfusion delays in bleeding and critically anaemic patients.			ds	Must have: Protocols Policies	
Date of Issue:	17-Jan-22	Reference No:	SHOT/2022/001		Conduct drills
This alert is for action by: NHS and independent (acute and specialist) sector where transfusions are carried out.			ut.	Investigate failures	
Access to blood com professions. Implem without executive boa	ponents and products is a co entation of this alert should b ards) and supported by their de	mplex safety critical issue that is e coordinated by an executive lea esignated senior leads for medical	relevant across many departments ader (or equivalent role in organisation, nursing and pathology teams.	and ons	investigate failures

https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103190



Right mechanism



High speed collision Penetrating trauma Post-partum hemorrhage

Bad hemodynamics

High heart rate Low systolic blood pressure Needing inotropes Cardiac arrest Poor response to fluids



Shock Index triggers for MHP activation

> 1 Obstetrics Child (all ages)

Heart Rate ÷ Systolic



Schroll et al. Injury 2018 Jan;49(1):15-19

Shock Index vs ABC score to predict MT



SI>1: Sens 68%, Spec 81%

ABC<u>></u>2: Sens 47%, Spec 89%

Schroll et al. Injury 2018 Jan;49(1):15-19

Do not activate the MHP to get uncrossmatched blood

- Just call blood bank for 2-4 units of uncrossmatched blood in a cooler
- The MHP is just for patients who will need at least 6 units of RBC and other components (plasma, platelets, fibrinogen concentrate/cryoprecipitate)



Callum JL, et al. CMAJ Open. 2019 Sep 3;7(3):E546-E561



GI Bleeds usually don't usually need an MHP

In the GI bleeding trial called TRIGGER (n=936) performed in the UK, 95% of patients got just RBCs

[52 patients also excluded for "massive bleeding"]

Jairath et al. TRIGGER. Lancet 2015;386(9989):137-44

You can still get plasma, platelets, fibrinogen replacement without activating the MHP



Activate the MHP via a planned Communications Pathway with distinct terminology

Here is how we do it at my hospital:

- Activated like a Code Blue
- Call 4444
- Say you are activating the Code Transfusion
- Stay on the line
- Blood Bank Tech will be conferenced in
- Answer the blood bank's questions so they know what to put in the blood coolers
- Code Transfusion will be announced overhead to alert hospital staff not to call blood bank except in emergencies
- Porter dispatched automatically





- Designate lead physician
- Designate lead nurse for communication to porter, labs and other clinical staff
- Consider having an MHP phone that travels with the patient
- Repeated drills and simulations improve care

Brydges R, Hatala R, Zendejas B, et al. Linking simulation-based educational assessments and patient-related outcomes: a systematic review and metaanalysis. *Acad Med* 2015;90:246-56.

Gjeraa K, Moller TP, Ostergaard D. Efficacy of simulation-based trauma team training of non-technical skills. A systematic review. *Acta Anaesthesiol Scand* 2014;58:775-87.

Team training matters

- Simulations have been successfully employed for training in obstetrical hemorrhage, pediatric hemorrhage, and trauma
- A systematic review of 33 studies involving 1,203 residents found simulation was associated with improved provider behavior and patient outcomes.
- A systematic review of 13 studies of trauma team training, both nontechnical skills and team-based performance improved
- Improvements from simulation extend to improved outcomes in trauma and cardiac arrest care



e.g. Box 1	Box 2	Box 3	Box 4+
4 units of RBC	4 units of RBC 4 units of Plasma	4 units of RBC 2 units of Plasma 4 grams fibrinogen	4 units of RBC 2 units of Plasma



Other items can be ordered as needed "à la carte" (e.g. more platelets, PCC, or fibrinogen)

Pediatric weight based coolers for kids

1:1 = 2:1

PROPRR

JAMA SURG HARVARD



Holcomb, JAMA 2015; 313: 471-482

Mesar, JAMA Surg 2017; March 8.

6 Give Tranexamic acid within 60 minutes

• Every 15 minute delay to tranexamic acid is associated with a 10% drop in survival benefit

Guyette FX, et al. JAMA Surg. 2020 Oct 5;156(1):11–20 Shakur H, et al. *Lancet.* 2010; 376:23-32 Gayet-Ageron A, et al. Lancet. 2018 Jan 13;391(10116):125-132

Tranexamic acid evidence

- Key trials:
 - CRASH-2 in 20,211 trauma patients
 - MATTERS in 896 military trauma patients
 - STAAMP in 927 pre-hospital trauma patients
 - CRASH-3 in 12,737 trauma patients with TBI
 - ROC-TXA in 1,280 pre-hospital trauma patients with TBI

Safe Reduces mortality Optimal <60 minutes

Shakur H, et al. *Lancet.* 2010; 376:23-32 Morrison et al. Arch Surg 2012;147:113-9 Guyette FX, et al. JAMA Surg. 2020 Oct 5;156(1):11–20 CRASH-3 trial collaborators. Lancet. 2019;394:1713-1723 Rowell SE, et al. JAMA. 2020 Sep 8;324(10):961-974

Systematic review – thromboembolic complications

Cause of death	No. of studies	Events in TXA group	Events in Control group	OR (95%CI)	P value	l ² statistic
Myocardial infarction	5	45/11,288 (0.4%)	64/10,982 (0.6%)	0.66 (0.45, 0.97)	0.03	0%
Stroke	5	73/11,288 0.6%)	76/10,982 (0.7%)	0.90 (0.65, 1.24)	0.50	40%
Thromboembolic events	6	67/1,308 (5.1%)	62/963 (6.4%)	0.89 (0.37, 2.11)	0.79	60%
Pulmonary embolism	5	137/12,112 (1.1%)	117/13,800 (0.8%)	1.57 (0.79, 3.13)	0.20	80%
Deep vein thrombosis	6	105/12,240 (0.9%)	105/13,925 (0.8%)	1.13 (0.51, 2.51)	0.77	83%

Al-Jeabory M, et al. J Clin Med. 2021 Mar 3;10(5):1030.

Systematic review (Mortality, Trauma)

Al-Jeabory M, et al. J Clin Med. 2021 Mar 3;10(5):1030

CRASH-3 plus ROC-TXA in traumatic brain injury

Figure 5: Evidence on the effect of tranexamic acid on head injury-related death RR=risk ratio.

TXA improves the coagulopathy

Table 3. Changes of Laboratory and ROTEM Values Between On-Scene and the ED					
	Changes From Admi	On-Scene to ED ission	Difference Between TXA and C		
	C, n = 24 Mean [SD]	TXA, n = 24 Mean [SD]	Difference in Means (95% CI)	P Value	
pH	0.00 [0.07]	0.02 [0.09]	-0.02 (-0.07 to 0.03)	.43	
Standard bicarbonate (mmol/L)	-0.3 [2.6]	-1.4 [2.8]	1.1 (-0.5 to 2.6)	.21	
Base excess	-0.3 [2.3]	-0.8 [2.1]	0.5 (-0.8 to 1.8)	.90	
Anion gap (mmol/L)	-0.9 [3.1]	-2.4 [3.1]	1.5 (-0.3 to 3.3)	.13	
Hemoglobin (g/L)	-21 [27]	-25 [19]	4 (-10 to 18)	.28	
Lactate (mmol/L)	-0.6 [1.3]	-1.2 [1.1]	0.6 (-0.1 to 1.3)	.03	
EXTEM MCF (mm)	-8.2 [4.1]	1.0 [2.5]	-9.2 (-11.2 to -7.2)	<.001	
EXTEM ML (%)	0 [4]	-12 [27]	12 (1–24)	<.001	
INTEM MCF (mm)	-7.7 [4.5]	-0.8 [2.7]	-6.8 (-9.0 to -4.7)	<.001	
INTEM ML (%)	-2 [16]	-11 [20]	9 (-3 to 22)	<.001	
FIBTEM MCF (mm)	-3.7 [1.8]	-0.2 [2.8]	-3.5 (-4.8 to -2.1)	<.001	
FIBTEM ML (%)	-1 [22]	-4 [31]	3 (–12 to 19)	.08	
Quick's value (%)	2 [16]	-6 [17]	7 (-2 to 17)	.14	
INR	0.0 [0.1]	0.0 [0.2]	-0.1 (-0.2 to 0.0)	.26	
Fibrinogen (g/L)	-0.4 [0.5]	-0.5 [0.5]	0.1 (-0.2 to 0.4)	.41	
Factor XIII activity (%)	-18 [18]	-17 [21]	-1 (-12 to 11)	.85	
Factor V activity (%)	-15 [23]	-18 [17]	3 (-9 to 14)	.51	
D-dimers (mg/dL)	3.9 [5.4]	0.1 [2.2]	3.9 (1.5 to 6.3)	.002	
Protein C activity (%)	-13 [18]	-11 [16]	-2 (-12 to 8)	.58	

Stein P, et al. Anesth Analg. 2018 Feb;126(2):522-529.

WOMAN Trial (n=20,060)

Figure 3: Death from bleeding by subgroup

*Heterogeneity p value. †One patient excluded from subgroup analysis because of missing baseline data.

Published online April 26, 2017 http://dx.doi.org/10.1016/S0140-6736(17)30638-4

Tranexamic acid

- Give 2 grams for all adults
 - 2 grams as a bolus/infusion
 - Or give 2 x 1 gram iv pushes one hour apart

J Emerg Crit Care Med 2021;5:15 | http://dx.doi.org/10.21037/jeccm-20-108

- Or if you are very sophisticated 1 gram bolus plus 1 gram infusion
- [kids: 15mg/kg IV bolus then 5mg/kg/hr IV infusion for 8 hours, to a maximum total dose of 2 grams]
- Don't bother if more than 3 hours from injury/bleed no residual benefit
- [Don't give to GI bleeds it doesn't work and causes more clots]

Shakur H, et al. *Lancet.* 2010; 376:23-32 HALT-IT Trial Collaborators. Lancet. 2020 Jun 20;395(10241):1927-1936

ROC-TXA infusion rate

5.2.7 Justification for dose selection

The dose selection for the study drug is as follows:

- Bolus/maintenance arm: 1 gram IV TXA in 250 mL administered wide open followed by a 1 gram maintenance IV TXA infusion over 8 hours (weight based equivalent: 50 kg person – bolus 20 mg/kg, maintenance 2.5 mg/kg/h; 75 kg person – bolus 13.3 mg/kg, maintenance 1.7 mg/kg/h; 100 kg person – bolus 10 mg/kg, maintenance 1.25 mg/kg/h)
- Bolus only arm: 2 grams IV TXA in 250 mL administered wide open followed by a maintenance placebo infusion over 8 hours (weight based equivalent: 50 kg person – bolus 40 mg/kg; 75 kg person – 26.7 mg/kg bolus; 100 kg person – bolus 20 mg/kg)

HALT-IT

HALT-IT Trial

-1936.

Collaborators.

Lancet. 2020 Jun

20;395(10241):1927

Tranexamic acid Placebo Risk ratio 95% Cl (n=5956) (n=5981) Time since onset 48 (4.9%) (0.75 - 1.61)≤3 h 52 (5.4%) 1.10178 (3.6%) 0.96 (0.78 - 1.18)>3 h 170 (3.4%) p=0.53 **Bleed** location 220 (4.1%) 0.97 (0.81 - 1.17)Upper 212 (4.0%) 6 (0.9%) 1.61 (0.59 - 4.40)Lower 10 (1.5%) • p=0.34 Variceal or liver 160 (5.5%) 165 (5.5%) (0.81 - 1.24)Yes 1.01No or unknown 62 (2.0%) 61 (2.1%) (0.70 - 1.40)0.99 p=0.94 Rockall score 1-2 17 (1.2%) 26 (1.9%) 0.64 (0.35 - 1.18)65 (2.8%) (0.70 - 1.38)3-4 63 (2.7%) 0.98 5-7 142 (6.3%) 135 (5.9%) 1.06 (0.84 - 1.33)p=0.32 Total 222 (3.7%) 226 (3.8%) 0.99 (0.82 - 1.18)1.6 0.35 1.0

Figure 3: Effect of tranexamic acid on death due to bleeding within 5 days

Blood work at activation and hourly

- Baseline:
 - BLOOD GROUP AND SCREEN
 - CBC, INR, PTT, fibrinogen
 - Electrolytes, ionized Ca, lactate
- Hourly or q4 units RBC:
 - CBC, INR, fibrinogen (no need to do hourly PTT if baseline concordant with INR)
 - K+, ionized Ca++ for monitoring for transfusion toxicity and lactate
- Ensure your lab calls back ALL hematology results and critical chemistry results

Use order groups in your EMR so you don't miss doing a test

Mortality increases at >1.2 Firth D, et al. J H and T 2010; 8: 1919-25

Baseline INR tells you how badly injured your patient is

Time from arrival in ED to critical levels

Gando & Hayakawa 2016

Two ways to test

VS.

INR, PTT, and fibrinogen done in the laboratory on a centrifuged plasma sample

Viscoelastic testing

ROTEM impact - Cardiac Surgery-related Hemorrhage Step-wedge cluster RCT (7402 patients)

Outcome	Relative Risk (95% CI)	P-value
Red cell transfusions	0.91 (0.84, 0.98)	0.01
Platelet transfusions	0.81 (0.72, 0.91)	<0.001
Plasma transfusions	1.04 (0.91, 1.18)	0.57
Cryoprecipitate or fibrinogen concentrate transfusions	1.19 (0.89, 1.59)	0.24
Major bleeding	0.86 (0.75, 0.98)	0.02
Major complications	1.01 (0.80, 1.26)	0.97

Karkouti et al. Circulation. 2016;1341152-1162

iTACTIC Trial (n=396) – TEG/ROTEM vs conventional clotting assays

Table 2 Secondary outcomes for the intention-to-treat population

	CCT (<i>n</i> = 195)	VHA (<i>n</i> = 201)	Odds ratio (95% CI)	<i>p</i> value
Mortality at 6 h—no. (%)	22/195 (11%)	22/201 (11%)	0.97 (0.52–1.80)	0.915
Mortality at 24 h—no. (%)	33/195 (17%)	29/201 (14%)	0.83 (0.48–1.42)	0.495
Mortality at 28 days—no. (%)	55/194 (28%)	50/201 (25%)	0.84 (0.54–1.31)	0.435
Mortality at 90 days—no. (%)	56/177 (31%)	53/179 (29%)	0.91 (0.58–1.42)	0.678
Death from exsanguination—no. (%)	17/56 (30%)	13/51 (25%)	0.78 (0.34–1.82)	0.576
Died before haemostasis—no. (%)	24/54 (44%)	19/50 (38%)	0.77 (0.35–1.67)	0.505

TEG/ROTEM patients **1.8-times** more likely to get non-RBC products

Baksaas-Aasen K, Gall LS, Intensive Care Med. 2021 Jan;47(1):49-59.

Transfuse to Target

BEWARE: Just because you are giving ratiobased resuscitation doesn't mean you will stay on target. Formula-based ratios are just for initial care.

Lab metric	Target
Hemoglobin	60-110 g/L Keep over 80 g/L if possible
Platelet count	Keep over 50 (over 100 for cardiac surgery and head trauma)
INR	Keep below 1.8 (or use similar cut off with viscoelastic testing, e.g. ROTEM CT>90 seconds)
Fibrinogen	Keep over 1.5 g/L (over 2.0 g/L for cardiac and obstetrics) (or use similar cut off with viscoelastic testing, e.g., FIBTEM<8-10)

Under and over transfusion are bad

Fig 1. The odds of death (Y-axis) based on the hemoglobin (HgB) value 24 ± 6 hours after anatomic hemostasis (X-axis). The odds of death are controlled for age, sex, and Charlson Comorbidity Score. The inflection points for increased mortality odds were >12.0 g/dL (pRBc overtransfusion) and <8.0 g/dL (undertransfusion). The ideal HgB range was defined as 8.0–12.0 g/dL.

Zielinski MD, et al. Surgery. 2016 Dec;160(6):1560-1567

Fibrinogen<2.0 g/L and PPH

[Pregnant patients without bleeding have fibrinogens between 3.5-6.5]

Charbit, et al. JHT 2006; 5: 266-73

Reverse anticoagulants

REVERSE ANTICOAGULANTS

Warfarin IV Vitamin K 10 mg INR 1.5 to 3.0 – 1000 IU PCC INR 3.0 to 5.0 – 2000 IU PCC INR > 5.0 - 3000 IU PCC Unknown INR – 2000 IU PCC

Dabigatran - Idarucizumab (Praxbind) 5 g IV

Xa Inhibitors - PCC 2000 IU Repeat at 1 hour if ongoing hemorrhage

Avoid hypothermia

- Keep temperature over 36°C
- Use blood warmer for all fluids
- Use active warming blankets
- Monitor temperature every 30 minutes

https://www.bairhugger.com/3M/en_CA/bair-hugger-ca/

https://belmontmedtech.com/rapid-infusion-pump

Hypothermia – Prevention & Management

- Minimal number of studies
- Poorly monitored during pre-hospital and pre-OR phase
- Temp <34°C associated with an increase in mortality
- Each 1°C increases blood loss by 16% and risk of transfusion by 22%
- In the pre-hospital phase, trauma patients with minor injury have a fall in temperature with passive warming (blankets), versus a rise with resistive warming blankets AND they are more comfortable on arrival

Reynolds BR, et al. J Trauma Acute Care Surg. 2012; **73**(2): 486-91. Dirkmann D, et al. Anesth Analg. 2008; **106**(6): 1627-32. Kober A, et al. Mayo Clin Proc. 2001; **76**(4): 369-75. Walpoth BH, et al. N Engl J Med. 1997; **337**(21): 1500-5. Lundgren P, et al. Scand J Trauma Resusc Emerg Med. 2011; **19**: 59.

- Terminate when hemorrhage control is achieved, hemodynamics improving, coagulation parameters improving, and rate of transfusion has slowed
- Call blood bank or designated communication route to terminate
- Return unused blood to blood bank immediately
- Bedside debrief talk about what the team did well and what did not go well – learn from your mistakes

- Keep the blood packed exactly as it comes from the blood bank
- Do not move blood from one cooler to another
- Don't put empties in your cooler they contaminate the other units and if not used, have to be discarded
- Don't write on the unit labels if you do they have to be discarded
- Return as soon as identified the products are not needed

Summary

- Activated promptly every 1 minute delay associated with 5% increase in mortality
- Right patient not all bleeding patients need an MHP activation, especially GI bleeds
- Activated through standardized communication process with clear terminology
- Team promptly assembled, team has been drilled, and a team lead is designated
- First RBC spiked within 15 minutes
- Tranexamic acid given within 60 minutes (excluding GI bleeds) 2 gm total dose for adults
- Blood work at activation and every 60 minutes or every 4 units of RBC
- Transfusion to target values and keep hemoglobin 80-120 g/L throughout
- Avoid hypothermia
- Terminate when hemorrhage is controlled, hemodynamics are improving, coagulation tests going in right direction, and rate of transfusion has slowed
- Don't waste blood we are the stewards of the blood system