CRITCARE BITES

BLEEDING AND MTP

SICM
Society of Intensive Care Medicine
SINGAPORE

MAD FOR MEDICINE

HEMOSTASIS

- Primary hemostasis
- Secondary hemostasis
- Fibrin stabilisation
- Fibrinolysis

PRIMARY HEMOSTASIS

- Vessel injury results in collagen/subendothelial matrix exposure causing vasoconstriction
- Blood flow impeded and platelets come into contact with damaged vessel wall
- Platelet adhesion, activation and aggregation occurs via VWF
- Leading to platelet plug formation at site of vascular injury

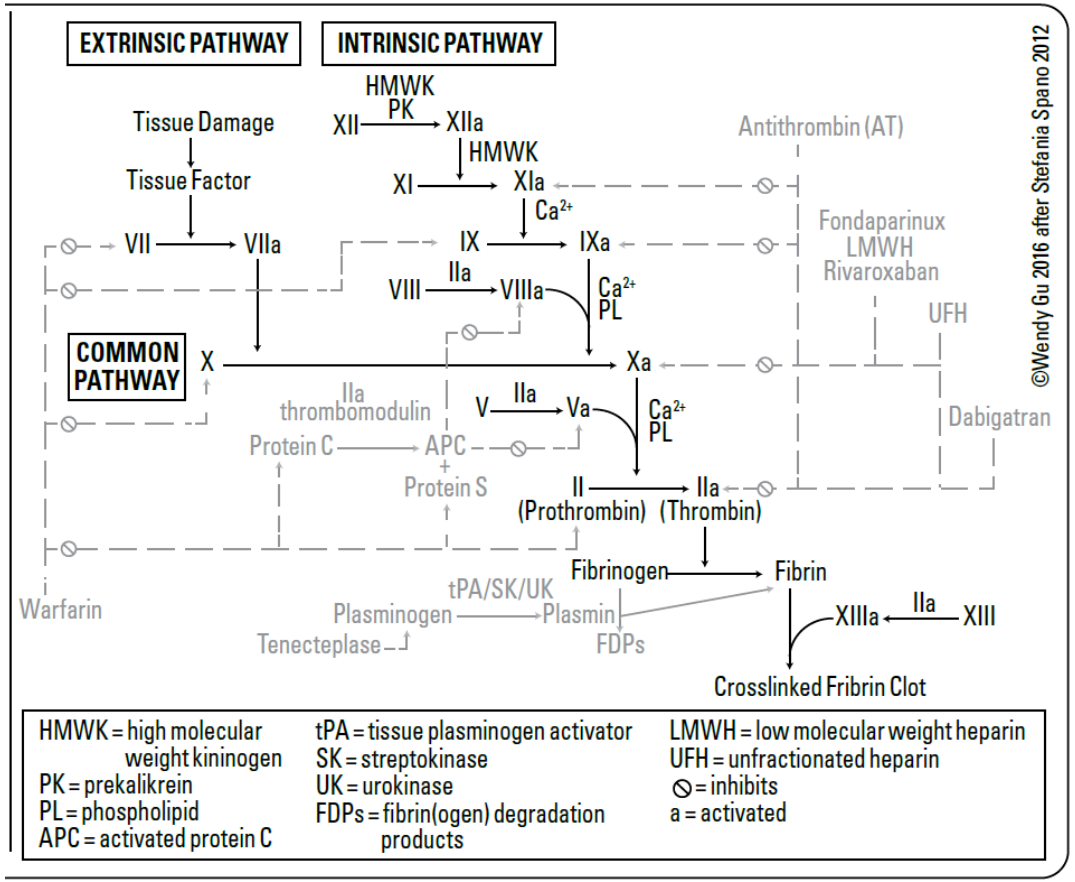
DISORDERS OF PRIMARY HEMOSTASIS

- Von Willebrand disease
- Platelet function disorders
- Thrombocytopenia
- Other rare conditions

SECONDARY HEMOSTASIS

- Platelet plug reinforced by production of fibrin clot
- Extrinsic pathway: initiation of coagulation in vivo
- Intrinsic pathway: amplification via positive feedback

SECONDARY HEMOSTASIS & FIBRIN STABILISATION



FIBRINOLYSIS

- Clot is eventually broken down
- Plasminogen converted to plasmin
- Plasmin degrades fibrin into soluble fragments

COAGULATION TESTS: PT | APTT | INR

- Prothrombin Time
  - Assess Extrinsic and common pathway
  - Validated for Warfarin monitoring
- Internationalised Normalise Ratio
  - Mathematically derived standardized PT result
- Activated Partial Thromboplastin time
  - Assess Intrinsic and common pathway
  - Validated for Heparin monitoring and haemophilia screening

ABNORMAL PT & APTT

Prolonged PT	Prolonged aPTT	Prolonged PT and aPTT
Factor 7 deficiency	Factor 8, 9, 11, 12 deficiency	Factor 2, 5, 10, Fibrinogen deficiency
Liver disease	Heparin Exposure	Liver disease
Warfarin therapy	Inhibitors	Supratherapeutic Warfarin
Vitamin K deficiency	Antiphospholipid ab	Vitamin K Deficiency
		DIC
		Thrombin Inhibitors

Hazim AZ, et al.
International Journal of Laboratory Hematology. 2022;44(1):209-215. doi:10.1111/ijlh.13727.

COAGULATION TESTS: FIBRINOGEN

- Fibrinogen key protein in fibrin clot formation
- Hypofibrinogemia commonly due to consumption, major bleeding or severe liver disease
- Fibrinogen is an acute phase reactant

owe GD et al, Annals of Clinical Biochemistry. 2004;41(Pt 6):430-40. doi:10.1258/0004563042466884.

COAGULATION TEST: VISCOELASTIC HEMOSTATIC ASSAY

- Evaluates cellular (primary) and plasma protein (secondary) hemostasis
- Reflect coagulation factor activity, platelet function and fibrinogen activity
- Real time comprehensive view of clot formation and dissolution

Carll T, Transfusion. 2020;60 Suppl 6:S1-S9. doi:10.1111/trf.16071.

VISCOELASTIC HEMOSTATIC ASSAYS

VHA

- Cellular and Plasma protein components
- Real time | Dynamic
- Shorter turnaround
- Detection of hypercoagulability and hyperfibrinolysis
- Guiding transfusion therapy
- More expensive

COAGULATION TESTS

- Plasmatic components only
- Static | Initiation phase only
- Longer turnaround

Carll T, Transfusion. 2020;60 Suppl 6:S1-S9. doi:10.1111/trf.16071.

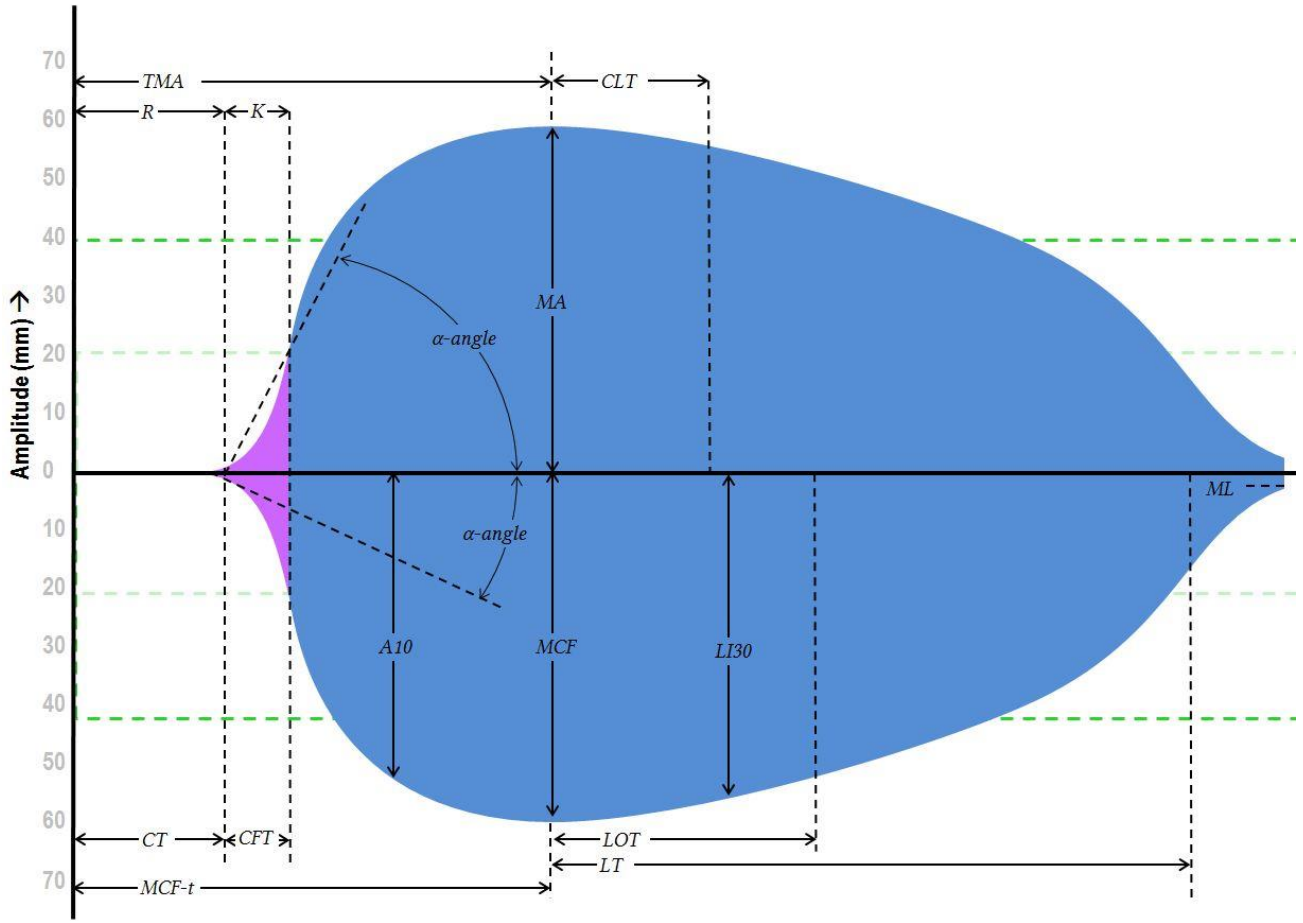
VHA- LIMITATIONS

- Insensitive to effects of antiplatelet agents
- Insensitive to effects of DOACs
- Insensitive to vWD | Anti thrombin III | Protein C/S | Factor V Leiden
- Hypothermia
- Hypocalcemia

Dias JD, et al. The Journal of Trauma and Acute Care Surgery. 2019;87(2):364-370. doi:10.1097/TA.0000000000002357.

TEG NOMENCLATURE

R = Reaction time (time from start to amplitude = 2mm)
K = Kinetics (time from amplitude = 2mm until amplitude = 20mm)
α-angle = slope from 2mm to 20mm amplitude
TMA = Time to Maximum Amplitude
MA = maximum amplitude
CLT = Clot Lysis Time (time taken for amplitude to decrease by 2mm from MA)



ROTEM NOMENCLATURE

CT = Clotting Time (time from start to amplitude = 2mm)
CFT = Clot Formation Time (time from amplitude = 2mm until amplitude = 20mm)
α-angle = slope of the line at 2mm amplitude
A10 = amplitude at 10 minutes; ...there can be any number of A(x) variables
MCF-t = Time to Maximum Clot Firmness
MCF = Maximum Clot Firmness
LOT = Lysis Onset Time (time taken for amplitude to decrease by 15% of MCF)
LT = Lysis Time (time taken for amplitude to drop to 10% of MCF)
LI30 = Lysis Index at 30 minutes (% drop in amplitude from MCF)
ML = Maximum Lysis (minimum amplitude achieved at the end of test run time)

https://derangedphysiology.com/main/required-reading/haematology-and-oncology/Chapter%20120/viscoelastic-tests-clotting-function-teg-and-rotem#:~:text=Both%20the%20TEG%20and%20ROTEM,platelet%20function%20and%20fibrinogen%20concentration.

VHA TERMINOLOGY

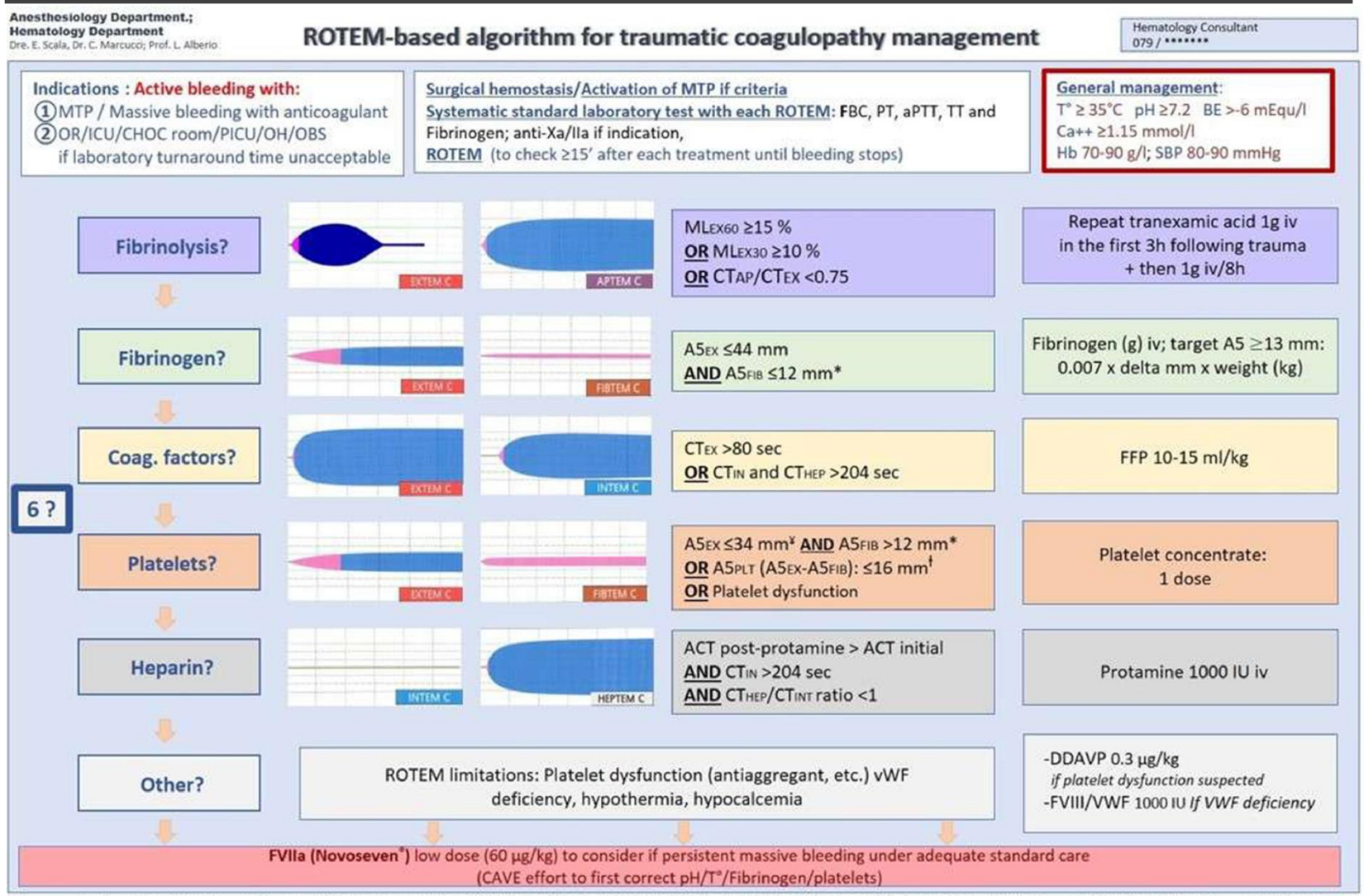
Description	Reflects	TEG	ROTEM
Time till fibrin formation	Clotting factors Anti Coagulation	Reaction Time (R Time)	Clotting time (CT)
Time taken to achieve certain level of clot (eg 20mm)	Clotting factors Fibrinogen Platelet	K- Time	Clot formation time (CFT)
Speed of fibrin build up | Slope at 2mm amplitude	Fibrinogen Platelet	Alpha Angle (α-angle)	Alpha Angle A
Maximum Strength of clot | thickness	Fibrinogen Platelet	Maximum Amplitude (MA)	Maximum Clot Firmness (MCF)
Amplitude of clot at specific intervals (Eg A5 = 5min)	Fibrinogen Platelet	A5 | A10 | A20	A5 | A10 | A20
Clot Lysis at 30mins | Maximum Lysis	Fibrinolysis	Lysis 30 (LY30) ML	LI30 Maximal Lysis (ML)

VHA: ROTEM AND TEG

Evaluates	TEG	ROTEM
Intrinsic Pathway	CKT (Kaolin)	INTEM (Ellagic Acid)
Extrinsic Pathway	-	EXTEM (Tissue Factor)
Rapid assessment of Coagulation	CRT (Kaolin + Tissue factor)	-
Heparin effect (Neutralise heparin via heparinase) In conjunction with CKT | INTEM	HTEG | CKH	HEPTEM
Fibrinogen contribution (Inhibit Plt function) In conjunction with CKT | EXTEM	CFF	FIBTEM
Effect of antifibrinolytic agent In conjunction with EXTEM	-	APTEM

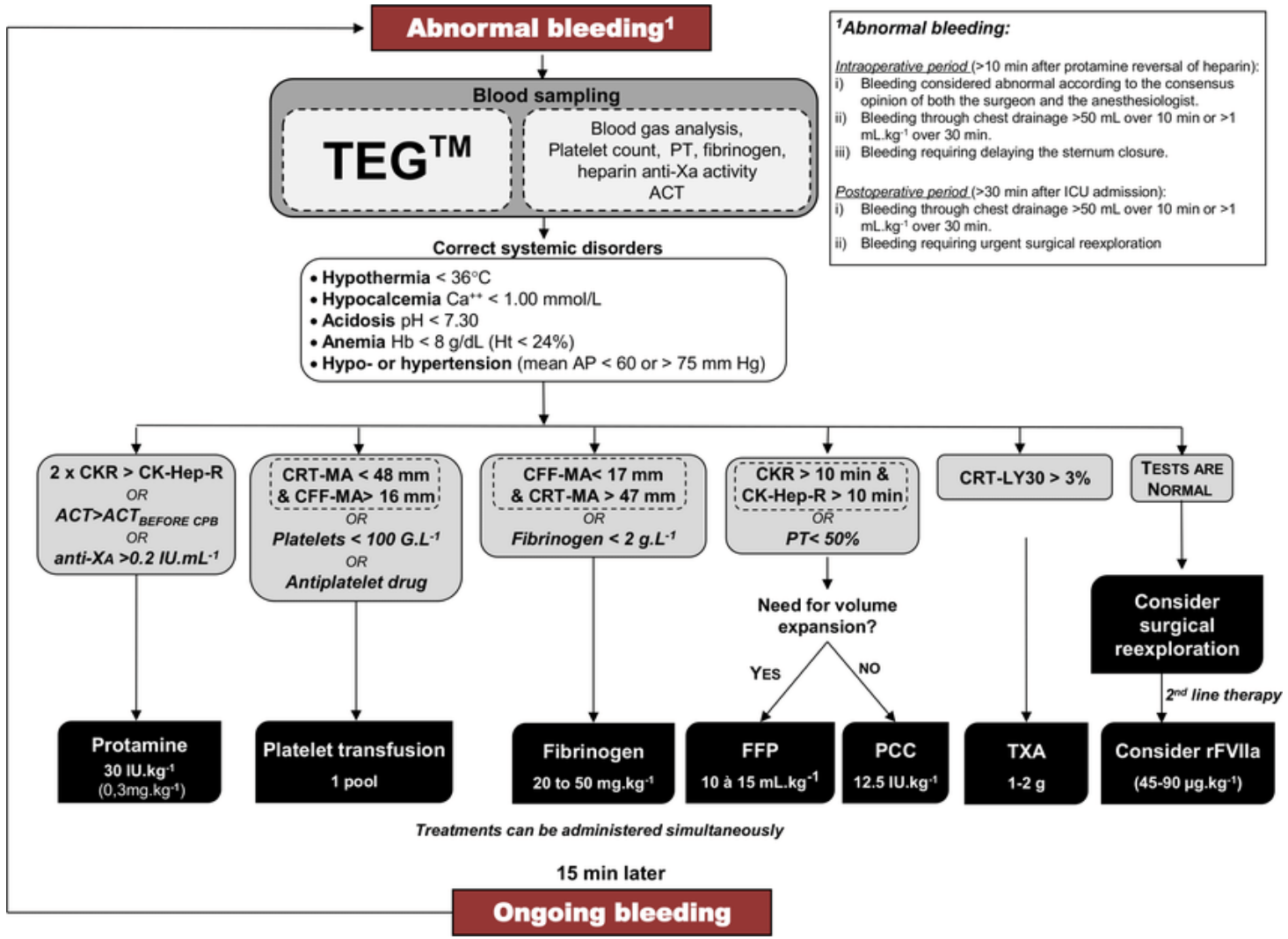
Whiting D American Journal of Hematology. 2014;89(2):228-32. doi:10.1002/ajh.23599.

ROTEM INTERPRETATION



https://doi.org/10.1053/j.jvca.2019.07.024

TEG INTERPRETATION



Rigal, Et al. BMJ Open. 9. e029751. 10.1136/bmjopen-2019-029751.

VHA USES

- Guide haemostatic therapy
  - Trauma
  - Cardiac surgery
  - Liver transplantation
  - Obstetrics
- Predict bleeding and thrombotic risks
- Assess anticoagulant effects

Reardon B Journal of Clinical Medicine. 2024;13(12):3612. doi:10.3390/jcm13123612.

DIC

- Precipitants
  - Sepsis | Trauma | Obstetric complications | Malignancy | Surgery
- Pathophysiology
  - Release of tissue factor activate clotting cascade
  - Production of excessive thrombin and fibrin clots
  - Widespread thrombosis and consumption of clotting factors and platelets
  - Leading to microangiopathic hemolytic anemia
- Lab features
  - Thrombocytopenia | prolonged PT/aPTT | Low fibrinogen | Elevated D-Dimer | Fragments

Levi M. Critical Care Clinics. 2005;21(3):449-67. doi:10.1016/j.ccc.2005.02.001.
Rubin RN et al Drugs. 1992;44(6):963-71. doi:10.2165/00003495-199244060-00005.

LIVER DISEASE

- Rebalanced hemostatic pathway
- Liver synthesize coagulation factors and anticoagulant proteins
- Bleeding
  - Reduced clotting factors
  - Thrombocytopenia | Platelet dysfunction
  - Hyperfibrinolysis | DIC
- Thrombosis
  - Elevated vWF and Factor 8
  - Reduced Protein C and S

Rautou PE et al, Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association. 2023;21(8):2110-2123.

CRITICALLY ILL BLEEDING MANAGEMENT

Massive Transfusion

GENERAL MEASURES

- Initial stabilisation – ABCs
- Haemostatic resuscitation (1:1:1 ratio)
- Restrictive transfusion targets
- Coagulopathy management
- Pharmacological adjuncts
- Correction of physiological derangements
- Haemostasis

INITIAL STABILISATION

- Airway
  - Secure airway early if concerns of massive bleeding
- Breathing
  - Supplement O2
- Circulation
  - Large bore IV cannula

HEMOSTATIC RESUSCITATION

- Permissive hypotension
- Balanced Blood product transfusion (1:1:1 ratio)
- Minimize crystalloids
- Antifibrinolytics
- Damage control surgery
- Avoid Hypothermia | Acidosis | Hypocalcemia

Tran A et al, The Journal of Trauma and Acute Care Surgery. 2018;84(5):802-808. doi:10.1097/TA.0000000000001816
Holcomb JB et al, Jama. 2015;313(5):471-82. doi:10.1001/jama.2015.12.

ANTIFIBRINOLYTIC AGENT

- Aminocaproic acid | Tranexamic acid - prevent clot breakdown
- Tranexamic acid
  - Uses: Trauma | Post Partum Haemorrhage | Surgical Bleeding – Cardiac / Orthopaedic | Burns | Liver transplantation
  - Dose: 1g followed by 1g over 8hours (Trauma)

Ockerman, A *et al.* Tranexamic acid for the prevention and treatment of bleeding in surgery, trauma and bleeding disorders: a narrative review. *Thrombosis Journal* **19**, 54 (2021)

ANTICOAGULANT REVERSAL

Anticoagulant	Reversal Agent	Dose
Warfarin (Dosed based on INR)	Viatmin K	10mg IV
	PCC	15-30u/kg
	FFP	10-20mls/kg
Direct Thrombin Inhibitor (Dabigatran)	Idarucizumab	5g IV
	PCC	25-50u/kg
	Dialysis	
Direct Factor Xa Inhibitor (Apixaban | Edoxaban | Rivaroxaban)	Andexanet alfa	400-800mg bolus > 4-8mg/min infusion for 120mins
	PCC	50U/kg

Anticoagulant	Reversal Agent	Dose
Thrombolytic	TXA	1g
	Cryoprecipitate	10u
	FFP	10-20mls/kg
Heparin	Protamine	1mg / 100u
Clexane	Protamine	1mg/mg

DDAVP

Indications

1) Uremic Platelet Dysfunction
2) Antiplatelet therapy
3) Hemophilia A
4) Von Willebrand Disease

Dose: 0.3-0.4mcg/kg infused over 20-30mins (Max 40mcg)

MASSIVE TRANSFUSION

- Definitions
  - Loss of one blood volume over 24hrs
  - Loss of 50% of blood volume over 3hours
  - Bleeding rate of >150ml/min
  - Transfusion of ≥10units of red cells over 24hrs
  - Bleed that causes a drop in SBP <90 and increase in HR >100 bpm

Hunt, *et al.* A practical guideline for the haematological management of major haemorrhage. *British Journal of Haematology* **170**, 788–803 (2015).

ABC SCORE

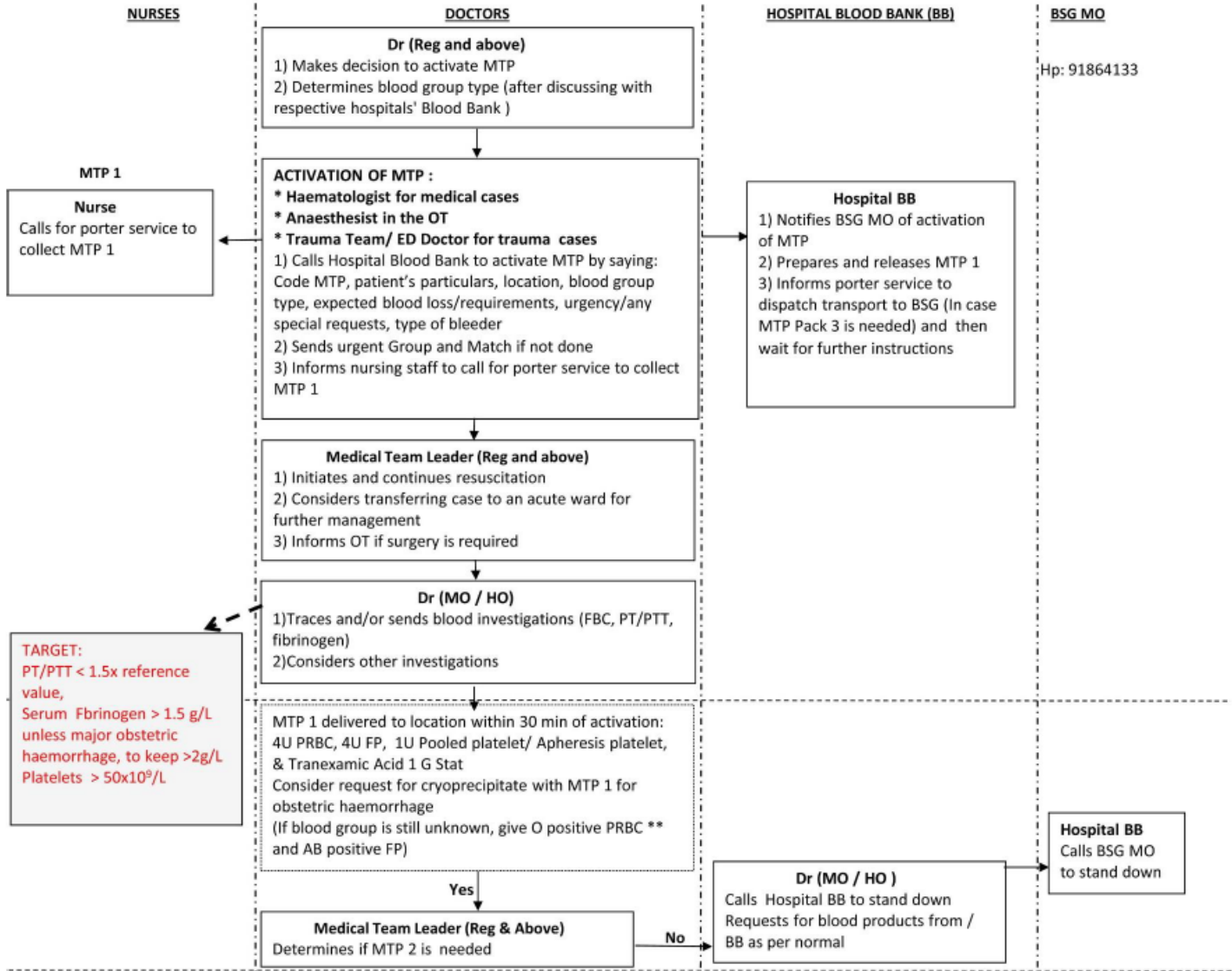
- Assessment of blood consumption score
- Predicts need for massive transfusion in trauma patients
- 4 components
  - SBP ≤ 90mmHg
  - HR ≥ 120bpm
  - Positive FAST
  - Penetrating mechanism of injury
- Score ≥ 2 predicts need for massive transfusion

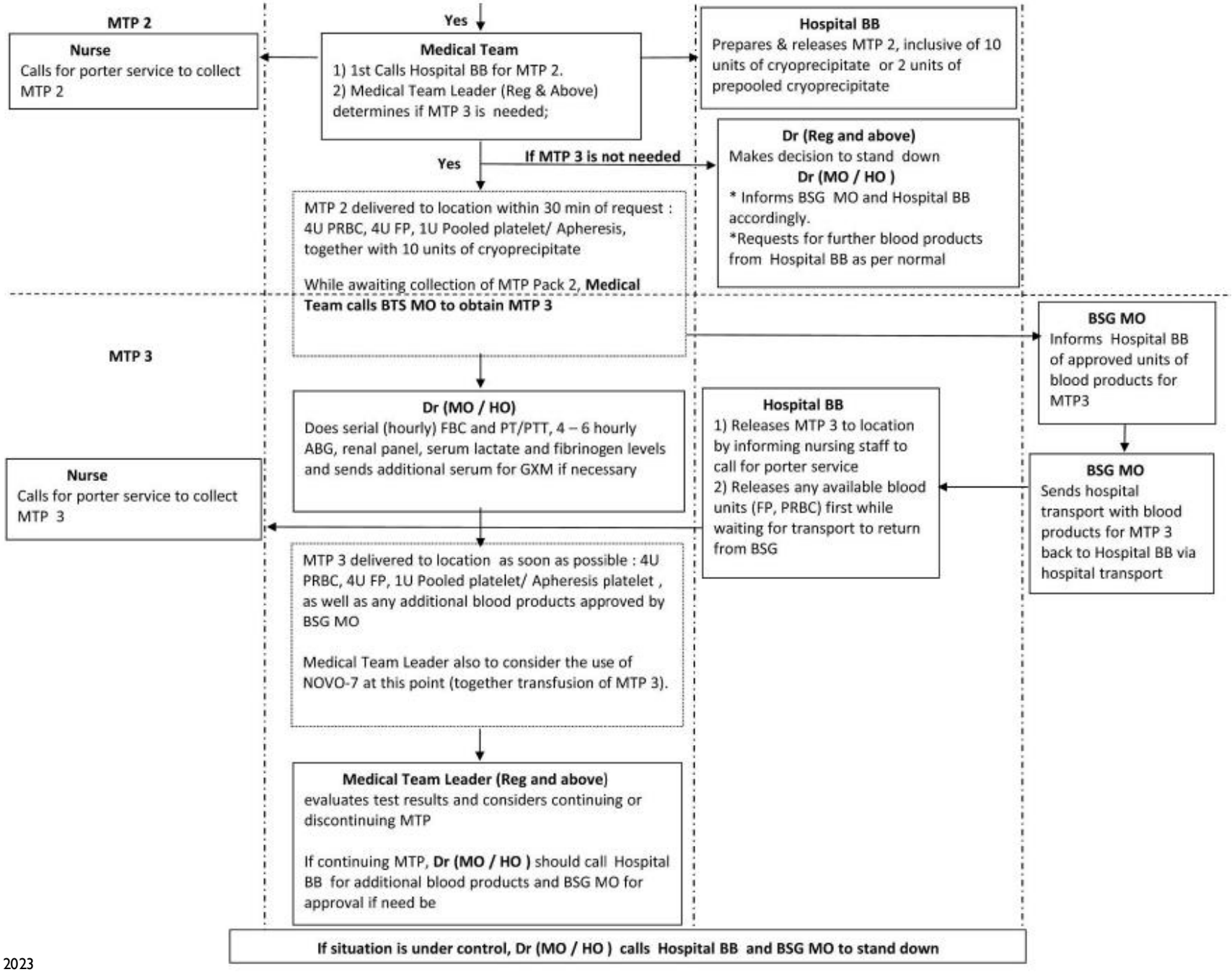
Nunez *et al.* Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)?*Journal of Trauma and Acute Care Surgery* **66**, 346–52 (2009).

COMMON NATIONAL MASSIVE TRANSFUSION PROTOCOL[4]

NB: Patients who are Rh D negative and who have positive red cell alloantibodies are excluded from this MTP. Attending doctor is to inform BSG MO and request for blood products in the usual manner.

If situation is under control, doctor (MO /HO) calls Hospital BB and BSG MO to stand down
PRBC **: packed red blood cells; FP: frozen plasma; BB: Blood Bank




MTP 2
Yes
Nurse
Calls for porter service to collect MTP 2
Medical Team
1) 1st Calls Hospital BB for MTP 2.
2) Medical Team Leader (Reg & Above) determines if MTP 3 is needed;
Hospital BB
Prepares & releases MTP 2, inclusive of 10 units of cryoprecipitate or 2 units of prepooled cryoprecipitate
Yes
If MTP 3 is not needed
Dr (Reg and above)
Makes decision to stand down
Dr (MO / HO)
* Informs BSG MO and Hospital BB accordingly.
*Requests for further blood products from Hospital BB as per normal
MTP 2 delivered to location within 30 min of request : 4U PRBC, 4U FP, 1U Pooled platelet/ Apheresis, together with 10 units of cryoprecipitate
While awaiting collection of MTP Pack 2, Medical Team calls BTS MO to obtain MTP 3
BSG MO
Informs Hospital BB of approved units of blood products for MTP3
MTP 3
Dr (MO / HO)
Does serial (hourly) FBC and PT/PTT, 4 – 6 hourly ABG, renal panel, serum lactate and fibrinogen levels and sends additional serum for GXM if necessary
Hospital BB
1) Releases MTP 3 to location by informing nursing staff to call for porter service
2) Releases any available blood units (FP, PRBC) first while waiting for transport to return from BSG
BSG MO
Sends hospital transport with blood products for MTP 3 back to Hospital BB via hospital transport
Nurse
Calls for porter service to collect MTP 3
MTP 3 delivered to location as soon as possible : 4U PRBC, 4U FP, 1U Pooled platelet/ Apheresis platelet , as well as any additional blood products approved by BSG MO
Medical Team Leader also to consider the use of NOVO-7 at this point (together transfusion of MTP 3).
Medical Team Leader (Reg and above)
evaluates test results and considers continuing or discontinuing MTP
If continuing MTP, Dr (MO / HO) should call Hospital BB for additional blood products and BSG MO for approval if need be
If situation is under control, Dr (MO / HO) calls Hospital BB and BSG MO to stand down

COMPONENTS OF MTP

Blood component	Indication	Threshold	Treatment
RBC	Maintain DO2	Refer to next slide	PRBC
Frozen plasma	Clotting factor replacement	PT/aPTT >1.5x ULN	15-20ml/kg FFP
Cryoprecipitate	Fibrinogen replacement	Fibrinogen <1.5-2g/l	10u cryoprecipitate
Platelets	Thrombocytopenia 2' consumption | Dilution	<50 <100 (ongoing bleeding)	1 unit of platelet
TXA	Anitfibrinolysis		

National guideline on clinical transfusion – HAS 2023

MTP – RBC

- O –ve considered in
  - Females <50yrs age (future or current future childbearing potential) + Indian | Caucasian | Middle Eastern | African origin with unknown ABO and RhD blood group
- O +ve
  - Male patients or Females patients with no current or future childbearing potential with unknown ABO and RhD blood groups

RBC TRANSFUSION TARGETS

Clinical Situation	Transfusion Trigger (g/dL)
Asymptomatic	<7
Critically ill	<7
Stable Post Op	<8
Unstable post Op	8-10, transfuse 1 PCT and assess efficacy
Stable Pre Existing CVD	<8
Unstable Pre Existing CVD	8-10
ACS	<8 8-10, if symptomatic, transfuse 1 PCT and assess efficacy

Hébert *et al.* A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. *New England Journal of Medicine* **340**, 409–417 (1999)
Docherty *et al.* Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. *Brisith Medical Journal* i1351–i1351 (2016).
Ducrocq *et al.* Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia. *Journal of American Medical Association* **325**, 552-560 (2021).
National guideline on clinical transfusion – HAS 2023

VHA GUIDED TRANSFUSION

- Standard Lab test
  - Long turnaround times
  - PT and aPTT not accurate
  - Limited value in predicting major bleeding

- VHA
  - Shorter turnaround time
  - Detect hyperfibrinolysis
  - Assess all phases of coagulation
  - Better predictive value in liver disease
  - Better outcomes in Cardiac surgery
  - Reduces number of blood products required
  - Reduced invasive haemostatic interventions
  - Reduced mortality in trauma patients

Wikkelsø A Anaesthesia. 2017;72(4):519-531. doi:10.1111/anae.13765.

VHA GUIDED FIBRINOGEN TRANSFUSION

	A5 Threshold	A5 Target
Severe bleeding	<9mm	>12mm
Liver	<12mm	> 14mm
Cardiac	<13mm	> 15mm

Target A5	Fibrinogen dose (ml/kg BW)	Fibrinogen concentrate (ml/kg BW)	Cryoprecipitate (ml/kg BW)
2	12.5	0.6 [1g/80kg]	1 [5u/80kg]
4	25	1.2 [1.2g/80kg]	2 [10u/80kg]
6	37.5	1.9 [3g/80kg]	3 [15u/80kg]
8	50	2.5 [4g/80kg]	4 [20u/80kg]
10	62.5	3.1 [5g/80kg]	5 [25u/80kg]
12	75	3.8 [6g/8kg]	6 [30u/80kg]

FC dose (g) = target increase AF Fibtem (mm) x BW (kg) 160

NUH Protocol

VHA GUIDED PLATELET TRANSFUSION

	Treatment
A5 Ex <25mm	1 Platelet concentrate
A5 Ex <15mm	2 Platelet concentrate
A5 Ex <5mm	2 Platelet Concentrate + Fibrinogen concentrate 4g

80 kg adult 1 pooled/apheresis PC increase A5 Ex by 8-10mm

VHA GUIDED PROTHROMBIN COMPLEX CONCENTRATE

- Dose 15IU/kg to 30IU/kg
- Repeat till correction of CT

COMPLICATIONS OF MTP

	Etiology	Consequence	Management
Dilutional coagulopathy	Large volume crystalloid | colloid | RBC transfusion	Coagulopathy	Minimise crystalloids 1:1:1 Transfusion
Hypothermia	Cold infusions Exposure	↓ Clotting Plt dysfunction	Normothermia Warm infusion Warm patient
Metabolic acidosis	Hypoperfusion Citrate overload Lactate release from RBC storage	↓ Clotting	Adequate perfusion
Hypocalcemia	Impaired citrate clearance	↓ Clotting ↓ Vasomotor tone	Monitor iCa 1-2hrly
Hyperkalemia	Extracellular K in RBC	Arrythmias	Monitor K

National guideline on clinical transfusion – HAS 2023

COMPLICATIONS OF BLOOD TRANSFUSION

Complications	Clinical Presentation	Additional Test	Management
Febrile Non hemolytic Transfusion reaction (FNHTR)	Fever during or within 4hrs Myalgia | Nausea | Rigors	Rule out bacterial contamination	Stop transfusion Antipyretics Mild – restart slowly Return blood component Use Leucoreduced (>2 FNHTRs)
Allergic reaction	Allergic reaction during or within 4hrs Mod: angioedema Severe: Anaphylaxis	IgA Deficiency	Stop transfusion Antihistamines | Steroids | Bronchodilator | Adrenaline Restart slowly (mild) Plasma reduced platelets Washed cellular blood components

National guideline on clinical transfusion – HAS 2023

COMPLICATIONS OF BLOOD TRANSFUSION

Complications	Clinical Presentation	Additional Test	Management
Acute hemolytic transfusion reaction (AHTR)	Fever | Chills | Rigors Facial Flushing | Chest pain Abdominal pain | N/V Hypotension Hemolysis – pallor | Jaundice DIC During or w/in 24hrs	Repeat ABO | RhD | Ab screen Direct antiglobin test Hemolysis testing	Stop transfusion ABC Organ support Return blood component
Delayed hemolytic transfusion reaction (DHTR)	Fever | Jaundice Inadequate rise in Hb 24hrs to 28d post transfusion	Direct antiglobin test Ab screen Hemolysis testing	Transfuse antigen negative and crossmatch compatible RBC
Transfusion Associated Circulatory Overload (TACO)	Fluid overload During or 12hrs after	X Ray BNP	Stop transfusion O2 supplement Diuretics Minimise crystalloids 1 unit at a time

National guideline on clinical transfusion – HAS 2023

COMPLICATIONS OF BLOOD TRANSFUSION

Complications	Clinical Presentation	Additional Test	Management
Transfusion related acute lung injury (TRALI)	Dyspnoea | Hypoxemia CXR – B/l infiltrates Absence of overload During to 6hrs after	Xray	Stop transfusion O2 supplementation Mech ventilation Return blood Blood bank notification
Transfusion associated Dyspnea (TAD)	Respiratory distress w/in 24hrs Not explained by other cause	Exclude TRALI | TACO | Allergic reaction	Stop transfusion O2 supplementation
Hypotensive transfusion reaction	Hypotension SBP ↓≥30mmHg and SBP ≤80mmHg Within 1hr of completing	Rule out allergic reaction	Stop transfusion Discontinue use of ACEi Avoid leucocyte filters

National guideline on clinical transfusion – HAS 2023