7^ Conferenza Nazionale dei Servizi Trasfusionali
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SIMTI

La coagulopatia nella trasfusione massiva

Elvira Grandone

I.R.C.C.S. Casa Sollievo della Sofferenza

e

Università degli Studi di Foggia

La sottoscritta, in qualità di Relatrice
dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:

- *Kedrion*
- *Rovi*
- *CSL Behring*
- *Sanofi*

Settings

- Trauma
- Peripartum hemorrhage
- Surgery/procedures
- Gastrointestinal bleeding

Massive Transfusion

Table 1. Definitions of massive transfusion (MT).

Massive Transfusion (MT)	Dynamic Massive Transfusion
Replacement of one entire blood volume within 24 hours	Transfusion of ≥ 3 units of PRBCs in 1 hour
Transfusion of ≥ 10 units of PRBCs in 24 hours	Transfusion of ≥ 4 units of PRBCs in 1 hour with active major bleeding
Transfusion of ≥ 20 units of PRBCs in 24 hours	Transfusion of any 4 blood components in 30 minutes
Rapid bleeding rate is documented or observed	Replacement of 50% of total blood volume within 3 hours

Napolitano LM. . Expert Rev Hematol. 2021 Feb;14(2):219-239.

Trauma

Trauma-induced coagulopathy (TIC) results from
1) **acute trauma coagulopathy (ATC)** related to tissue injury and **shock** which occurs immediately
&
2) resuscitation coagulopathy (RC) related to **fluid/blood product resuscitation, hypothermia, acidosis and hypocalcemia**

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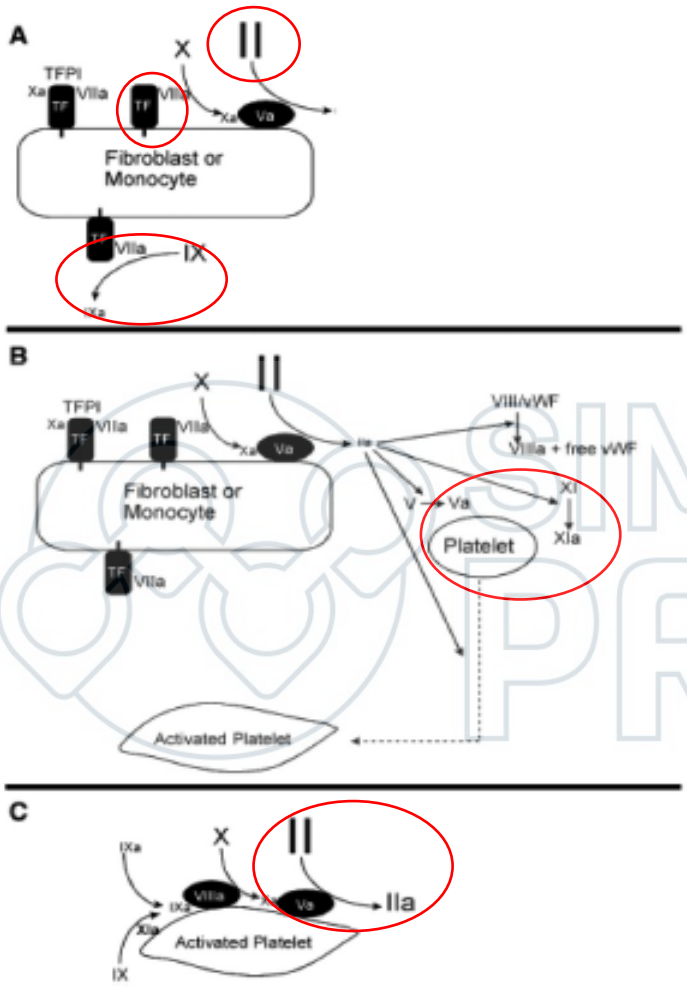
Steps in a cell-based model of coagulation and hemostasis



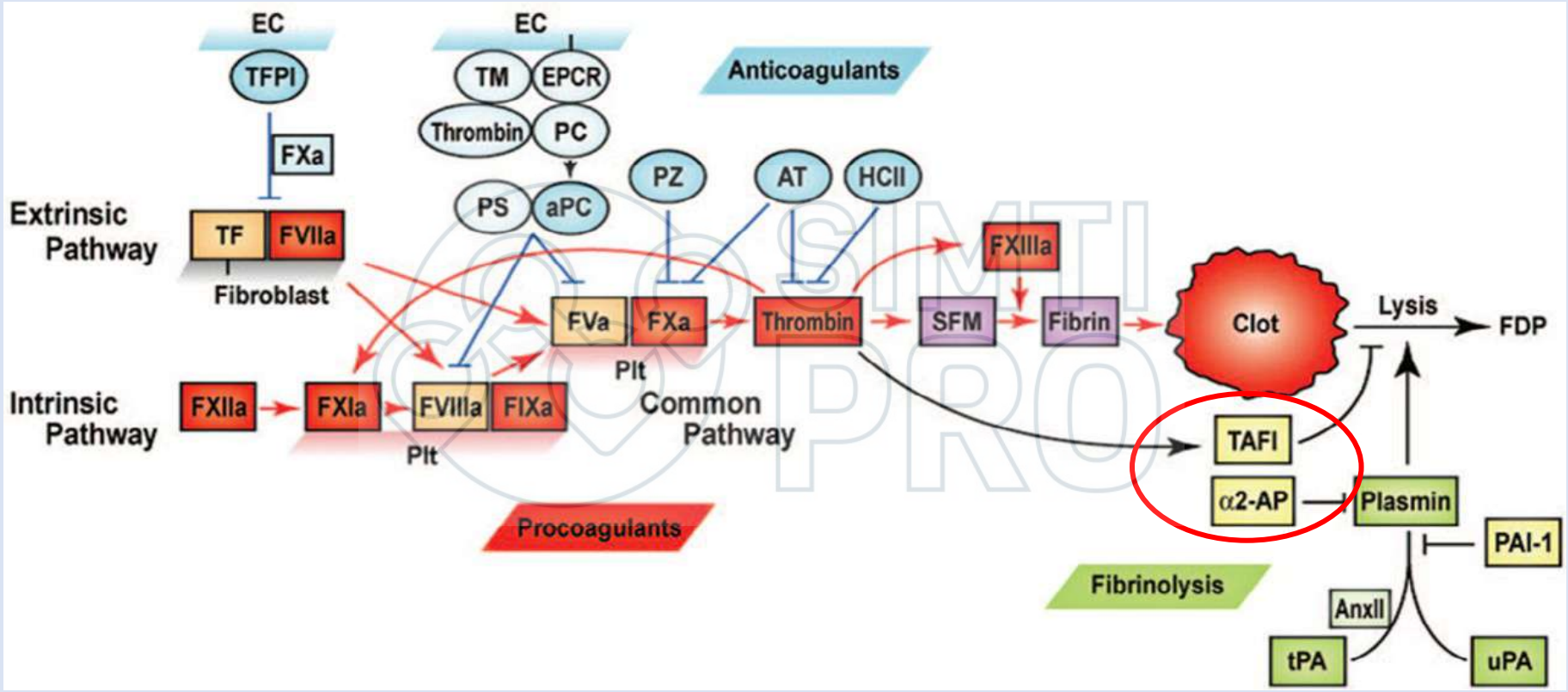
FVII-TF
IX
→ IIa

Plt
XI

IIa

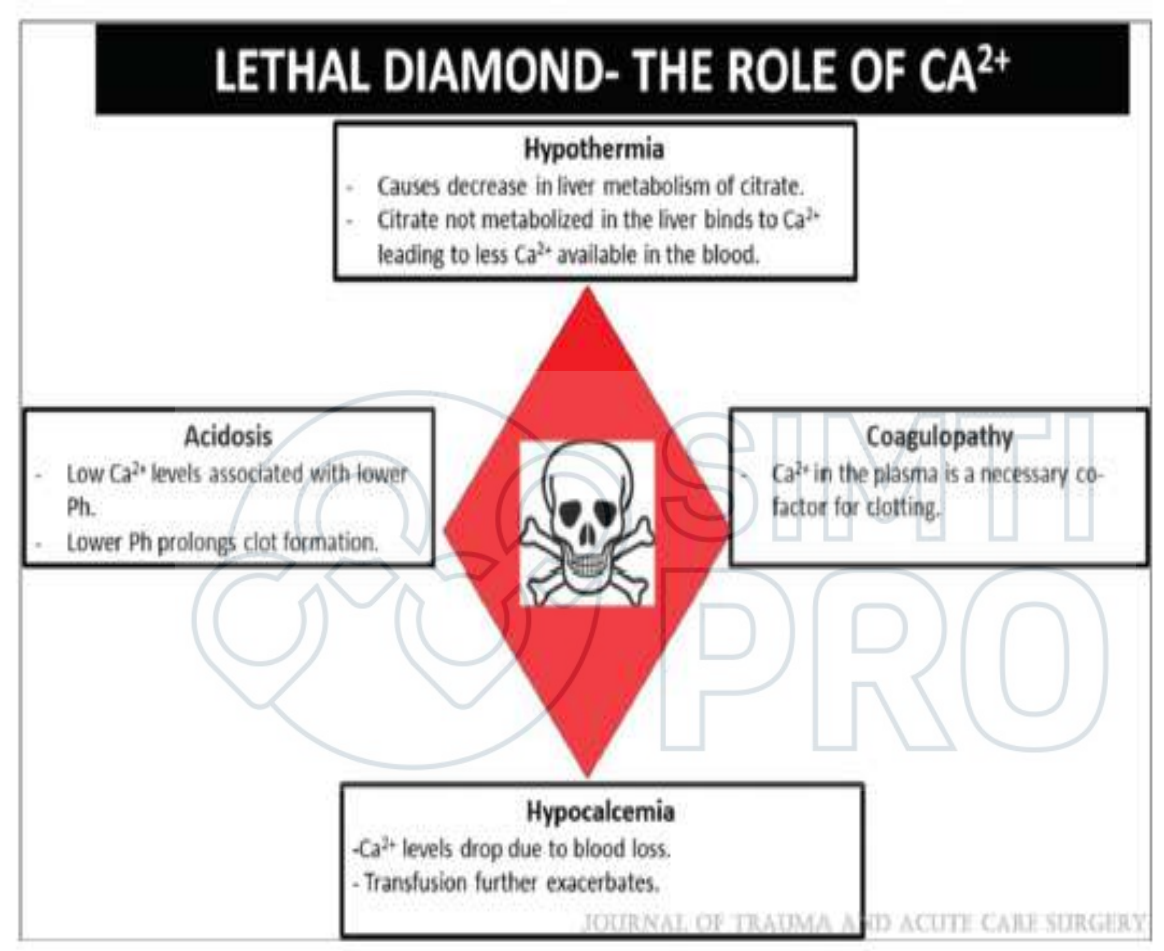
Hoffman M, et al.: A modern view of hemostasis. Hematol Oncol Clin North Am 2007 Feb;21(1):1–11.

The complexities of the coagulation pathways are illustrated here.



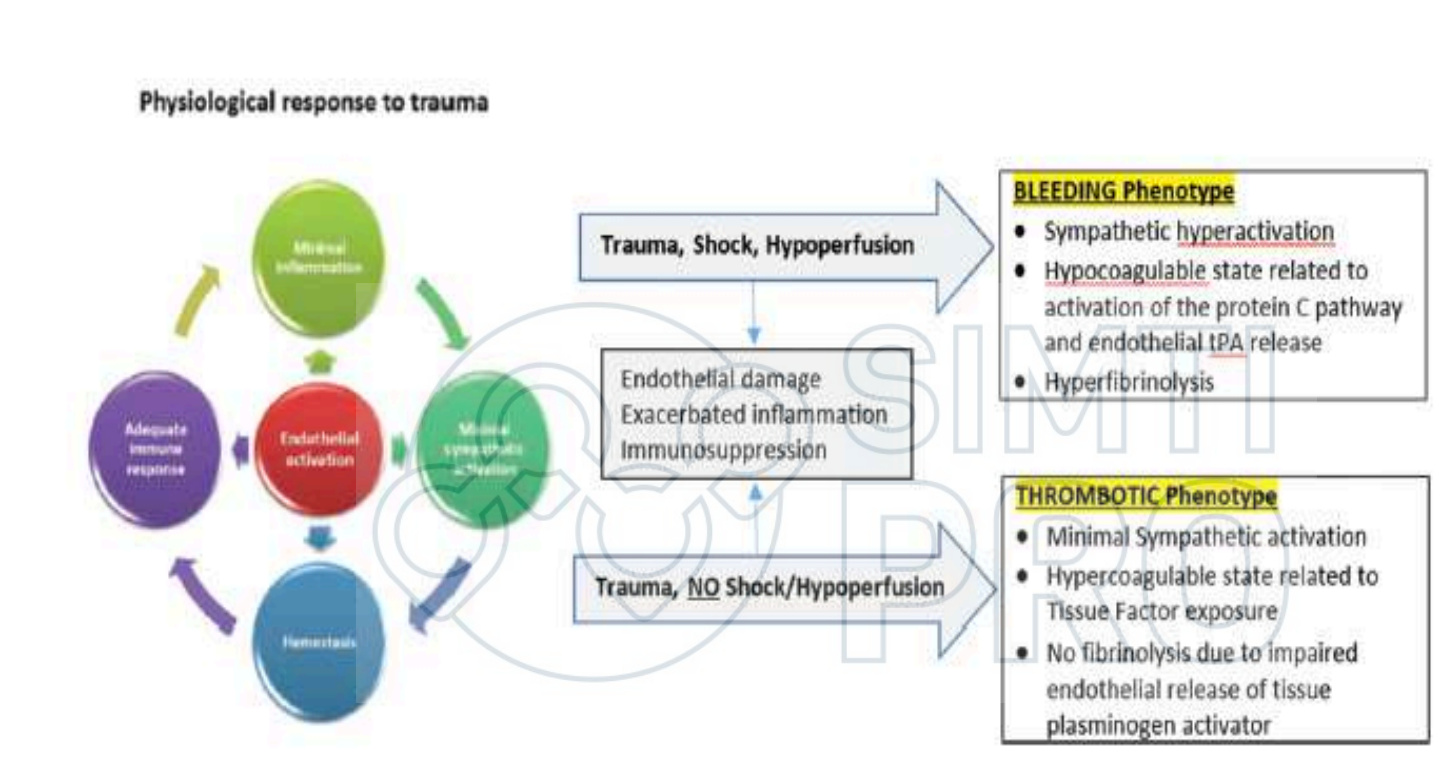
Mark J. Fisher Stroke. 2013;44:3275-3285

Interaction of calcium with the ‘lethal triad’



Ditzel RM et al. J Trauma Acute Care Surg. 2020 Mar;88(3):434–439

Physiological Response to Trauma



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PPH: thrombotic and haemorrhagic phenotypes

Table IV - *Clinical characteristics of two women with post-partum pulmonary embolism*

	Pt 1	Pt 2
Age	33	36
Previous pregnancies, n	1	2
Previous CS	1	2
Previous pregnancy loss	0	0
Previous pre-eclampsia	0	0
Personal/family history VTE	No	No
Other pregnancy complications	No	No
Pre-pregnancy weight (kg)	55	57
Weight at delivery	66	67
Gestational week	38	38
Delivery mode	CS	CS
Neonate sex	Male	Female
Birth weight (g)	3,300	3,080

Pt: patient; CS: caesarean section; VTE: venous thromboembolism.

Grandone E, et al. Blood Transfus. 2020 Jan;18(1):13-19.

PPH: thrombotic and haemorrhagic phenotypes

Table V - *Laboratory investigations in patients with pulmonary embolism-index pregnancy.*

PATIENT 1					
Date	**Before CS 19/6**	**After CS 19/6**	**PE 23/6**	**Discharge 11/7**	**N.V.**
RBC (×10¹²/L)	4.09	2.87	3.15	4.28	4.2-5.4 (10^6/μL)
Hb (g/dL)	12.1	8.3	9.4	12.6	12-16 (g/dL)
Plt (×10⁹/L)	128	114	116	150	130-400 (10^3/μL)
WBC (×10⁹/L)	7.23	7.42	4.43	2.97	4.3-10.8 (10^3/μL)
PT **INR**	138% 0.9	71% 1.1	/	39* 1.67*	70-130% 0.8-1.2
aPTT **ratio**	27.9 1.07	/	/		20-32 sec 0.8-1.2
PATIENT 2					
Date	**Before CS 25/10**	**After CS 6/11**	**Pre-hysterectomy 6/11**	**Discharge 24/11**	**N.V.**
RBC (×10¹²/L)	3.48	3.36	2.38	3.56	4.2-5.4 (10^6/μL)
Hb (g/dL)	11.8	10.0	7	10.9	12-16 (g/dL)
Plt (×10⁹/L)	176	73.000	55	373	130-400 (10^3/μL)
WBC (×10⁹/L)	8.77	19.7	20.5	7.19	4.3-10.8 (10^3/μL)
PT **INR**	/	98 1.0	122 1.1	/	70-130 % 0.8-1.2
aPTT **ratio**	/	30.7 1.2	33.5 1.4	/	20-32 sec 0.8-1.2

*During anticoagulation. CS: caesarean section; PE: pulmonary embolism; N.V.: normal values; sec: seconds; RBC: red blood cells; Hb: haemoglobin; Plt: platelets; WBC: white blood cell count; PT: prothrombin time; aPTT: activated partial thromboplastin time.

Grandone E, et al. Blood Transfus. 2020 Jan;18(1):13-19.

PPH: thrombotic and haemorrhagic phenotypes

Patient (age)	PRBC (n)	FFP (n)	PC (n)	Reason for transfusion	Timing
Pt 1 (33 years)	9	7	/	Haemoperitoneum after CS	Post-partum
Pt 2 (36 years)	6	2	1	Uterine atony after CS	Post-partum
Pt 3 (32 years)	2	/		Anaemia after CS	Intra-partum
Pt 4 (45 years)	2	/	/	Uterine atony after CS	Post-partum
Pt 5 (29 years)	1	/	/	Uterine atony after CS (bigeminy pregnancy)	Post-partum
Pt 6 (25 years)	2	/	/	PPH after VD	Post-partum
Pt 7 (26 years)	2	/	/	Vaginal haematoma after VD (episiotomy)	Post-partum
Pt 8 (31 years)	2	/	/	Anaemia at admission (IUGR foetus), VD	Pre-labour
Pt 9 (17 years)	2	/	/	Uterine atony after CS (mechanical dystocia)	Post-partum
Pt 10 (31 years)	3	/	/	PPH after VD (retained placenta)	Post-partum
Pt 11 (30 years)	2	/	/	Anaemia at admission, CS	Post-partum
Pt 12 (35 years)	3	/	/	Anaemia at admission, VD	Pre-labour

Grandone E, et al. Blood Transfus. 2020 Jan;18(1):13-19.

Trombosi e Supporto trasfusionale

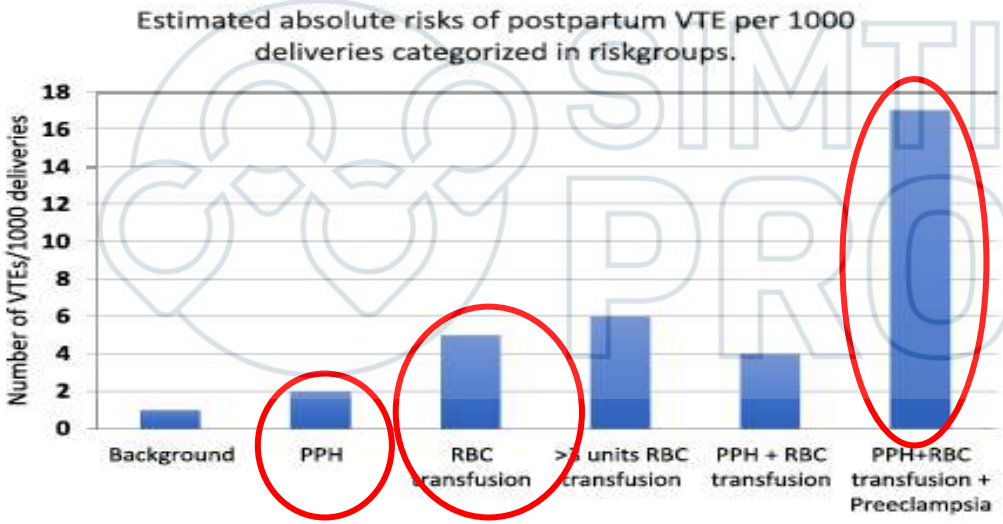

Fig. 2. Estimated absolute risks of postpartum VTE per 1000 deliveries categorized in different risk groups. VTE = Venous thromboembolic event, PPH = postpartum hemorrhage, RBC = Red blood cell.

Thurn L, Thromb Res 2018

Phenotypes in Trauma Induced Coagulopathy

- Distinct phenotypes exist in TIC, including 'Bleeding' or 'Thrombotic' phenotypes
- Distinct fibrinolysis phenotypes exist in TIC, including hyperfibrinolysis, normal, and fibrinolysis shutdown, with both abnormal phenotypes associated with higher mortality

Napolitano LM. . Expert Rev Hematol. 2021 Feb;14(2):219-239

Initial management

Initial management of severe bleeding requires early massive transfusion protocol (MTP) use and damage control resuscitation (DCR)

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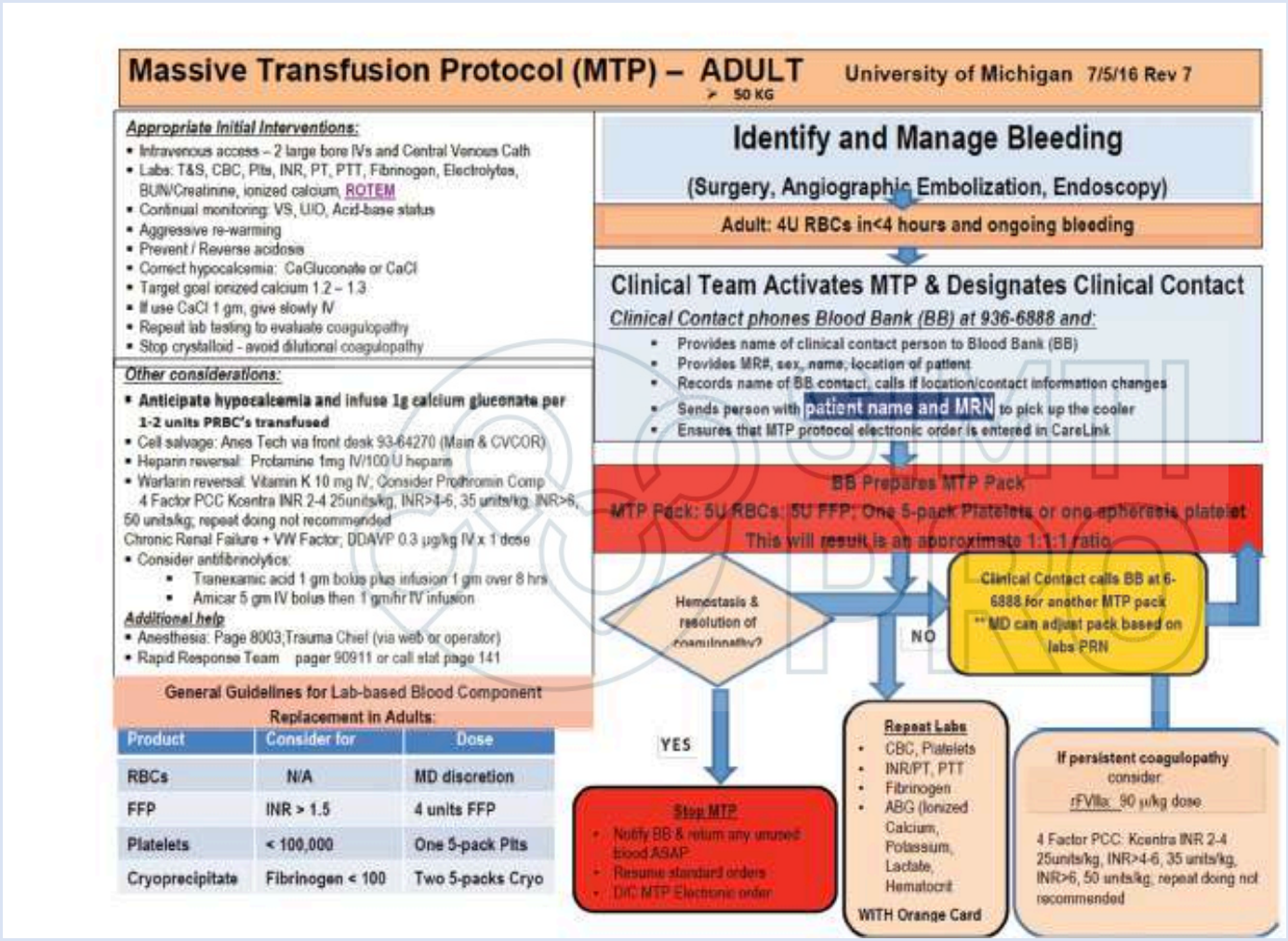

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Damage control resuscitation

DCR : A strategy of rapid control of hemorrhage and restoration of intravascular volume, which includes

- **minimizing blood loss**
- keeping **blood pressure at approximately 90 mm Hg** until definitive hemostasis is achieved
- **hemostatic balanced resuscitation with a 1:1:1 ratio of RBCs, plasma and platelets using MTP**
- **minimize crystalloid infusion**
- **hemostatic adjuncts** to promote hemostasis at sites of injury.

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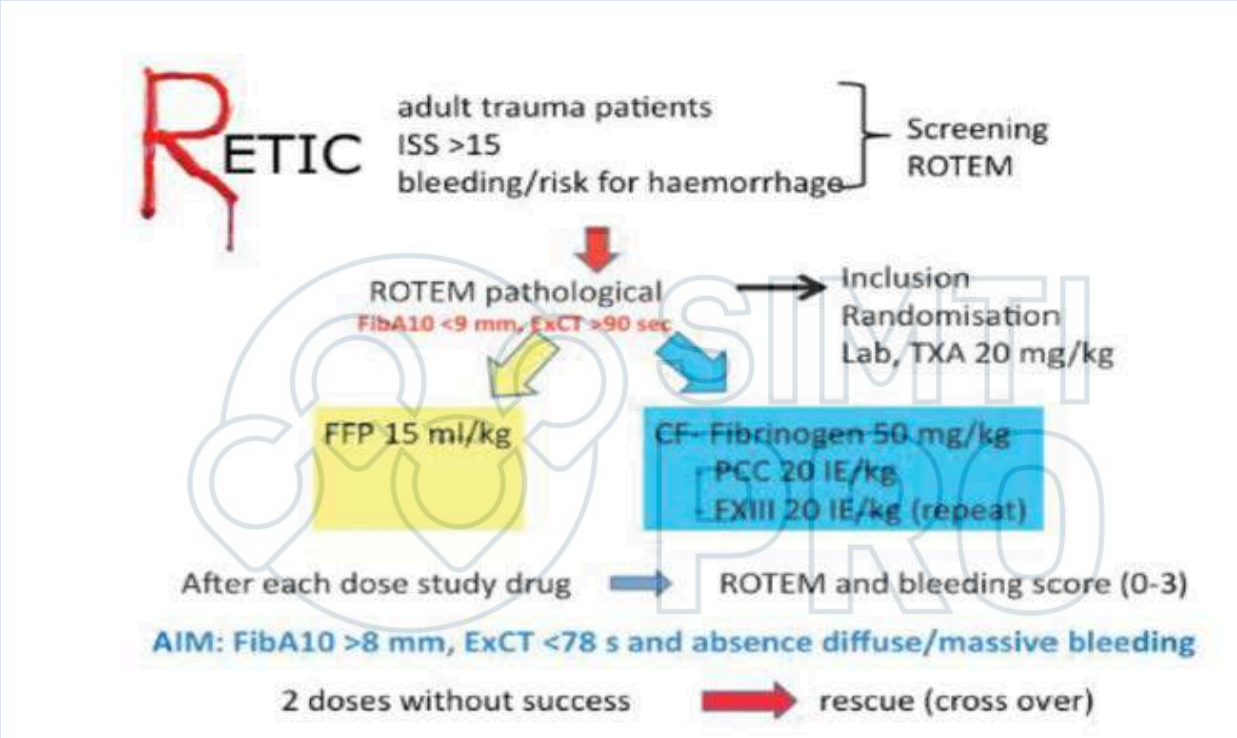
Damage control resuscitation

DCR also includes important efforts to stop the bleeding (tourniquet, hemostatic dressings, direct pressure) and prioritize definitive surgical or angiographic hemostasis.

Cannon JW. Hemorrhagic Shock. NEJM 2018

RETIC trial



Innerhofer P, et al. Lancet Haematol. 2017 Jun;4(6):e258–e271.

RETIC: main findings

- The odds for receiving massive transfusion were 3-fold higher with plasma (NNT 5.7, i.e. 10 of 57 patients treated initially with FFP would need MT which would not have occurred with initial coagulation factor treatment).

- In-hospital mortality was low at 7.4% and similar in both groups

Innerhofer P, et al.Lancet Haematol. 2017 Jun;4(6):e258–e271

Bleeding control bundle of care

- Prehospital plasma resuscitation
- Hospital Damage Control Resuscitation
- Hospital Massive Transfusion Protocol
- Tranexamic acid (TXA) for patients with severe hemorrhagic shock and fibrinolysis
- Coagulation monitoring with conventional coagulation testing and viscoelastic testing (ROTEM/TEG)
- Early definitive hemorrhage control (decrease time to operating room/interventional radiology)
- Goal-directed Hemostatic Resuscitation,individualized based on coagulation testing and ROTEM/TEG

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Adapted from: Oyeniyi BT, et al. Injury. 2017 Jan;48(1):5–12.

DCR guidelines

- Early use of TXA in appropriate patients (bleeding phenotype, < 3 hours from injury, severe hemorrhagic shock, evidence of fibrinolysis)
- Calcium repletion in patients at risk of hypocalcemia
- Prevention of acidosis and hypothermia
- Expeditious delivery to a damage control surgical capability

Joint Trauma System Clinical Practice Guideline (JTS CPG) for Damage Control Resuscitation 2019. https://jts.amedd.army.mil/ assets/docs/cpgs/JTS_Clinical_Practice_Guidelines_(CPGs)/ Damage_Control_Resuscitation_12_Jul_2019_ID18.pdf. Accessed 2020 Jan 9.

Summary

- In patients with major bleeding, particularly those requiring massive transfusion, hemostasis may be significantly impaired.

- Tissue injury and systemic ischemia cause distinct impairments in several hemostatic mechanisms to induce coagulopathy (TIC) in the trauma patient.

- These include acquired quantitative and qualitative platelet defects, hypocoagulable and hypercoagulable states, and dysregulation of the fibrinolytic system.

Early diagnosis

Early diagnosis of hemostatic defects and coagulopathy is imperative in order to provide the best treatment strategy for stable clot formation and definitive control of hemorrhage.

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Among many open questions....

- What is the best laboratory test to diagnose hemostatic defects, coagulopathy and TIC?
- Is viscoelastic testing superior to conventional coagulation testing for TIC treatment?
- Are factor concentrates superior to blood component therapy for patients with coagulopathy?

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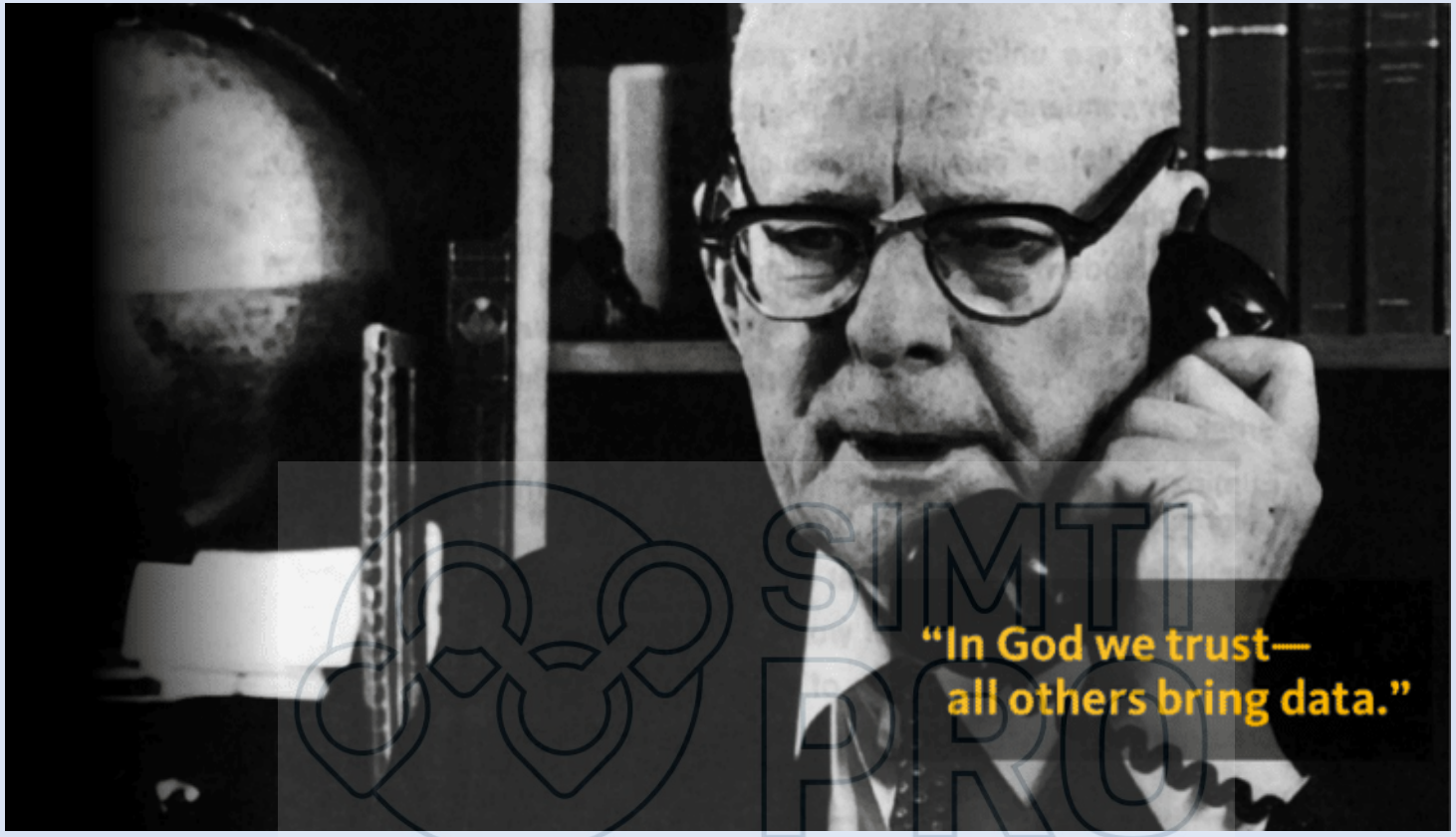

W. Edwards Deming, 1900-1993