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Conferenza Nazionale dei Servizi Trasfusionali

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La coagulopatia nella trasfusione massiva

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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

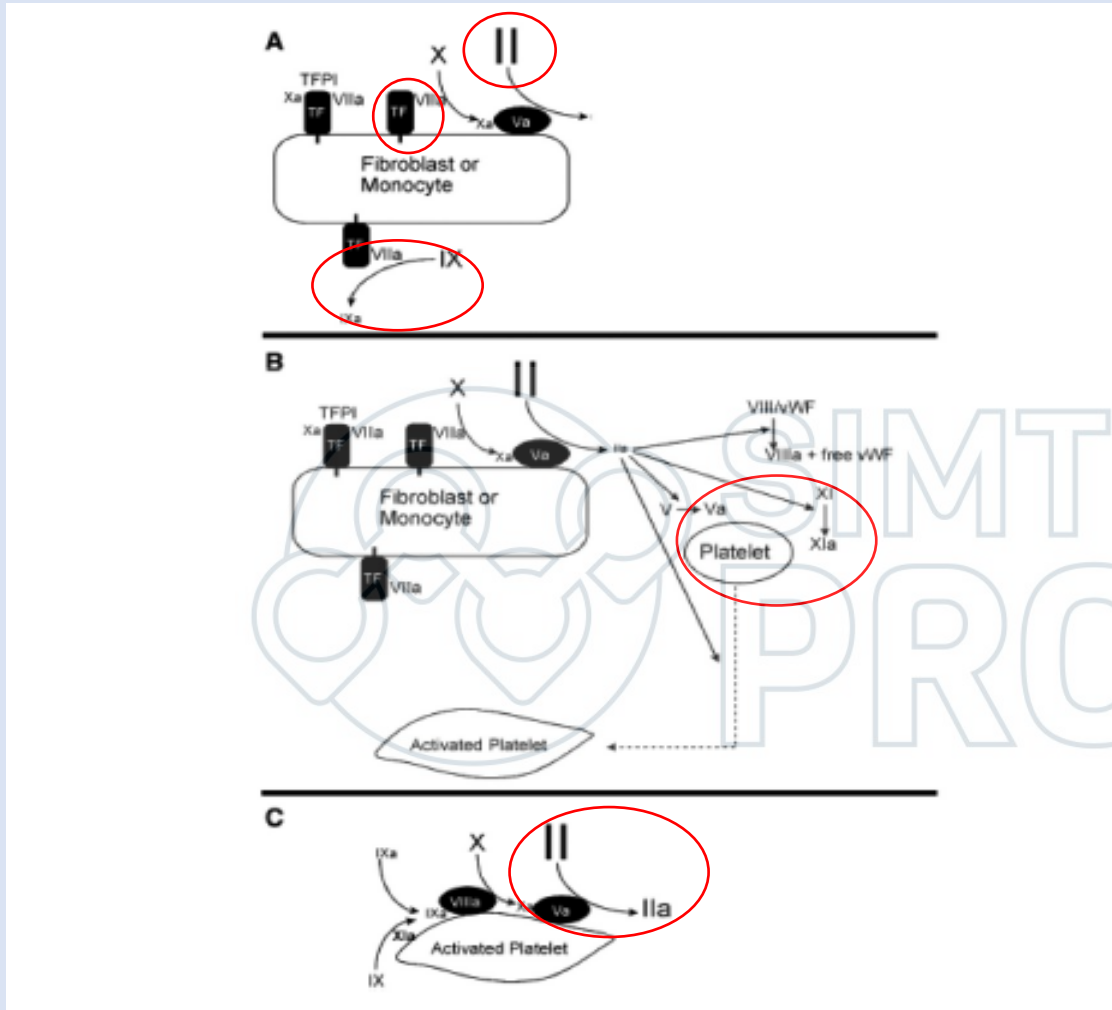
1) **acute trauma coagulopathy (ATC)** related to tissue injury and **shock** which occurs immediately

&

2) **resuscitation coagulopathy (RC)** related to **fluid/blood product resuscitation, hypothermia, acidosis and hypocalcemia**

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

Steps in a cell-based model of coagulation and hemostasis



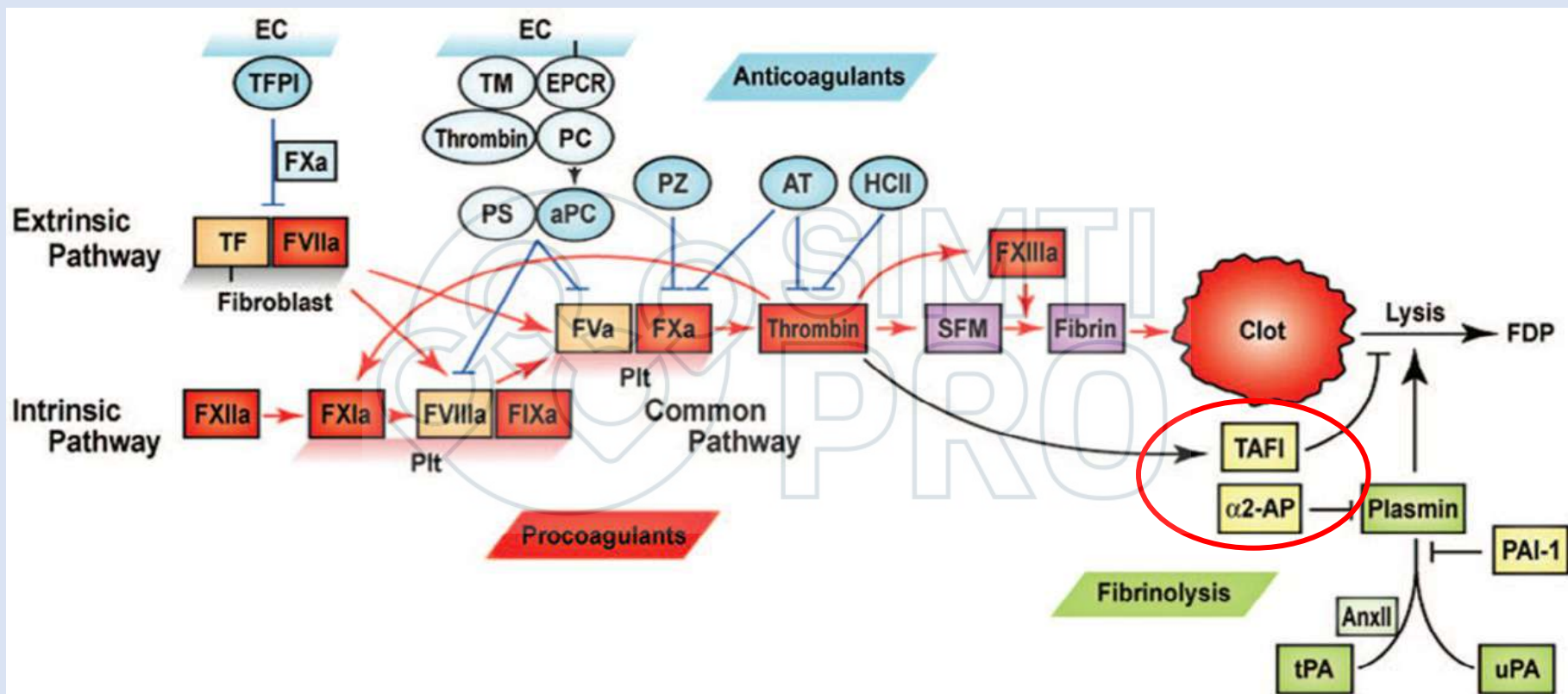
FVII-TF
IX → IIa

Plt
XI

IIa ★

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

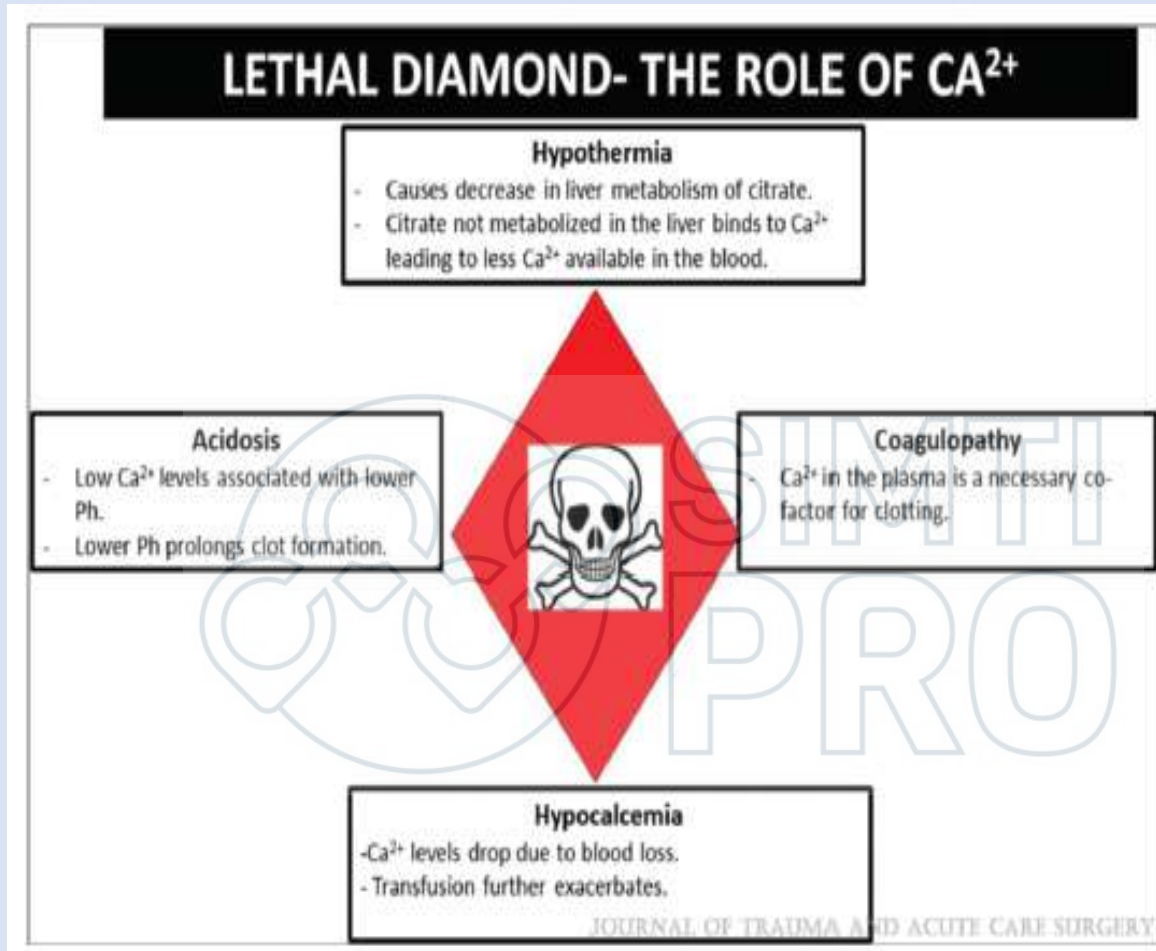
The complexities of the coagulation pathways are illustrated here.



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

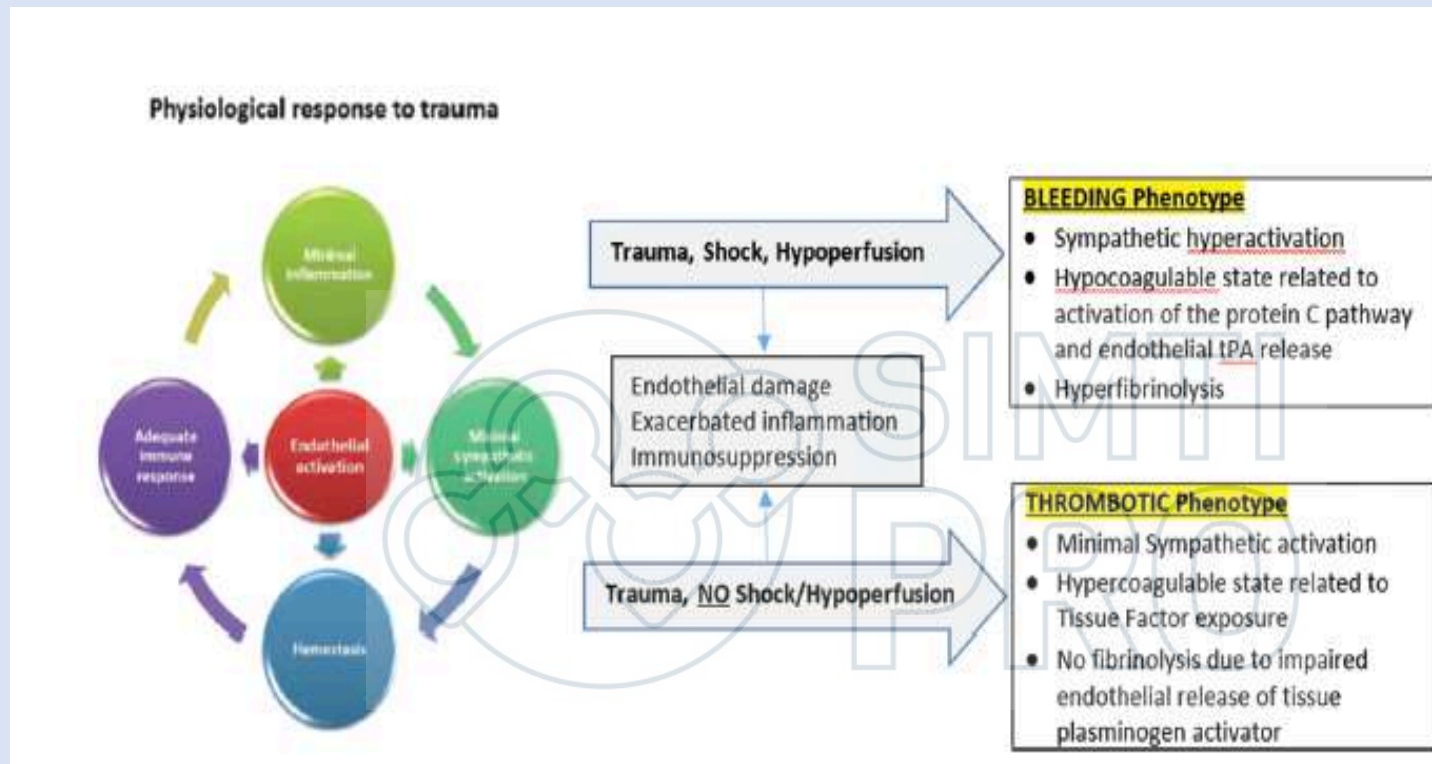
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Interaction of calcium with the 'lethal triad'



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

Physiological Response to Trauma



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

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.

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 ($\times 10^{12}/L$)	4.09	2.87	3.15	4.28	4.2-5.4 ($10^6/\mu L$)
Hb (g/dL)	12.1	8.3	9.4	12.6	12-16 (g/dL)
Plt ($\times 10^9/L$)	128	114	116	150	130-400 ($10^3/\mu L$)
WBC ($\times 10^9/L$)	7.23	7.42	4.43	2.97	4.3-10.8 ($10^3/\mu L$)
PT	138%	71%	/	39*	70-130%
INR	0.9	1.1	/	1.67*	0.8-1.2
aPTT	27.9	/	/	/	20-32 sec
ratio	1.07	/	/	/	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 ($\times 10^{12}/L$)	3.48	3.36	2.38	3.56	4.2-5.4 ($10^6/\mu L$)
Hb (g/dL)	11.8	10.0	7	10.9	12-16 (g/dL)
Plt ($\times 10^9/L$)	176	73.000	55	373	130-400 ($10^3/\mu L$)
WBC ($\times 10^9/L$)	8.77	19.7	20.5	7.19	4.3-10.8 ($10^3/\mu L$)
PT	/	98	122	/	70-130 %
INR	/	1.0	1.1	/	0.8-1.2
aPTT	/	30.7	33.5	/	20-32 sec
ratio	/	1.2	1.4	/	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.

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

Trombosi e Supporto trasfusionale

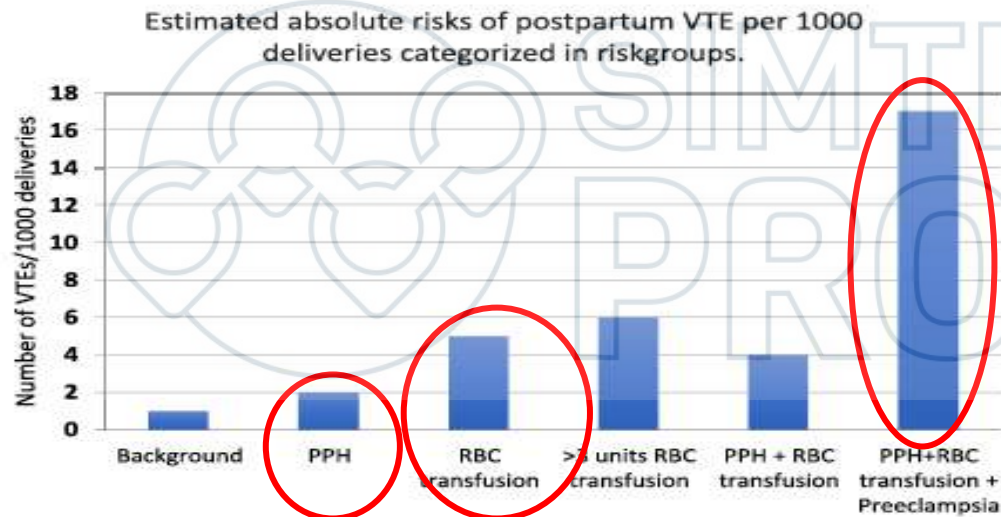


Fig. 2. Estimated absolute risks of postpartum VTE per 1000 deliveries categorized in different risk groups. VTE = Venous thromboembolic event, PPH = postpartum hemorrhage, RBC = Red blood cell.

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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Massive Transfusion Protocol (MTP) – ADULT University of Michigan 7/5/16 Rev 7

> 50 KG

Appropriate Initial Interventions:

- Intravenous access – 2 large bore IVs and Central Venous Cath
- Labs: T&S, CBC, Pits, INR, PT, PTT, Fibrinogen, Electrolytes, BUN/Creatinine, ionized calcium, **ROTEM**
- Continual monitoring: VS, U/O, Acid-base status
- Aggressive re-warming
- Prevent / Reverse acidosis
- Correct hypocalcemia: CaGluconate or CaCl
- Target goal ionized calcium 1.2 – 1.3
- If use CaCl 1 gm, give slowly IV
- Repeat lab testing to evaluate coagulopathy
- Stop crystalloid - avoid dilutional coagulopathy

Other considerations:

- Anticipate hypocalcemia and infuse 1g calcium gluconate per 1-2 units PRBC's transfused
- Cell salvage: Anes Tech via front desk 93-64270 (Main & CVCOR)
- Heparin reversal: Protamine 1mg IV/100 U heparin
- Warfarin reversal: Vitamin K 10 mg IV, Consider Prothromin Comp
- 4 Factor PCC Kcentra INR 2-4 25units/kg, INR>4-6, 35 units/kg, INR>6, 50 units/kg; repeat doing not recommended
- Chronic Renal Failure + VW Factor, DDAVP 0.3 µg/kg IV x 1 dose
- Consider antifibrinolytics:
 - Tranexamic acid 1 gm bolus plus infusion 1 gm over 8 hrs
 - Amicar 5 gm IV bolus then 1 gm/hr IV infusion

Additional help

- Anesthesia: Page 8003, Trauma Chief (via web or operator)
- Rapid Response Team: pager 90911 or call stat page 141

General Guidelines for Lab-based Blood Component

Replacement in Adults:

Product	Consider for	Dose
RBCs	N/A	MD discretion
FFP	INR > 1.5	4 units FFP
Platelets	< 100,000	One 5-pack Pits
Cryoprecipitate	Fibrinogen < 100	Two 5-packs Cryo

Identify and Manage Bleeding

(Surgery, Angiographic Embolization, Endoscopy)

Adult: 4U RBCs in <4 hours and ongoing bleeding

Clinical Team Activates MTP & Designates Clinical Contact

Clinical Contact phones Blood Bank (BB) at 936-6888 and:

- Provides name of clinical contact person to Blood Bank (BB)
- Provides MR#, sex, name, location of patient
- Records name of BB contact, calls if location/contact information changes
- Sends person with **patient name and MRN** to pick up the cooler
- Ensures that MTP protocol electronic order is entered in CareLink

BB Prepares MTP Pack

MTP Pack: 5U RBCs, 5U FFP, One 5-pack Platelets or one apheresis platelet.

This will result in an approximate 1:1:1 ratio

Hemostasis & resolution of coagulopathy?

NO

Clinical Contact calls BB at 6-6888 for another MTP pack
*** MD can adjust pack based on labs PRN

YES

Stop MTP

- Notify BB & return any unused blood ASAP
- Resume standard orders
- Do NOT MTP Electronic order

Repeat Labs

- CBC, Platelets
- INR/PT, PTT
- Fibrinogen
- ABG (Ionized Calcium, Potassium, Lactate, Hematocrit)

WITH Orange Card

If persistent coagulopathy consider rFVIIa: 90 µg/kg dose.

4 Factor PCC: Kcentra INR 2-4 25units/kg, INR>4-6, 35 units/kg, INR>6, 50 units/kg, repeat doing not recommended

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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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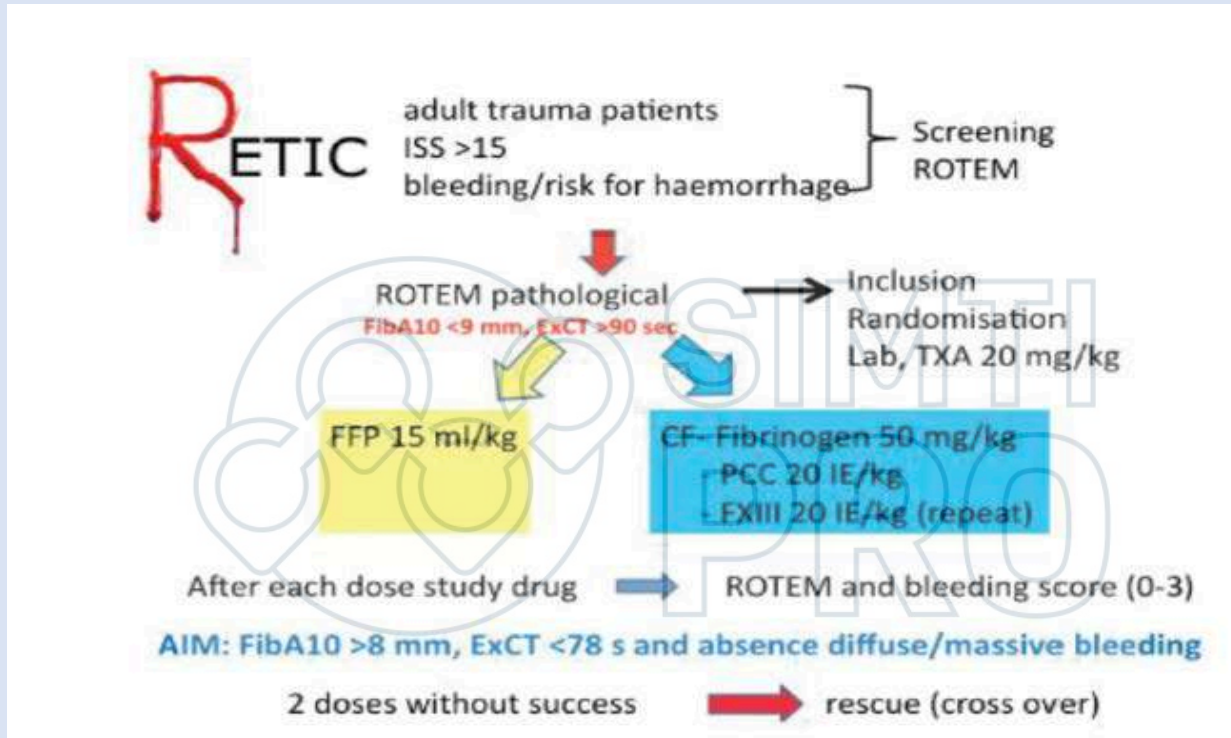
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Damage control resuscitation

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

Adapted from: Oyeniya 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](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

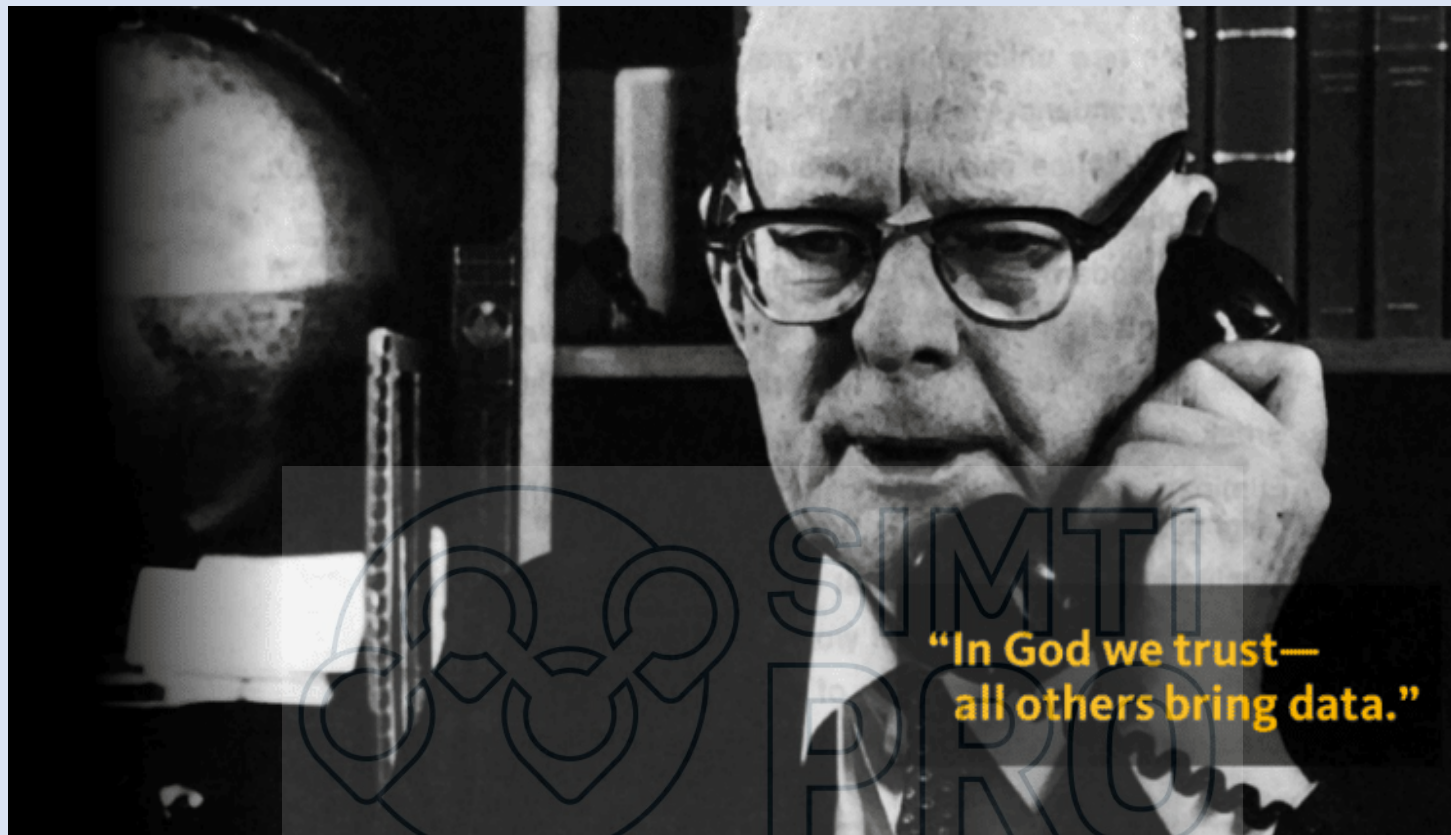
Early diagnosis of hemostatic defects and coagulopathy is imperative in order to provide the best treatment strategy for stable clot formation and definitive control of hemorrhage.

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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