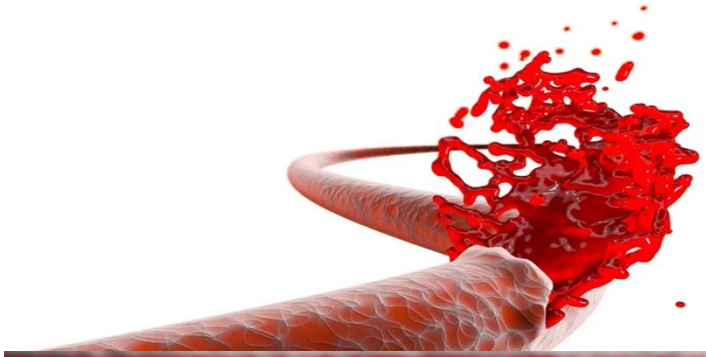
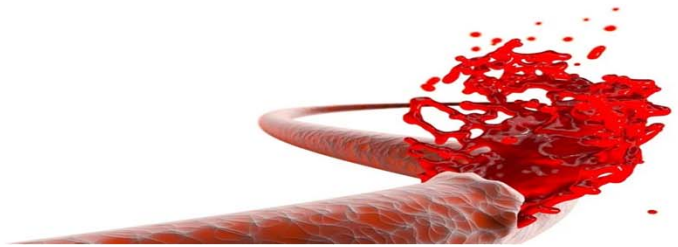
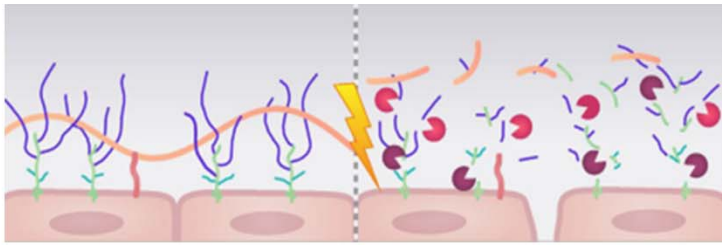


Μεταπτυχιακό Πρόγραμμα ΕΚΠΑ
"Επείγουσα Χειρουργική & Τραύμα"

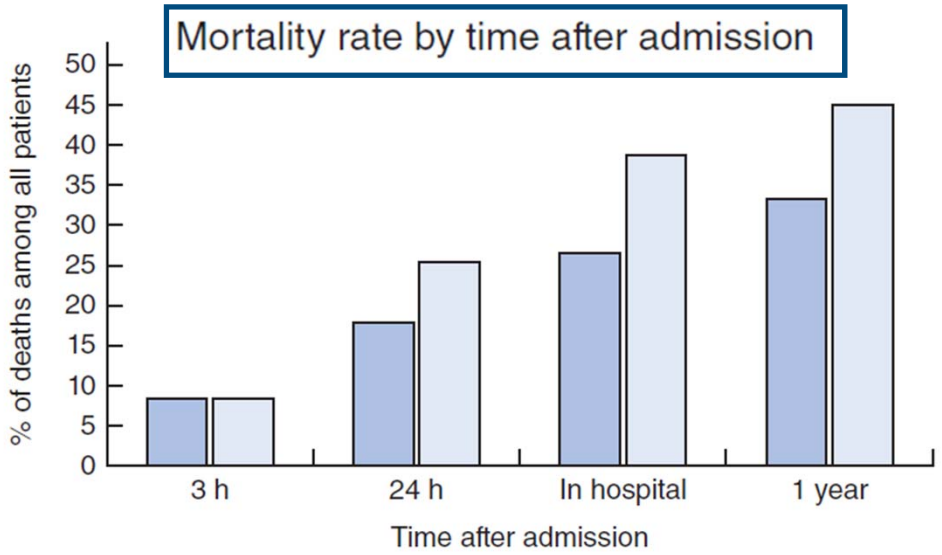
Bleeding Disease Glycocalyx

Βαρβάρα Φυντανίδου
Αναισθησιολόγος-Επειγοντολόγος
Αν. Καθηγήτρια Επείγουσας Ιατρικής
Διευθύντρια Κλινικής Επείγουσας Ιατρικής ΑΠΘ
ΠΓΝΘ "ΑΧΕΠΑ"

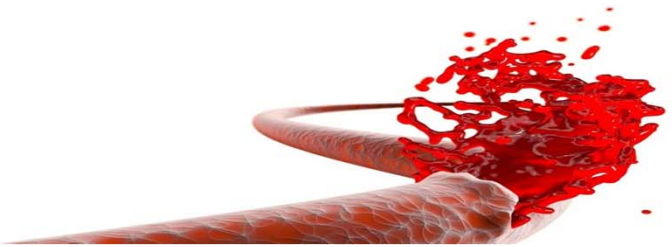


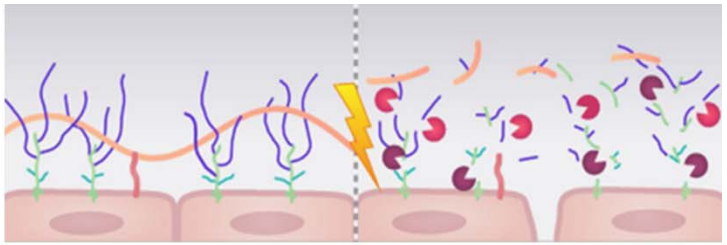


Mortality from trauma haemorrhage and opportunities for improvement in transfusion practice



BJS 2016; **103**: 357–365



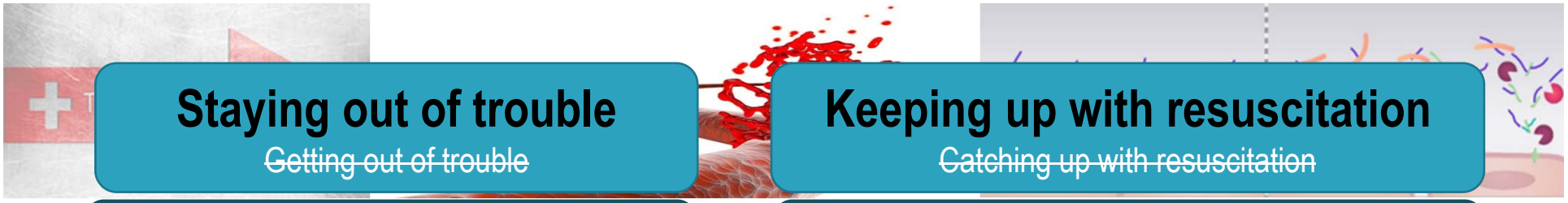


Mortality from trauma haemorrhage and opportunities for improvement in transfusion practice

Mortality rate by time after admission

Overall the outcomes from trauma haemorrhage were poor One in four patients with major haemorrhage died in hospital, rising to over one in three for those with massive haemorrhage. Seventy-nine patients died within the first 24 h, representing 67·5 per cent of all in-hospital deaths More than half of the deaths on the first day occurred within the first 4 h of arrival.

BJS 2016; **103**: 357–365



Staying out of trouble

~~Getting out of trouble~~

Keeping up with resuscitation

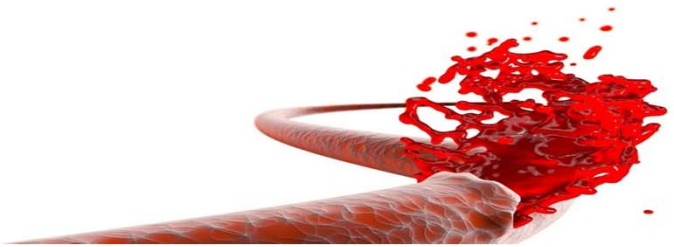
~~Catching up with resuscitation~~

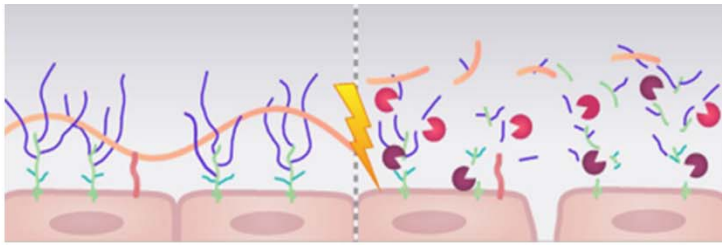
Damage Control Surgery

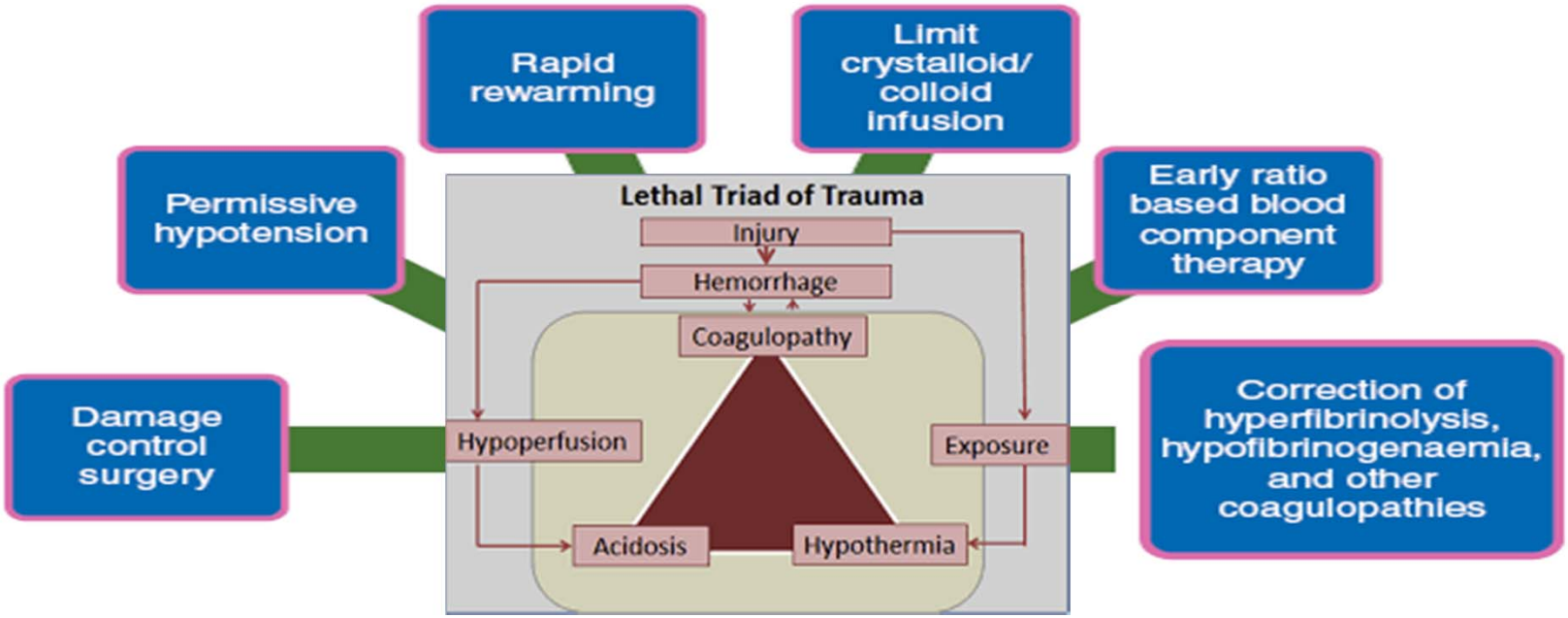
Damage Control Anaesthesia

Damage control resuscitation

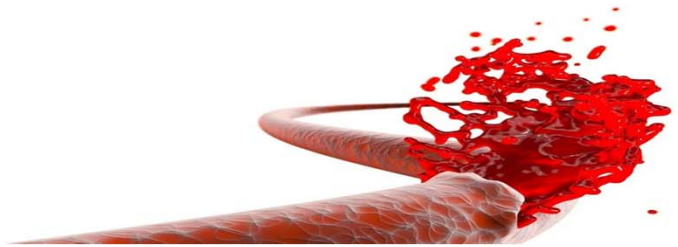

TRAUMA

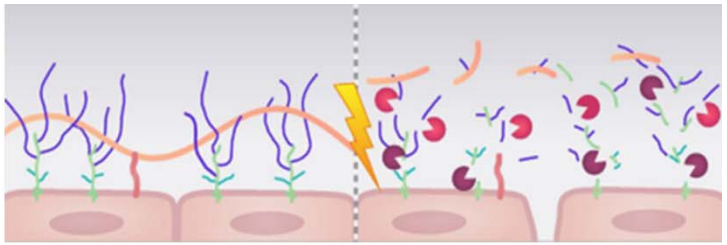


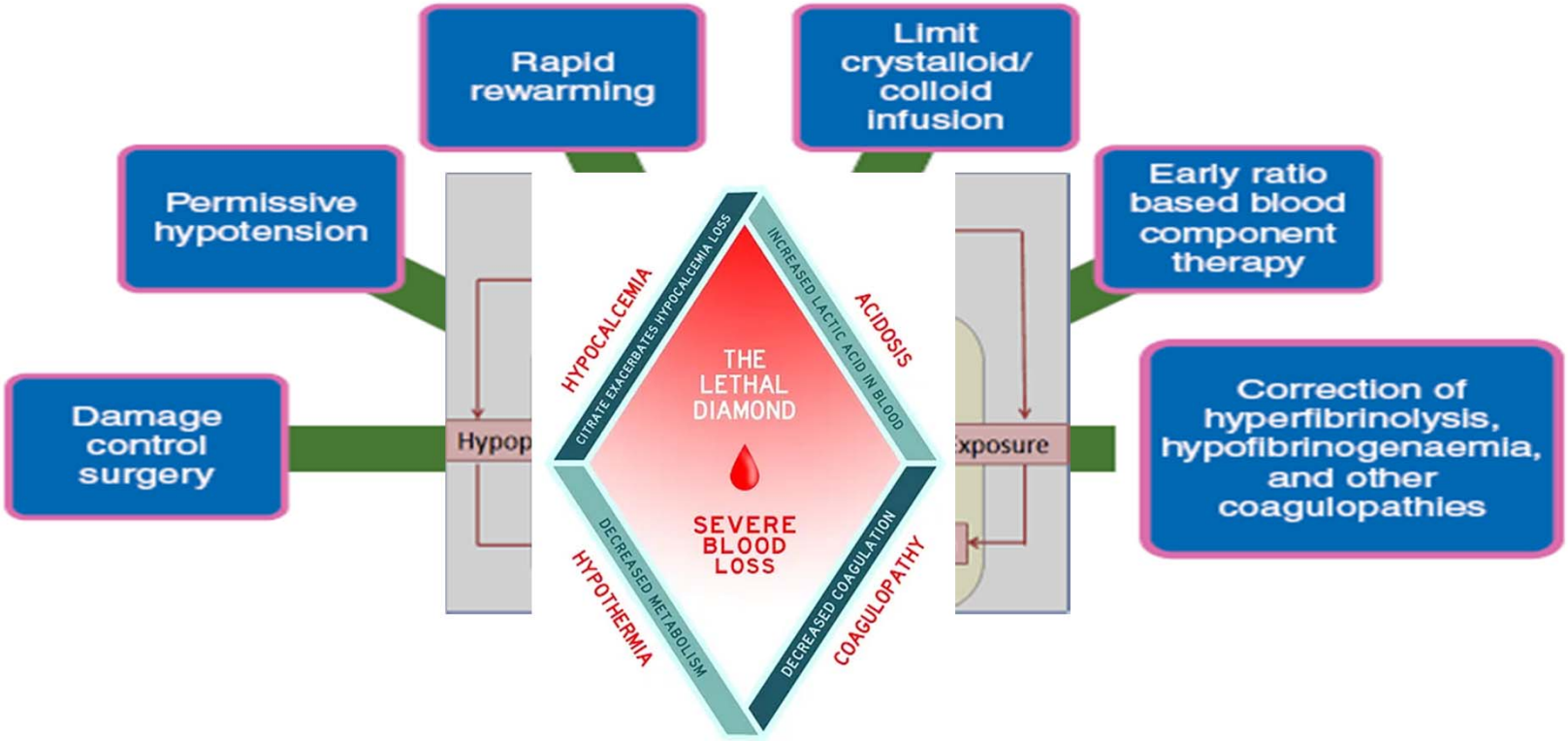



Rapid rewarming
Limit crystalloid/ colloid infusion
Permissive hypotension
Early ratio based blood component therapy
Lethal Triad of Trauma
Injury
Hemorrhage
Coagulopathy
Damage control surgery
Hypoperfusion
Exposure
Correction of hyperfibrinolysis, hypofibrinogenaemia, and other coagulopathies
Acidosis
Hypothermia


TRAUMA



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Damage control surgery
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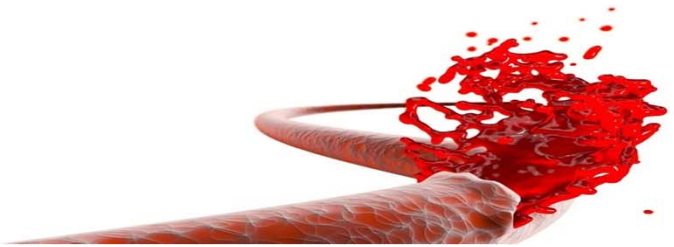
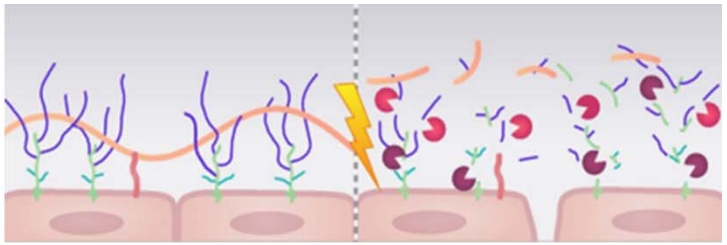
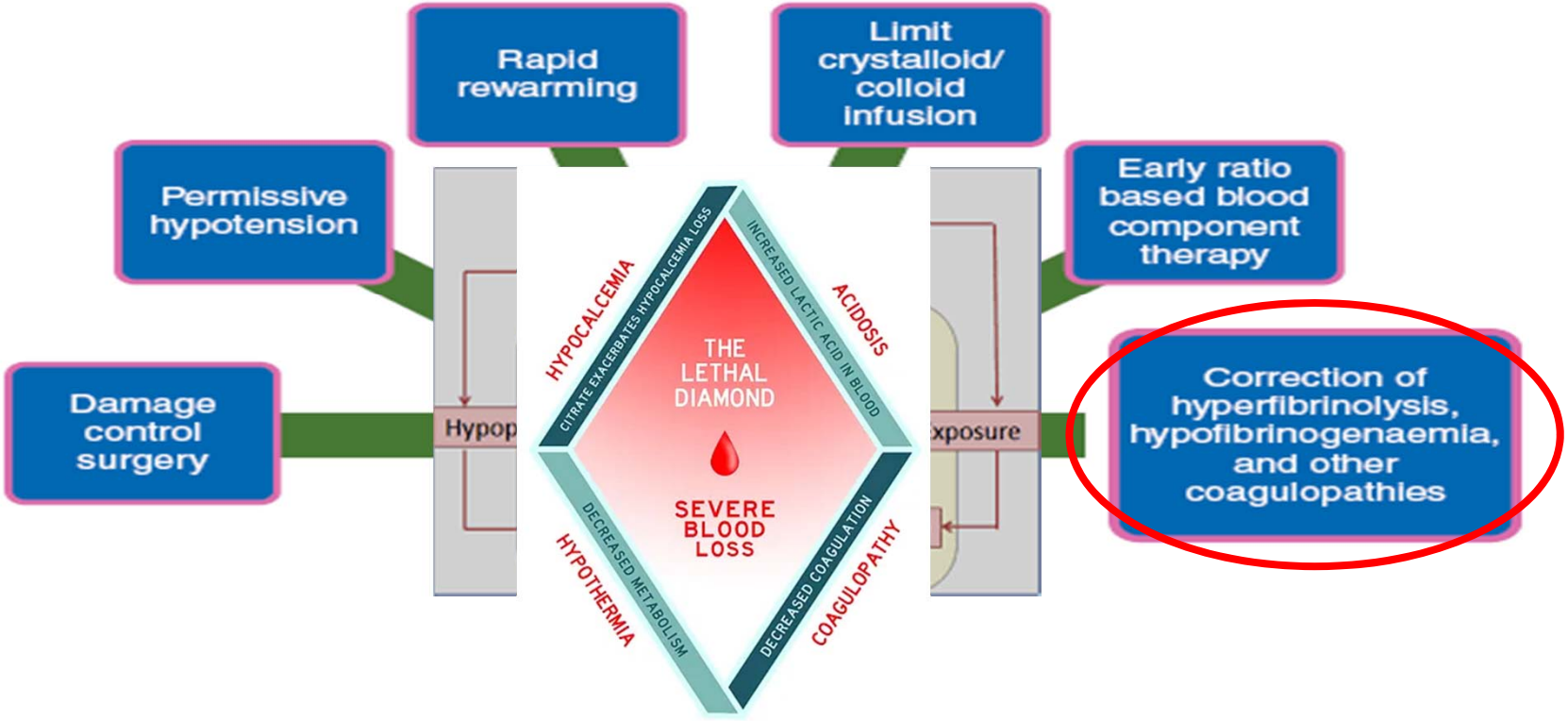
THE LETHAL DIAMOND
SEVERE BLOOD LOSS
HYPOCALCEMIA
CITRATE EXACERBATES HYPOCALCEMIA LOSS
ACIDOSIS
INCREASED LACTIC ACID IN BLOOD
HYPOTHERMIA
DECREASED METABOLISM
COAGULOPATHY
DECREASED COAGULATION


TRAUMA



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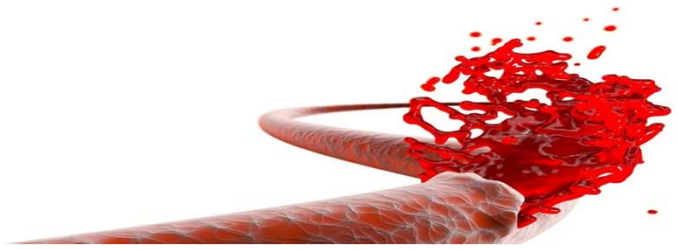
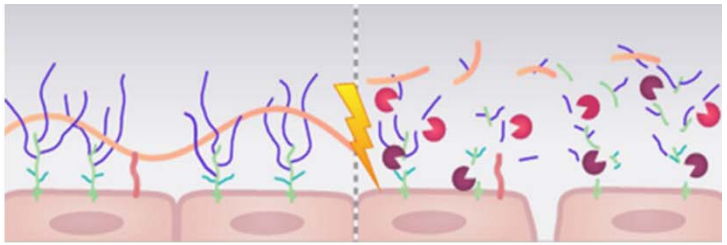
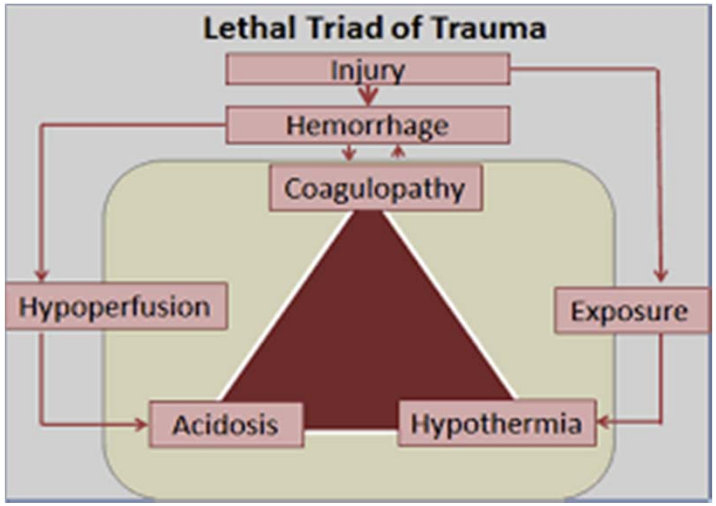
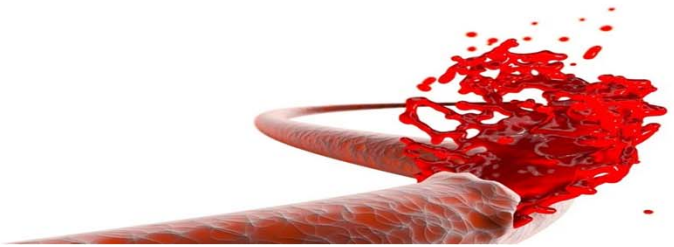


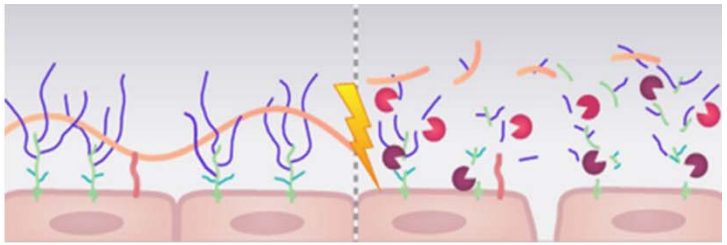


Until 2003

- ☑ Bleeding
- ☑ Dilution
- ☑ Hypothermia
- ☑ Acidosis







After 2003

- ☑ Bleeding
- ☑ Dilution
- ☑ Hypothermia
- ☑ Acidosis

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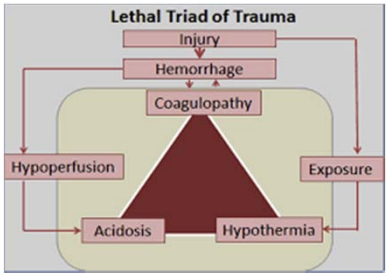

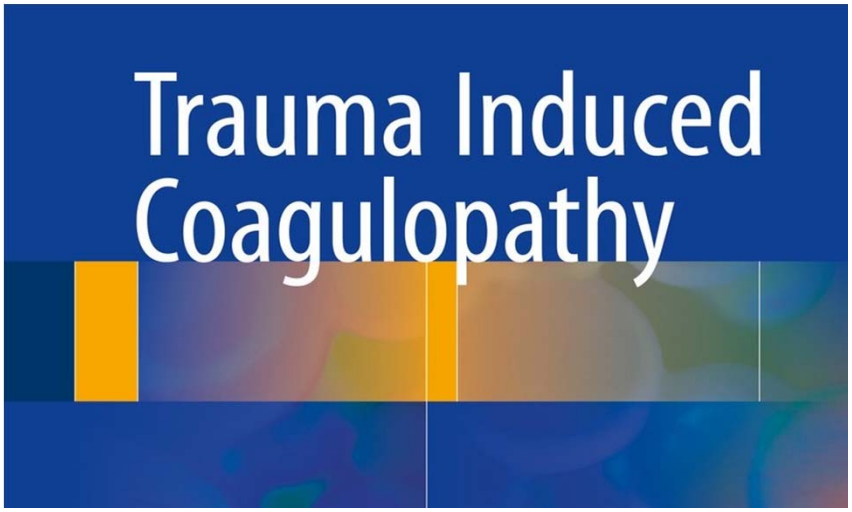

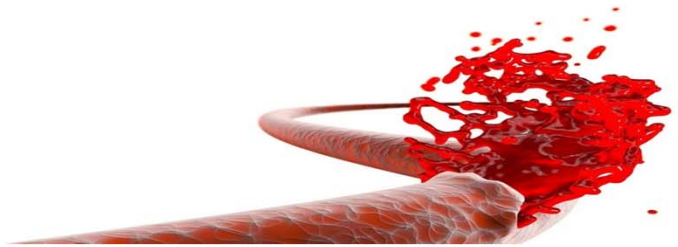

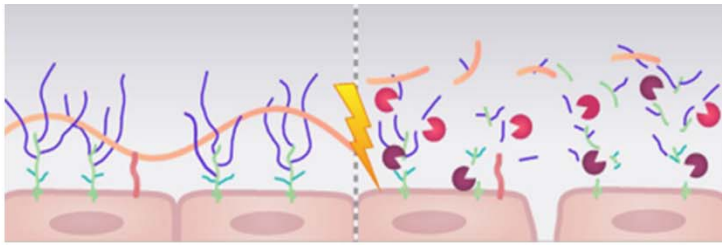

After 2003

- ☑ Endogenous
- ☑ 25% trauma
  - ➲ INR≥1.3
- ☑ ⬆⬆Mortality
  - ➲ x 3-4
- ☑ ⬆ Outcome
  - ➲ FFP/PLT/Fibrinogen

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Acute Traumatic Coagulopathy *J Trauma.* 2003;54:1127–1130.

Karim Brohi, BSc, FRCS, FRCA, Jasmin Singh, MB, BS, BSc, Mischa Heron, MRCP, FFAEM, and Timothy Coats, MD, FRCS, FFAEM

ORIGINAL ARTICLES

Acute Traumatic Coagulopathy: Initiated by Hypoperfusion Modulated Through the Protein C Pathway?

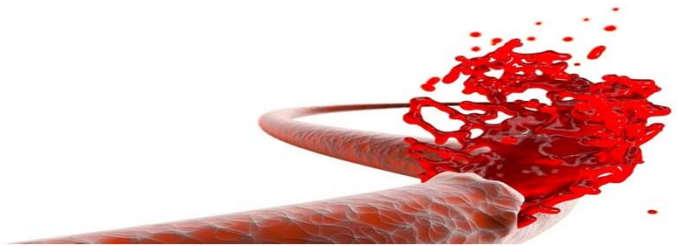
Brohi, Karim FRCS, FRCA*; Cohen, Mitchell J. MD*; Ganter, Michael T. MD†; Matthay, Michael A. MD‡; Mackersie, Robert C. MD*; Pittet, Jean-François MD†‡

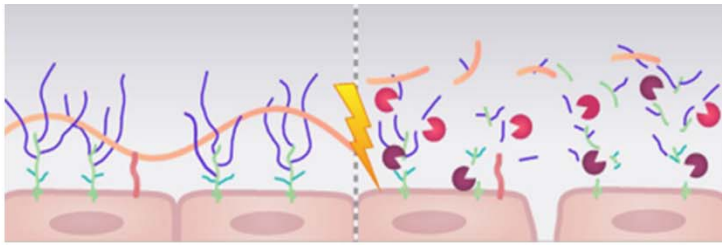
Annals of Surgery: May 2007 - Volume 245 - Issue 5 - p 812-818
doi: 10.1097/01.sla.0000256862.79374.31

Acute coagulopathy of trauma: mechanism, identification and effect

Brohi, Karim[a]; Cohen, Mitchell J[b]; Davenport, Ross A[a]

Current Opinion in Critical Care: December 2007 - Volume 13 - Issue 6 - p 680-685
doi: 10.1097/MCC.0b013e3282f1e78f

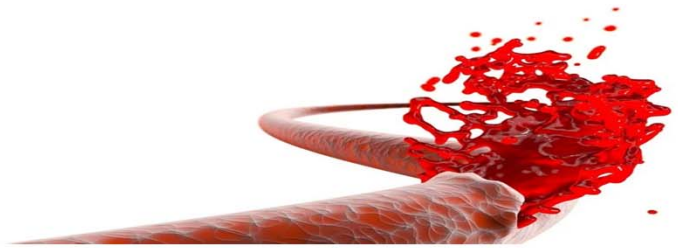


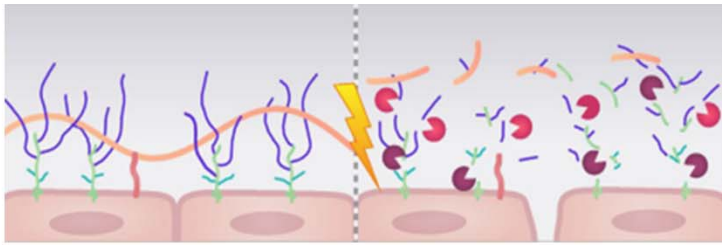


Evolving beyond the vicious triad: Differential mediation of traumatic coagulopathy by injury, shock, and resuscitation

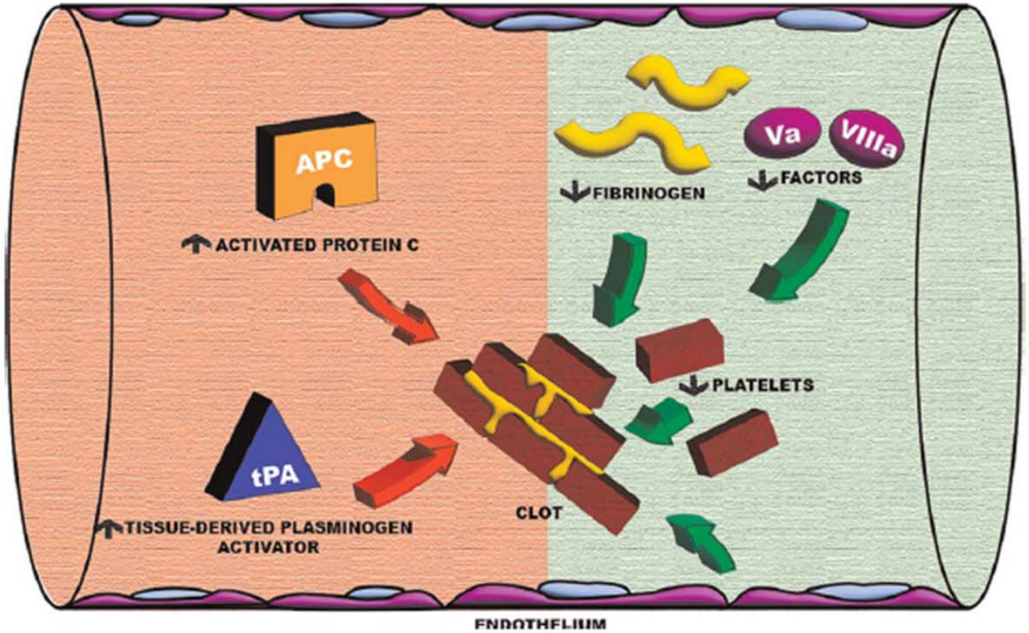
Increasing awareness exists that a subset of patients with critical injury and shock develop abnormal coagulation immediately after injury, despite normothermia, and before the onset of acidosis or hemodilution by crystalloid administration.[1–3] This phenomenon, termed *acute traumatic coagulopathy* (ATC), is associated with significant early and long-term morbidity and mortality.

J Trauma Acute Care Surg
Volume 78, Number 3
DOI: 10.1097/TA.0000000000000545

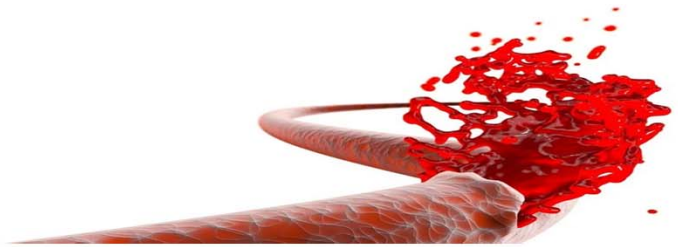


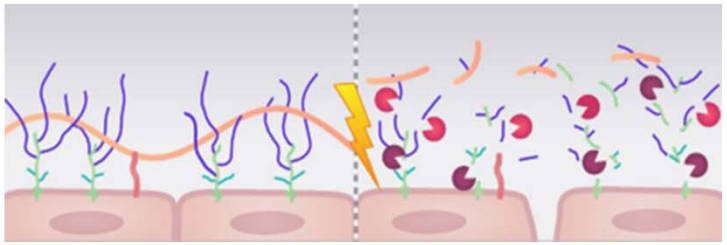


TACTIC® Trauma-induced coagulopathy: What you need to know



J Trauma Acute Care Surg
Volume 96, Number 2





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Acute coagulopathy of trauma: mechanism, identification and effect

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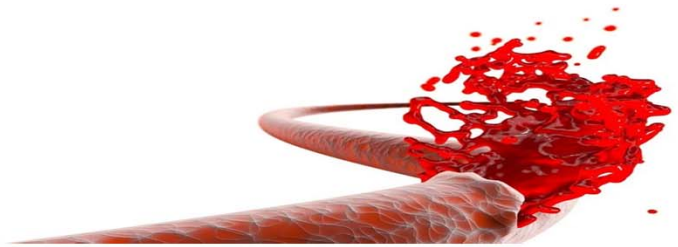
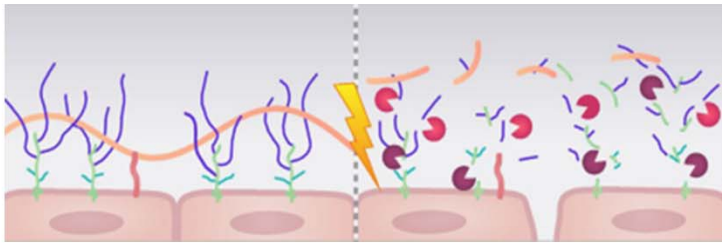
doi: 10.1097/MCC.0b013e3282f1e78f

- ☑ Damage of external + internal barriers
- ☑ Elicits immune responses
  - ➲ In a an attempt to clear damaged tissues
- ☑ Activates repair mechanisms
  - ➲ Restoring cells & tissues to pre-injury state
- ☑ This response is further bolstered
  - ➲ Acidic / Hypoxic enviroment





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Acute coagulopathy of trauma: mechanism, identification and effect

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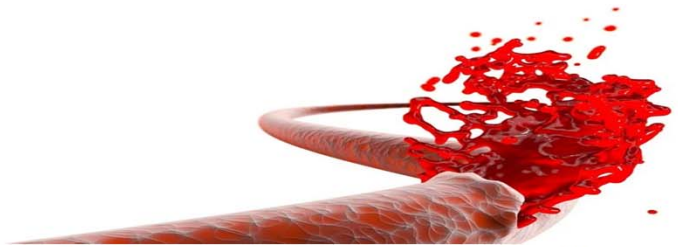
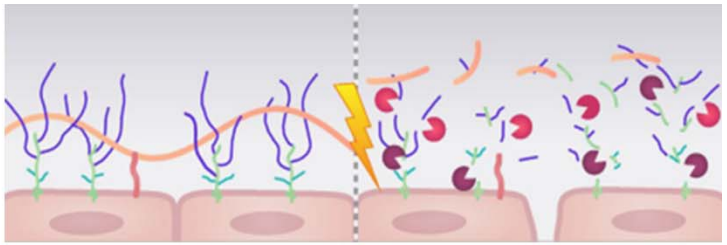
Current Opinion in Critical Care: December 2007 - Volume 13 - Issue 6 - p 680-685
doi: 10.1097/MCC.0b013e3282f1e78f

- ☑ **Hemorrhagic shock + Extended surgical intervention**
  - ➲ **Escalation of immune response**
    - ✓ **Coagulopathy**
    - ✓ **Inflammation**

  - ➲ **Organ Dysfunction**





Evolving beyond the vicious triad: Differential mediation of traumatic coagulopathy by injury, shock, and resuscitation

Coagulopathy [INR>1.3] requires BOTH

Tissue Injury [ISS>15] ✚ Shock [BD>6 or Lactate≥4mmol/L]

Mortality requires BOTH

Tissue Injury [ISS>15] ✚ Shock [BD>6 or Lactate≥4mmol/L]

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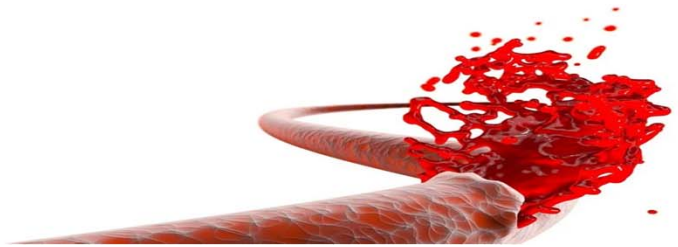
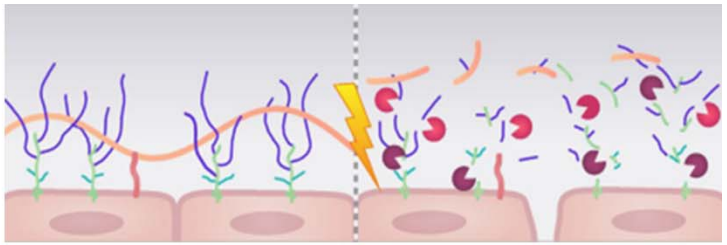
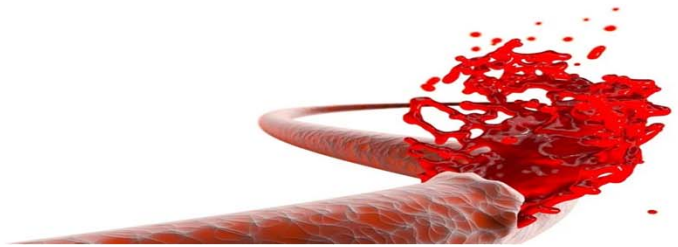


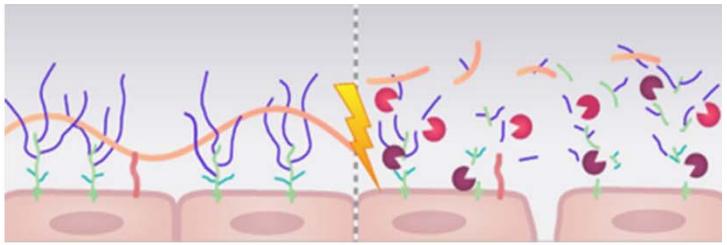


BLOOD

ORGAN

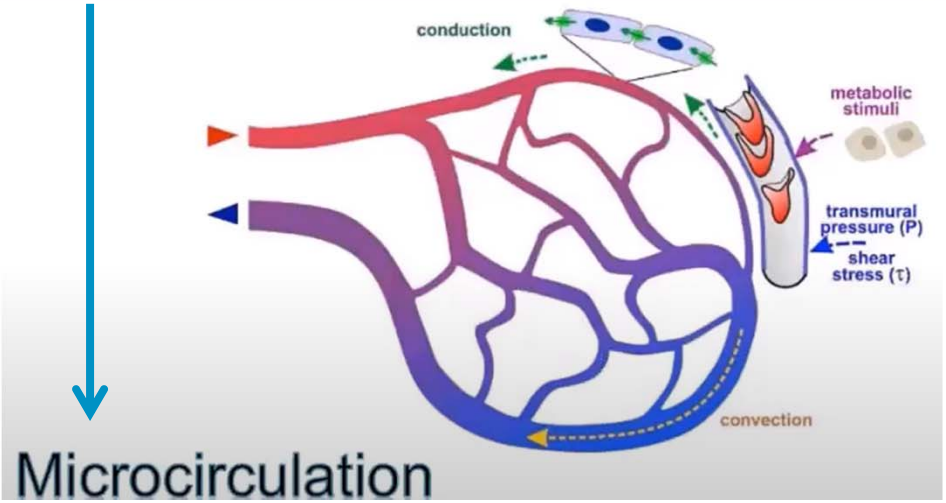
Sensitive

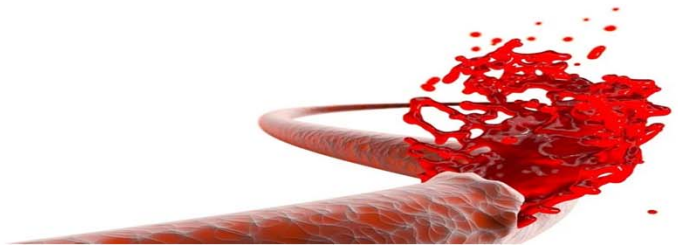


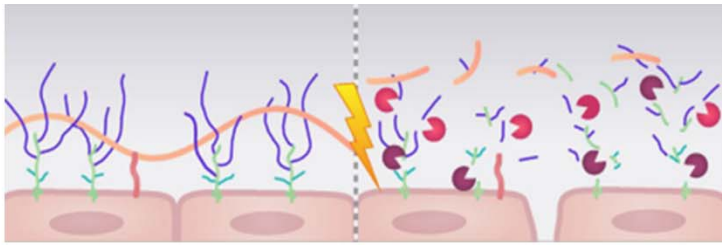


The microcirculation: linking trauma and coagulopathy

Endothelium: 1kilo (4-7.000 m^2)

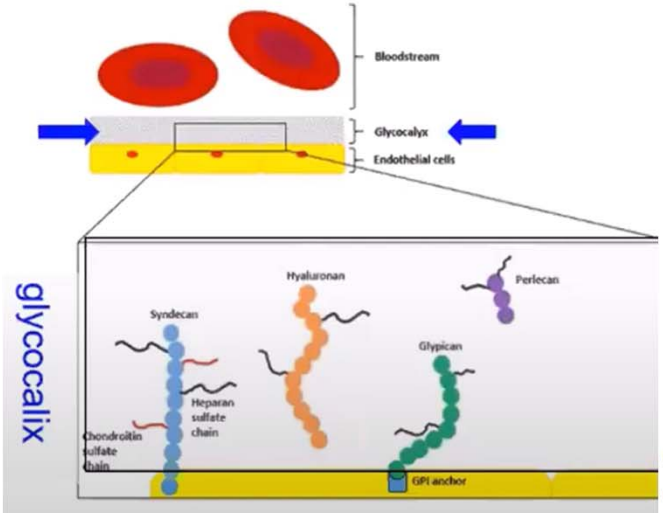




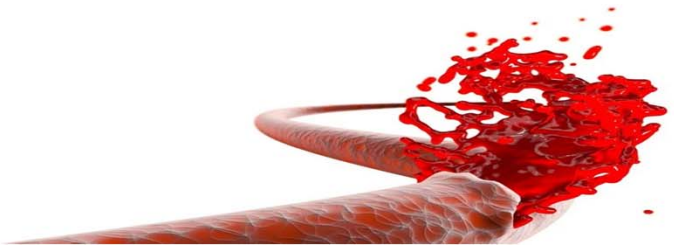


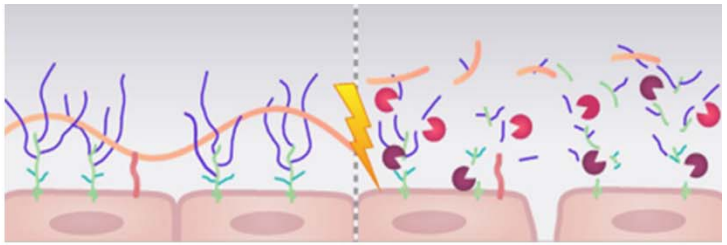
The endothelial glycocalyx and its disruption, protection and regeneration: a narrative review

Endothelium [1kg] is protected by glycocalyx [1L]



Schött *et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* (2016) 24:48
DOI 10.1186/s13049-016-0239-y

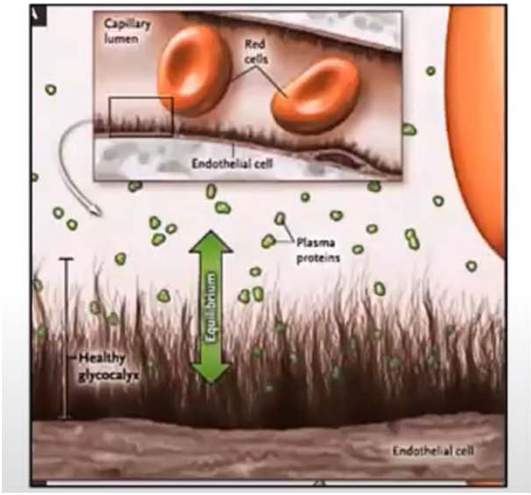




TRAUMA AND ENDOTHELIAL GLYCOCALYX: THE MICROCIRCULATION HELMET?

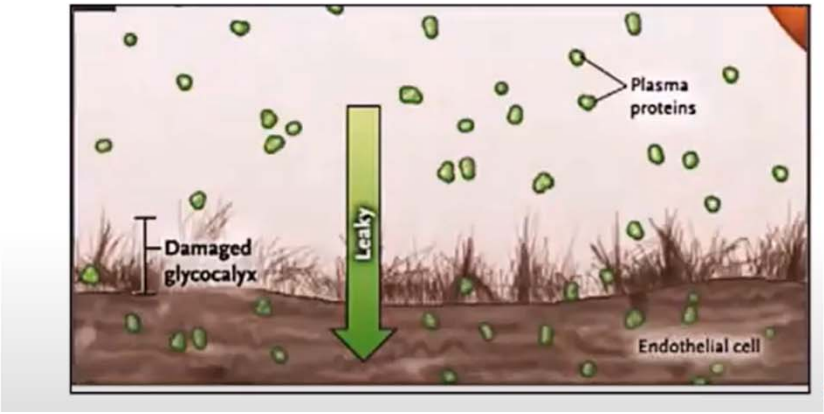
HEALTHY glycocalyx

- Not permeable
- *ANTI*-coagulant
- Does NOT leak

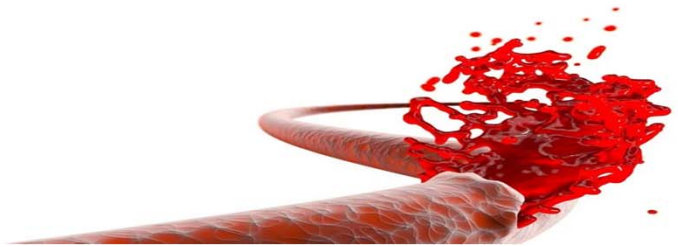
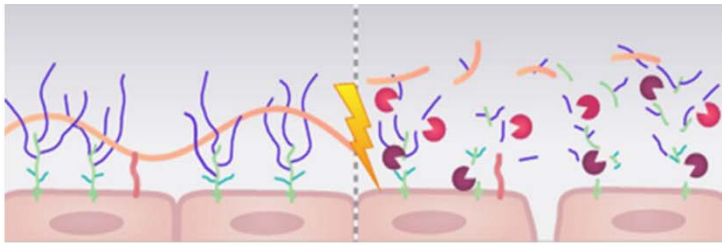


DAMAGED glycocalyx

- *PRO*-coagulant (thrombin + platelet adhesion)
- Permeable (leaky, tissue edema)
- Releases its *ANTI*-coagulant factors in the circulation



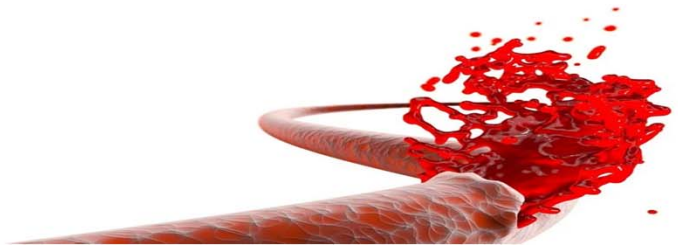
SHOCK, Vol. 46, No. 4, pp. 352–357, 2016

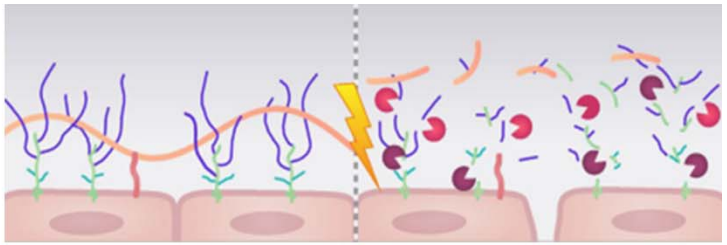



THOR Position Paper on Remote Damage Control Resuscitation: Definitions, Current Practice and Knowledge Gaps

Survivors of hemorrhagic shock (HS) demonstrate an "endotheliopathy of trauma (EoT)" which is a systemic response resulting in disturbances of coagulation, inflammation, and endothelial barrier integrity

Shock. 2014 May ; 41(0 1): 3–12.





"endotheliopathy of trauma (EoT)"

Shock induced endotheliopathy (SHINE) in acute critical illness - a unifying pathophysiologic mechanism

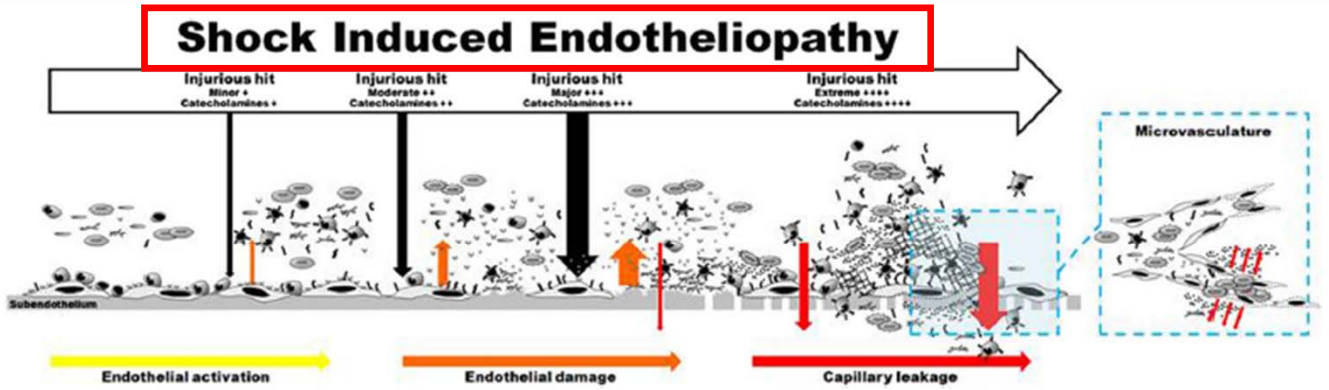
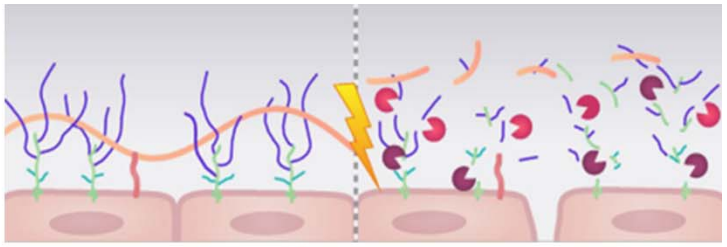


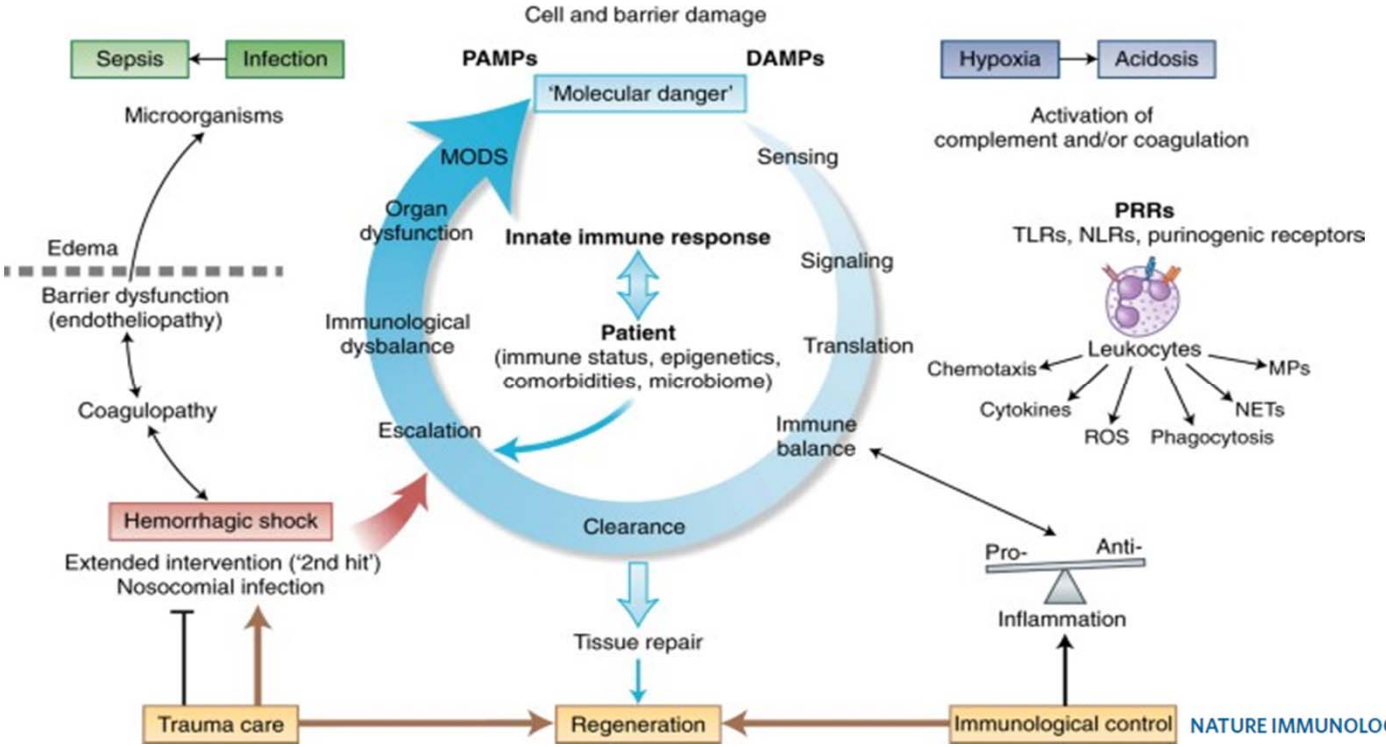
Fig. 1 Shock-induced endotheliopathy (SHINE). Schematic illustration of the changes in the vascular compartment with increasing disease severity and increasing sympatho-adrenal activation (Original figure)

Johansson *et al. Critical Care* (2017) 21:25
DOI 10.1186/s13054-017-1605-5

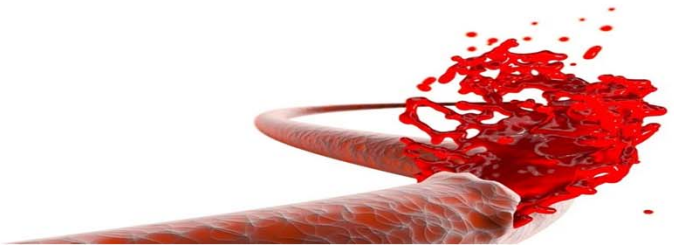


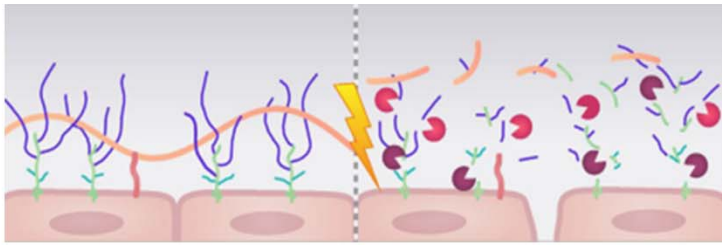
Innate immune responses to trauma

Markus Huber-Lang[1]*, John D. Lambris[2] and Peter A. Ward[3]



NATURE IMMUNOLOGY | VOL 19 | APRIL 2018 | 327–341



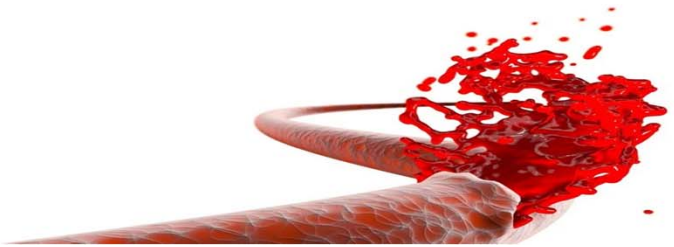


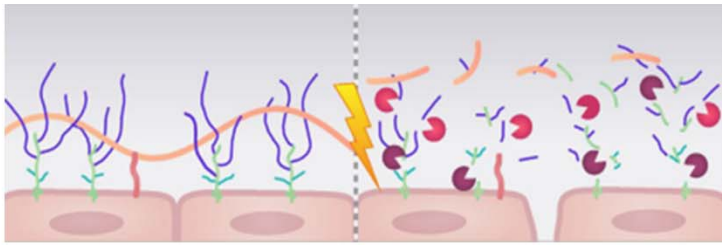
Plasma for prevention and treatment of glycocalyx degradation in trauma and sepsis

The overlapping pathophysiology of sepsis and trauma

Similar to sepsis, traumatic hemorrhage also involves a systemic disruptive inflammatory response that damages the glycocalyx, leading to organ dysfunction and worsening disease, which has been termed the Endotheliopathy of Trauma (EoT)

Kravitz *et al. Critical Care* (2024) 28:254



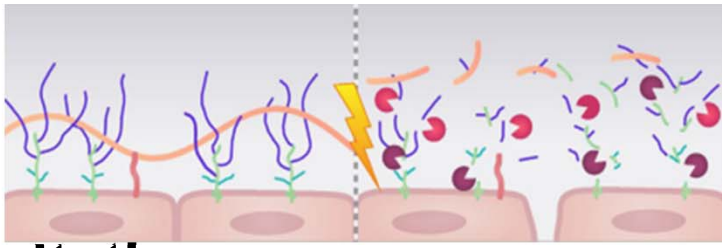


Plasma for prevention and treatment of glycocalyx degradation in trauma and sepsis

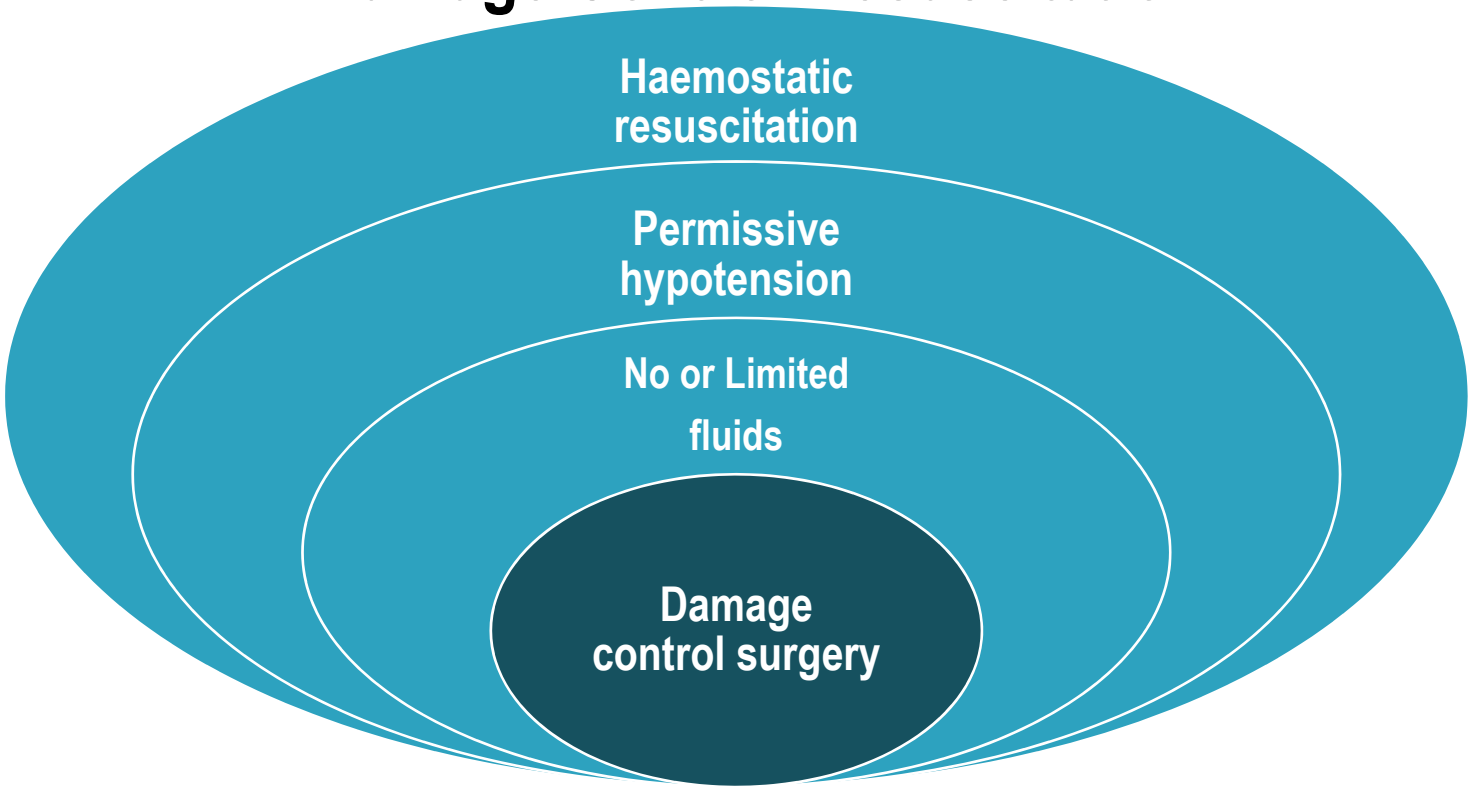
The overlapping pathophysiology of sepsis and trauma

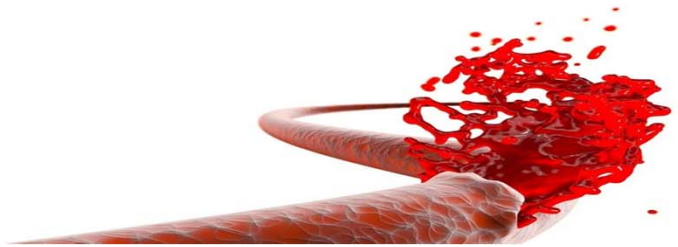
Both sepsis and trauma are syndromes characterized by sympatho-adrenal hyperactivation, leading to endothelial cell activation and glycocalyx degradation (endotheliopathy).

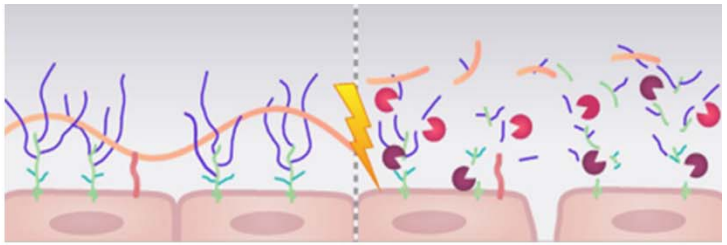
Kravitz *et al. Critical Care* (2024) 28:254



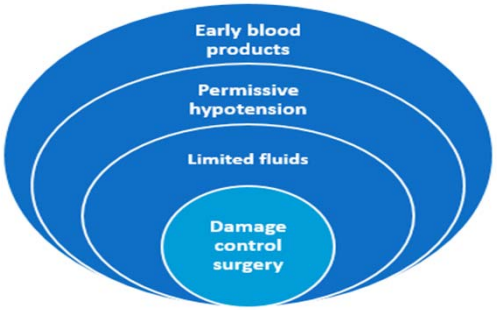
Damage Control Resuscitation



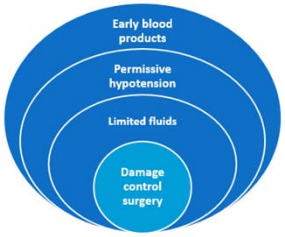




Limited Fluids



The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition

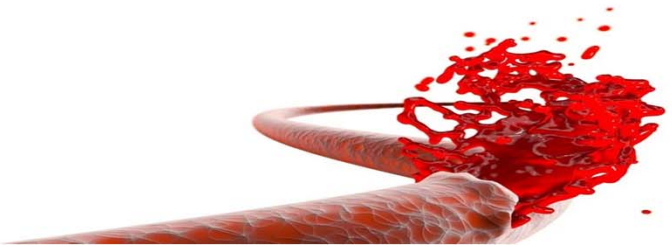


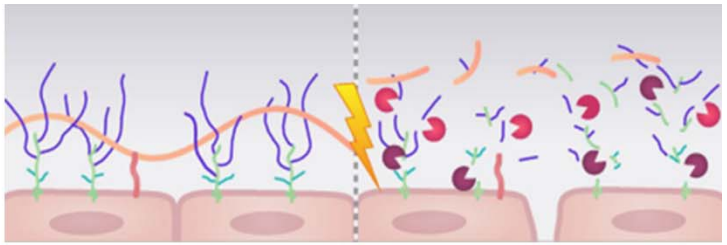
IN DCR

Restricted use of CRYSTALLOIDS [Isotonic]

Absolutely NO use of SYNTHETIC COLLOIDS

Rossaint *et al. Critical Care* (2023) 27:80
https://doi.org/10.1186/s13054-023-04327-7



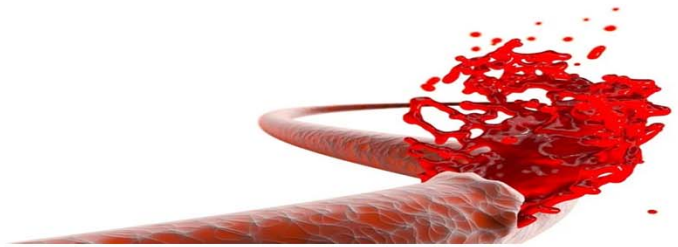


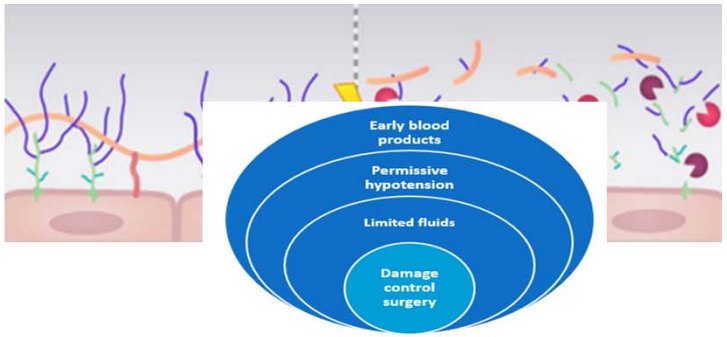
THOR Position Paper on Remote Damage Control Resuscitation: Definitions, Current Practice and Knowledge Gaps

We and others have shown that crystalloids, either saline or lactated Ringers (LR), fail to restore glycocalyx functional integrity following hemorrhagic shock

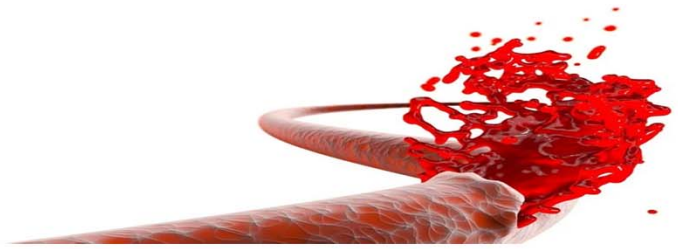
Overall, resuscitation with crystalloid solutions (saline or LR) caused glycocalyx damage and worsened permeability.

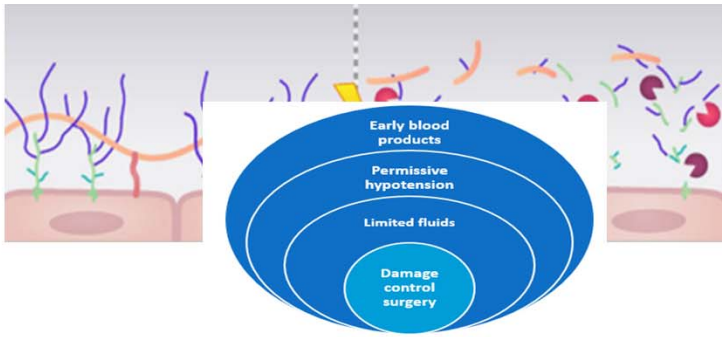
Shock. 2014 May ; 41(0 1): 3–12.





Permissive Hypotension

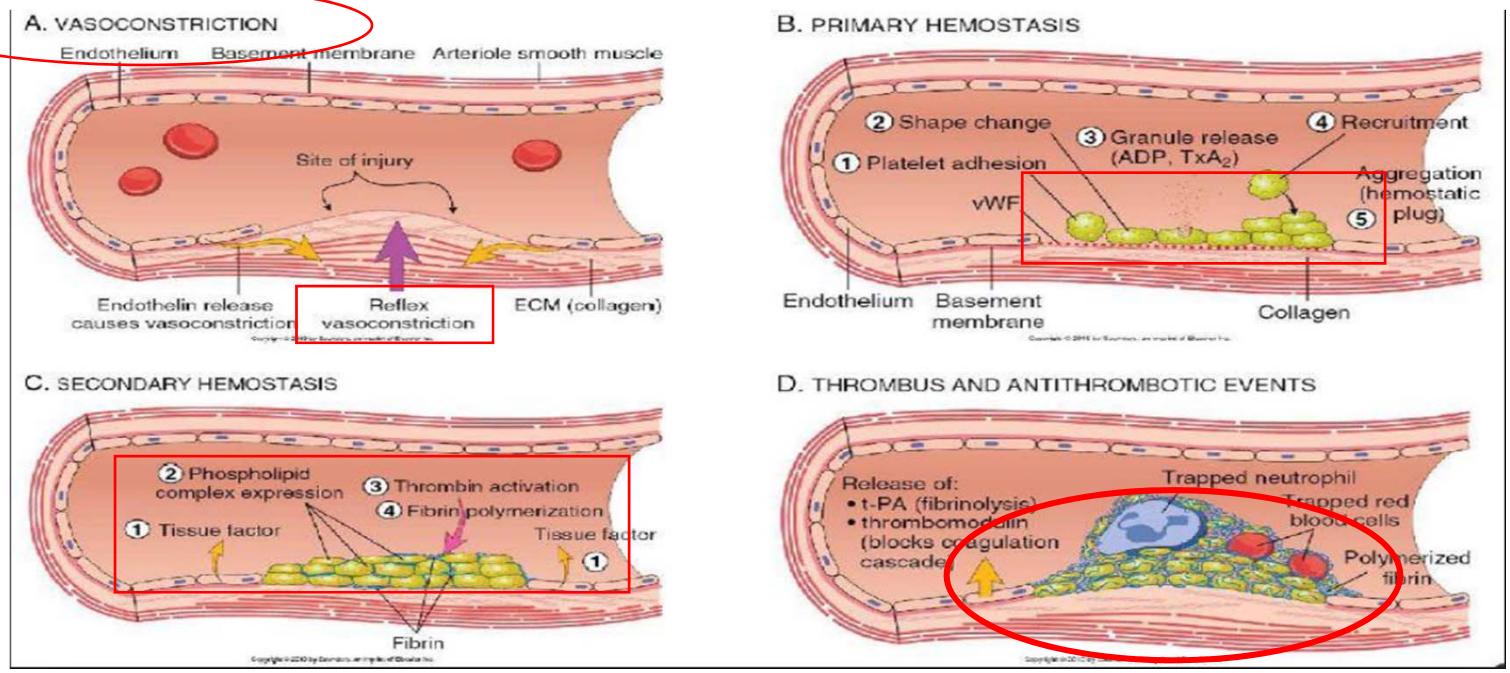




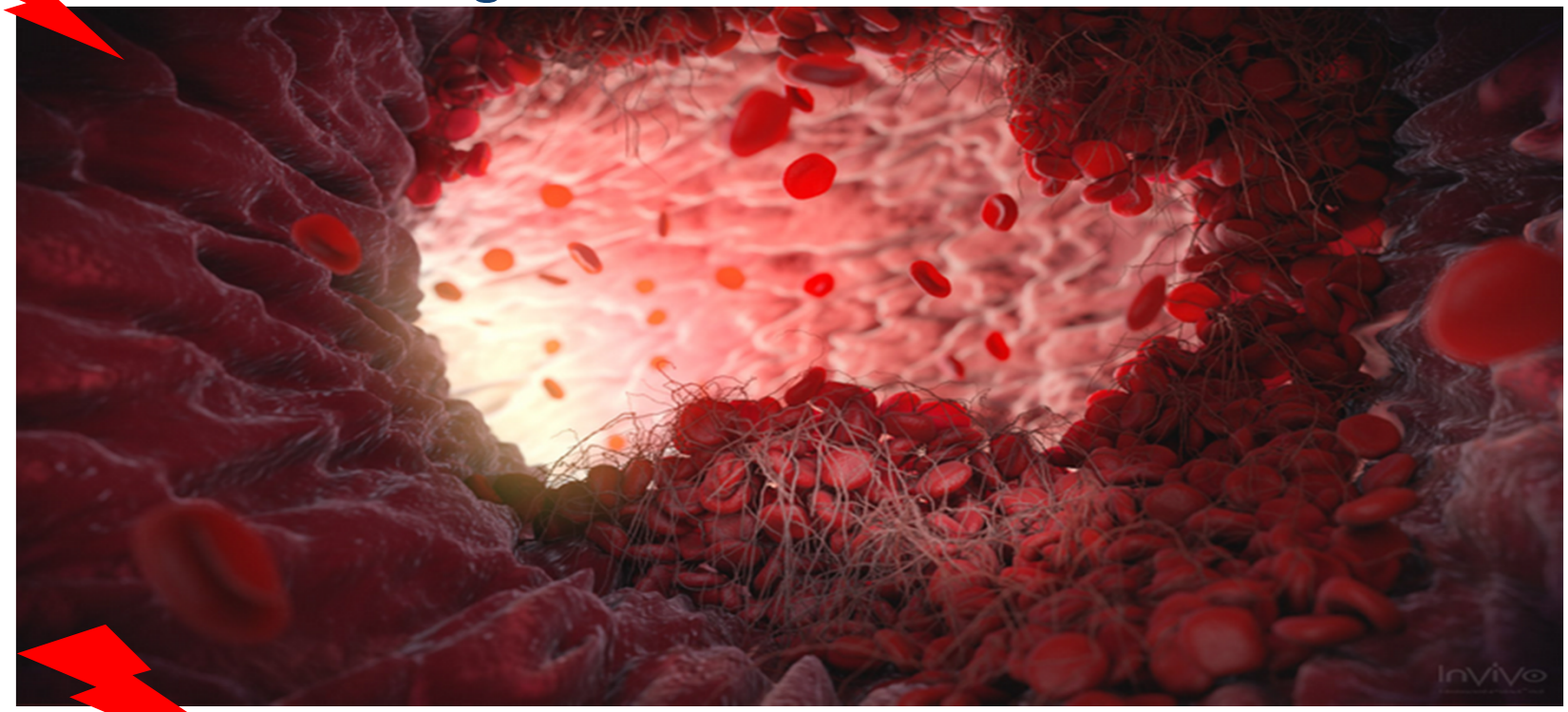
Permissive Hypotension

Tolerate systemic blood pressures below normal values until control of bleeding

Local vasoconstriction initiating primary haemostasis



Counteracting local vasoconstriction



“Popping” the clot

The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition

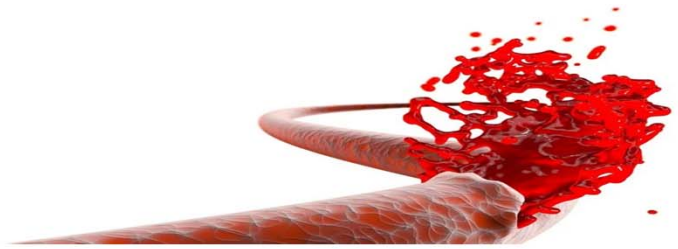
Recommendation 13 We recommend permissive hypotension with a target systolic blood pressure of 80–90 mmHg (mean arterial pressure 50–60 mmHg) until major bleeding has been stopped in the initial phase following trauma without brain injury. (Grade 1C)

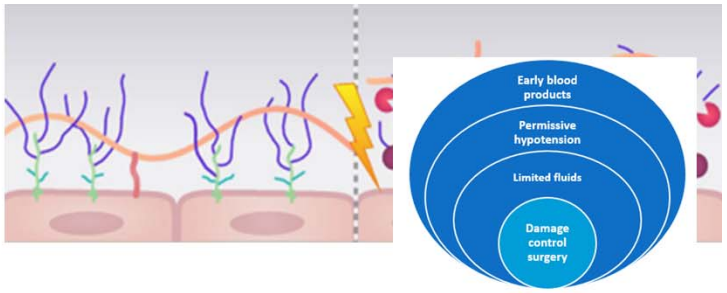
Rossaint *et al. Critical Care* (2023) 27:80
https://doi.org/10.1186/s13054-023-04327-7

The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition

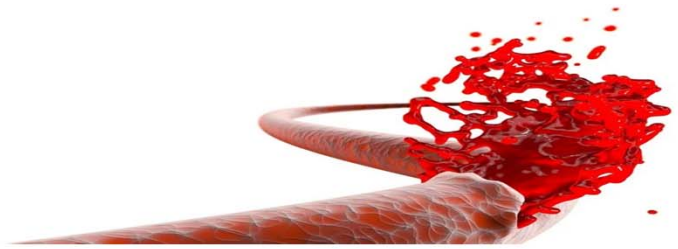
In patients with severe TBI (GCS ≤ 8), we recommend that a mean arterial pressure ≥ 80 mmHg be maintained. (Grade 1C)

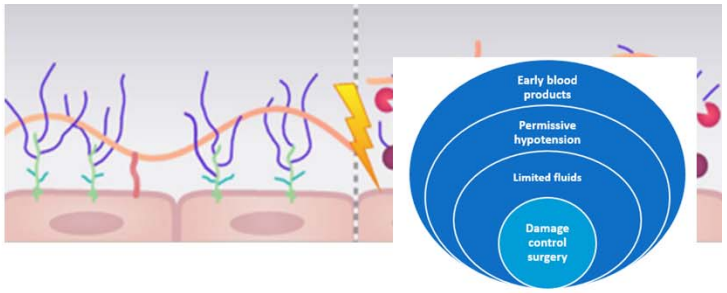
Rossaint *et al. Critical Care* (2023) 27:80
https://doi.org/10.1186/s13054-023-04327-7



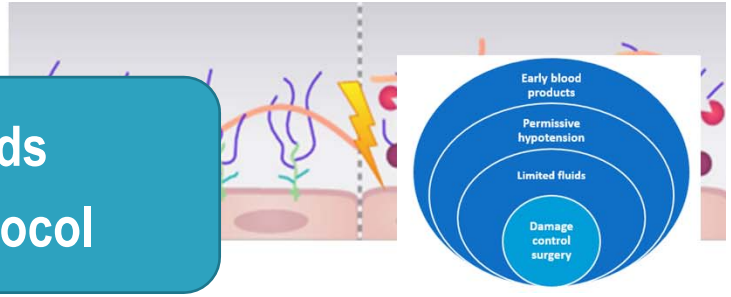


- **Haemostatic Resuscitation**





- Early Blood Products

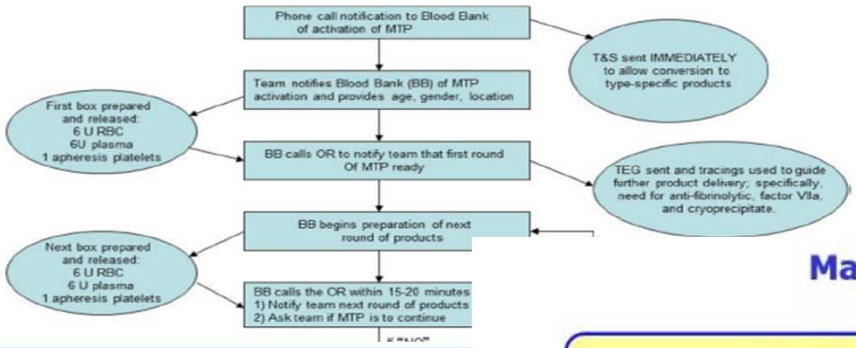


Massive Transfusion needs a Massive Transfusion Protocol

- MTP is necessary at every hospital to coordinate actions
- MTP coordinates actions
- MTP is associated with improved survival
- MTP enables mobilization of blood and blood products [blood bank]
- MTP serves the concept Haemostatic Resuscitation

HAEMOSTATIC RESUSCITATION

- Early administration of blood & blood products
- Aggressive administration of blood & blood products
- Lost blood volume should be replaced by blood volume



Recognise blood loss and trigger major blood

Take baseline blood samples before trans

- Full blood count, group and save, clotting screen includi
- Near-patient haemostasis testing if available

If trauma and <3h from injury, give tranexa bolus over 10 minutes followed by IV infusion (consider tranexamic acid 1 g bolus in non

Team leader to coordinate management an a member of team to liaise with transfusio

- State patient unique identifier and location when reques
- To limit use of Group O NEG: until patient group known, females and consider O POS in males
- Use group-specific blood as soon as available
- Request agreed ratio of blood components (e.g. 6 units RBS and 4 units FFP). Send porter to lab to collect urgently

Major Haemorrhage Managemen

Give: 10 mls/kg of warmed Saline, Plasmalyte or PPS
Contact Theatre or ED and ask for blood warmer as an emergency

Request additional products if required

Cap refill > 2secs

Cap refill < 2secs

Reassess **ABC**

Reassess **ABC**

Give 20mls/kg blood
20mls/kg FFP
+ 5mls/kg cryo
when available

Continue transfusion to achieve:
Hb > 80g/l
Platelets > 75 x 10^9
Fibrinogen > 1.5 g/l
APTT/PT <1.5 x midpoint of normal

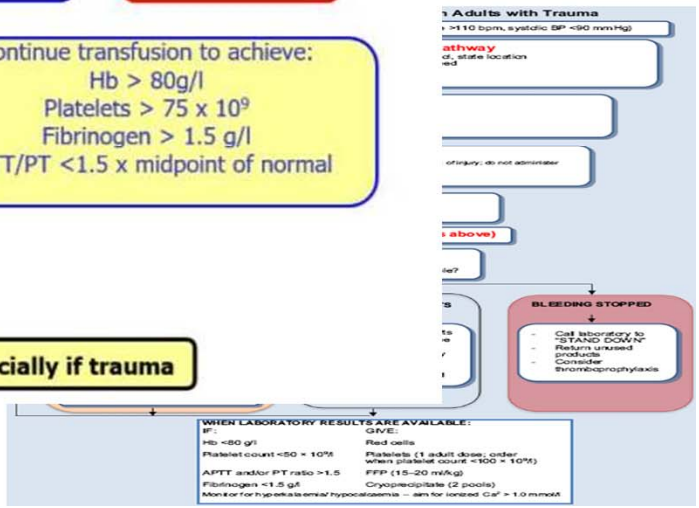
Check ABG if possible and core temp

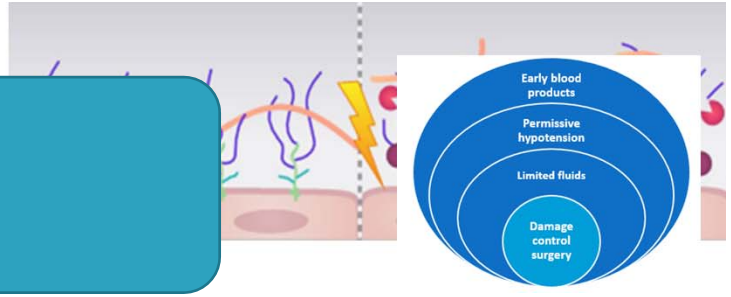
Give 10 mls/kg platelets when available

Consider Tranexamic acid 15mg/kg especially if trauma

Until lab results are available:

- Give further FFP 1L (4 units) per 6 units red cells
- Consider cryoprecipitate (2 pools)
- Consider platelets (1 adult therapeutic dose (ATD))





MTP

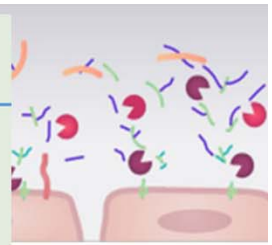
What is the best ratio?

PROPPR trial
680 patients

- **Tendency to use higher ratios of FFP and platelets**
- **Initial Fixed Ratio ➲ 1:1:1**
- **Lost blood volume should be replaced by blood volume**

Deliver **near ”normal” whole blood**

CONCEPT
Start with predermined packages, and
move to a goal directed strategy as soon as coagulation tests are available

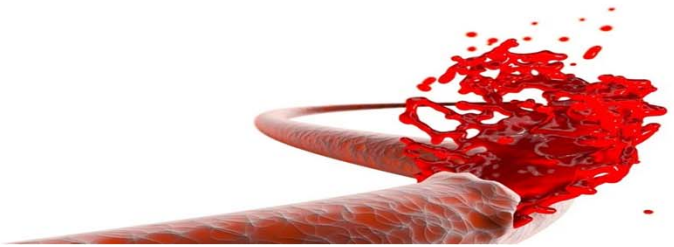


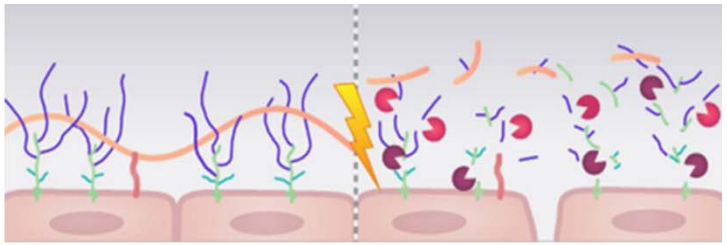
JOINT TRAUMA SYSTEM CLINICAL PRACTICE GUIDELINE (JTS CPG)

Damage Control Resuscitation

This CPG provides evidence–based guidance to minimize variation in resuscitation practices and improve the care of massively hemorrhaging, severely injured casualties.

- Fully TTD tested (performed in FDA registered testing facility/FDA approved) whole blood
- Blood components at a 1:1:1:1 ratio (plasma:platelets:RBC:CRYO)
  Note that apheresis platelets may be collected in theater and therefore are not FDA approved and fully tested prior to transfusion.
- Whole blood from a recently tested donor (***NOTE:*** *this option is only acceptable in the hospital for emergency indications when full component therapy is not available)*
- RBCs plus plasma=1:1 ratio
- Plasma with or without RBCs
- RBCs alone



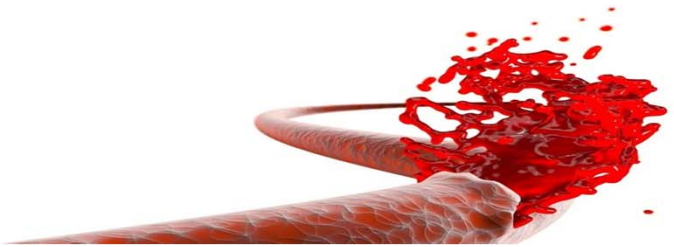


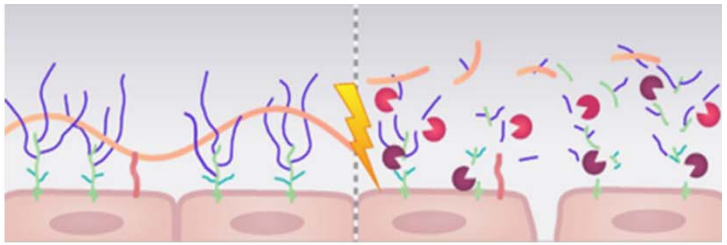
Resuscitative Strategies to Modulate the Endotheliopathy of Trauma: From Cell to Patient:

demonstrated that endothelial glycocalyx thickness was only partially restored by albumin, but was completely restored by FFP

Resuscitation with fresh whole blood or plasma evoked protection, and albumin had an intermediate effect

Shock. 2020 May ; 53(5): 575–584.



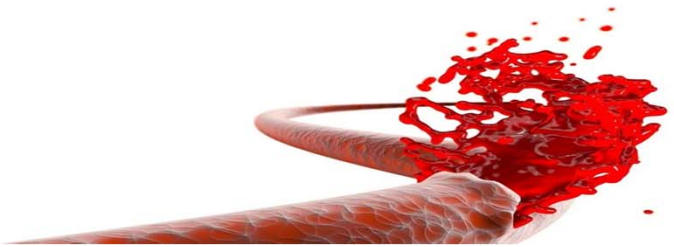


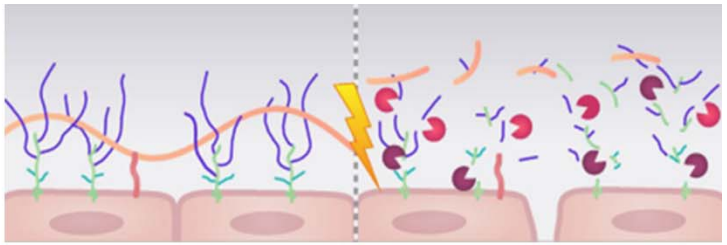
Resuscitative Strategies to Modulate the Endotheliopathy of Trauma: From Cell to Patient:

We demonstrated degradation of the glycocalyx after hemorrhagic shock, which was partially restored at three hours by plasma but not LR

Additionally, a clinically relevant effect of plasma was suggested by the observation that plasma resuscitation required significantly less volume to maintain the mean arterial pressure (MAP)

Shock. 2020 May ; 53(5): 575–584.

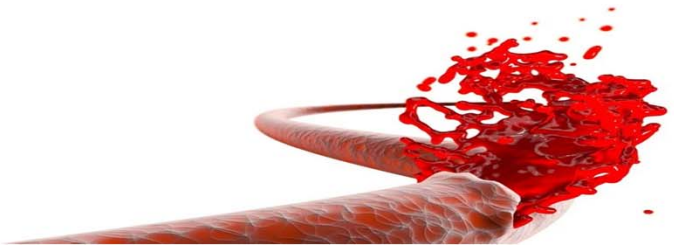


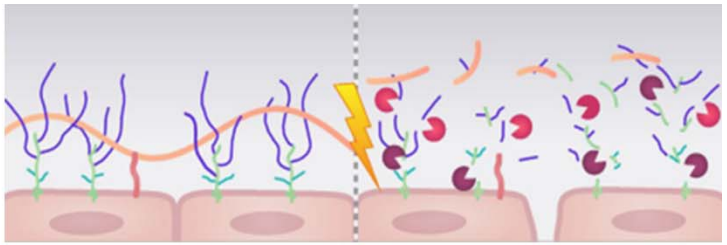


Resuscitative Strategies to Modulate the Endotheliopathy of Trauma: From Cell to Patient:

Naumann et al demonstrated that the endotheliopathy of trauma occurred within five to eight minutes of injury (68). This finding suggests that the early use of plasma after injury may be beneficial.

Shock. 2020 May ; 53(5): 575–584.

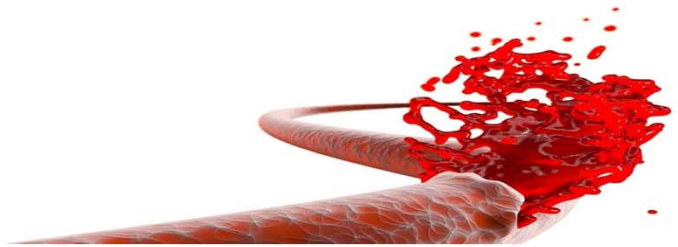


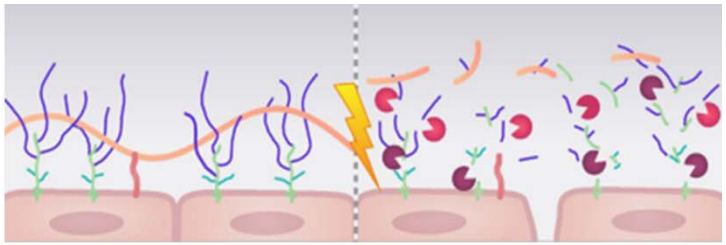


Resuscitative Strategies to Modulate the Endotheliopathy of Trauma: From Cell to Patient:

Indeed, Diebel et al demonstrated in their *in-vitro* biomimetic model of endothelial vascular barrier dysfunction following shock that the early use of plasma restored the endothelial glyocalyx and reduced syndecan-1 shedding, while the late use was comparable to shock alone

Shock. 2020 May ; 53(5): 575–584.

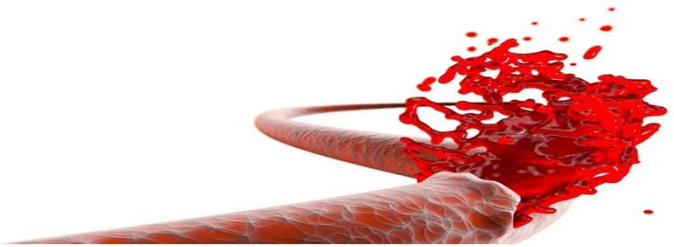


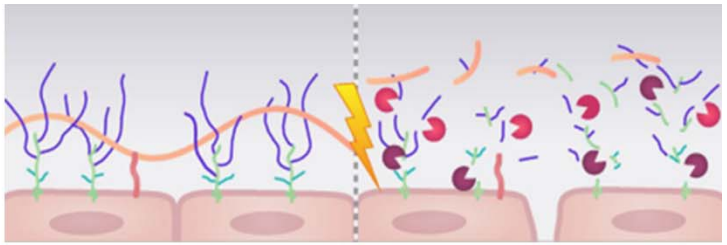


Resuscitative Strategies to Modulate the Endotheliopathy of Trauma: From Cell to Patient:

This supports the concept that the early transfusion of plasma is important to outcomes after hemorrhage.

Shock. 2020 May ; 53(5): 575–584.

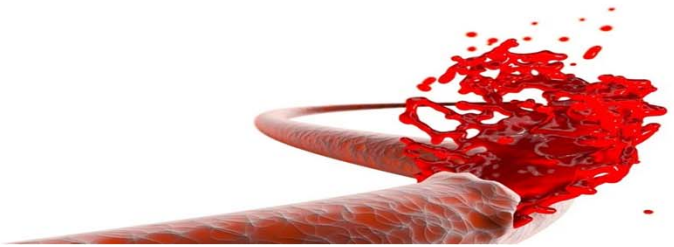


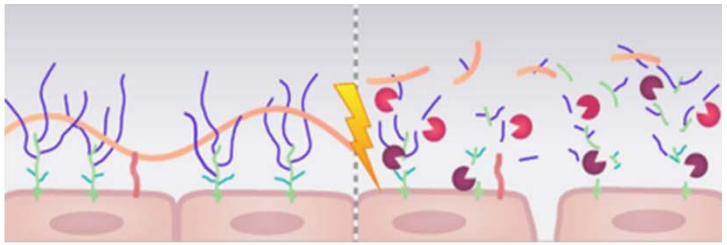


Plasma for prevention and treatment of glycocalyx degradation in trauma and sepsis

Plasma transfusion is commonly used for the replenishment of coagulation factors and as a component of a balanced massive transfusion protocol in the setting of hemorrhage, alongside red blood cells and platelets

Kravitz *et al. Critical Care* (2024) 28:254

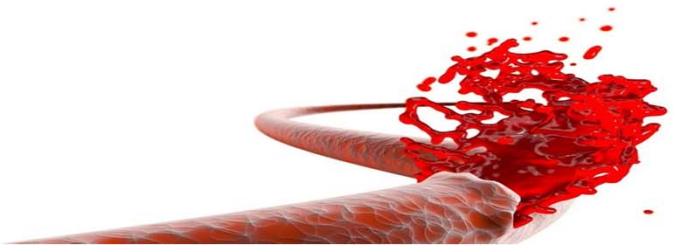


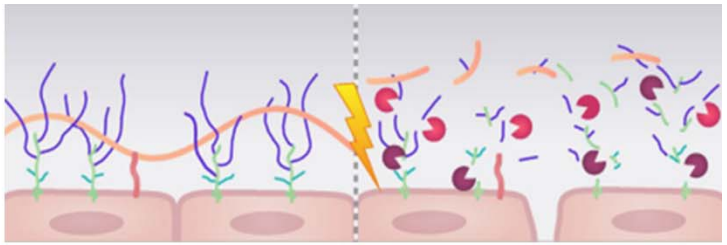


Plasma for prevention and treatment of glycocalyx degradation in trauma and sepsis

Yet, plasma, the non-cellular component of blood, also contains numerous other biologically-active components that influence homeostatic and pathogenic pathways other than coagulation.

Kravitz *et al. Critical Care* (2024) 28:254

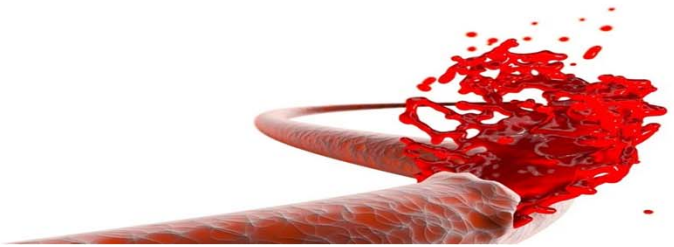


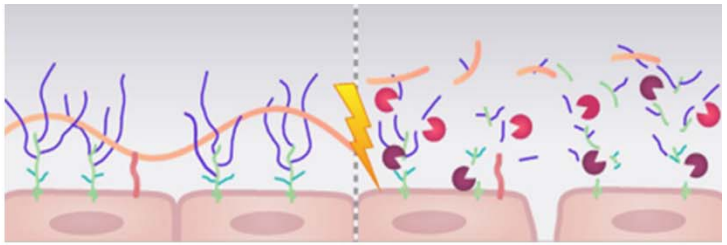


Plasma for prevention and treatment of glycocalyx degradation in trauma and sepsis

These bioactive components, which include sphingosine-1 phosphate, antithrombin, and adiponectin, may prevent and restore damage to the glycocalyx, reduce endothelial cell permeability and leukocyte adhesion, and decrease inflammation in critical illnesses

Kravitz *et al. Critical Care* (2024) 28:254

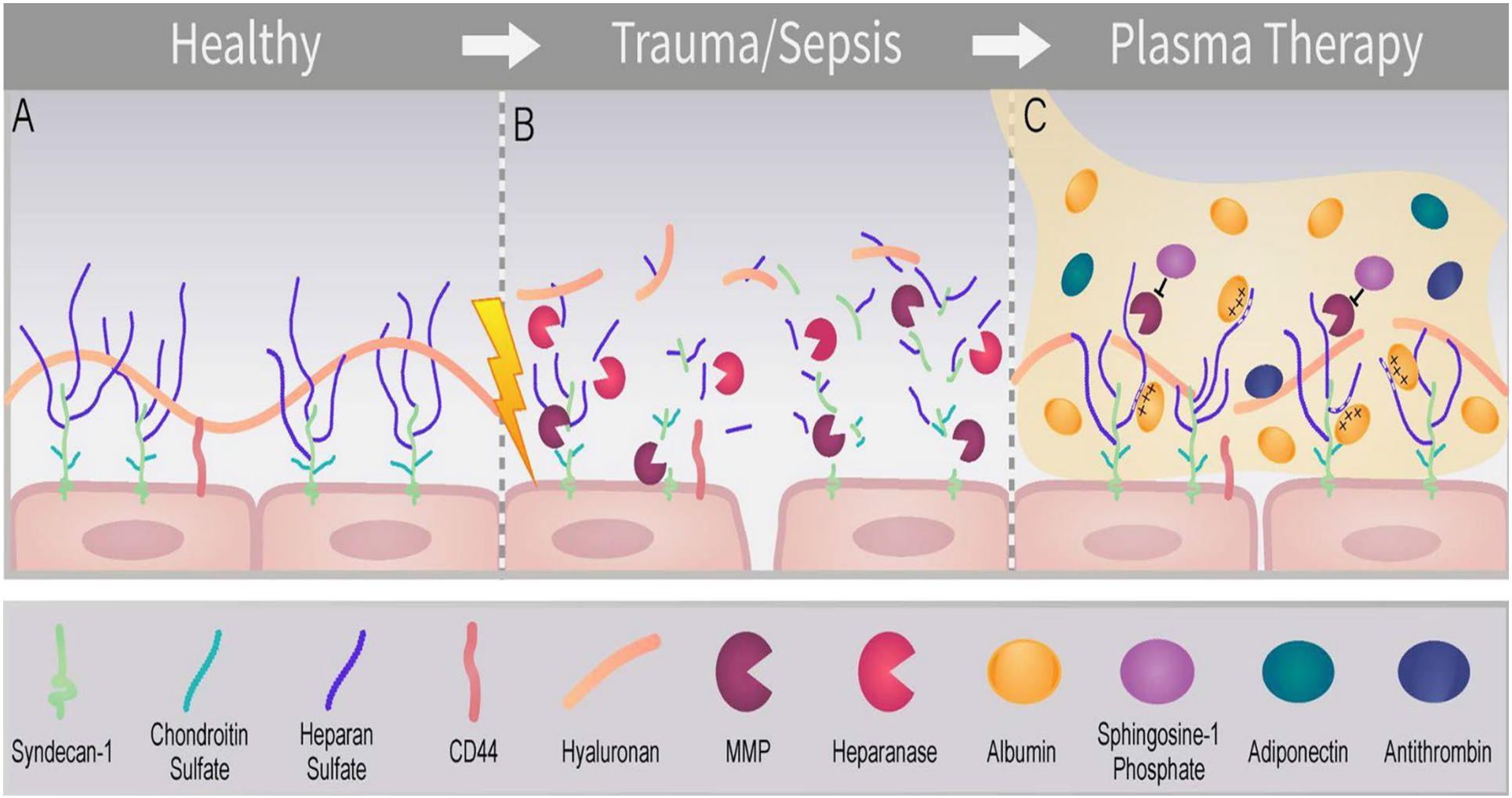




Plasma for prevention and treatment of glycocalyx degradation in trauma and sepsis

plasma is a potential therapeutic, and glycocalyx sparing, agent in trauma and sepsis (beyond treatment of coagulopathy), through its potential protective and restorative effects on the glycocalyx.

Kravitz *et al. Critical Care* (2024) 28:254



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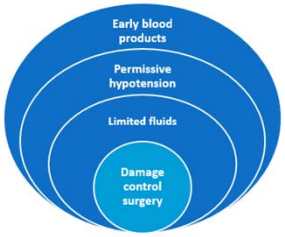
Haemostatic Resuscitation

Fibrinogen

The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition

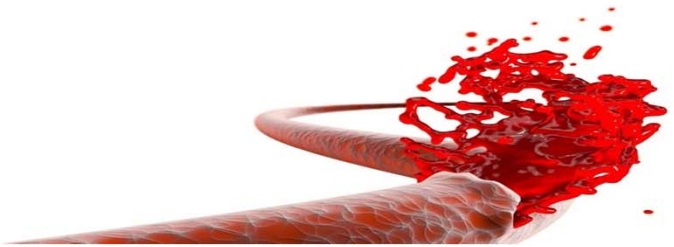


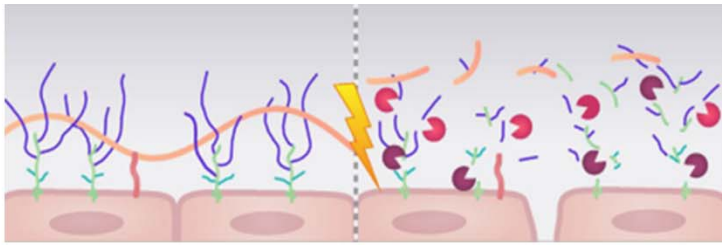
Fibrinogen supplementation

Recommendation 29 We recommend treatment with fibrinogen concentrate or cryoprecipitate if major bleeding is accompanied by hypofibrinogenemia (viscoelastic signs of a functional fibrinogen deficit or a plasma Clauss fibrinogen level ≤ 1.5 g/L) (Grade 1C)*

We suggest an initial fibrinogen supplementation of 3–4 g. This is equivalent to 15–20 single donor units of cryoprecipitate or 3–4 g fibrinogen concentrate. Repeat doses should be guided by VEM and laboratory assessment of fibrinogen levels (Grade 2C).

Rossaint *et al. Critical Care* (2023) 27:80
https://doi.org/10.1186/s13054-023-04327-7





Resuscitative Strategies to Modulate the Endotheliopathy of Trauma: From Cell to Patient:

Fibrinogen plays a key role in hemostasis by acting as an endogenous substrate for fibrin formation, promoting clot formation and platelet aggregation by binding platelet glycoprotein IIb/IIIa receptors. Hypofibrinogenemia is known to be associated with worse outcomes after trauma ; and the degree of hypofibrinogenemia is correlated with increased injury severity

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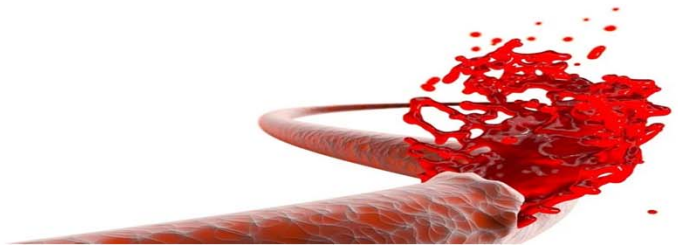

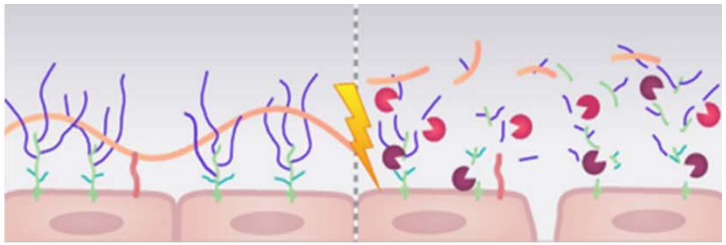

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As fibrinogen is the first coagulation factor to fall below a critical value during massive bleeding, it seems plausible that it should be the first protein to be given to patients with trauma.

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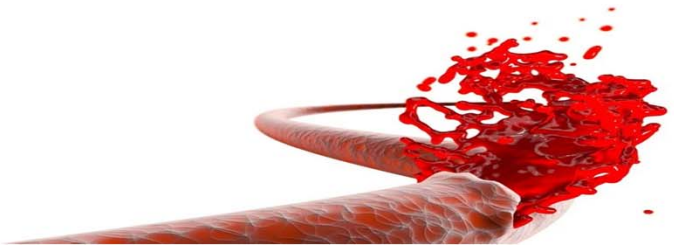

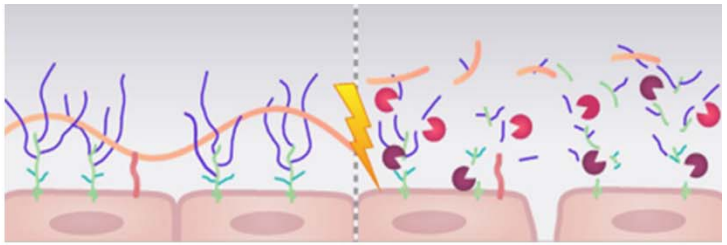

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These results demonstrate an endothelial barrier protective effect for fibrinogen, which may support the early use of fibrinogen as a therapeutic intervention for hemorrhagic shock. Indeed, other studies also demonstrated that fibrinogen-derived peptide B-beta (15–42) preserves endothelial barrier function in shock

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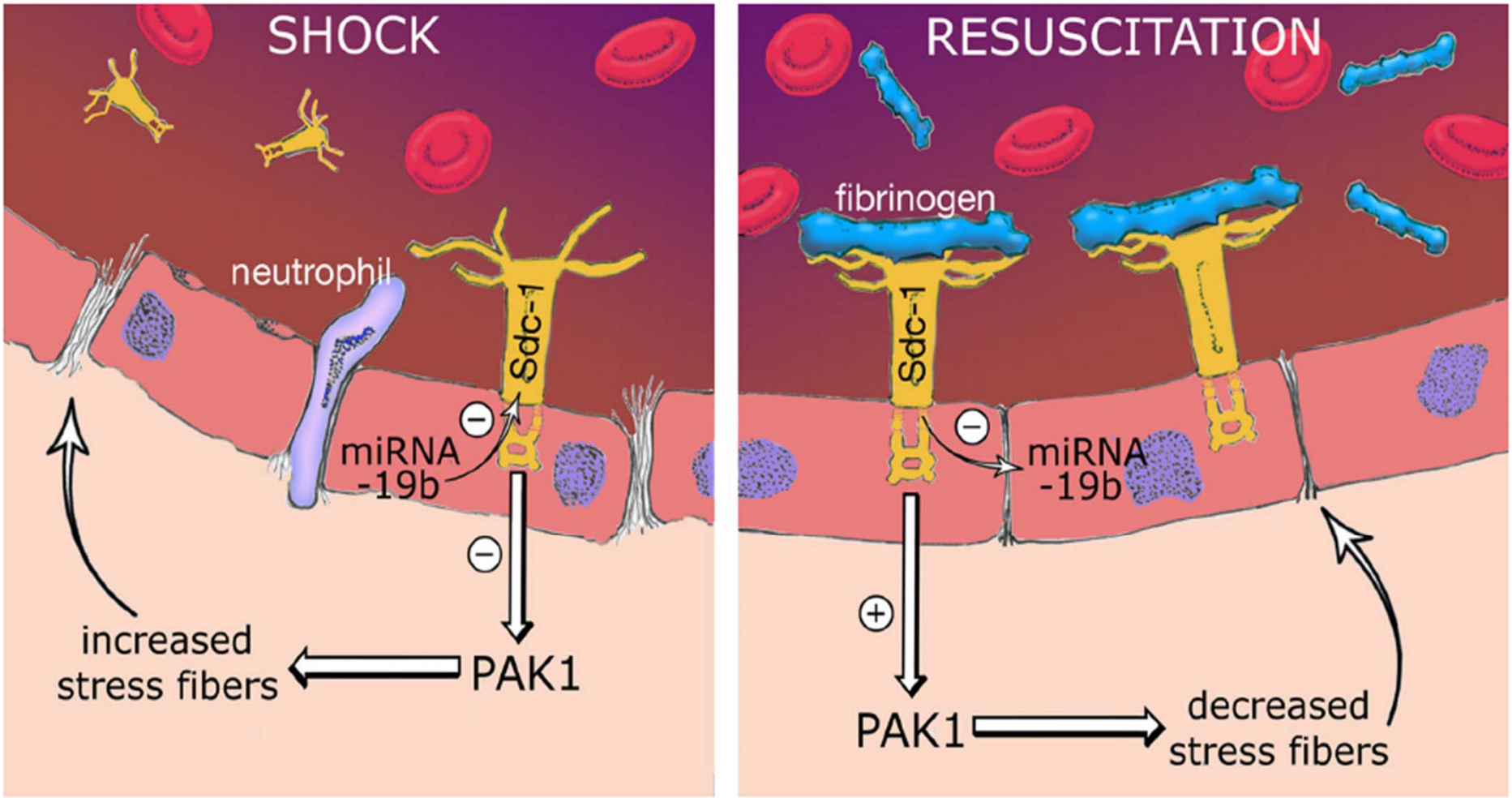

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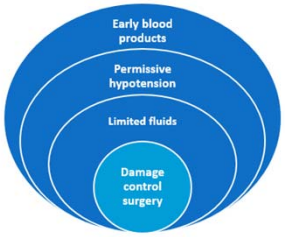
The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition



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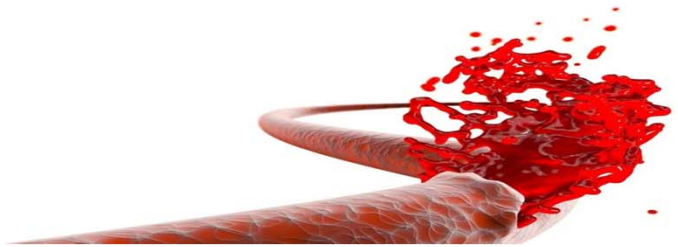

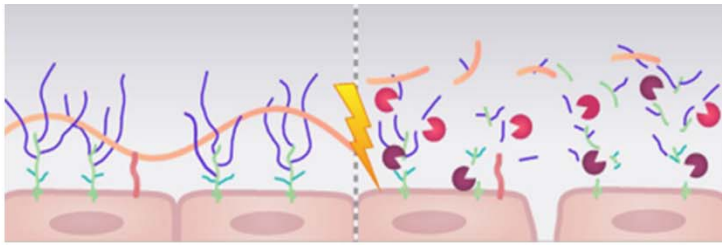

Chemical sympathectomy attenuates inflammation, glycocalyx shedding and coagulation disorders in rats with acute traumatic coagulopathy Blood Coagulation and Fibrinolysis 2015, 26:152–160

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Journal of Thrombosis and Thrombolysis
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Resuscitation After Hemorrhagic Shock in the Microcirculation: Targeting Optimal Oxygen Delivery in the Design of Artificial Blood Substitutes

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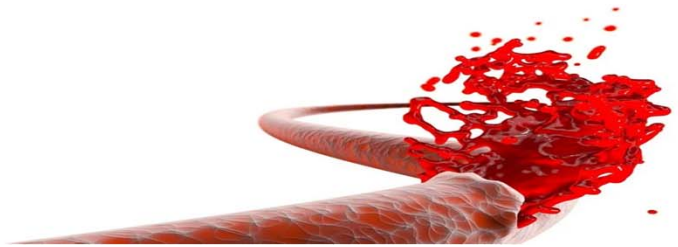

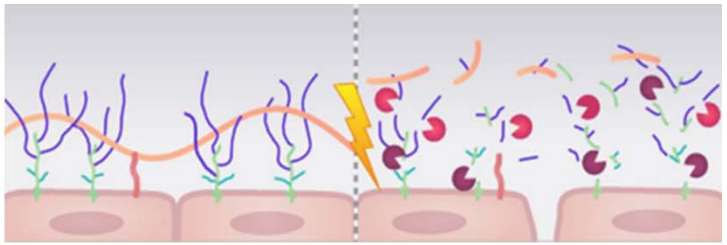

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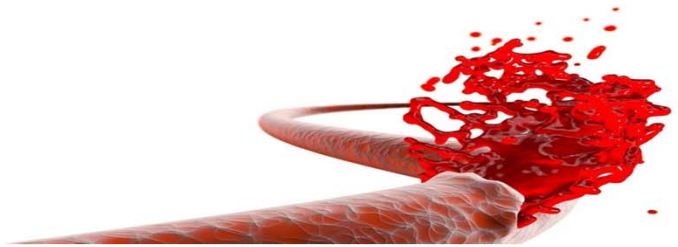

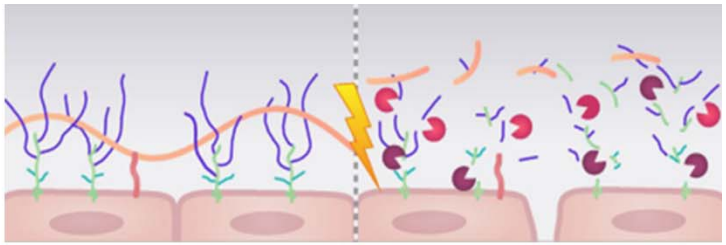

Bleed STOP

Stop the bleeding & Correct Oxygen debt

Treat Coagulopathy

Observe response to interventions

Prevent secondary coagulopathy