Disclosures

I have nothing to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation.
Objectives

• Describe the physiology of trauma and its effect on normal coagulation processes

• Discuss the concept of balanced resuscitation and massive transfusion

• Review literature related to pharmacologic agents used to promote normalization of hemostasis

• Summarize the role of the pharmacist in the management of acute traumatic coagulopathy (ATC)
Epidemiology

5.8 million trauma deaths worldwide annually

4th leading cause of death among all ages

Leading cause of death in US children and adults under 45 years of age

https://www.cdc.gov/injury/images/lc-charts/leading_causes_of_death_age_group_2015_1050w740h.gif
The “Golden Hour” of Trauma

Described by R. Adams Cowley in 1975

“The first hour after injury will largely determine a critically injured person’s chances for survival”

Patient Case

AF is a 47 yo F brought in by EMS after she was reportedly struck by an SUV while crossing the street. Patient has a GCS of 15 and was hemodynamically stable in the field. On arrival she is complaining of rib pain, leg pain, and has an obvious L femur deformity.
Self-assessment Question

Which of the following statements is true regarding death from traumatic injury?

A. Two of the most common causes of early death after trauma are hemorrhage and devastating brain injury.
B. Trauma deaths follow a bimodal distribution where the majority of fatalities occur in the immediate and early phases after injury.
C. Coagulopathy, acidosis, and hypothermia are referred to as the “lethal triad” or “triad of death”.
D. All of the above.
Trimodal to Bimodal Distribution

1983 classification of immediate, early, and late trauma deaths:

<table>
<thead>
<tr>
<th>Deaths</th>
<th>Trimodal Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>Historical</td>
</tr>
<tr>
<td>Early</td>
<td>2005</td>
</tr>
<tr>
<td>Late</td>
<td></td>
</tr>
</tbody>
</table>

Acute Traumatic Coagulopathy

“Coagulopathy initiated by hemorrhagic shock and tissue injury that leads to activation of the anticoagulant and fibrinolytic pathways…”

tPA

Plasminogen → Plasmin

Stable fibrin clot → Fibrin breakdown products
Acute Traumatic Coagulopathy

Hemostatic equilibrium disrupted by injury
- Tissue injury
- Blood loss

Exacerbated by medical interventions
- Fluid and product resuscitation
- Medication administration
- Surgical procedures

AF was found to have decreased breath sounds on the L side and the CXR below. A chest tube is emergently placed and 1200 cc’s of blood is removed. Her BP is 112/80 and her heart rate is 118. What class of hypovolemic shock would describe this patient?

A. I  
B. II  
C. III  
D. IV
Hypovolemic Shock

- Hemorrhage is most common cause of shock after traumatic injury
- Adult blood volume = 7% body weight or 5L

<table>
<thead>
<tr>
<th>Actual or Relative Hypovolemic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Blood loss</td>
</tr>
<tr>
<td>Blood loss (% BV)</td>
</tr>
<tr>
<td>Pulse rate</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Pulse pressure</td>
</tr>
<tr>
<td>Respiratory rate</td>
</tr>
<tr>
<td>Urine output</td>
</tr>
<tr>
<td>CNS/Mental status</td>
</tr>
</tbody>
</table>

Cite ATLS book here
Fluid Resuscitation

- The Advanced Trauma Life Support (ATLS) recommends aggressive crystalloid resuscitation on presentation
  - Balanced crystalloid solution
  - Worsening coagulopathy…..
  - Transient or non-responders progress to PRBCs
- Damage control resuscitation
Massive Transfusion (MT)

• >10 units pRBCs within first 24 hours
• Goal: provide optimal clotting substrates 1:1:1 or 1:1:2? Who knows!

[Image of PROPPR study]
## Complications of MT

<table>
<thead>
<tr>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume overload</td>
</tr>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Dilutional coagulopathy of factors and platelets</td>
</tr>
<tr>
<td>Transfusion related acute lung injury</td>
</tr>
<tr>
<td>Hyperkalemia/hypocalcemia</td>
</tr>
</tbody>
</table>
Calcium

- Essential cofactor in clotting cascade
- Cardiac contractility
- Skeletal muscle contractility
- Systemic vascular resistance
Calcium Replacement

- Citrate anticoagulant in blood products
  - FFP and platelets with highest content
- Each unit of PRBC contains 3g citrate
  - Metabolized in 5 minutes by healthy liver
  - Metabolism impaired in low flow states
  - Citrate toxicity $\rightarrow$ hypocalcemia
- Replaced when ionized $<0.9$ mmol/l $(1.1-1.3)$
  - Calcium chloride

http://www.trauma.org/archive/resus/massive.html
Thromboelastography

Thromboelastography

Thromboelastography (TEG) is a viscoelastic technique used to assess and monitor clot formation and function. It measures the time and strength of clot formation, providing a comprehensive overview of hemostasis. The TEG curve, which is generated by a computer, reflects the coagulation and fibrinolysis processes.

Key parameters include:
- **Coagulation**:
  - **Kinetics of clot development**
  - **Angle**: Reflects the speed of clot formation.
  - **R**: Reaction time, first significant clot formation.
  - **K**: Achievement of certain clot firmness.
  - **MA**: Maximum amplitude — maximum strength of clot.
  - **LY30**: Percent lysis 30 minutes after MA.

- **Fibrinolysis**:
  - **LY**: Percent lysis at a given time point, indicating the rate of fibrin degradation.

Normal
R;K;MA;Angle = Normal

Anticoagulants/hemophilia
Factor Deficiency
R;K = Prolonged;
MA;Angle = Decreased

Platelet Blockers
Thrombocytopenia/
Thrombocytopathy
R ~ Normal; K = Prolonged;
MA = Decreased

Fibrinolysis (UK, SK, or t-PA)
Presence of t-PA
R ~ Normal;
MA = Continuous decrease
LY30 > 7.5%; WBCL30 < 97.5%;
Ly60 > 15.0%; WBCLI60 < 85%

Hypercoagulation
R;K = Decreased;
MA;Angle = Increased

D.I.C
Stage 1
Hypercoagulable state with secondary fibrinolysis

Stage 2
Hypocoagulable state
“Death Diamond”?  

Pharmacologic Interventions

Anti-fibrinolytics
- Tranexamic acid (TXA)

Clotting Factors
- Factor VIIa
- Prothrombin complex concentrate (PCCs)
AF has received 2L of crystalloid for resuscitation. Her BP subsequently dropped to 85/59 and her HR increased to the 130s. The physician states she has a positive FAST exam and a pelvic fracture on X-ray. 2 units of PRBCs are ordered stat. The patient responds transiently and an additional 2 units are ordered. What intervention can you consider at this point?

A. Calcium chloride 1g IV  
B. TXA 1g bolus followed by 1g over 8 hours  
C. Recombinant Factor VIIa 1mg  
D. 1L lactated ringers bolus
TXA

- Antifibrinolytic
- Inhibits plasminogen activation
A Normal fibrinolysis occurs by binding of plasminogen to fibrin and subsequent activation to plasmin via the interaction with plasminogen activator. Plasmin bound to fibrin results in degradation of fibrin into fibrin degradation products.

B Antifibrinolytic medications such as aminocaproic acid and tranexamic acid bind to the site where plasminogen binds to fibrin, thereby preventing activation of plasminogen on the surface of fibrin. Fibrinolysis is therefore blocked. (Adapted with permission.)

https://pbrainmd.wordpress.com/2015/10/15/1335/
Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

CRASH-2 trial collaborators*

All cause mortality significantly reduced
• 14.5% v. 16% (p=0.0035) at 28 days

Mortality due to hemorrhage reduced
• 4.9% v. 5.7% (p=0.0077)

No difference blood product use, surgery, or rate of thromboembolic events

What about patients treated >3h from injury?

Figure 1: Mortality due to bleeding by subgroups

Figure 3: All-cause mortality by subgroups

Military Application of TXA

Population and Treatment

| 896 combat injured patients | TXA 1g, repeated prn |

Endpoints

| 24 hour/48 hour/ inhospital mortality | Transfusion requirements | VTE events |

896 patients admitted to Camp Bastion with a combat injury requiring a transfusion

293 received TXA

125 received TXA and massive transfusion

603 no TXA

195 received no TXA but had massive transfusion

**MATTERS**

Table 2. All-Cause Mortality Rates of Patients in Massive Transfusion Groups With and Without Early Early TXA Administration

<table>
<thead>
<tr>
<th>End Point</th>
<th>No TXA</th>
<th>TXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.304</td>
<td>0.303</td>
</tr>
<tr>
<td>&lt;24 h</td>
<td>0.301</td>
<td>0.291</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>0.027</td>
<td>0.027</td>
</tr>
<tr>
<td>&lt;48 h</td>
<td>0.359</td>
<td>0.359</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>17.228</td>
<td>17.228</td>
</tr>
</tbody>
</table>

Figure 4. Kaplan-Meier survival curve of the massive transfusion group receiving tranexamic acid (TXA) or no TXA. \( P = .004 \), Mantel-Cox log-rank test.

TXA

Decreased mortality in civilian/military trauma

• Greatest benefit in more severely injured patients

Administration should occur early

• Less than 3 hours from injury

Number needed to treat?

• 67 or 7?
European Guidelines

Give TXA 1g over 10 minutes followed by 1g over 8 hours as early as possible to the trauma patient who is bleeding or at risk of significant hemorrhage. Grade 1A

Give TXA within 3 hours of injury. Grade 1B

Suggest protocols consider TXA administration en route to the hospital. Grade 2C

Rossaint et al. Critical Care (2016) 20:100
Fibrinolytic Shutdown

180 severely injured trauma patients (ISS >15)

Fibrinolytic Shutdown

Association for Academic Surgery

Tranexamic acid is associated with increased mortality in patients with physiological fibrinolysis

Hunter B. Moore, MD, a,* Ernest E. Moore, MD, a,b
Benjamin R. Huebner, MD, a Gregory R. Stettler, MD, a
Geoffrey R. Nunns, MD, a Peter M. Einersen, MD, a
Christopher C. Silliman, MD, PhD, a,c and Angela Sauaia, MD, PhD a,d

Should we be more selective of which patients receive TXA?

Coming in 2018

CRASH3
- Early administration of TXA on death and disability in patients with traumatic brain injury
- Goal N >10,000 patients

PATCH
- Pre-hospital administration of TXA for control of hemorrhage
- CRASH II dosing of TXA
Recombinant Factor VIIa (NovoSeven®)

- FDA approved use in hemophilia A and B with inhibitors
- Congenital Factor VII deficiency

Prothrombin Complex Concentrates

- Lyophilized concentrate of Vitamin K dependent clotting factors
- Originally approved for hemophilia B
- Now used for warfarin reversal
- 3 and 4 factor PCC products

<table>
<thead>
<tr>
<th>Vitamin K dependent coagulation factors</th>
<th>Recombinant Factor VIIa</th>
<th>Fresh Frozen Plasma</th>
<th>Three-Factor Prothrombin Complex Concentrate</th>
<th>Four-Factor Prothrombin Complex Concentrate</th>
<th>Factor Eight Inhibitor Bypass Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
</tr>
<tr>
<td>IX</td>
<td>![Checkmark]</td>
<td></td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
</tr>
<tr>
<td>VII</td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
</tr>
<tr>
<td>II</td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
<td>![Checkmark]</td>
</tr>
</tbody>
</table>

AF is taken emergently to the OR for a damage control laparotomy for suspected pelvic hemorrhage. MTP is started and she receives the following resuscitation:

21 PRBCs; 14 FFP; 2 platelets (6-packs); 1 cryoprecipitate (10 units); 4 L cell saver

Her post-op labs were as follows:

H/H 9.3/31
Platelets 124
Fibrinogen 240
INR 1.24
Ca(i) 0.84
Return to Patient Case

Based on her current labs, what intervention should be considered at this point?

A. 25 u/kg 4-factor PCC
B. Sodium bicarbonate 50mEq IV
C. Calcium chloride 1g IV
D. Another dose of TXA 1g IV
## Summary

<table>
<thead>
<tr>
<th>Early goal directed resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Appropriate fluids and blood products</td>
</tr>
<tr>
<td>• Permissive hypotension, platelets &gt;50k, Hgb &gt;7, INR &lt;1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Massive Transfusion Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mimic whole blood transfusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TEG guided resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May assist in selection of product replacement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early administration of TXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1g over 10 minutes followed by 1g over 8 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcium replacement as needed</th>
</tr>
</thead>
</table>
The research agenda for trauma critical care

Karim Asehnoune\textsuperscript{1,2*}, Zsolt Balogh\textsuperscript{7}, Giuseppe Citerio\textsuperscript{3,4}, Andre Cap\textsuperscript{9}, Timothy Billiar\textsuperscript{8}, Nino Stocchetti\textsuperscript{5}, Mitchell J. Cohen\textsuperscript{10}, Paolo Pelosi\textsuperscript{6}, Nicola Curry\textsuperscript{11}, Christine Gaarder\textsuperscript{12}, Russell Gruen\textsuperscript{13}, John Holcomb\textsuperscript{14}, Beverley J. Hunt\textsuperscript{15}, Nicole P. Juffermans\textsuperscript{16}, Mark Maegele\textsuperscript{17}, Mark Midwinter\textsuperscript{18}, Frederick A. Moore\textsuperscript{19}, Michael O’Dwyer\textsuperscript{20}, Jean-François Pittet\textsuperscript{21}, Herbert Schöchl\textsuperscript{22}, Martin Schreiber\textsuperscript{23}, Philip C. Spinella\textsuperscript{24}, Simon Stanworth\textsuperscript{25}, Robert Winfield\textsuperscript{26} and Karim Brohi\textsuperscript{20}

Abstract

In this research agenda on the acute and critical care management of trauma patients, we concentrate on the major factors leading to death, namely haemorrhage and traumatic brain injury (TBI). In haemostasis biology, the results of randomised controlled trials have led to the therapeutic focus moving away from the augmentation of coagulation factors (such as recombinant factor VIIa) and towards fibrinogen supplementation and administration of anti-fibrinolytics such as tranexamic acid. Novel diagnostic techniques need to be evaluated to determine whether an individualised precision approach is superior to current empirical practice. The timing and efficacy of platelet transfusions remain in question, while new blood products need to be developed and evaluated, including whole blood variants, lyophilised products and novel red cell storage modalities. The current cornerstones of TBI management are intracranial pressure control, maintenance of cerebral perfusion pressure and avoidance of secondary insults (such as...
References


• https://www.cdc.gov/injury/images/lc-charts/leading-causes-of-death-age-group_2015_1050w740h.gif


