Halting the Hemorrhage: Pharmacologic Management of Severe Traumatic Bleeds

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Financial Disclosures

- Nothing to disclose
Learning Objectives

- Explain the mechanisms of trauma-induced coagulopathy.
- Describe the pharmacology of medications used to treat acute hemorrhage.
- Discuss appropriate treatment strategies for patients with acute hemorrhage.
Outline

- Coagulation cascade
- Trauma-induced coagulopathy
- Massive transfusion protocols (MTPs)
- Therapies for trauma-induced hemorrhage
- Therapies for drug-related hemorrhage
Trauma

- Leading cause of mortality world-wide
- > 1,000,000 deaths from motor vehicle collisions (MVCs) world-wide each year
- #1 cause of death in US for ages 1 – 46 years
- #3 cause of death across all age groups
- 30% of all life years lost in US from trauma
- 192,000 deaths in 2014
- $585 billion/year
- 45 million people disabled each year
- > 90% of trauma deaths in low-middle income countries
- 1/3 of in-hospital trauma deaths from hemorrhage
- Sports injuries, natural disasters, falls, traumatic brain injuries (TBI)

Peden M, et al.; Centers for Disease Control and Prevention
Trauma

- Body Regions
  - Head/Neck/Spine
  - Face
  - Thoracic (chest, back)
  - Abdominal/Pelvic
  - Extremities
  - External

- Types
  - Penetrating
  - Blunt
  - Crush
  - Burn
  - Amputation

Brunett, et al.
Trauma

- 3 peak times for trauma death
  - Immediate
    - Massive head injury/decapitation, high C-spine injury, cardiac laceration, aortic rupture, laceration of great vessels (carotids/jugulars), airway obstruction
  - Early (minutes-hours) ("The Golden Hour")
    - Subdural/epidural hematomas, lacerated/ruptured spleen & liver, hypovolemic shock, pelvic long-bone fractures, hemo/tension pneumothorax, cardiac tamponade, aortic dissection/rupture
  - Delayed – multiorgan system failure, SIRS/sepsis

Brunett, et al.
Trauma

- Clotting cascade & hemostatic system maintain circulation after severe vascular injury
  - Trauma & surgery
- Severe blood loss challenges hemostatic system
- Stimulation of clot breakdown = fibrinolysis
  - Too much/pathological = hyperfibrinolysis
- Too little fibrinogen = excessive hemorrhage → hypoperfusion of tissues → cell death → multiorgan system failure

Together, coagulation, anticoagulation, and fibrinolysis maintain a delicate physiological balance.

Plasminogen activator

Plasminogen

PAI1

Vitronectin

Plasminogen activator inhibitor complex

Plasmin dissolves fibrin clots

Endothelial cells

Clot
Coagulopathy in Trauma

- Trauma patient with coagulopathy upon presentation
  - Massive blood transfusion
  - Multi-organ failure
  - 4x risk of death

- Definition
  - Inability of trauma patient’s blood to clot appropriately & cease hemorrhage
  - Prolonged PT/INR or PTT in the setting of trauma not known to be from another cause (ex: pharmacologic anticoagulant)

Coagulopathy in Trauma

Definition of trauma-induced coagulopathy?

- Early trauma-induced coagulopathy (ETIC)
- Prolonged PT/PTT/INR upon admission
- Injury → release of tissue factor → thrombin & fibrin generation → DIC
- Hypoperfusion & ischemia → activated protein C → consumes plasminogen activator inhibitor (PAI-1) → inhibits clotting cascade → systemic anticoagulation & hyperfibrinolysis
- Excessive crystalloid administration → iatrogenic/secondary coagulopathy (hemodilution of clotting factors)

Lethal “Triad”

- “Downward spiral”

Alam HB; Miller TE
Treatment

- 3 Principles of trauma management
- Fluid resuscitation to replace lost blood volume & improve hemodynamics to maintain oxygen delivery to tissues
- Blood products to replace those that are lost from trauma and are diluted by IV fluids
- Pharmacologic therapy to assist blood products and cease hemorrhage

Brunett, et al.
MTP/MRP

- Massive transfusion/resuscitation protocols – very between institutions
- At discretion of ED physician or trauma surgeon
- Blood services are delivered in “rounds” containing RBCs, platelets, plasma, whole blood until protocol is deactivated
- Shown to decrease mortality
  - Earlier transfusions, decrease in time to first transfusion of products
- Risk factors for MTP: SBP < 90 mm Hg and base deficit > 10 units
- Saves > $2,200 per patient
- Variability in protocols between institutions

Miller TE
MTP/MRP

- Mortality benefits with blood product ratios
  - Observational studies
  - Plasma:RBC > 1:2
  - Platelets:RBC = 1:1
- Damage control resuscitation (DCR) – 1:1:1 RBC:plasma:platelets
  - Confirmed with PROPPR trial 2015
- Warm fresh whole blood > products?
  - Full amounts of platelets, clotting factors, and fibrinogen
- Caution: citrate in blood → hypocalcemia
- Target Hgb: 7-9 g/dL

Holcomb, et al; Miller TE
MTP/MRP

- Point of care testing
  - Hgb, PT/PTT/INR, CBC/platelet count, fibrinogen
  - Thromboelastography (TEG) & thromboelastometry (TEM)
  - Cochrane review 2015
    - No evidence on the accuracy of TEG & TEM
    - Too few studies, concerns of bias
    - PT/INR are imperfect, but are the best options in clinical practice today
  - 2013 European Guidelines - useful for testing of oral anticoagulants? (1C recommendation)
  - *Ann Surg* 2016: use of TEG-guided MTP to resuscitate severely-injured pts improves survival vs MTP guided by conventional coagulation assays; less FFP & platelets during early resuscitation
  - POC machine (TEG 6s)

Massive Transfusion Protocol (MTP) Doctor’s Orders

Emergency Department
1. Unit secretary to initiate Red Code group page (if not already done)
2. Unit secretary dial “11” to initiate Massive Transfusion Protocol (MTP) group page
3. ED Charge Nurse to be the contact nurse for Transfusion Services, extension 3360.
4. Type and crossmatch STAT
5. Send transporter with patient label and recipient number to Transfusion Service to pick up transport cooler
6. Contact trauma nurse to order additional units.
7. Notify Transfusion Service when patient is transferred
8. Level 1 Rapid Infuser/Warmer at bedside for blood/blood product administration
9. Bair Hugger at bedside, goal temperature 37.0°C
10. Insert foley catheter, capable of temperature measurement. Monitor and record temperatures on arrival and every 15 minutes and PRN
11. Initiate ED/OR/ICU MTP Fluid/Blood/Blood Product Tracker Form
12. Hand-off of blood products Emergency Department nurse to Operating Room nurse

Respiratory Department
1. Intubation if necessary
2. Insert arterial line
3. STAT ABG

ED/Trauma Surgeon
1. Insert central line in subclavian or femoral vein if needed, AVA 3xi if possible
2. Consider the use of Tranexamic Acid for patients that arrive < 3 hours from time of injury.
   Adult Initial dose: Tranexamic Acid 1000 mg (10 mL) IV in 100 mL Normal Saline and infuse over 10 minutes, then administer the maintenance dose of 1000 mg (10 mL) IV in 250 mL Normal Saline and infuse over 8 hours
3. Consider Factor VII order (recommended 90 mcg/kg)
4. Initiate anticoagulation reversal guidelines per Pharmacy protocol

Transfusion Service
1. 2 units uncrossmatched blood delivered to ED per Red Code orders
2. Issue initial MTP blood/blood products in transport cooler.
3. After the Red Code units are issued, additional blood products from Transfusion Service will continue to be prepared and issued as follows:
   Standard MTP pack (adults and pediatric > 50kg)
   6 units PRBC (uncrossed until cross matched blood is available)
   6 units FFP
   1 unit pheresis platelets
4. Administer Massive Transfusion Packs in a 1:1:1 ratio
   Pediatric MTP pack (pediatric patients < 50kg)
   See chart on page 2
5. Continue to release blood/blood products until MTP cancelled
   continued on next page
## Pediatric MTP Pack

<table>
<thead>
<tr>
<th>Less Than or = 30 kg</th>
<th>Greater Than 30 kg - 50 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pack 1</strong></td>
<td><strong>Pack 1</strong></td>
</tr>
<tr>
<td>3 PRBC unit</td>
<td>5 PRBC unit</td>
</tr>
<tr>
<td>3 FFP unit</td>
<td>6 FFP unit</td>
</tr>
<tr>
<td>1 apheresis platelet unit</td>
<td>1 apheresis platelet unit</td>
</tr>
<tr>
<td><strong>Pack 2</strong></td>
<td><strong>Pack 2</strong></td>
</tr>
<tr>
<td>3 PRBC unit</td>
<td>5 PRBC unit</td>
</tr>
<tr>
<td>3 FFP unit</td>
<td>6 FFP unit</td>
</tr>
<tr>
<td>1 Cryo</td>
<td>1 apheresis platelet unit</td>
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<tr>
<td><strong>Pack 3</strong></td>
<td><strong>Pack 3</strong></td>
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<tr>
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<tr>
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<td>1 apheresis platelet unit</td>
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<td><strong>Pack 4</strong></td>
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<tr>
<td>1 Cryo</td>
<td>2 Cryo</td>
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<tr>
<td><strong>Pack 5</strong></td>
<td><strong>Pack 5</strong></td>
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<tr>
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<td>6 PRBC unit</td>
</tr>
<tr>
<td>3 FFP unit</td>
<td>6 FFP unit</td>
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<td>1 apheresis platelet unit</td>
</tr>
<tr>
<td><strong>Pack 6</strong></td>
<td><strong>Pack 6</strong></td>
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<td>1 apheresis platelet unit</td>
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<td><strong>Pack 9</strong></td>
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<td>6 PRBC unit</td>
</tr>
<tr>
<td>6 FFP unit</td>
<td>6 FFP unit</td>
</tr>
<tr>
<td>1 apheresis platelet unit</td>
<td>1 apheresis platelet unit</td>
</tr>
</tbody>
</table>

Suggested plan for product administration for pediatric patients:

- PRBC 10-20 mL/kg
- FFP 10-20 mL/kg
- Apheresis platelets 10 mL/kg
- Cryo 10 mL/kg

Administer massive transfusion packs in a 1:1:1 ratio of PRBC:FFP:Platelets when immediately available.
Operating Room
1. Notify Cell Saver Service of MTP initiation
2. OR nurse team to ED for transfer patient to OR
3. Establish primary contact OR nurse and provide phone extension to Transfusion Service.
   If OR contact nurse unavailable, contact OR charge nurse, extension 4350.
4. Complete MTP Fluid/Blood/Blood Product Tracker Form
5. Hand-off of blood products OR nurse to ICU nurse
6. Notify transfusion Service of patient transfer
7. CBC, PT/PTT/INR, Fibrinogen, ABG, lactate, ionized calcium every 2 hours

ICU
1. Establish primary contact ICU nurse and provide phone extension to Transfusion Service
2. Receive blood transport cooler from OR nurse and sign
   MTP Fluid/Blood/Blood Product Tracker Form
3. CBC, PT/PTT/INR, Fibrinogen, ABG, lactate, ionized calcium every 2 hours
4. Calcium gluconate 1 gram/10 mL slow IV push on arrival
5. Bair Hugger, goal temperature 37.0°
6. Level 1 Rapid Infuser/warmer at bedside

Blood/Blood Products Administration
1. Transfusion of blood/blood products will be as follows:

   Standard MTP pack (adults and pediatric > 50kg)
   6 units PRBC (uncrossed until cross matched blood is available)
   6 units FFP
   1 unit pheresis platelets

   Pediatric MTP pack (pediatric patients < 50kg)
   See chart on page 2
   1. Continue blood/blood products administration until discontinued by physician
   2. Consider 1 mL/kg/min rate of infusion for FFP & platelets
   3. Consider 2 mL/kg/min for PRBC

Discontinuation of Protocol
1. Call “11” to initiate “MTP cancelled” group page
IV Fluids & Vasopressors

- Rapid infusion of 2 L of LR or NS; target 80-99 mm Hg until major bleeding has stopped
  - Avoid LR for head trauma; MAP ≥ 80 mm Hg for shock & TBI
- Colloids? - Controversial
- Plasma-Lyte A® & Normosol R®
  - 140 mEq sodium, 5 mEq potassium, 3 mEq magnesium, 98 mEq chloride, 27 mEq acetate, and 23 mEq gluconate per 1 L
  - Calcium-free balanced crystalloids improve acid-base status and cause less hyperchloremia at 24 hours post-injury.
  - N = 46
  - No data on clinical outcomes
- Vasopressors: norepinephrine, phenylephrine

Spahn, et al; Young, et al
Recombinant Factor VII

- NovoSeven® RT, rFVIIa
- Approved indications: hemophilia A & B, acquired hemophilia, deficiencies in factor VII
- 90 mcg/kg every 2-3 hours
- Conflicting evidence of utility in hemorrhagic trauma
- Risk of thrombosis, especially in geriatric patients
- pH < 7.2 → activity of FVIIa is blunted
  - > 90% decrease in action pH < 7.0
- Use should be restricted; utility is highly questionable; only when bleeding persists despite standard attempts for control
- Risk in patients with intracerebral bleed from head trauma
- COST: $2.29/mcg → dose for 90 kg = $18,500!!!
Tranexamic Acid

- TXA, Cyclokapron®
- Synthetic lysine analogue; anti-fibrinolytic
- Competitively inhibits plasminogen/plasmin
- Widely distributes throughout all tissues
- Half life: 2 hours
- Approved indications: tooth extraction in hemophiliacs, menorrhagia
- Off-label uses: hereditary angioedema, blood loss in knee arthroplasties & total hip replacements, prevention of dental bleeds in patients using oral anticoagulants, trauma-induced hemorrhage
- Cost: $65 per 1000 mg

Levi M; Roberts, et al
CRASH-2

Shakur, et al.
CRASH-2

Shakur, et al.
## CRASH-2 Deaths

<table>
<thead>
<tr>
<th>Category</th>
<th>TXA</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death, any cause</strong></td>
<td>1463 (14.5%)</td>
<td>1613 (16.0%)</td>
<td>0.91 (0.85-0.97)</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>489 (4.9%)</td>
<td>574 (5.7%)</td>
<td>0.85 (0.76-0.96)</td>
</tr>
<tr>
<td><strong>Thromboembolic events</strong></td>
<td>33 (0.3%)</td>
<td>48 (0.5%)</td>
<td>0.69 (0.44-1.07)</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>209 (2.1%)</td>
<td>233 (2.3%)</td>
<td>0.90 (0.75-1.08)</td>
</tr>
<tr>
<td>Head injury</td>
<td>603 (6.0%)</td>
<td>621 (6.2%)</td>
<td>0.97 (0.87-1.08)</td>
</tr>
<tr>
<td>Other cause</td>
<td>129 (1.3%)</td>
<td>137 (1.4%)</td>
<td>0.94 (0.74-1.20)</td>
</tr>
</tbody>
</table>

Shakur, et al.
CRASH-2

- 1 g IV 10 minutes, then 1 g IV over 8 hour within 8 hours of injury
- No difference
  - Vascular occlusive events (fatal & nonfatal)
  - Blood product transfusions
  - Surgical interventions
  - GI bleeding
- 1.5% reduction in 28-day all-cause mortality in adult trauma patients with signs of bleeding
- NNT ~ 70

Shakur, et al.
CRASH-2

- Sub-analysis 2011
  - **Greatest benefit within 1 hour of injury** (5.3% TXA vs 7.7% placebo, RR 0.68, p<0.0001)
  - Between 1 and 3 hours post-injury: decreased risk of death due to bleeding (4.8% TXA vs 6.1% placebo, RR 0.79, p=0.03)
  - > 3 hours from injury: increased risk of death due to bleeding (4.4% TXA vs 3.1% placebo, RR 1.44, p=0.004).
  - Incremental cost of giving TXA compared with not giving TXA was $48,002; incremental cost per life year gained of administering TXA = $64

- Tranexamic acid should be given as early as possible to bleeding trauma patients.

- More support: MATTERS and MATTERS II trials

Levi M; Morrison et al; Morrison et al; Roberts set al; Roberts et al; Shakur, et al; Spahn et al
“ITLS believes that there is sufficient evidence to support the use of TXA in the management of traumatic hemorrhage in the adult patient, pursuant to system medical control approval. Following initial resuscitation including control of external bleeding and stabilization of airway, consideration should be given to administration of TXA during early stages of transport.”

Alson, et al.
Looking Forward

- Pre-hospital administration?
  - The United Kingdom
  - Newark, OH Fire Department (The Ohio State University Medical Center)
  - Prehospital TXA Administration Protocol
  - PATCH trial in Australia

- CRASH-3
  - Assess the effect of TXA on risk of death or disability in patients with TBI; is tranexamic acid an effective treatment for patients with TBI?; anticipated results in 2018

- Pediatrics?
  - 5 patients in CRASH-2 < 16 years of age
  - PED-TRAX trial
  - Currently expert opinion suggests its use

Alson R, et al; Eckert et al; Strosberg, et al; Yutthakasemunt et al
Patient Case

• JD is a 54 year-old male presenting to the ED with a chief complaint of trauma. Pt arrives via ambulance after having a van fall onto his lower body from 5-6 feet high from lift. EMS reports 4 inch laceration on his lower back and states he has been awake, alert, and oriented the whole time. They state his pelvis felt unstable but he did not complain of pain when they palpated it. They add that the patient screams when his legs move. He arrived on a back board with c-collar in place, with his legs drawn up in flexion at the hips and knees.
Patient Case

• ROS: injury to his lower back; negative HA, SOB, neck pain, or LOC
• PMH: none
• PSH: hernia repair
• SH: smokes tobacco, drink alcohol
• Allergies: NKA
• Home medications: none
• VS: HR 135 bpm, RR 27 breaths/min, BP 101/68, Temp 37.2 deg C, O2 sat 97% ra, Pain 10/10, Wt 68 kg
Patient Case

- PE: two large round 2 cm open wounds to the right lower back with active bleeding; palpation reveals bone fragments within them and that they are fairly deep with subcutaneous tracking as well as what appears to be tracking into the retroperitoneal areas; crepitus to the lower lumbar pelvic region
- CBC: WBC 13,000/mm², Hgb 14.9 g/dL, Hct 45.7%
- Chem-8: glucose 185 mg/dL, calcium 6.8 mg/dL
- INR: 1.7
- BAC: negative
Patient Case

• JD is given 1 mg of hydromorphone upon arrive to the ED. He becomes non-cooperative, combative, and agitated when the trauma surgeon arrives and tries to assess his injuries. He is administered 20 mg of etomidate and 70 mg of rocuronium for RSI, followed infusions of propofol and fentanyl for pain control and sedation and a urethral Foley catheter. His FAST exam is negative. His wounds are packed by the trauma surgeon. An arterial-line is placed by the RT.
• ABG: pH 7.16, pCO2 66 mm Hg, pO2 525 mm Hg, HCO2 23 mEq/L
Patient Case

• X-rays & CTs:
  • **Lumbar spine crush comminuted fractures**, transverse processes, posterior elements of L5, and right portion of the sacrum as well as the articular margin of the L5-S1 level. Slight subluxation of L5 on S1 suggesting facet subluxation. Also **compression injury of the right portion of the ileum**.
  • A **significant degree of hemorrhage**, at the site of compression injury at the L5-S1 level, epidural extent with epidural bubbles of air extending along the lumbar spine.
  • Large laceration with packing along the posterior right lower flank at the level of the crush fracture of the left portion of the ileum.
Patient Case

- X-rays & CTs:
  - Subcutaneous air, retroperitoneal air, and significant retroperitoneal hemorrhage
  - Vascular blush/acute hemorrhage above the right kidney, cannot exclude tear of the adjacent diminutive IVC, upper pole of the right kidney and/or adrenal gland; associated hemorrhage in Morisons pouch, and fluid surrounding the IVC and within the porta hepatis region.
  - Bilateral rib fractures
  - Small left-sided pneumothorax
Patient Case

• JD is has two large bore IV sites established, and 2 L of NS are huge wide open with pressure bags.

• The trauma surgeon is very concerned about JD’s severe open lumbar pelvic fracture and orders 2 units of PRBCs, 1 unit of FFP, and 1 unit of platelets, which are infused using the Level-1 rapid infuser. The ED physician places a triple-lumen subclavian central line, for which 2 more L of NS are infused. The orthopedic PA helps to stabilize JD’s pelvis by wrapping it in sheets with towel clamps.

• VS: HR 130 bpm, RR 20 breaths/min, BP 120/80 mm Hg, Temp 37.0 deg C
Administering a calcium-free crystalloid IV fluid (Plasma-Lyte A®/Normosol R®) instead of normal saline to JD might provide him with which of the following benefits?

A. Less risk of mortality and long-term sequelae
B. Improved hemodynamics and cardiac output
C. Improved acid/base status and less risk of hyperchloremia
D. Less risk of excessive hemorrhage and need for blood products
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JD receives a total of 6 units of PRBCs, 4 units of FFP, and 2 units of platelets per order of the trauma surgeon. His Hgb = 12.0 g/dL, Hct is 36.2%. Arrangements are being made to transport JD to a level I trauma center for further care, with instructions to infuse 2 more units of PRBCs if needed en route. It is now 1.5 hours after the time of injury.

Which of the following interventions is best for JD?

A. Administer 6100 mcg of rFVIIa IV
B. Administer 1 g of TXA IV over 10 minutes, then 1 g over 8 hours
C. Infuse cryoprecipitate 10 units
D. Infuse 2 more units of PRBCs through the Level-1
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D. Infuse 2 more units of PRBCs through the Level-1
What is the mechanism of action of tranexamic acid (TXA) for the treatment of trauma-induced hemorrhage?

A. Inhibiting the binding of plasmin to fibrin clots
B. Enhancing the conversion of fibrinogen into fibrin
C. Inducing the activation of factor VII
D. Inhibiting tPA from binding to plasminogen
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Treatment of Drug-Related Hemorrhage
Background

- Anticoagulants are commonly used medications for multiple medical conditions.

- Life-threatening complications include:
  - Intracranial hemorrhage
  - Gastrointestinal bleed
  - Need for urgent surgery or procedure requiring reversal of anticoagulation

- New agents in clinical trials may provide new antidote therapy for DOACs.
Review of Coagulation Cascade

[Diagram showing the coagulation cascade]

Antiplatelet-Induced Bleeds

- Aspirin, clopidogrel (Plavix®), ticagrelor (Brilinta®), prasugrel (Effient®), NSAIDs
- No specific antidote for antiplatelet agents
- Management:
  - Supportive therapy
  - Platelet transfusion may be considered for severe bleeds
  - Desmopressin (DDAVP) may be considered
    - 0.3-0.4 mcg/kg IVPB over 30 minutes
  - MOA: Increases plasma levels of factor VIII activity in hemophilic individuals and patients with von Willebrand's disease type I

Warfarin (Coumadin®)

- Vitamin K antagonist
- MOA:
  - Competitive inhibition of vitamin K epoxide reductase complex (VKORC1)
  - Reduces synthesis of vitamin K-dependent clotting factors (Factors II, VII, IX, X)
- Indications:
  - Prevention/treatment of VTE
  - Prevention of embolic complications from atrial fibrillation or cardiac valve replacement
- Monitoring: INR

Warfarin Reversal Strategy

- **Antidote: Vitamin K**
- **Mechanism:** promotes liver synthesis of vitamin K-dependent clotting factors (II, VII, IX, X)
- **Dosing:**
  - Variable; based on INR and presence of bleeding
  - Generally 2.5-10 mg
- **Administration:** PO, IV
  - IV: administer via slow IV infusion; monitor for anaphylactic reactions
  - Do NOT administer IM

<table>
<thead>
<tr>
<th>INR Level</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR 4.5-10</td>
<td>Suggest against the use of vitamin K</td>
<td>2B</td>
</tr>
<tr>
<td>No evidence of bleeding</td>
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<tr>
<td>INR &gt;10</td>
<td>Oral vitamin K</td>
<td>2C</td>
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<td>No evidence of bleeding</td>
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<td>Major bleeding at any</td>
<td>Rapid reversal with 4-factor PCC</td>
<td>2C</td>
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<tr>
<td>INR</td>
<td>Vitamin K 5-10 mg IV</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4-factor PCC (Kcentra®)

- **Prothrombin complex concentrate (PCC)**
  - Factors II, VII, IX, X, protein C, protein S
- **Indication:** vitamin K antagonist reversal in patients with acute major bleeding or urgent need for surgery/invasive procedures
- **Dosing:**

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>2 - &lt;4</th>
<th>4-6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (units of factor IX) per kg body weight</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose (units of factor IX)</td>
<td>2500</td>
<td>3500</td>
<td>5000</td>
</tr>
</tbody>
</table>

4-factor PCC (Kcentra®)

- **Administration:**
  - Administer reconstituted product via IV infusion at a maximum rate of 210 units/min

- **Contraindications:**
  - Disseminated intravascular coagulopathy (DIC), heparin-induced thrombocytopenia (HIT) – contains heparin, known hypersensitivity
Patient Case

- AB – 53 year old Hispanic female (70 kg) presented with a chief complaint of ground-level fall; struck her head
- History of multiple ischemic strokes, on warfarin 5 mg PO daily
- Head CT revealed a large right cerebellar intraparenchymal hemorrhage
- INR=13.55 upon admission

- Options for AB?
Is 4-factor PCC indicated in this patient?

- Yes
- No
Is 4-factor PCC indicated in this patient?

- Yes
- No
What is an appropriate dose of 4-factor PCC (Kcentra®) for this patient?

A 5000 units  
B 1750 units  
C 3500 units  
D 2450 units
What is an appropriate dose of 4-factor PCC (Kcentra®) for this patient?

A 5000 units
B 1750 units
C 3500 units
D 2450 units
Is IV vitamin K indicated in this patient?

- Yes
- No
Is IV vitamin K indicated in this patient?

- Yes
- No
Is IV TXA indicated for this patient?

✅ Yes
❌ No
Is IV TXA indicated in this patient?

☐ Yes

☒ No (lack of evidence for trauma patients to receive both PCC and TXA)

☒ Severe drug-drug interaction between agents
Target-Specific Oral Anticoagulants

- Target-specific/direct oral anticoagulants (DOACs)
  - Direct thrombin inhibitors
    - Dabigatran (Pradaxa®)
  - Factor Xa inhibitors
    - Rivaroxaban (Xarelto®)
    - Apixaban (Eliquis®)
    - Edoxaban (Savaysa®)

- Indications:
  - Venous thromboembolism prophylaxis* and treatment
  - Nonvalvular atrial fibrillation (stroke and systemic embolism prevention)

*Edoxaban, dabigatran not FDA approved for VTE prophylaxis in U.S.
Direct Thrombin Inhibitor

- **Dabigatran (Pradaxa®)**
- **Mechanism of action:**
  - Reversible direct thrombin inhibitor
  - Inhibits free and fibrin-bound thrombin
- **Monitoring:**
  - No routine monitoring necessary

A patient presents with tarry stools and hematemesis after starting dabigatran two weeks ago for atrial fibrillation. How would you best manage this patient's bleeding?

A. IV vitamin K
B. Idarucizumab
C. PCC/aPCC
D. Dialysis
A patient presents with tarry stools and hematemesis after starting dabigatran two weeks ago for atrial fibrillation. How would you best manage this patient’s bleeding?

A. IV vitamin K – no role
B. Idarucizumab – may consider
C. PCC/aPCC – limited data
D. Dialysis – may consider
Dabigatran Reversal

- Early administration of charcoal may reduce absorption
- Hemodialysis may be considered
- aPCCs and coagulation factors not routinely recommended or studied
  - Limited data for off-label use of PCC (KCentra®) & aPCC (FEIBA®)
- New antidote – idarucizumab (Praxbind®)

Anti-inhibitor Coagulant Complex (FEIBA®)

- Activated prothrombin complex concentrate (aPCC)
- Factor Eight Inhibitor Bypassing Activity
- Contains mainly non-activated factors II, IX, X; mainly activated factor VII

Mechanism:
- Restores impaired thrombin generation of hemophilia patients with inhibitors

Off-label indication: life-threatening hemorrhage associated with dabigatran (case reports)
- No established dose, range 25-100 units/kg

Idarucizumab (Praxbind®)

- Monoclonal antibody fragment
- Binds free and thrombin-bound dabigatran with 350x affinity compared to thrombin
- Idarucizumab neutralizes the activity of dabigatran
- Nearly immediate and complete reversal of dabigatran without pro-coagulant effects
- Classified as a breakthrough agent
- ~$3500 per dose

RE-VERSE AD Trial

- Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD)

- Current status: Phase 3 trial, expected completion in 2017

- Patient population: adults (≥18 years old) taking dabigatran
  - Group A: uncontrollable or life-threatening bleeds
  - Group B: requiring invasive procedure or surgery

- Treatment: 5 g IV idarucizumab
  - 50 mL bolus x 2 (each containing 2.5 g idarucizumab)
  - Administered no more than 15 minutes apart
  - Rapid IV infusion over 5-10 minutes

RE-VERSE AD Trial

❖ **Primary endpoint:**
  - Maximum percentage reversal of dabigatran’s anticoagulant effect within 4 hours

❖ **Secondary endpoints (clinical outcomes):**
  - Group A
    - Extent of bleeding and hemodynamic stability
    - Outcome of patients with intracranial hemorrhage
  - Group B
    - Degree of hemostasis during the intervention
    - Thrombotic events or deaths

RE-VERSE AD Trial

- **Preliminary results:** (n=90 patients)
  - Median maximum % reversal (Groups A and B) = 100%
  - Rapid and complete reversal of anticoagulant activity in 88-98% of patients assessed
  - Median time to cessation of bleeding = 11.4 hours

- **Limitations:**
  - Lack of control group

Factor Xa Inhibitors

- Rivaroxaban (Xarelto®), apixaban (Eliquis®), edoxaban (Savaysa®)

- Mechanism of action:
  - Inhibit platelet activation and fibrin clot formation through direct inhibition of factor Xa

- Monitoring:
  - No routine monitoring necessary

Reversal Strategies – Factor Xa Inhibitors

- No FDA approved antidote for factor Xa inhibitors
- Human and animal trials have shown potential benefit of PCC administration
- New antidote – **andexanet alfa**
  - Benefit in LMWH & fondaparinux bleeds?

Andexanet Alfa

- Modified recombinant factor Xa
- Binds to direct factor Xa inhibitors
- Phase II: andexanet alfa decreased anti-factor Xa activity in a dose-dependent manner
- Classified as a breakthrough agent – NOT FDA approved YET

Connolly, et al. Andexanet alfa for acute major bleeding associated with Factor Xa inhibitors. NEJM.2016 [Epub ahead of print]
ANNEXA-A and ANNEXA-R

- Phase III: 67 pts with acute major bleeding within 18 hours of factor Xa inhibitor; 400 or 800 mg IV bolus, & 800 or 960 mg infusion (depending on last dose of Xa inhibitor)

- Preliminary results:
  - Rapid and sustained near reversal of factor Xa inhibitors with bolus dosing of IV andexanet alfa and/or followed by continuous infusion
  - **Near complete reversal** of factor Xa inhibition (89-93%)
  - Effective hemostasis in 79% of pts

- Limitations:
  - Reversal of factor Xa activity ≠ improved clinical outcomes
  - Concern for potential immunogenicity

Connolly, et al. Andexanet alfa for acute major bleeding associated with Factor Xa inhibitors. NEJM.2016 [Epub ahead of print]
Potential Reversal Strategies

- Dabigatran
  - Activated charcoal
  - Hemodialysis
  - aPCC
  - Idarucizumab
  - Supportive therapy

- Factor Xa inhibitors
  - Activated charcoal
  - Hemodialysis ineffective
  - aPCC
  - Supportive therapy
  - Eventually,andexanet alfa…

(True or False)
Andexanet alfa has shown complete rivaroxaban reversal in clinical trials.

✅ True
❌ False
Non-specific antidote – Cirpatantag (aripazine; PER977)

- Phase II trial assessing edoxaban reversal
- Small synthetic molecule
- Combines directly with UFH, LMWH, and other anticoagulants (including DOACs) to neutralize their effects in animal studies
- Further studies are needed to assess safety and efficacy
- Phase III trial planned for this year

Key Takeaways

- **Key Takeaway #1**
  - Trauma-induced coagulopathy contributes to hemorrhage, exsanguination, and death.

- **Key Takeaway #2**
  - Resuscitation with IV fluids and blood products is critical for treating severe trauma-induced hemorrhage, but finding the right amounts of each can be challenging.

- **Key Takeaway #3**
  - Future confirmation into effectiveness of TEG-monitoring and how it impacts therapeutic decisions

- **Key Takeaway #4**
  - Tranexamic acid should be administered early in the time course for patients experiencing significant hemorrhage from trauma.
Key Takeaways

❖ Key Takeaway #5
  • Anticoagulant-induced severe bleeding and/or the need for emergent surgery requires urgent reversal of drug therapies

❖ Key Takeaway #6
  • Existing management strategies and antidotes depend on the specific agent and mechanism of action

❖ Key Takeaway #7
  • New agents (idarucizumab, andexanet alfa, ciraparatantag) may serve as life-saving antidotes for DOACs
Thanks for listening!
References (Trauma-Induced Hemorrhage)

- Alam, HB. To TEG, or not to TEG: that is the question. *Ann Surg.* 2016;263:1060-1.
References

References

- Hunt H, et al. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding. *Cochrane Database of Systemic Reviews*. 2015;2
References

References

References (Drug-Related Hemorrhage)


References


