All Bleeding Stops... Eventually

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Hemorrhage

• Uncontrolled hemorrhage remains the leading cause of preventable death in trauma
• Coagulopathy of trauma is present at time of admission in 25% of patients and associated with a 5 time higher mortality
• Traumatic coagulopathy is multifactorial
Combination of massive tissue injury and shock results in early coagulopathy

Field resuscitation of high chloride containing crystalloids at room temperature exacerbate by inducing acidosis, hemodilution and hypothermia with further alterations in platelet function, fibrinolysis, and endothelial function
ATLS classification of hypovolemic shock

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>CLASS I (MILD)</th>
<th>CLASS II (MILD)</th>
<th>CLASS III (MODERATE)</th>
<th>CLASS IV (SEVERE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate blood loss</td>
<td>&lt;15%</td>
<td>15-30%</td>
<td>31-40%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Heart rate</td>
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<td>↑</td>
<td>↑↑↑</td>
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<tr>
<td>Blood pressure</td>
<td>--</td>
<td>--</td>
<td>↑↑↑</td>
<td>↓</td>
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<tr>
<td>Pulse pressure</td>
<td>--</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>--</td>
<td>--</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Urine output</td>
<td>--</td>
<td>--</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td>--</td>
<td>--</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Base deficit</td>
<td>8 to -3 mEq/L</td>
<td>-2 to -6 mEq/L</td>
<td>-6 to -10 mEq/L</td>
<td>-10 mEq/L or less</td>
</tr>
<tr>
<td>Need for blood products</td>
<td>Monitor</td>
<td>Possible</td>
<td>Yes</td>
<td>Massive Transfusion</td>
</tr>
</tbody>
</table>

Resuscitation

- Judicious IVF volume
- Permissive hypotension
- Early use of blood and blood products
- Management of coagulopathy
- TXA
- Control source of hemorrhage
Resuscitation

- Advocate for 1:1:1
- May not be realistic for some centers

- Goals of resuscitation/MTP:
  - HGB > 10g/dL
  - PT < 18 seconds
  - aPTT < 35 seconds
  - Platelet count >150
  - Fibrinogen level >180g/L

Whole Blood

- Used in military settings with patients 10x more likely to survive than those who don’t receive it after correcting for injury severity
- Warm whole blood not FDA approved for civilian use primarily due to the fact that absence of pathogens cannot be confirmed prior to transfusion
- Cold whole blood stored at 1-6 C being studied and considered fresh if transfused within 48 hours. It can be stored in solution for up to 21 days and if adenosine is added can be stored for 35 days
- Research ongoing in regards to leukoreducing the blood, how to manage emergency transfusion to women of childbearing age with unknown Rh status and the need to transfuse low titer blood when using O type as a universal donor as well as whether whole blood from women can be utilized due to concerns about TRALI
• Replaces all coagulation factors
  – Hemostasis usually requires factor levels ~30%
  – Factor IX may only reach 20%
• Obtained from whole blood and frozen at -20°C within 8 hours of donation
• Can be stored for up to 1 year
• Takes 30 minutes to thaw and not optimal for 1:1:1
• Thawed FFP often used for massive transfusion as it is immediately available and can be stored for up to 5 days

• Liquid plasma now being used at some trauma centers
• Never frozen and can be stored for 26 days
• Avoids factor degradation associated with the freeze-thaw cycle
• Some reduction in Factors V and VIII but the hemostatic efficacy remains stable throughout storage time
**Dried Plasma**

- Produced by lyophilization, freeze drying or spray drying creating a powder that can be stored and reconstituted with water as needed in nearly any environment
- Ideal for prehospital, austere, rural or wartime scenarios
- In early FDA trials
- German and French products being used by US Special Forces medics

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**Prehospital Plasma**

- Prehospital Air Medical Plasma (PAMPer) Trial
  - Severe hypotension (SBP <70) or hypotension (SBP < 90) and tachycardia (HR >108)
  - 2u thawed plasma completely transfused prior to any other IVF
  - 13 of 27 air transport teams carried 2u RBC to be given if persistent hypotension or obvious bleeding
  - 30 day mortality 9.8% lower in those receiving prehospital plasma
- Number needed to treat is 10 to save 1 life
Cold Stored Platelets

- Platelets currently stored at 22C with gentle agitation for no longer than 5 days
- Storage time limited due to risk of bacterial infection
- Cold storage of platelets abandoned in 1970s due to evidence that room temp stored platelets would survive in circulation longer
- Recent work by the US Army Institute of Surgical Research reveals cold storage at 4C exhibit increased aggregation, more rapid clot formation and increased clot strength as well as increased platelet activation markers but decreased release of pro-inflammatory markers
- Can be stored for much longer and produce improved hemostasis
- Could be advantageous for rural and austere conditions

Cryoprecipitate

- Prepared from plasma
- Stored frozen and must be transfused within 6 hours of thawing
- Contains fibrinogen, von Willebrand factor, factor VIII, factor XIII and fibronectin
- Transfuse when fibrinogen levels < 100mg/dL
- Most institutions use a standard dose of 10 units
• Anti-fibrinolytic drug with evidence that it reduces blood loss and transfusion requirement in perioperative situations including cardiac, orthopedic, oral, gynecology and urologic surgeries with no apparent increase in vascular occlusive events

• Acts in a reversible and competitive manner to plaminogen and the blocking results in a reduced affinity of plasminogen to bind to fibrin resulting in a reduced plaminogen to plasmin conversion

• Potentially beneficial in trauma patients as it prevents the development of DIC associated with the fibrinolytic phenotype

• CRASH-2 trial 2010
  – 20,2011 patients, 274 hospitals in 40 countries
  – Adult trauma patients who were within 8 hours of injury with significant hemorrhage or considered to be at risk of significant hemorrhage
  – Overall benefit seen if given within 3 hours of injury and SBP < 80 mmHg, with moderate or penetrating TBI
  – No difference seen in blood product transfusion or surgery
  – Limitations of overpowered study, bleeding still the cause of death in 5% of the patients, most countries were low income with limited resources, no specific transfusion protocols, no information regarding ISS or coagulopathy
• MATTERs trial (Military Application of TXA)
  – 896 military patients at a single facility in Afghanistan
  – Reported lower in hospital mortality but no difference in 24 hour mortality
  – Higher requirement for pRBC/FFP/platelets/cryo
  – Higher rate of DVT

• If you are going to give:
  – 1g IV within 6 hours, best within 3 hours of injury
    • Administer over 10 minutes
    • If bolused in the field, follow up infusion of TXA 1g over 8 hours at time of admission
  – Has been added to 2018 ATLS
Anticoagulant/Antiplatelet Agents

• Indicated for prevention of arterial and venous thromboembolic events
• Atrial fibrillation currently affects 2.3 million people in the US and they are at a fivefold increase risk for stroke with oral anticoagulants reducing this risk by two-thirds
• Individuals 65 or older make up only 15% of the general population but undergo ~40% of all surgical procedures performed

Anticoagulants/Antiplatelet Agents

• HISA-HT
  – Hold further doses
  – Investigate for bleeding source
  – Supportive treatment
  – Consider Antidote
  – Hemostatic measures
    • Local/topical agents, TXA, surgical intervention, IR
  – Transfusion
<table>
<thead>
<tr>
<th>NAMES</th>
<th>ELIMINATION HALF-LIFE</th>
<th>REMOVED BY HD</th>
<th>STRATEGIES TO REVERSE OR MINIMIZE DRUG EFFECT</th>
</tr>
</thead>
</table>
| Apixaban (Eliquis) -direct Xa inhibitor | 5-12 hours Longer in renal impairment | NO | Treatment- FACTOR Xa inhibitors  
• If ingested within 2 hours:  
  -Administer activated charcoal (consider within 6 hours)  
• In life-threatening situations:  
  -Consider 4-factor PCC (Kcentra)  
  50 units/KG (max 5000 units)  
• NOTES:  
  -Drug activity can be assessed with anti-factor Xa assay  
  -PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown |
| Rivaroxaban (Xarelto) -direct Xa inhibitor | Healthy 5-9 hours Elderly 11-13 hours Longer in renal impairment | | |
| Argatroban -direct thrombin inhibitor | 40-50 minutes =20% | | Treatment- turn off infusion  
• Notes: degree of reversal can be assessed with aPTT, ACT, and/or plasma-diluted thrombin time |
| Dabigatran (Pradaxa) -direct thrombin inhibitor | 12-17 hours Up to 34 hours in severe renal impairment | ~65% | Treatment  
• If ingested within 2 hours, administer activated charcoal  
• For life-threatening bleeding or emergency surgery, consider idarucizumab (Praxbind) 5mg IV  
Notes  
• Drug activity can be assessed with PT, INR, aPTT and/or plasma-diluted thrombin time  
• Idarucizumab will likely correct aPTT and plasma-diluted thrombin time, but the correction of the lab results with improved outcome is not established  
• Plasma Dabigatran concentrations can increase more than 12-24 hours after idarucizumab, likely due to re-distribution from the extravascular compartment  
• The risks and benefits of repeat idarucizumab administration is not known |
| Fondaparinux (Arixtra) -direct Xa inhibitor | 17-21 hours Longer in renal impairment | NO | Treatment  
• Consider recombinant factor VIII (Novoseven) 90mcg/kg however minimal evidence of efficacy  
Notes  
• Drug activity can be assessed with anti-factor Xa assay, PT and aPTT  
• rFVIIa will not affect the anti-factor Xa activity, but it will partially normalize the prolonged aPTT and PT |
### NAME ELIMINATION HALF-LIFE REMOVED BY HD STRATEGIES TO REVERSE OR MINIMIZE DRUG EFFECT

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</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>2.1 – 3.1 hours (IV)</td>
<td>~20%</td>
<td>Treatment</td>
</tr>
<tr>
<td></td>
<td>3 – 5 hours (SQ)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Longer in renal impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin (Lovenox)</td>
<td>2-4 hours IV</td>
<td>~20%</td>
<td>TREATMENT</td>
</tr>
<tr>
<td></td>
<td>4.5-7 hours SQ</td>
<td></td>
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<tr>
<td></td>
<td>Longer in severe renal impairment</td>
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</tbody>
</table>

#### Time since last dose of dalteparin
- **Dose of protamine for each 100 units of dalteparin with max single dose = 50 mg**

<table>
<thead>
<tr>
<th>Time since last dose of dalteparin</th>
<th>Dose of protamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 hours</td>
<td>1 mg</td>
</tr>
<tr>
<td>If the aPTT measured 2-4 hours after the first infusion remains prolonged, a second infusion may be given</td>
<td>0.5 mg</td>
</tr>
</tbody>
</table>

Note: Degree of reversal can be assessed with anti-factor Xa activity

#### Time since last dose of enoxaparin
- **Dose of protamine for each 1 mg of enoxaparin administered (Max single dose 50mg)**

<table>
<thead>
<tr>
<th>Time since last dose of enoxaparin</th>
<th>Dose of protamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 hours</td>
<td>1 mg</td>
</tr>
<tr>
<td>8-12 hours</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Or if the aPTT measured 2-4 hours after the first infusion remains prolonged, a second infusion may be given</td>
<td></td>
</tr>
<tr>
<td>&gt;12 hours</td>
<td>Unlikely to be beneficial</td>
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## NAME

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</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>30-90 minutes</td>
<td>Partial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Time since last dose of heparin</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Immediate</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>30 minutes - 2 hours</td>
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<td></td>
<td></td>
<td></td>
<td>&gt;2 hours</td>
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</tbody>
</table>

### Warfarin (Coumadin)

<table>
<thead>
<tr>
<th>NAME</th>
<th>TREATMENT</th>
<th>INR</th>
<th>CLINICAL SCENARIO</th>
<th>MANAGEMENT/REVERSAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;4.5</td>
<td>No bleeding</td>
<td>Hold warfarin until INR therapeutic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5-10</td>
<td>No bleeding</td>
<td>Hold warfarin until INR therapeutic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>May consider Vitamin K 2.5 – 5 mg PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;10</td>
<td>No bleeding</td>
<td>Hold warfarin until INR therapeutic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Give Vitamin K 2.5 mg PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consider Vitamin K 2.5 – 5 mg IV</td>
</tr>
<tr>
<td></td>
<td>ANY INR</td>
<td>Procedure requiring reversal</td>
<td>Hold warfarin</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Procedure start within 12 hours</td>
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<td></td>
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<td></td>
<td>-consider Vitamin K 5 – 10 mg IV</td>
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<td></td>
<td></td>
<td></td>
<td>Procedure start after 12 hours</td>
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<td></td>
<td></td>
<td></td>
<td>-consider Vitamin K 5 -10 mg PO</td>
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### INR >10

<table>
<thead>
<tr>
<th>NAME</th>
<th>TREATMENT</th>
<th>INR</th>
<th>CLINICAL SCENARIO</th>
<th>MANAGEMENT/REVERSAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-life-threatening bleeding</td>
<td>Hold warfarin</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Give Vitamin K 5 -10 mg IV</td>
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<td></td>
<td></td>
<td></td>
<td>Consider FFP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serious or life-threatening bleeding</td>
<td>Hold warfarin</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Give Vitamin K 5 -10 mg IV</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Give 4-factor PCC (KCentra)</td>
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<td></td>
<td></td>
<td></td>
<td>-INR 2 – 3.9: 25 units/kg (max 2500 units)</td>
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<td></td>
<td>-INR 4 – 6: 35 units/kg (max 3500 units)</td>
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<td></td>
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<td>-INR &gt;6: 50 units/kg (max 5000 units</td>
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<td></td>
<td></td>
<td>FFP may be used in place of Kcentra in non-life-threatening situations</td>
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</tbody>
</table>

**NOTE:**
- The effect of vitamin K can last for days or even weeks
- Vitamin K half-life range ~26-193 hours
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</tr>
</thead>
</table>
| Clopidogrel (Plavix) | 7 - 10 hours however drug effects are seen for 3 - 10 days after last dose due to the lifecycle of platelets | NO            | • PFA  
• 1 apheresis unit of platelets transfused initially with 0.3mcg/kg of desmopressin (DDAVP) and platelets are then transfused Q12 hour for the next 48 hours |
| And Prasugrel (Effient) |                                                                                       |               |                                                                                     |
| Ticagrelor (Brilinta)| 7 – 9 hours                                                                           | NO            | Is a reversible inhibitor so platelet function normalizes after drug clearance       |

**KCENTRA**

- 4 factor PCC
- Rapid reversal of warfarin in bleeding patients
- Must be given with Vitamin K IV when used for warfarin reversal
- Do NOT give a repeat dose
- Contraindicated in active HIT with thrombosis.
- Does contain a small amount of heparin
- Content:
  - Factor 2, Factor 7, Factor 9, Factor 10, Protein C and S, Heparin
KCENTRA

• Dose based on patient’s weight and INR
• Correction of Vitamin K antagonist - impairment of hemostasis is reached at 30 minutes after the injection and will persist for ~ 6 – 8 hours. However, the effect of Vitamin K if given simultaneously is usually achieved within 4 – 6 hours. Thus, repeat dosing with human 4-Factor PCC is not usually required

Hartford Consensus

• Formally known as The Joint Committee to Create a National Policy to Enhance Survivability from Intentional Mass Casualty and Active Shooter Events
• American College of Surgeons, Department of Homeland Defense, FBI, Police Departments and Committee of Tactical Combat Casualty Care
• Integrated response directed primarily at the control of life-threatening hemorrhage
• THREAT
• Threat suppression
• Hemorrhage control
• Rapid Extrication to safety
• Assessment by medical providers
• Transport to definitive care

Law enforcement officers represent first responders to each and every active shooter/intentional mass casualty event
• Hemorrhage control now needed as a core law enforcement skill
• Since October 2013, more than 225,000 law enforcement officers covering more than 85 million Americans are now capable of effective hemorrhage control
Hartford Consensus II

• A Call to Action
• The public—uninjured bystanders or minimally injured victims—can have a critical role as rescuers
• Promote the training of the general public in the techniques of hemorrhage control with a focus on the use of tourniquets, pressure dressings and hemostatic agents until transport and definitive treatment

Hartford Consensus III

• Continued emphasis on the role of the immediate responder— the inadvertent bystander— in controlling life-threatening external hemorrhage
• Window of opportunity to save a life by controlling major arterial bleeding from an extremity wound may be as short as 5 minutes
Hartford Consensus III

- Bystanders need to be trained and empowered
- Every bystander carries a set of tools at all times to control hemorrhage: his or her hands
- “See Something, Do Something”
- “Stop the Hemorrhage, Save a Life”

Hartford Consensus III

- A call for better equipment capabilities, better education and increased resources for communities
- White House National Security Council
- The Stop The Bleed Initiative
Hartford Consensus IV

• Building a national resilience by outlining strategies to educate the public to become immediate responders
• National survey to assess the public’s ability and willingness to serve as immediate responders
• Next focus is on enhancing citizen resilience and continued community training

Tourniquets

• ACS and U.S. Department of Transportation
• Tourniquets should be used in the pre-hospital setting for the control of significant extremity hemorrhage WHEN direct pressure is ineffective or impractical
• A tourniquet properly applied in the pre-hospital setting should not be released until the patient reaches definitive care
When Tourniquet is Appropriate

- Pulsatile or steady bleeding from the wound
- Blood is pooling on the ground
- Overlying clothes are soaked with blood
- Bandages and makeshift bandages used to cover the wound are ineffective and steadily becoming soaked with blood
- Traumatic amputation of the arm or leg
- Prior bleeding and the patient is now in shock
  – Unconscious, confused, pale

Teaching Points

- Waiting too long to apply is a mistake
- Apply just proximal to the site of the severe bleeding, never directly over a joint
- Tightened as necessary to stop the bleeding
- A second tourniquet can be applied proximal to the first to further control bleeding
- Recheck periodically to ensure the tourniquet is still working
- Write a T on the persons forehead and the time it was placed
• Needs to be an effective arterial tourniquet and not an ineffective venous tourniquet as this will cause an increase in bleeding
  – Not making the tourniquet tight enough
• Using for minimal or minor bleeding
• Waiting too long to apply
• Not re-evaluating
• Periodically loosening
Hemostatic Agents

• Topical hemostatic agents should be used in combination with direct pressure for the control of significant hemorrhage in the pre-hospital setting when sustained direct pressure is ineffective or impractical

• Topical hemostatic agents in a gauze can be used to enhance wound packing