The Bleeding Trauma Patient
Objectives

- Define Shock, mostly as it relates to bleeding
- Options and evidence for tools of resuscitation
- Understand a little about coagulation and coagulopathy
- 1:1:1
- “New advances”
Definition of Shock

- Reduced perfusion of vital organs leading to inadequate oxygen and nutrients necessary for normal tissue and cellular function. (1,5)

- Cellular level:
  - Reduction of mitochondrial oxygen
  - Anaerobic glycolysis of ATP
  - Accumulation of pyruvate
  - Lactic Acidosis
“Normal Vital Signs” DO NOT EQUAL ADEQUATE PERFUSION

MAP = 75

MAP = 55
“Normal Vital Signs” DO NOT EQUAL ADEQUATE PERFUSION

\[ Q = \frac{\pi \Pr^4}{8\eta l} \]
Acidosis
“Shock”
- Le Dran, 1731: *secousse* (jarring)
- Sparrow: “shock”

1920 Blalock showed that shock after trauma was due to blood loss
- Bluntly traumatize dog’s legs
- Increased weight in the legs showed enough blood volume loss to account for the shock.
History

- Hardaway (Ann Surg 1963)
  - Porcine Model
  - Trauma alone to one thigh produced no mortality.
  - Hemorrhage alone to 40mm hg systolic for 4hrs produced zero mortality.
  - Combined trauma *and* hemorrhagic shock produced 91% mortality

- Vietnam Wound Analysis (J. Trauma 1978)
  - Soldiers often died of shock despite being adequate treated with IV fluids and appropriate surgical procedures.
History

- Hardaway (1990 Crit Care)
  - Pig Study
  - 60 blows to each thigh
  - Produced 100% mortality within 48hrs
    - Even though normal blood volume was maintained with IV fluids.
  - Pigs died of DIC and ARDS
Shock

- More complicated
- Trauma
- +
- Bleeding
- +
- Trauma
- =
- DIC & ARDS = DEATH
Sources of hemorrhage

- Chest
- Abdomen
- Retroperitoneal
- Muscle compartments
- Street
## Classes of acute hemorrhage*

<table>
<thead>
<tr>
<th></th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood loss</strong></td>
<td>&lt; 750 cc 0-15%</td>
<td>750-1500 15-30%</td>
<td>1500-2000 30-40%</td>
<td>&gt;2000cc &gt;40%</td>
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<tr>
<td><strong>HR</strong></td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td><strong>PP</strong></td>
<td>Normal</td>
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<td><strong>BP</strong></td>
<td>Normal</td>
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<tr>
<td><strong>UOP</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
<td>Negligible</td>
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<tr>
<td><strong>Mental</strong></td>
<td>Normal</td>
<td>Anxious</td>
<td>Confused</td>
<td>Lethargic</td>
</tr>
<tr>
<td><strong>Fluid</strong></td>
<td>Crystalloid</td>
<td>Crystalloid</td>
<td>Crys+blood</td>
<td>Crys+blood</td>
</tr>
</tbody>
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*ATLS; 2004. 70kg male*
 Fluids

- Wiggers 1950s: Animal models (7,8,9)
  - Blood taken out through a catheter until set blood pressure was reached.
  - Re–Administration of shed blood did not improved morbidity and mortality.
Shires 1970s$^{(7,8,9)}$:
- Large extracellular fluid deficit was greater than could be attributed to vascular refill alone.
- Only infusion of both shed blood and lactated ringers to replace the ECF deficit showed improved outcome.
Fluids

- “Third space” loss into interstium and tissues
  - 3:1 rule of crystalloid for every 1 ml of blood loss

- ATLS: 2 liters of crystalloid through large bore IV for early treatment of hemorrhagic shock.
Resuscitation

Vigorous fluid resuscitation
Hemodilution increased
Recurrent Hypotension
“Injection of a fluid that will increase blood pressure has dangers in itself ... If the pressure is raised before the surgeon is ready to check any bleeding that might take place, blood that is sorely needed may be lost.”

Cannon, JAMA 70:618–621, 1919
Early Advice about IV Fluids

“Injection of a fluid that will increase blood pressure has dangers in itself ... If the pressure is raised before the surgeon is ready to check any bleeding that might take place, blood that is sorely needed may be lost.”

Cannon, JAMA 70:618–621, 1919
Permissive Hypotension

- Dogma has come under question for *uncontrolled* hemorrhage.
  - Shires and similar animal models:
    - Controlled hemorrhage (8)
  - Newer animal and human resuscitation studies
    - Uncontrolled hemorrhage
  - **Permissive hypotension**
Permissive Hypotension

- **Bickell** (8)
  - Porcine model
  - Aggressive replacement of blood loss with three times the volume of crystalloid
  - *Increased* hemorrhage and *decreased* survival.

- **Stern and Kowalenko** (19)
  - Pigs bled through femoral catheter and aortotomy
  - Resuscitated to systolic blood pressure of 40, 60, 80mmHg.
  - Most bleeding and highest mortality occurred in the 80mmHg group.
Permissive Hypotension

Riddez (12)
- Dog aortotomy
- 4 resuscitation groups
  - No fluid
  - 1:1 replacement blood loss with LR
  - 2:1
  - 3:1
- Aortic blood flow and blood loss increased with the amount of fluid used
- Highest mortality in no fluid and 3:1 fluid group
Permissive Hypotension

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Permissive Hypotension

- **Riddez** \(^{(12)}\)
  - Dog aortotomy
  - 4 resuscitation groups
    - **No fluid** \(\rightarrow\) shock
    - 1:1 replacement blood loss with LR
    - 2:1
    - **3:1** \(\rightarrow\) Rebleeding
  - Aortic blood flow and blood loss increased with the amount of fluid used
  - Highest mortality in **no fluid** and **3:1** fluid group
Bickell & Mattox (NEJM 1994)

- Randomized prospective trial of 598 patients with penetrating torso injuries
- Immediate vs delayed resuscitation group
- Immediate group average of 900ml LR
- Delayed group 100ml

- Better survival to discharge rate (70% vs. 62% p=0.04)
- Fewer overall complications.
Permissive Hypotension

- Delaying massive fluid resuscitation until the time of surgery prevents:
  - Exacerbating uncontrolled internal hemorrhage
  - Clot dissolution / “popping the clot”
  - Dilution of clotting factors
  - Hypothermia
Permissive Hypotension

- Caveats
  - Brain injury
    - CPP=MAP–ICP
    - SBP>100 mmHg
  - Fast evacuation to definitive surgical care
  - Unclear results for non-penetrating trauma
  - Elderly patients
Fluids

- Blood
- Crystalloid
- Colloid
- Hypertonic saline
LR vs. NS

- Lowery 1971 (Surg Gynecol Obstet)
  - Vietnam war study LR v NS
  - Healthy soldiers
  - No difference in outcome
LR vs. NS

- Waters 2001 (Aneth Analg)
  - Patients undergoing aortic aneurysm repair
  - NS
    - More volume (~500–1000ml)
    - Hyperchloremic acidosis
    - Dilutional coagulopathy

- Todd (J. Trauma 2007; 62:636–9)
  - Swine bled via liver injury & resuscitated to MAP 90mmHg
  - NS
    - More volume
    - Hyperchloremic acidosis
    - Dilutional coagulopathy
Conclusion
  ◦ No mortality difference
  ◦ LR
    • Lower overall volume
    • More buffering capacity
  ◦ NS
    • Metabolic acidosis
    • Dilutional coagulopathy
  ◦ Preferred fluid outside of US
  ◦ Probably no difference for prehospital or early fluid resuscitation.
Isotonic crystalloids

Advantages
- Cheap
- Easy to store and warm
- Established safety
- Predictable rise in cardiac output

Disadvantages
- Large volumes needed
- Dilutional coagulopathy
- Increase cytokine activation
- No oxygen carrying capacity
- May Increase ICP
Colloids

Proposed Benefits (15)

- Smaller volume
  - Less pulmonary edema
- Stays in the intravascular space
  - Quicker return to normal hemodynamics
- Smaller package
- Antioxidant and anti-inflammatory effects
Disadvantages (16)
- Transmission of diseases
- Increased bleeding
- Hypersensitivity reactions
- Renal failure
- Accumulation
  - Taken up by RES
  - Dose limit (20–50mL/kg)
- Cost
Colloids

- Schierhout and Robertson; BMJ 1998
  - 30 total studies, 7 trauma studies
  - Albumin, dextran, gelatin v Crystalloid
  - Colloids associated with 4% increased risk of mortality

- Cochrane meta analysis; BMJ 1998
  - 63 trials total; 4 trauma studies (1977, 1978, 1983)
  - Albumin, 23 trials; Hydroxyethyl Starch (HES), 16 trials; Gelitin, 16 trials; Dextran, 9 trials
  - 6% increased mortality
  - Albumin “kills our patients” (1 out of 17)
Colloids

- Wilikes (2001 Ann Int Med)
  - 27 studies: trauma and surgical pts
  - Albumin v crystalloid
  - No effect of albumin on mortality

- Choi et al. (1999 Crit Care Med)
  - All kinds of colloids v crystalloids
  - No difference in mortality
Colloids

Cochrane Review 2006

“As colloids are not associated with improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use can be justified outside the context of RCTs.”
- Double blind RCT, 7000 pts, 16 ICUs, 18 month period
- 4% albumin v 0.9% normal saline
- First 4 days volume albumin to saline (1:1.4)
- No difference in 2 groups in 28 all day cause mortality
- Sub group analysis: difference between trauma and sepsis patients
  - RR of death pts with severe sepsis = 0.87
  - Overall trauma mortality higher for albumin v saline (13.5% v 10%)
    - TBI separated, no difference in mortality
  - SAFE brains study proposed
Conclusion

- Most studies do not show reduction of mortality
- Possible risk of increased mortality
- Increased cost
- Routine use of colloids not supported in Trauma
- May be beneficial in Septic patients, SBP, ARDS
- Promise with HES and newer colloids (16)
- Further RCT trials needed
Hypertonic Saline

- Rapid plasma volume expansion (17)
  - Pull of fluid to vascular space secondary to increased concentration gradient
- Decreases ICP
  - Potential benefits in TBI patients
- Military use
  - Weighs less
    - 1 liter NS bag = 2744 cm³ in volume and 1.1 kg
  - Storage space for helicopters and ground ambulances
Hypertonic Saline

- Adverse effects
  - Hyperosmolar coma
  - Hypernatremia
  - Seizures
  - Arrhythmias
  - Tissue necrosis
  - Allergic reactions
Hypertonic saline

- Australian prehospital study (JAMA 2004)
  - Double blind prospective RCT, 229 pts
  - SBP<100
  - Blunt head trauma
  - Excluded polytrauma pts
  - HTS v LR
  - Conclusion
    - Both groups received same volume of fluids
    - No difference in survival, length of stay, neurologic outcome
Wade et al; 1997 meta analysis
- 11 studies
- Hypertonic saline alone and with dextran v isotonic saline
- No difference for HS v isotonic saline
- HSD showed slight improvement in survival
  - Especially with TBI pts and penetrating injuries
Blood Disadvantages

- Cost
- Compatibility/error\textsuperscript{18}
  - Incorrect blood\textendash{}1:40,000 (death 1:2million)
- Immune complications\textsuperscript{18}
  - 1:40,000
- Infection\textsuperscript{19}
  - Sepsis 1:500,000 (RBCs) 1:50,000 (platelets)
  - Hep B 1:250,000
  - Hep C & HIV 1:2million
- Storage requirements
- Citrate toxicity
- Hypocalcemia
- Hyperkalemia
Clotting takes time (2–10 minutes in the best of circumstances)
Clots are physically weak
There is limited clotting material to work with (even in the whole body)
- 10 grams of fibrinogen total
- 15 mL of platelets total in normal individuals
Human blood clotting is weak because it has to be!

- Ten times more people die from clotting than from bleeding (heart attacks, strokes, pulmonary emboli, etc).
- Moderate bleeding is an uncommon event, but clotting is a continuous threat.
- The body evolved to deal with bruising and minor to moderate bleeding.
Bleeding

- Blood loss (volume) = area x rate x time
- Area is determined by the extent of initial injury or the need for surgical exposure.
- Rate of blood loss is a function of the tissues involved and the blood pressure
- Time of bleeding is a function of the rate of blood loss with subsequent fall in blood pressure, the rate of blood coagulation, and the effect of interventions
CLOT
The Classic Coagulation Cascade

Intrinsic Pathway tested with the PTT

MacFarlane, Nature 1964
Davie & Ratnoff, Science 1964

Extrinsic Pathway tested with the PT

Common pathway
Causes of Coagulopathy in the Massively Injured

- Loss
- Dilution
- Hypothermia
- Acidosis
- Consumption
- Fibrinolysis

Coagulopathy of Trauma

DIC
Figure 1. Causes of coagulopathy in trauma patients.
Acute Traumatic Coagulopathy

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

- Derangements in coagulation occur rapidly after trauma even after adjusting for ISS
- By the time of arrival at the ED, 1/3 of trauma patients had a coagulopathy associated with a poor outcome
Early Coagulopathy Predicts Mortality in Trauma

Method

Wire turns 4.75° back and forth. Clot elasticity but not blood viscosity torque the wire.

Normal values

\[ R = 6-8 \text{ min} \]
\[ R + K = 10-12 \text{ min} \]
\[ \alpha > 50^\circ \]
\[ MA = 50-70 \text{ mm} \]
\[ A_{60} = >85\% \text{ MA} \]
Normal values

\( R = 6\text{–}8 \text{ min} \)
\( R + K = 10\text{–}12 \text{ min} \)
\( \alpha = >50^\circ \)
\( \text{MA} = 50\text{–}70 \text{ mm} \)

\( A_{60} = >85\% \text{ MA} \)
\( F = >300 \text{ min} \) – \( F \) is a measure of the rate of clot lysis
TEG Patterns in Pathologic States
Recruitment of clotting activity by rVIIa in a trauma patient

- 17 y/o male shot in porta hepatis
- massive TX in course of damage control surgery
- TEGs before and after rVIIa show increased activity in plasma and platelet phases

**TEG before rVIIa**
- R = 11 min, a = 12°, MA = 12 mm

**TEG after rVIIa**
- R = 3.3 min, a = 60°, MA = 44 mm
A symposium held at the U.S. Army Institute of Surgical Research, 26–27 May 2005
If clinically evident coagulopathy is prevented by the early use of FFP, subsequent blood product consumption is likely to be less.

In massive transfusion, early 1:1:1
- PRBC : Plasma : platelets are indicated
Malone DL, Hess JR, Fingerhut A. Comparison of practices around the globe and suggestion for a massive transfusion protocol.

J Trauma, 2006

- Reviewed massive transfusion protocols from well-developed trauma systems in Denver, Houston, Helsinki, Sydney, and Baltimore.
- This group then presented a massive transfusion protocol based on the best data from their review.

  1:1:1
Effect of FFP : RBC Ratio on Overall Mortality in 252 Massively Transfused Trauma Patients (long term outcomes)

- Chi Square
  - RB: p=0.006
  - RG: p<0.001
  - BG: p=0.034

FFP : RBC Ratio

- 0:22 - 1:4: 65% (n=31)
- 1:3.9 - 1:2.1: 34% (n=56)
- 1:2 - 1:0.59: 20% (n=165)
Component Therapy vs. What we bleed

So Component Therapy Gives You
1U PRBC + 1U PLT + 1U FFP

• Hct 29%
• Plt 87K
• Coag activity 65%
• 950 mg fibrinogen

• Armand & Hess, Transfusion Med. Rev., 2003
Whole blood 500 mL
(Hct 38%–50%; Plts 150 K–400 K;
Plasma coagulation activity100%)

1 Unit PRBC
(335 mL, Hct 55%)

1 Unit Plasma
(275 mL, coagulation activity 80%)

1 Unit Platelets
(50 mL, 5.5 x 10^{10} plts)

150 mL anticoagulant added; centrifuged

Patient Receives 650 mL fluid:
Hct 29%, Plts 88 K, 65% coagulation activity
Hemostatic Resuscitation

- Act prior to the onset of coagulopathy
  - INR still normal
  - Less than 1 blood volume transfusion
- Strive to maintain clotting
  - Plasma (uncrossmatched?)
  - Platelets
  - Normothermia
  - Adequate HCT
Any fluid which does not clot or carry oxygen should be suspect.
FVIIa
The Ideal Hemostatic Agent

- Is easy to store and use
- Stops inappropriate hemorrhage
- Does not clot working vessels
- Has no side effects
- Is free
Recombinant human product
Facilitates cell-based coagulation, triggering thrombin burst on platelet surface
In large doses, requires only Factor I (Fibrinogen), II (Thrombin) and platelets to produce clotting
Licensed only for use in hemophiliacs with inhibitors to Factor VIII or IX, or patients with FVIIa deficiency
Change in PT

Prothrombin Time (sec)

Pre PT       Post PT
TEG Before and After FVIIa
Procedure

- “Off-label” use requested by attending physician
- Gatekeeper approval required
  - Life threatening hemorrhage
  - Coagulopathy
  - Failure of conventional therapy
  - Non-futile
- Periodic data analysis approved by the IRB

Dosing

- 100 mcg/kg
  - Shock
  - Rapid bleeding

- 1.2 mg (smallest possible dose)
  - No shock
  - Slow or no bleeding
Outcome

- 20% no response (futile)
- 80% response rate (hemostasis)
  - 50% die
    - Traumatic brain injury (average 5.5 day LOS)
    - Multiple organ system failure (average 32 day LOS)
  - 50% survive to discharge
- Overall survival about 40%

LOS, length of stay.
FVIIa is a potent pro–coagulant
Thrombotic complications will be highly patient dependant:
- Unstable atherosclerotic disease
- Blunt vascular injury (carotid, mesenteric arteries)
- Extracorporeal circulation
- Other pro–coagulants?
Probably not dose dependant!
Other “New Stuff”

- Looking into hemoglobin substitutes as oxygen carriers.
- Nothing FDA approved yet
- Hemostatic dressings, liquids, etc.
- Suspended animation
Summary

- All bleeding stops
- Try to stop the bleeding before the heart stops beating
- Resuscitate before a coagulopathy develops
- 1:1:1
- A little hypotension is a good thing
- Control the chaos
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