ACUTE COAGULOPATHY OF TRAUMA: BACKGROUND, THEORIES, UPDATES AND INNOVATIONS

WHY DO WE HAVE THIS TALK? BECAUSE THIS ISN’T GOING AWAY

INTRODUCTION

- Many of those that lose their blood volume before care is rendered will die as 40% of trauma deaths are associated with hemorrhage.
- This exceeds all other causes of death in persons <36 years old.
- Continued work in the field of trauma shows that the mechanisms in traumatic bleeding are different from what we have traditionally assumed.

COAGULOPATHY: OLD SCHOOL/NEW SCHOOL

- The understanding of the mechanisms of bleeding have exploded in the past decade.
- Teaching of the classic coagulation cascade has been integrated into the more dynamic cell based theory of coagulation.
- This knowledge has spilled into the trauma arena and has helped to develop theories for the Acute Coagulopathy of Trauma.

BEDSIDE TO BENCH: CELL BASED THEORY, IMPROVED RESUSCITATION.
INTRODUCTION

- First we must remember that ‘bleeding’ is not the same as ‘coagulopathy’.
- But coagulopathies that develop are obviously of paramount importance when dealing with the acutely injured individual.

Even for those who survive the initial traumatic insult, the physiologic sequela often leads to organ injury, sepsis and death.

Recently, a better understanding of the coagulopathy associated with trauma and its timeline have helped to change treatment for the most critical of patients.

SENTINEL ARTICLES OUT OF DH


TIMELINE OF TRAUMA THEORY:

- Early 1990s: Bloody Vicious Cycle
- Late 1990s: Damage Control Surgery and Cell based theory of coagulation
  - Staged Laparotomy
- Early 2000s: Damage Control Resuscitation via military outcome studies.
  - 1PRBC/1FFP/1plts
- Mid 2000s: ACOTS
- Late 2000s: Goal Directed Resuscitation

“BLOODY VICIOUS CYCLE”
CIRCA 1995

- Hemorrhage
- Coagulopathy
- Fluid Resuscitation with crystalloids
- Hypothermia

TRIAD OF DEATH

- This bloody vicious cycle creates what has been called the triad of death:
  - Acidosis
  - Hypothermia
  - Coagulopathy
EARLY FINDINGS

- The original papers dealing with the coagulopathy from in the 1990s found 4 major risk factors for developing a coagulopathy.
  - Ph<7.1
  - Core Temp< 34 degrees
  - ISS >25
  - SBP<70mmHg

- Patients with none of these risk factors on arrival had a less than 1% risk of developing coagulopathy.
- A single risk factor had a 10-40% risk of developing coagulopathy.
- Multiple risk factors increased this substantially

EARLY FINDINGS

- So some simple, observational science had come out of the traditional treatments used for the trauma patient. Not a lot of attention given to the hypotension on admission.
- The problem was that these coagulopathies were just thought to be the bad luck of the care rendered:
  - “massive transfusion that is used to treat hypovolemia leads to a coagulopathy itself.”

- ‘Damage Control’ surgery was the a theory coined in the mid-90s.
- Much of it born at Denver Health (DG)
- This grew out of a theory about how best to handle the Bloody Viscous Cycle.
- ‘... progressive coagulopathy is the most prevalent reason for staged laparotomy as the coagulopathy can often not be controlled in the OR.’

DAMAGE CONTROL RESUSCITATION

- ‘Damage Control Resuscitation’ was a phrase coined in the early 2000s.
- At the same time the development of the cell based theory of coagulation was taking hold in the scientific literature.
- Also, the military observational evidence about trauma patients noted that many of these critically injured patients were suffering from a coagulopathy when they arrived at the hospital.

- The massive injuries and the observation that these coagulopathies were present on arrival, started the wheels turning regarding looking for a new mechanism.
- Damage Control Resuscitation addresses the lethal triad at admission which was a much more proactive approach.

**DAMAGE CONTROL RESUSCITATION: IN A NUT SHELL**

- Resuscitation is limited to keep SBP about 90mmHg, not more, in an attempt to prevent renewal of bleeding from recently clotted vessels.
- Intravascular volume is replenished with FFP as a primary resuscitation fluid. Empiric FFP was given and Factor VII was given ‘as needed’.
- If the bleeding continued, a MTP was initiated with 6PRBCs/6FFP/6plts/10 cryo, and crystalloid was used basically as a carrier.
- The worst patients even received FWB.

**STOP AND THINK?**

- It seems simple now, but the theory had always been that coagulopathy was initiated by resuscitation, not endogenous.
- AKA ‘It’s Always Anesthesia’s Fault’.
- 7%-10% of Military combat injuries require massive transfusion vs. 1%-2% of civilian trauma.
- The severity of military injuries are much greater than in a civilian arena.

**MAYBE THERE IS SOMETHING TO THIS?**

- LR and NS increased reperfusion injury and leukocyte adhesion.
- Maybe standard pre hospital resuscitation guidelines were actually worsening the prehospital acidosis and coagulopathy?
- They certainly were being shown to increased the risk of ARDS, SIRS, MOF.

**DAMAGE CONTROL RESUSCITATION ORIGINS**

- But this is the military, in the real world ‘Damage Control Resuscitation’ was slightly different, but the point was to be proactive and address the coagulopathy earlier than we had before.
- Now the Anesthesiologist was much more active in the care of the trauma patient vs. ‘Just get them to the ICU’.
- What was great about this observation was the advent of the MTP.

**MTPS ARE FANTASTIC, EVERY HOSPITAL SHOULD HAVE ONE**

- But the liberal use of FFP has been shown to be harmful to patients and increase ICU days, MODS.
- The civilian arena had less acute coagulopathy patients than the military arena. The MTPs, while essential, were useful for a smaller group.
- But lessons from the use of MTP helped pave the way for individualized transfusion therapy.

**ACOT/ACOTS/ECT/ATC/TIC**

- Continued evaluation of the military trauma data confirmed that traditional dilutional explanations for coagulopathy in trauma are no longer sufficient.
- Coagulation was being shown to be an integral part of the inflammation cascade.
- ‘Acute Coagulopathy of Trauma’ has been confirmed (not just hypothesized) in 25% of trauma patients on arrival to the ED.
ACUTE COAGULOPATHY OF TRAUMA/SHOCK

IS THE PREDOMINATING PHRASE NOW

ACUTE COAGULOPATHY OF TRAUMA/SHOCK 'BLOODY VICIOUS CYCLE 2.0'

This coagulopathy is multifactorial:
- Tissue trauma
- Shock
- Hemodilution
- Hypothermia
- Acidemia
- Inflammation

ACOTS: TISSUE TRAUMA

- Tissue trauma initiates coagulation as endothelial damage in the area of injury leads to exposure of subendothelial Type III collagen and TF.
- The tissue factor or recombinant factorVIIa complex activates plasma coagulation proteases resulting in thrombin and fibrin formation

ACOTS: SHOCK

- A direct relationship has been found between the severity of tissue hypoperfusion and degree of admission coagulopathy as measured by PT/PTT.
- A base deficit >6 has also been associated with coagulopathy in 25% of patients.
- Platelets are ‘generally’ unaffected by shock.

- Patients without symptoms of shock have been found to have normal coagulation studies despite poor ISS scores.
- The shock state appears to make patients relatively anticoagulant and hyperfibrinolytic.
- This is theorized to be because of widespread endothelial disruption.
ACUTE COAGULOPATHY OF TRAUMA/SHOCK

- In combination, direct tissue trauma and shock with systemic hypoperfusion appear to be the primary factors driving the coagulopathy in the immediate post injury phase.

ACOTS: HEMODILUTION

- It can’t be ignored and is part of what we do during a resuscitation.
- Also, during the shock state, reduced intravascular hydrostatic pressure results in a shift of fluid deficient in coagulation factors from the cellular and interstitial spaces into the plasma.

ACOTS: HYPOTHERMIA

- Hypothermia inhibits coagulation protease activity and platelet function.
- TF or FVIIa complex decreases linearly with temperature, yet platelets are probably more sensitive to hypothermia as low temperature states decrease platelet activation.
- vWF traction on Glycoprotein Ib/IX, which mediates the signal transduction from initial adhesion to activation decreases precipitously.

ACOTS: ACIDEMIA

- Acidemia is common in the trauma patient especially if a low flow state also exists and excessive chloride has been given. Acidemia also leads to increased degradation of fibrinogen.
- The activity of FXa/Va complex is reduced 50% at pH7.2.

ACOTS: INFLAMMATION

- Trauma has also been shown to be an inducer of inflammation and SIRS.
- Endothelial activation and injury leads to activation of elements of the immune system.
- Activation of coagulation proteases can induce inflammation through transmembrane protease receptors on cell surfaces and complement activation.
ACOTS: INFLAMMATION

- Degranulating platelets also potentiate immune responses by activation of neutrophils.
- In turn, inflammation also leads to derangements of coagulation. Monocytes express tissue factor and can adhere to platelets at the site of injury disrupting the formation of a platelet plug.

PROTEIN C

- Tissue injury and Shock (together) have been shown to result in a decrease in Protein C and a ‘derepression’ of fibrinolysis.
- This is due to a very early activation of Protein C pathway, and a subsequent depletion of Protein C much earlier than expected.
- This loss of protein C has been associated with a loss of cytoprotectivity and further endothelial cell disruption.

CROSSTALK BETWEEN INFLAMMATION AND COAGULATION

SO THAT ALL SOUNDS BAD . . . MANAGEABLE, BUT BAD.

ACOTS: ‘WHEN GOOD TIMES GO REALLY BAD’

- Fibrinolysis is common after trauma and is a direct consequence of both tissue trauma and shock.
- Endothelial injury results in increased fibrinolysis because of direct release of tPA.

ACOTS: ‘WHEN GOOD TIMES GO BAD’

- Fibrinolysis is exacerbated in trauma because of the combined effects of endothelial tPA release from ischemia and inhibition of plasminogen activator inhibitor-1 (PAI-1). And fibrin monomers are more susceptible to cleavage by plasmin in the presence of reduced thrombin.
**HOW DO WE KNOW THIS?**


- What our group was able to confirm was that some form of fibrinolysis was associated with 46% of trauma patients who presented in need of transfusion.
- This fibrinolysis differentiated by severity into primary, transient, incidental.
- Watching in real time on the TEG, one could see the fibrinolysis and determine immediate therapy.

**ACOTS: ‘WHEN GOOD TIMES GO BAD’**

- For a localized injury this is protective, as the hyperfibrinolysis is presumably to limit clot propagation to site of the vascular injury.
- With wide spread injury and endothelial disruption, this localization is lost.

**APPLES AND ORANGES**

- Nearly all incoming severe trauma patients have ISTH scores that would denote DIC.
- But no pathologic evidence to support the diagnosis were found in studies as no microvascular thrombi were found within the first 24 hours.
- Treatment for the fibrinolysis of ACOTS is with antifibrinolics which are generally contraindicated in DIC.

**DIC**

- Early reduction in platelet count
- Drop in fibrinogen and increasing coagulation times.
- Major Consumption of factors V and VIII.

**ACOTS**

- Platelet count generally stable.
- Stabilized within 6 hours.
- Factor V dropped while VIII remained high.

**ACOTS: FIBRINOLYSIS TREATMENT**

- Through early TEG based studies the trauma community was able to recognize a need to emergently treat the fibrinolysis associated with ACOTS.
- In 2005-06 we initiated our use of Amicar (Epsilon-Aminocaproic Acid).
- It had previously not been universally adopted as most assumed this consumptive coagulopathy was a DIC like state.
CRASH II: Clinical Randomization of an Anti-Fibrinolytic in Significant Hemorrhage II Trial.
- 274 hospitals, 40 countries, >20,000 patients, 2005-2011.
- Randomized to TXA vs. Placebo.

TXA arm decreased 28 day mortality.
- Prompt Therapy initiation <1 hour – significant decrease in death due to bleeding
- 1-3 hours showed decrease yet not significant
- >3 hours > slight increase

Why:
- Treatment needs to be initiated early, as ACOTS changes over time into a procoagulant state where these drugs are unwarranted.
- Yet overall, as long as TXA was initiated within first 8 hours, the mortality decreased with no apparent increase in vascular occlusive events.

AMICAR/TXA
- Lysine analogs that are antifibrinolytic and inhibit both plasminogen activation as well as plasmin activity. They prevent clot breakdown vs. promoting new clot (DeNovo VII).
- TXA is 10X more potent than Amicar and had previously been associated with greater prothrombotic risks.

ACOTS: FIBRINOLYSIS TREATMENT DOSING
- Epsilon-Aminocaproic Acid (Amicar): 5 gram loading dose; infusion of 1 gm/hour.
- Tranexamic Acid (TXA): 1 gram loading dose; 1 gram/8 hours.

GOAL DIRECTED RESUSCITATION
- About the same time as CRASH II was finishing we published data regarding the success of POC testing to treat ACOTS.
- The use of r-TEG allowed us to maintain what we termed a ‘Goal Directed Resuscitation’, tailored to each patient.
- By adopting this philosophy, we were not bound by predetermined ratios put forth in the standard ‘Damage Control Resuscitation’ thinking.
GOAL DIRECTED RESUSCITATION

- r-TEG results have been known to come back up 30 minutes faster than conventional 'STAT' coagulation studies.
- Speed and a diligent tailored resuscitation by the anesthesia service was able to decrease our facility’s use of blood components while theoretically improving our patient care due to the decrease in products.

SUMMARY

- The ACOTS is a theory that has developed and taken root through advances in basic science and at the bedside.
- The cell based model opened the door for better understanding of the implications widespread endothelial injury.
- This lead to changes in thinking of how to care for these patients via Damage Control Surgery and Resuscitation.

TAKE HOME

- Hopefully the background and diagnosis of ACOTS has been elucidated.
- Every Hospital should have some form of MTP
- Not all places are fully prepared with POC testing for Goal Directed Resuscitation, but as seen in CRASH II early administration of antifibrinolytics has been shown to save lives.
- We have altered our protocol towards the use of TXA

QUICK SAMPLE CASE

- 48 Y.O. Female Run over 2x by "Monster Truck"
- 30 PRBcs/16FFP/1Cryo/2Plts
- 5 Grams Amicar

SUMMARY

- Clinical observations from the military theatre helped advance the theory of ACOTS and the need for MTPs worldwide.
- Work at our institution has helped to fine tune that proactive approach.
- With the aid of POC testing we have helped pioneer Goal Directed Resuscitation for the life threatening coagulopathy in the trauma patient.

THANKS
REMEMBER: THERE ARE NO FRIENDS (OR LECTURES) ON A POWDER DAY!!!!

Look up Grand rounds reading list for bibliography

ACOTS RELATED RESEARCH

RESEARCH: PLATELET MAPPING

- Platelet Mapping measures clot strength as Maximal Amplitude and enables a quantitative evaluation of platelet function by evaluating the contribution of adenosine diphosphate (ADP) and thromboxane A2 receptors to clot formation.
- This is done by the addition of platelet agonist to a patient sample before the TEG is run. Simply put these additives (ADP, or Arachadonic Acid) allow a measurement of percentage of platelet inhibition.
**PLATELET MAPPING: NEUROTRAUMA**
- Study out of DH (2013) shows possible improvement of care via ‘platelet mapping’ at the POC.
- Platelet mapping showed early platelet dysfunction to be prevalent after TBI.
- The formal mechanism responsible still remains to be elucidated.

**PROPOSED OBSTETRICS TRIAL AT DHHA**
- Multidisciplinary study with 4 Thrombelastogram blood draws at 4 specific times throughout pregnancy.
  - Initial visit
  - Triple Screen
  - Labor
  - 8 weeks post partum
- Will include sophisticated platelet mapping and the associated MA values.
- Endpoints of evaluating the changes in platelet function over the course of pregnancy.

**RESEARCH: FRESH WHOLE BLOOD**
- Certainly has had documented success on the battlefield.
- Civilian arena:
  - Storage, Testing, Utility.
  - Logistics, Logistics, Logistics.

**RESEARCH: R-TEG VS. COAGS**
- COMIRB# 10-0477 : “A Prospective, Randomized Comparison of rTEG and Conventional Coagulation Testing For Guiding the Diagnosis and Hemostatic Resuscitation of Trauma Patients at Risk for Post Injury Coagulopathy”
- Current Clinical study at DHHA. Evaluating Conventional Coagulation tests vs. rTEG guided therapy in Massive Transfusion patients.

**COMIRB# 10-0477**
- Draws at specific times including ‘field sticks’.
- Alternating weekly rotation of traumas being conducted at a single institution: Conventional Coag guided/ r-TEG guided.
- No head to head tests have been done with a single lab. Physicians send both tests but are blinded to one.

**RESEARCH: C.O.M.B.A.T.**
- COMBAT trial: Control Of Major Bleeding After Trauma.
  - The study is sponsored by the Department of Defense’s Telemedicine & Advanced Technology Research Center (TATRC) and is being conducted in collaboration with DHHA & University of Colorado.
  - AB-FP24 will be given in the field rather than crystalloid for major trauma.