After traumatic injury, if signs of shock are present, CONTROL THE BLEEDING FIRST, if at all possible. Hemorrhage control takes precedence over infusion of fluids.
Hemostasis

- The process by which bleeding stops

- Three inherent physiologic processes
  - Vascular constriction
    - Vessels constrict to slow bleeding
  - Platelet plug formation
    - Platelets get ‘sticky’ and plug hole
  - Coagulation
    - Proteins in blood combine to make ‘cement’ for platelet plug
Coagulation

- Protein ‘cement’
  - Prothrombin activator initiated by chemicals released by injured tissue
  - Prothrombin $\rightarrow$ thrombin
  - Thrombin causes Fibrinogen $\rightarrow$ fibrin
  - Fibrin strands help plug the primary platelet clot

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Coagulation

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Coagulation

- Clot retraction
  - More solid and pulls edges of wound together
Fibrinolysis

- Process that prevents blood clots from growing and becoming problematic
  - Constant balance between too much clot and too little
- Plasminogen $\Rightarrow$ Plasmin
  - Tissue plasminogen activator (tPA)
- Plasmin cleaves the strands of fibrin to break down clot

Hemostasis

Controlling Internal Hemorrhage
The problem:

- How do you fix the leaky bucket when you cannot even see the hole?

Military Medical Innovations

- Novel approaches have been developed to address the current complexity and severity of military trauma with great success on casualty survival

Damage Control Resuscitation

- New strategy in trauma resuscitation based on addressing the lethal triad
  
  - ‘Lethal triad’ describes the mutually perpetuating combination of:
    - Acute coagulopathy
    - Hypothermia
    - Acidosis
Lethal Triad

- Hypoperfusion leads to:
  - Decreased oxygen delivery
  - Switch to anaerobic metabolism
  - Lactate production
  - End result is metabolic acidosis.

Acidosis

- In vitro studies have shown substantially reduced clot formation rate in normal blood brought down to a pH of 7.0
- Platelets incubated in a:
  - Low pH (5.5) form spheres devoid of aggregating tendency.
  - High pH (9.0) have increased aggregation properties.
- Varying degrees of acidosis have been clinically linked with coagulopathy and poorer outcomes in trauma patients
Lethal Triad

- Shock = Anaerobic metabolism
- Anaerobic metabolism
  - Limits endogenous heat production
  - Exacerbates hypothermia caused by exposure and injudicious administration of cold resuscitative fluids and blood

Hypothermia

- Severely injured trauma patients with hemorrhagic shock typically have uncoupling of normal metabolic pathways.
  - Casualty cannot generate own body heat
  - Can be exacerbated in prehospital setting:
    - Environmental factors
    - Prolonged extrication or scene time
    - Intoxication
    - Convective and conductive heat loss
**Hypothermia**

- Presence of hypothermia on arrival linked with increased mortality.
- Severe trauma-related hypothermia (temp<32°C) has been associated with 100% mortality.
- Moderate hypothermia (32°C-34°C) directly reduces coagulation factor activity and markedly affects platelet function.

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**Lethal Triad**

- Acute Coagulopathy of Trauma-Shock
  - NOT be induced as thought from bleeding loss of coagulation proteins and massive IVF dilution
  - Observational studies have shown that 25% of trauma patients have established early coagulopathy on arrival to ED
  - Now understood to be complex process related to tissue damage
Summary: Lethal Triad

- Acidosis causes abnormal clotting which increases bleeding = DEATH
- Hypothermia causes abnormal clotting which increases bleeding = DEATH
- Coagulopathy IS abnormal clotting which increases bleeding = DEATH

New novel approach to management of severe trauma

Addressing the Lethal Triad

- Emphasis on the recognition and prevention of hypothermia
- Temporization of acidosis (or at least prevention of worsening acidosis).
- Emphasis on immediate correction of abnormal clotting
Hypothermia

- Easier to prevent than treat!!
  - Remove wet clothing
  - Place pt onto an insulated surface asap
  - Cover the casualty with commercial warming device, dry blankets, or anything that will retain heat and keep the casualty dry
  - Warm fluids are preferred if IV fluids are required.

Hypothermia

- Improvised
  - Vapor barrier
  - Insulating layer
  - Reflective heat shield

- Commercial options
  - APLS Thermal Guard
  - HPMK

Acidosis

- Treatment is challenging at best in severely injured patients

- Exogenous bicarbonate??
  - Alone appears insufficient in reversing acidosis-induced coagulopathy
  - Creates CO₂ in system causing increased minute ventilation
  - Decreases serum calcium concentrations
Acidosis

- Prevention may be more important than treating
  - Avoid Hypoventilation
  - Judicious use of resuscitation fluids:
    - NS: pH 4.5
    - LR: pH 6.0.

Acidosis

- Ultimate treatment is to restore end organ perfusion
  - Cannot be done until hemorrhage is controlled

- New pharmacologic agents on horizon?
  - Tris(hydroxymethyl)aminomethane

Coagulopathy

- Unlike hypothermia and acidosis, there are a number of effective therapies and products available to directly treat coagulopathy.

- Of the three parts of the lethal triad, coagulopathy is probably the most readily treatable
  - Hemostatic resuscitation
  - Options: FFP, TXA, targeted factor replacement
**Damage Control Resuscitation**

- New aggressive theory of complete resuscitation addressing the lethal triad
- Integrates the treatment modalities of:
  - Damage control surgery
  - Permissive hypotension
  - Hemostatic resuscitation

**Damage Control Surgery**

- Damage control surgery is a surgical strategy aimed at restoring normal physiology rather than anatomical integrity

**Permissive Hypotension**

- New strategy is to defer or restrict fluid resuscitation until hemorrhage is controlled while accepting a limited period of suboptimal end-organ perfusion
- Studies show fluid resuscitation may interfere with hemostatic mechanisms
  - Houston: 8% reduction in deaths for hypotensive penetrating torso trauma patients who received delayed IVF
Permissive Hypotension

- Limited prospective evidence supports use
  - Recommended for patients with uncontrolled hemorrhage
  - Especially torso penetrating trauma but applicability in hypotensive blunt trauma patients as well

Permissive Hypotension

- NIH has endorsed permissive hypotension in civilian pre-hospital setting and advises against fluid administration in patients without head injury who have a radial pulse
- Civilian TECC, ATLS, PHTLS/ITLS, and military TCCC Guidelines now all emphasize judicious use of fluids

Permissive Hypotension

- Foundation set by minimizing intravenous fluids in casualties who have a palpable radial pulse and normal mental status
  - Goal for resuscitation is radial pulse and mentation
  - Correlates with systolic ~80mmHg
Hemostatic Resuscitation

- DCR concept of resuscitation that emphasizes:
  - Early use of blood and blood products as primary resuscitation fluids
  - Treating intrinsic acute traumatic coagulopathy
  - Prevent the development of dilutional coagulopathy

Fresh Frozen Plasma to treat coagulopathy

- Busy trauma centers in Afghanistan routinely thaw fresh frozen plasma each morning.
  - Delivered to trauma bay and OR in standard resuscitation packs for delivery early in severely injured trauma patient’s course.
- Baltimore Shock Trauma Center currently thaws FFP each morning, allowing for the immediate transfusion of FFP once a trauma patient requiring transfusion arrives.

Other Alternatives for Coagulopathy

- Freeze dried plasma
- Recombinant Factor VIIa
- Tranexemic Acid
Researchers are also exploring the use of freeze-dried plasma products or use of purified protein concentrates that use variable amounts of factors.

- Potentially safer from ID perspective.
- Target factor replacement without the additional volume.
- Logistically appealing given their small size.

Martinaud C et al, J Trauma 2012

- Prospective study of use of Freeze Dried Plasma at French MTF in Kabul
- 87 patients transfused on average 3.5 FDP units
  - PT significantly decreased after transfusion
- Users reported ease of use, shelf life of 2 years, observed efficacy of FFP
- No reported adverse effects

Recombinant Factor VIIa
Recombinant Factor VIIa

- Considerable debate about:
  - Appropriate timing of drug delivery.
  - Selection of patients to receive the drug.
  - Whether additional blood components can be delivered with the drug to enhance its effect.
  - Cost benefit

- Reports of increased thromboembolic events

- Conclusion: Jury still out but unlikely to be recommended

Tranexamic Acid

What is it:
- Synthetic derivative of the amino acid lysine

How does it work:
- Inhibits breakdown of fibrin strands in clot by blocking the lysine binding site that converts plasminogen to plasmin
  - No plasmin = no breakdown of fibrin clot
TXA – FDA Approval

IV:
- Short term use for prevention / reduction in bleeding in patients with hemophilia undergoing dental procedures

Oral:
- Control of heavy menstrual periods

TXA

Extensively Studied:
- Intraoperative and post operative bleeding, hemophilia, GI bleeds, traumatic hyphema, and hereditary angioedema

Trauma Literature:
- CRASH-2 - Lancet 2010
- Matters Trial – Archives of Surgery 2011

Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2)

Study Design:
- Effect of early administration of TXA on death, vascular occlusive events, and receipt of blood transfusion
- 274 hospitals
- 40 countries
- 20,211 trauma patients within 8 hours of injury were randomized
CRASH 2

Eligibility:
- Adult trauma patient
- Within 8 hours of injury
- “Significant hemorrhage” (SBP<90 and/or heart rate >110)
- Risk of significant hemorrhage

CRASH 2

Results:
- All causes of death reduced 1.5%
  - TXA 14.5 / 16%
- Death from bleeding reduced 0.8%
  - TXA 4.9 / 5.7%
- No increased vascular occlusive events
  - TXA 0.3 / 0.5%

CRASH 2

Assets of the Study:
- Huge RCT
- 1.5% decreased death rate – all comers
### CRASH 2

**Liabilities:**
- Clinical decision about “hemorrhage”
  - Hypotension/tachycardia or considered to be at risk of significant hemorrhage
- Half the patients didn’t even get an operation
- Half didn’t even get blood products
- No reduction in blood products used in TXA arm

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**Liabilities:**
- NNT 67 for all cause mortality
- NNT 125 for mortality from bleeding
- Worse outcome if given over 3 hours post injury
  - TXA 4.4 / 3.1%

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**Assets Sub Group Analysis:**
- Suggests more benefit if treated within 3 hrs
- Suggests more benefit if SBP < 75 mm Hg

**Post Hoc Analysis:**
- 1.3% decreased death from bleeding if TXA given between 1 and 3 hours
- Worse outcome if given over 3 hours post injury
**TXA and Head Injury**

**CRASH-2 Intracranial Bleeding Study:**
- Prospective randomized, nested study within CRASH 2
- 270 patients with GCS < 14 and abn head CT
- 9% decreased death from traumatic head injury if given TXA
- CRASH-3 will further examine TXA with TBI

**Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study**

**Study Design:**
- Retrospective cohort at a single UK surgical Hospital in Afghanistan (Bastion)
- Consecutive trauma patients receiving at least one unit pRBC’s within 24 hrs of admission following combat trauma
- 896 patients, 293 received TXA within 1 hour of injury (mean dose 2.3 gms)

**MATTERS**

**Results:**
- 6.5% reduction in all causes of death
- 13.7% reduction in massive transfusion cohort deaths
- NNT 7 in massive transfusion group
MATTERS

Assets:
- Clearly defined trauma population
- Population receiving TXA was sicker
  - Higher ISS
  - More severe extremity trauma
  - Lower GCS
  - More hypotension
- NNT 7 in massive transfusion group

MATTERS

Liabilities:
- Increased venous thromboembolic events with TXA
  - Pulmonary embolism TXA 2.7 / 0.3
  - Deep vein thrombosis TXA 2.4 / 0.2
- Higher transfusion requirement with TXA
  - 11.8 Units pRBCs / 9.8
  - FFP, Cyro, and platelets too

What Do the “Experts” Say?
Cochrane Review 2011
- "The review concluded that tranexamic acid safely reduces mortality in bleeding trauma patients without increasing the risk of adverse events."
- "Our results strongly endorse the importance of early administration of tranexamic acid in bleeding trauma patients and suggest that trauma systems should be configured to facilitate this recommendation."

TXA for Trauma Patients: A Critical Review of the Literature
- "This inexpensive and safe drug should be incorporated into trauma clinical practice guidelines and treatment protocols"
  - Cost $5.70 per dose
- "...TXA should be adopted for use in bleeding trauma patients because it is the only drug with prospective clinical evidence to support this action"

  J Trauma Jul 2011

Does the Admin of Antifibrinolytic Drugs in Acute Trauma Reduce Deaths?
Take-Home Message
- "The use of tranexamic acid may reduce the risk of death in bleeding trauma patients."

Annals of Emergency Medicine
March 2012
Hemorrhage Control Summary

- **Priority:** Fix the leaky bucket first!!!
  - Cannot fill the tank if it is continually leaking...

- **External bleeding**
  - Rapidly control with:
    - Direct pressure first (every drop counts!!)
    - Tourniquet
    - Pack and pressure dressing
    - Hemostatic agents
    - Junctional tourniquets

Hemorrhage Control Summary

- **Priority:** Fix the leaky bucket first!!!
  - Cannot fill the tank if it is continually leaking...

- **Internal Hemorrhage**
  - Minimize using Damage Control Resuscitation
    - Hypothermia prevention kits
    - TXA
    - Permissive hypotension
    - ?FFP or FDP in the future

Hemorrhage Control Summary

- THEN... Fill the bucket!!
  - IVF, blood transfusion... another lecture!!