Resuscitation: Past Beliefs and Current Clinical Trials

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Resuscitation

- Goals of treatment have evolved
  - Volume resuscitation
  - Oxygen delivery
  - Hemostasis

Spectrum: Saline to Fresh Whole Blood

Theory of Disease

- For centuries theories concerned **spirits** to explain disease.

The error in reasoning

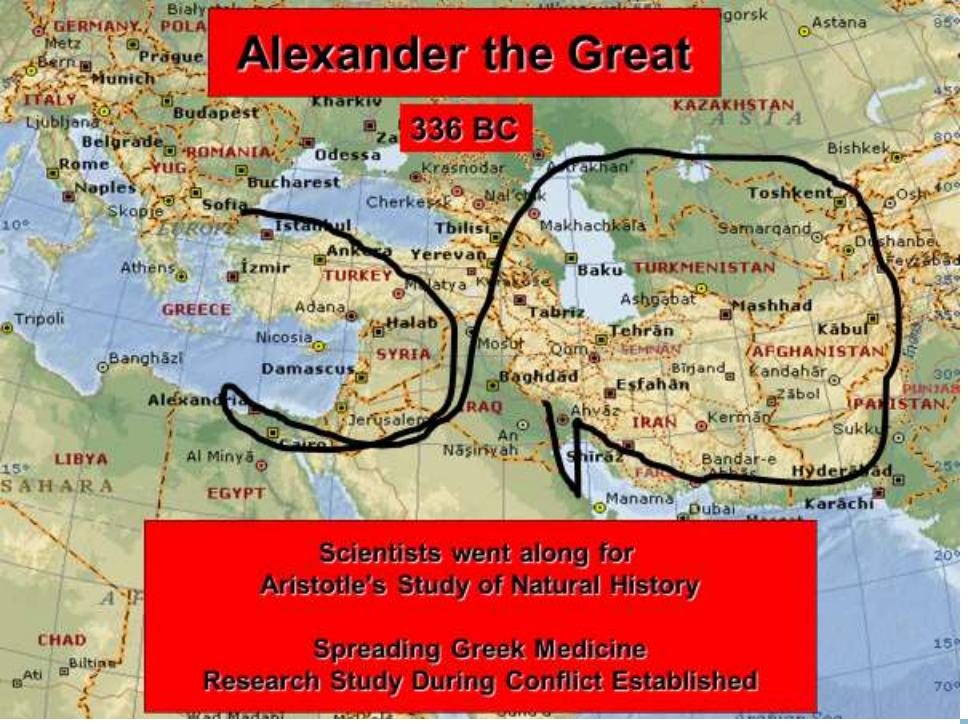
- A man gets sick: he takes medicine: he gets well
  - Something happens after another
- Does not mean the second happened because of the first.

- **"Post hoc Ergo propter hoc"**
- **After it; therefore because of it**

This will take 4000 years to over come

Resuscitation – Greek Medicine

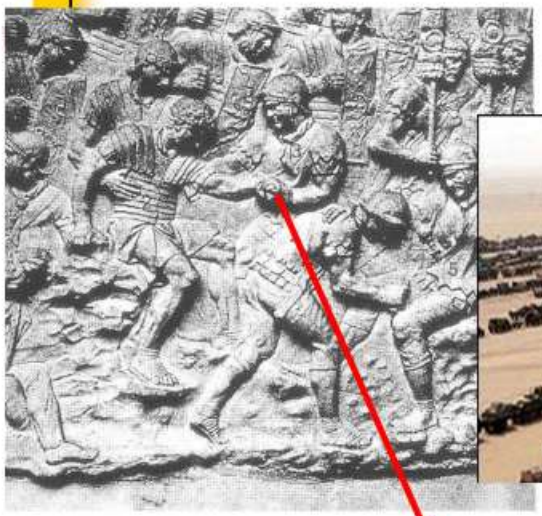
- Homer – the Iliad 800 BC
  - 147 wounds described
  - 114 died
- Mortality – 77%
  - Treatment
    - Application of herbs
    - Removing arrows
    - Casting fractures



Galen – Blood letting

- Born 131 AD
  - MD training – 149 AD
- Galen's Theory
  - Food to liver→ blood → artery → heart → veins
- Draining blood "therapeutic"

Roman Military Care: Organized System



Far Forward Care Established

World Changes

Christianity 400-500

Galen principles Dominated

Latin to Arabic
Galen to Avicenna
Bled on opposite side

Islam 700-800

Avicenna's Canon – 980-1037 Medical Encyclopedia

"it should be used in it's natural state upon uncomplicated disease….**that two opposed cases be observed ….and that study be made of the time of action and of the reproducibility of the effects……**.the experimentation must be done with the human body for testing a drug on a lion or a horse might not prove anything about it's effect on man"

The Modern Clinical Trial

Medicine Returns to Europe

- 1010- Constantine of Carthage
  - Learned medicine in Arabia and India - mistrusted
- Escaped to Salerno
  - Translated Arabic to Latin
- First medical school - Return of Dissection

Origin of Chairman

Franciscan Roger Bacon: Apology

- "for it is exceedingly difficult and dangerous to perform operations on the human body….for the practical sciences which do their work on the insensate bodies can multiply their experiments till they get rid of deficiency and errors**…but a physician cannot do this because of the nobility of the material in which he works….physicians are to be excused for their defects more than are workers in the sciences**"
- Endorsement of empiric therapy…- 1275AD

Early Gun Shot Wounds

- Pare` 1507- focus infection
- Poisoned - gunpowder
  - Boiling oil - "diseases not curable by knife were curable by fire"
- New Concept - Turpentine and Rosehips

Shock still not a priority

1492- Blood Letting Calendar Second publication Gutenberg press

Barber - Surgeons

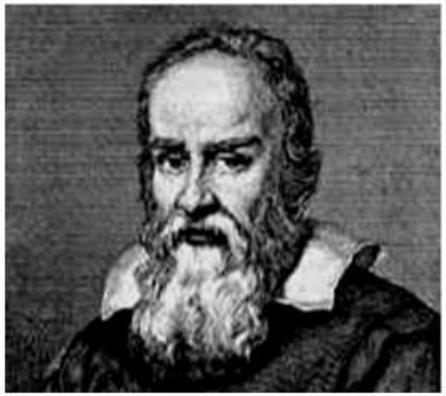
- 1534- Company-Guild joined
  - Henry VIII
- Given 4 executed criminals/year for dissection

Critical Development: Anatomy Vesalius - Rejected

- 1543 - De Fabrica Humani Corporis – 300 woodcuts
  - Pupils left, burned his manuscripts, gave up anatomy
- Could not explain R → L passage of blood.

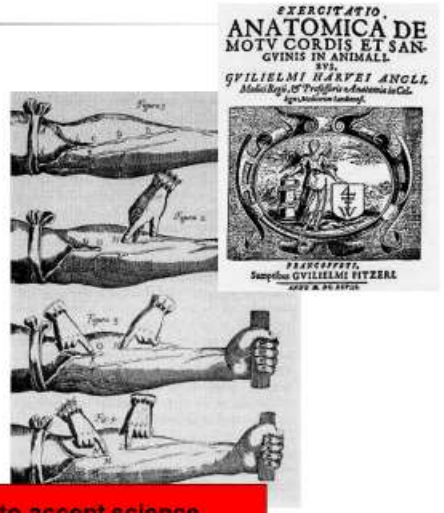
Critical Development Physiology: Galileo - 1581

- Imprisoned by Pope for views about earth orbiting sun
- Medical School @ Pisa
- Watched pendulum
  - Timed pulse



Critical Development Anatomy Meets Physiology

- Harvey – challenged Galen
  - No pores in the heart
  - Demonstrated venous return
  - Calculated ejection volume HR x 60cc x 1440 minutes
  - 16 tons in 24 hours - impossible
  - 1628 - Must circulate

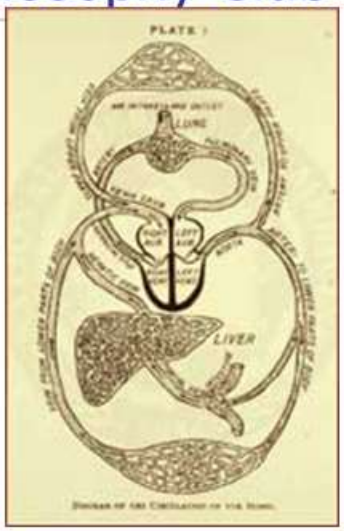


The world was starting to accept science

Right time - Right place
Experimental Philosophy Club

- 1630's-1650's Oxford
  - Harvey member
- Wren-Architect
  - Quill and bladder syringe
- Boyle-Chemist
- Injected antimony and opium in dogs
  - Vomiting and Sedation

Intravenous injections circulate



First Transfusion

- 1665 – Lower
  - Wren and Boyle medical student
- Dog shock model and resuscitation
  - Artery to vein
- "One animal may live with the blood of another"

Blood Transfusion History

- Jean Batista Denys
  - December 19, 1667
- Transfused Antoine Maury - **lambs blood**
  - Third transfusion
    - Died, wife sued
    - Trial – Absolved Denys
- French Parliament and Pope banned transfusion

Blood Letting Ruled

Sued 1799

Bled on deathbed

Continued practice

Crystalloid - Colloid History

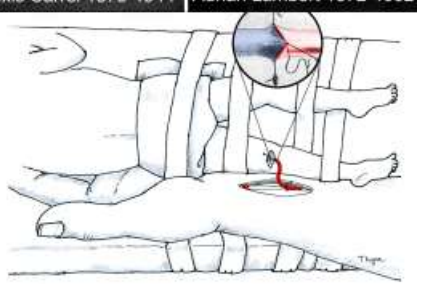
- 1831-O'Shaughnessy
  - Described **cholera deficit**
- 1832-Latta
  - Gave **normal saline**
- 1882-Ringer
  - Described components
- 1898-Thomas
  - Obstetrical hemorrhage
- 1910's – Colloid: **Gum of acacia**
- 1931-Hartman
  - Sodium lactate added

First Operative Transfusion

- 1908-Carrel summoned by Lambert
  - Brothers (surgeons)
- Father to baby transfusion success
  - Carrel - no license
  - Celebrated birthday 21 years later


Alexis Carrel 1873-1944


Adrian Lambert 1872-1952



Agglutination and Hemolysis and Anticoagulation

- Landsteiner - Vienna
- 1900 Published work
- 1912 – Ottenberg
  - Mt Sinai – simplified test
  - Reduced hemolysis to zero.
- 1915 Lewisohn - Mt. Sinai
  - Na citrate
- "The technique of blood transfusion…was suddenly made as simple…as saline infusion…"

Shock Theory -Walter Cannon

- Studied American Forces
- MD physiologist – Harvard
- Traumatic Shock
  - Shock – dilated capillary region – exemia
  - Neuro-endocrine theories confused volume resuscitation role

Cannon – World War I

- "The injection of a fluid that will increase blood pressure has dangers in itself. Hemorrhage may not have occurred to a marked degree because the blood pressure has been too low to overcome the obstacle offered by a clot."
- **"Pop the Clot"**

"with this method of blood transfusion, I know that at this hospital we have saved lives by its use which would otherwise have been lost…. Lieutenant A. M. Hansen to Dr. Cannon 1918

Shock Theory-Alfred Blalock

- 1925 – Joined Harrison
  - Vanderbilt Chief Residents
  - Vivien Thomas – 1929
- Defined relationship of blood loss to shock
- Volume resuscitation critical
- **Theory largely ignored for 30 Years**

1924-5 Global Instability

Colloid Resuscitation - WW II

- Blood needed – Carrel asked
- Blood would not survive the transatlantic journey
- Shifted focus **plasma**
  - Committee on Transfusion 1940 - Walter B. Cannon
- **Albumin** first used
  - Pearl Harbor- I. Ravdin

World War II

- 1943 - Churchill- Harvard
  - **"Plasma not a blood substitute"**
- Described over zealous shock resuscitation
- Pushed for blood with great personal political risk

Korea Blood Program

- Military program collapsed
- No blood first 70 days
- First changes in coagulation reported
  - Small transfusion volumes

Vietnam-Coagulation Disorders

- First description: **coagulopathy**
- Described relation of shock and acidosis
- 9% of massive transfusions
  - Simmons and Collins

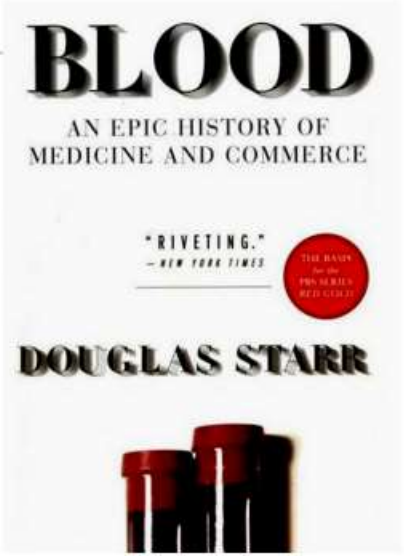
Hx Coagulapathy Treatment

- **Needs** as **function of** blood volume **loss**
  - Volume @ 0.2 BV
  - Red Cells @ 0.6 BV
  - Albumin @ 1.2 BV
  - Coag fact. @ 1.8 BV
  - Platelets @ 2.2 BV
- Treatment by component in order
  - Volume
  - Red cells
  - Albumin
  - Coagulation factors
  - Platelets

Collins 1974

1960s - Civilian Use

- Blood like oil – wildcatters
- Unregulated
  - Fractionation for drugs
  - Big money
- Inappropriate collection - rampant
- Hepatitis emerged
- AIDS – not yet present



1970s :Crystalloid: 3 TO 1

- Original studies
  - Shires, 1963
  - Three isotope model
- **Extracellular repletion - essential for survival**

Trends in Resuscitation:1980s Goal Directed Oxygen Delivery

- Supernormal O_2 del.
  - Shoemaker et al.
- 7 randomized studies - no difference
- **Increased Compartment Syndromes**

Significant Developments Trauma Systems

- Paramedic Training
- Regional EMS systems
- 911
- ATLS
- Trauma Care standards
- Verification

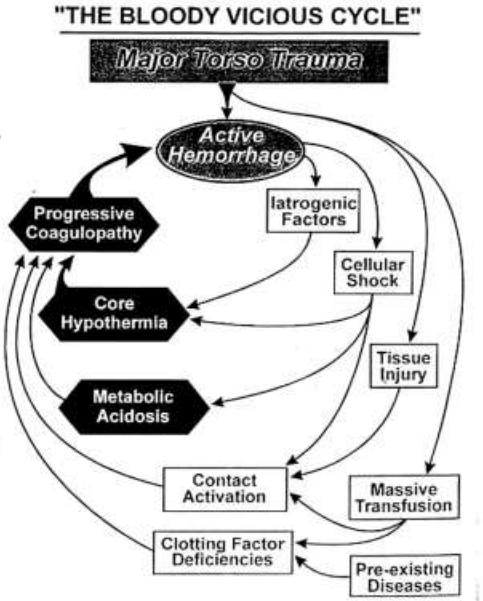
Saw sicker patients earlier

New Concept Damage Control

- Damage Control Surgery
  - Operational logistics
    - Shunts
    - Stapling bowel and lung - temporary
    - Solid organ tamponade – temporary
    - Temporary closure

Factors - Triggers

- Factors
  - Hypothermia
  - Acidosis
  - Coagulopathy
- Triggers
  - Transfusion of 10 units
  - Decreased platelets
  - PT of >16 secs
  - PTT of >50 secs
  - Diffuse nonsurgical bleeding



Strategy

- Staged Decisions in Management
  - I - Pt selection - indications
  - II - Intraoperative assessment
  - III - Physiologic restoration
    - **Coagulation control**
  - IV - Return-operating room
  - V - Abdominal closure

NIH Trauma Working Group

- Expand Basic, Translational, and Applied Focused Research
- **Trauma Working Group - July 14th -15th,2003**
- **NHLBI, NIGMS, NINDS, NICHD**
  - **Cosponsored by ACSCOT,DOD,CDC,FDA, AAST**
- Scope:
  - 70 scientists and clinicians
  - Gaps/frontiers in basic science of injury
  - Areas ready for translational research

Goals: 1)National Center for Resuscitation Research
2)Build a multicenter network for clinical trials

Critical events - 2003

ROC
RESUSCITATION OUTCOMES CONSORTIUM

RFA 2004

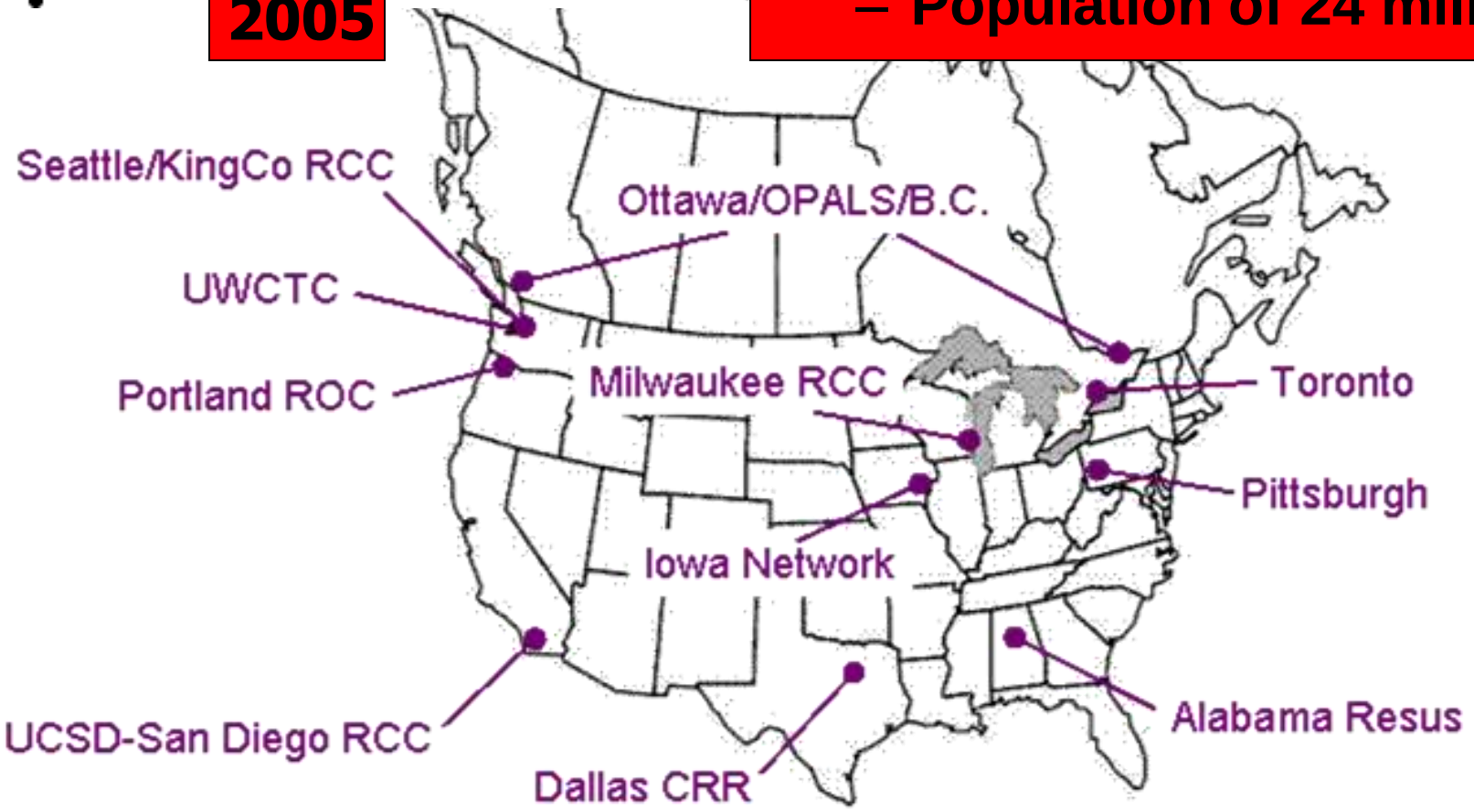
Resuscitation Research Network

ROC

RESUSCITATION OUTCOMES CONSORTIUM

2005

- **264 EMS/fire agencies**
- **194 hospitals**
- **Greater than 100 IRBs**
- **36,000 EMS/fire personnel**
- **Population of 24 million**



Resuscitation Strategies 2018

- **Should we resuscitate**
- Ringer's lactate and NS
- HTS
- Colloids
- Hemoglobin solutions
- Blood
- Other additives or strategies

The Question

- While there is still a hole in a named blood vessel, what is the best fluid resuscitation strategy to keep the victim alive until hemostasis can be achieved, and to promote intact survival?

	N	24-Hour Mortality	
		N	%
Limited	96	5	5.2
Standard	95	14	14.7

2015 - Low vs. Conventional Resuscitation Trial Completed

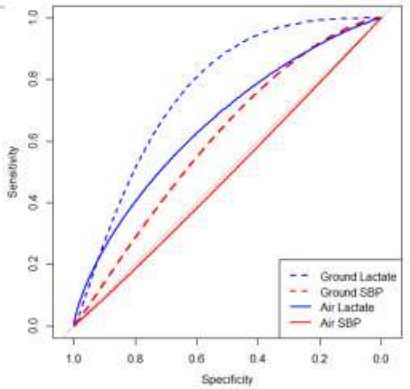
- ROC pilot – field and early ED
- 250cc vs. normal
  - Hypotensive pts
- Challenge – get difference in two groups

ROC
RESUSCITATION OUTCOMES CONSORTIUM

ROC
RESUSCITATION OUTCOMES CONSORTIUM

BLAST -2015

- **Biomarker Lactate Assessment of Shock in Trauma** compared point of care lactate to BP<90 to predict **resuscitative care**



	AUC (95% CI)	
	Ground	Air
P-LAC	0.78 (0.73-0.83)	0.66 (0.58-0.73)
SBP	0.59 (0.53-0.66)	0.49 (0.42-0.57)
P Value	< 0.001	0.004

Resuscitation Strategies 2018

- Should we resuscitate
- **Ringer's lactate and NS**
- **HTS**
- **Colloids**
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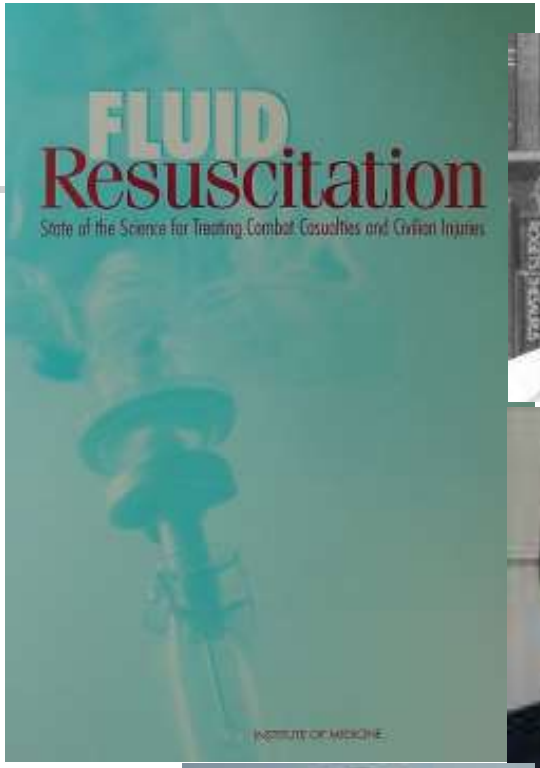
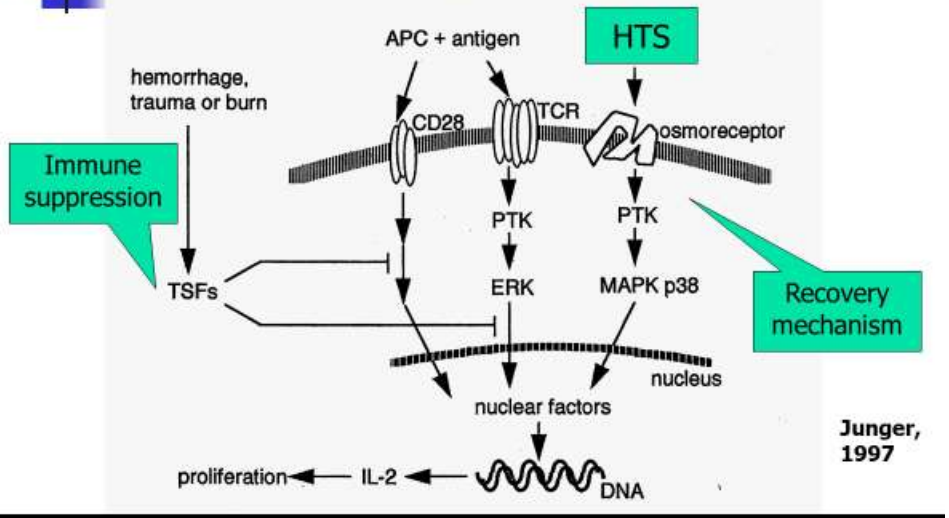
Fluid **Type** Concerns

- Concerns with R.L. and NS
  - Pro-inflammatory
  - Hyperchloremic acidosis
- HTS -Immunologic advantage
  - **1984 – attempting to isolate shock factor with affinity chromatography and t-cell suppression – NACL eluent +++**
  - Logistic advantage
    Higher pressure for same volume



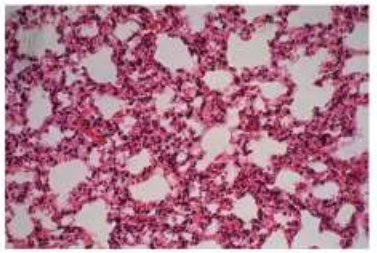
Senescent Signaling

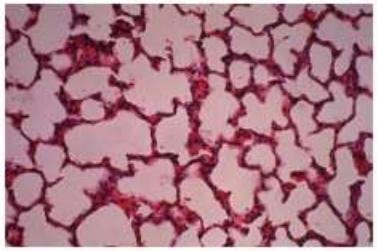


Does early fluid **type** effect MOF?

In vivo Effects

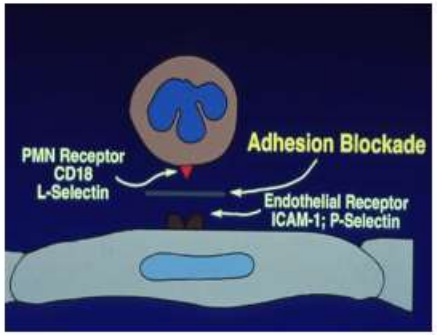
- HTS vs. RL
- Animal model – 2hit
  - Hemorrhage
  - Peritonitis
- Outcomes
  - Survival
  - Organ function
- Survival
  - HTS group 76.9%
  - RL group 14.3%
    - Coimbra,1997





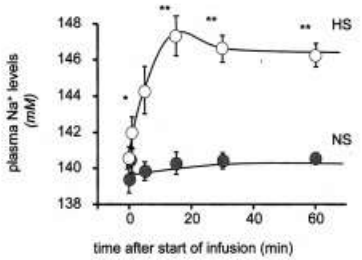
HTS- PMN

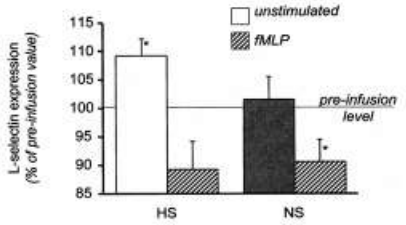
- HTS – adhesion expression
  - **Decreases neutrophil L selectin expression**, not endothelial P and E
  - CD 11b unchanged
    - Angle,1998
- HTS vs. RL- **Decreased H_2O_2**
  - Angle,1998
  - Rhee, 1998

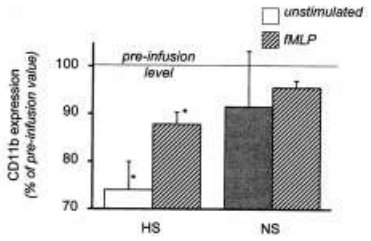


HTS Effects- Humans

- 4ml/kg 7.5% over 15 min.
- Immune function studied
  - Angle, 2000

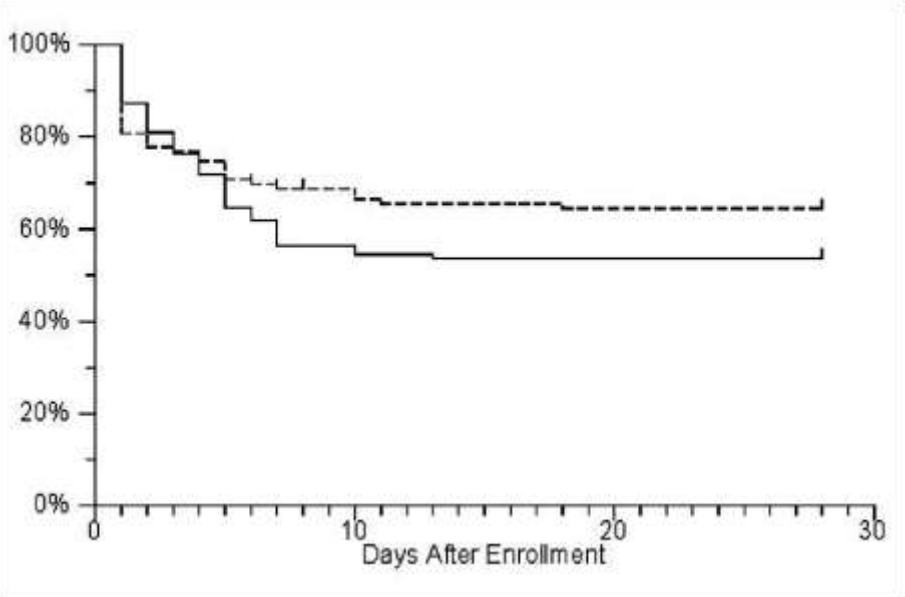


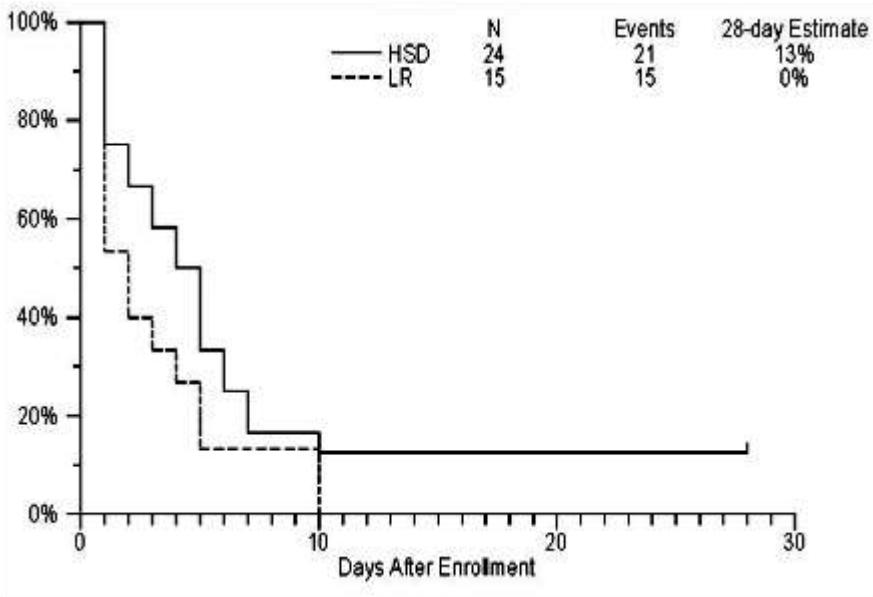




Phase II trial 2005

ARDS-free Survival



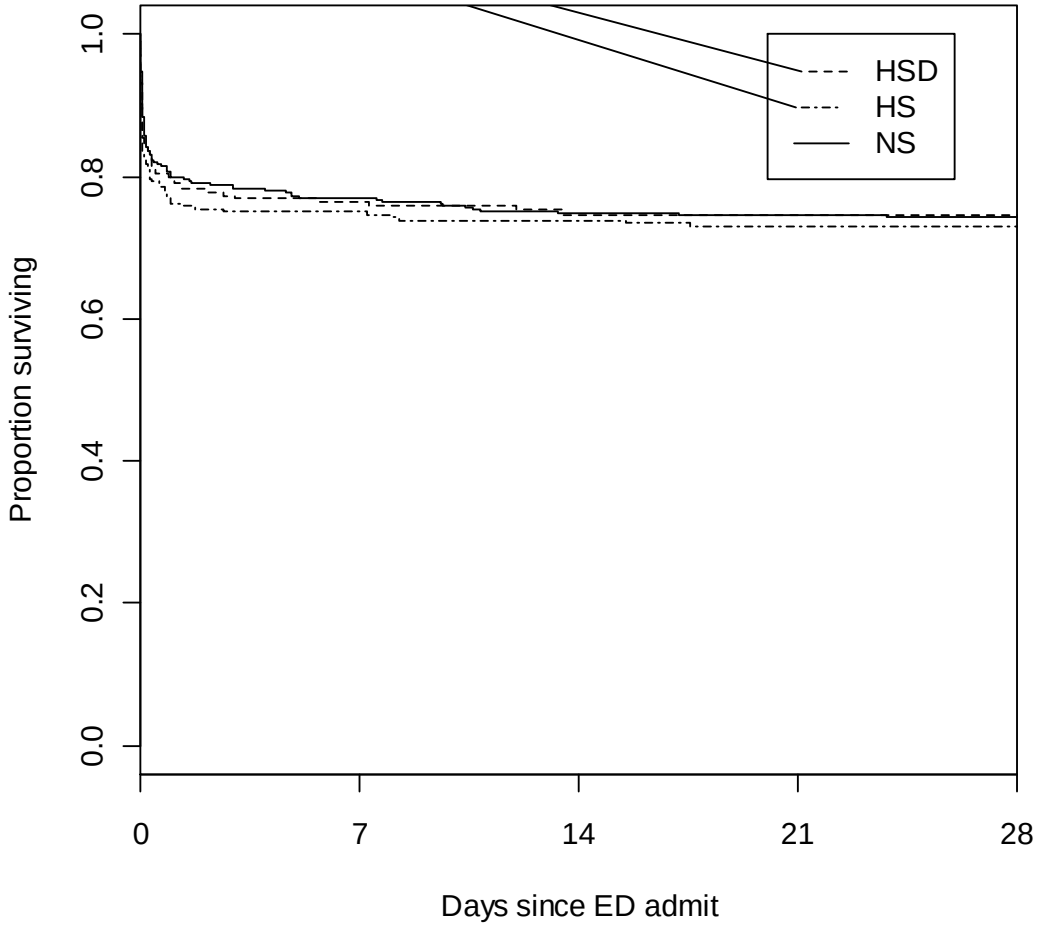


N=209
Unadjusted HR: 0.75 (95% CI: 0.49-1.15)
Log rank: p=0.16

Massive transfusion subgroup

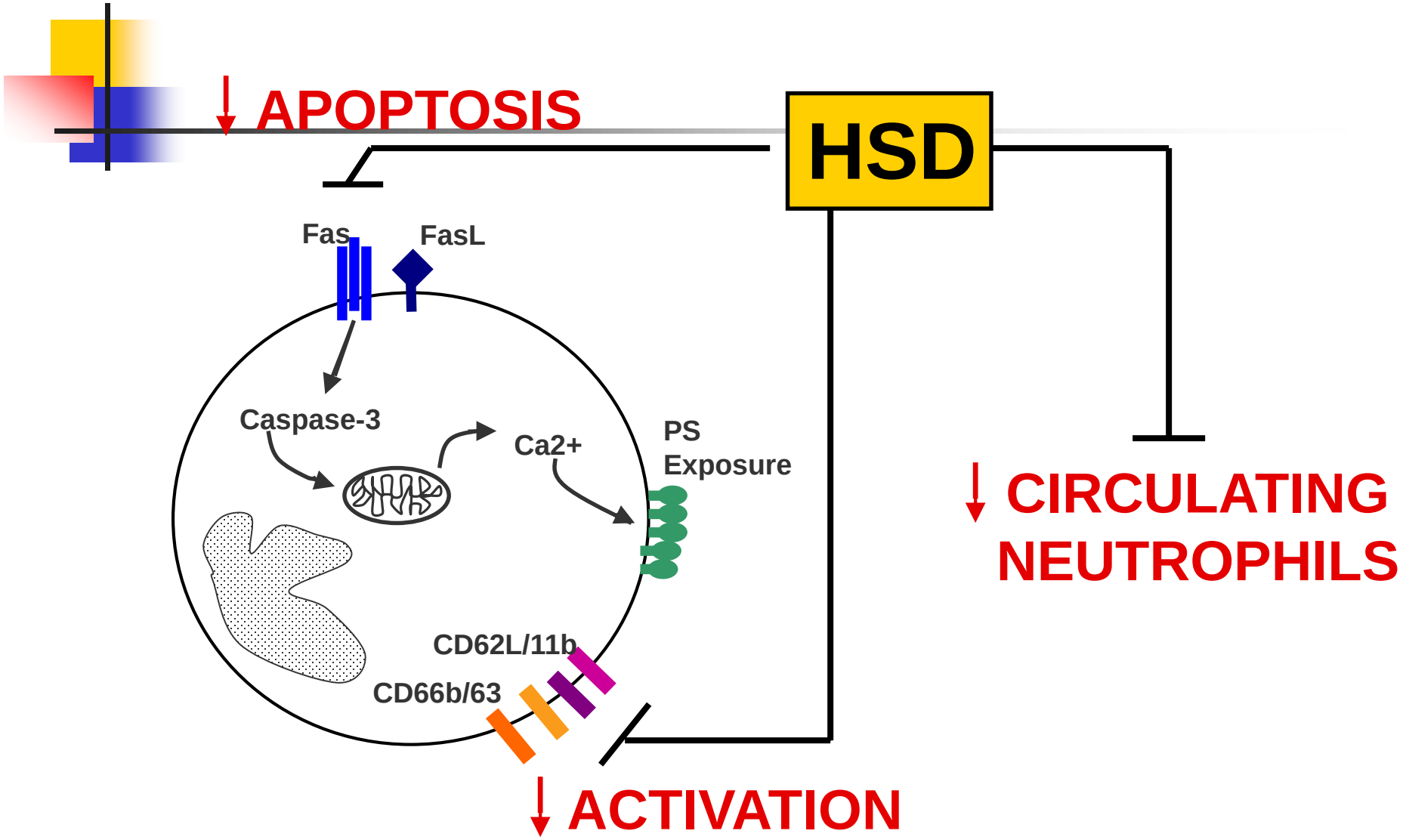
NIH, R01HL73233-01, Bulger et al, Arch Surg 2008

Phase III Trial - 2010
28 day survival



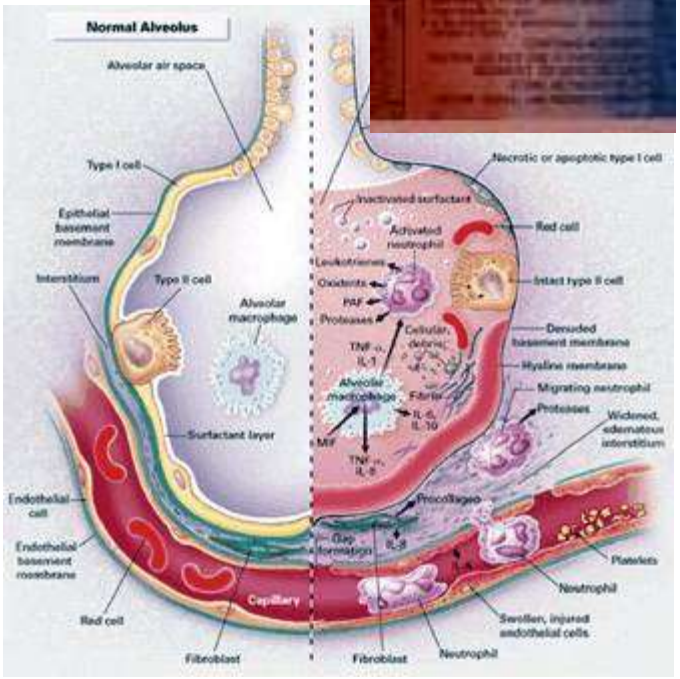
Treatment	28 day survival
HSD	74.5%
HS	73.0%
NS	74.4%
P value	0.91

Immune Effects Realized



Colloid Studies

- CoTCCC 2001 & 2010
  - Hetastarch chosen
  - Logistic advantage
  - Guidelines not really followed – 60% get RL or NS
- Multiple studies (> 50)
  - Albumin equal other colloids
  - **Colloids equal to crystalloid**



Resuscitation Strategies 2018

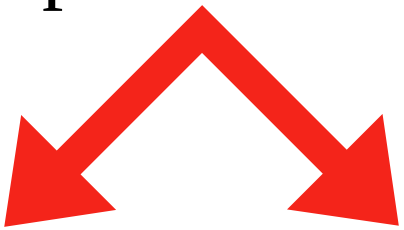
- Should we resuscitate
- Ringer's lactate and NS
- HTS
- Colloids
- **Hemoglobin solutions**
- Blood
- Other additives or strategies

Human Polymerized Hemoglobin Ambulance Infusion

500ml, 10g/dl
P50 = 28-30 torr
T1/2 = 1 day
Shelf-life > 1 year

Results: Study Overall

714 patients
82 patients died



349 Received
PolyHeme®
46 Deaths (13%)

365 Received
Control
36 Deaths (10%)

NO Difference

Resuscitation Strategies 2018

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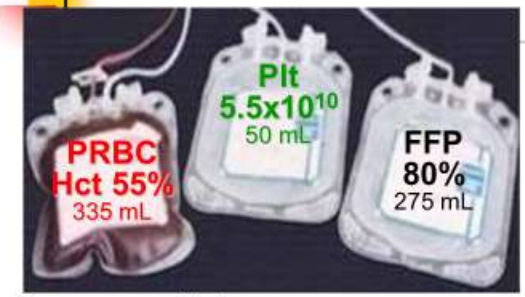
Weve Had a Debate

- When to use:
  - Fresh whole blood
  - Whole blood
  - Fresh frozen plasma
  - Platelets
  - Cryoprecipitate
    - Fibrinogen

You Can Get Close With Reconstitution

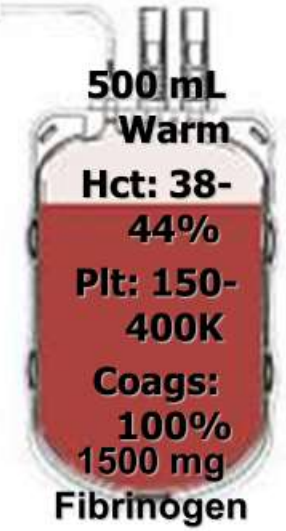


Component Therapy

1U PRBC + 6U PLT + 1U FFP + 10 pk Cryo

- ***Hct 29%***
- ***Plt 87K***
- ***Coag activity 65%***
- ***750 mg fibrinogen***

- **Armand & Hess, Transfusion Med. Rev., 2003**



Historical View

- Measure coagulation and platelet counts
- Give plasma when INR or aPTTr $\geq$ 1.5
- Give platelets when platelet count < 50K
- Give cryoprecipitate or fibrinogen when fibrinogen is < 100 mg/dL
  - College of American Pathologists
  - English National Blood Service

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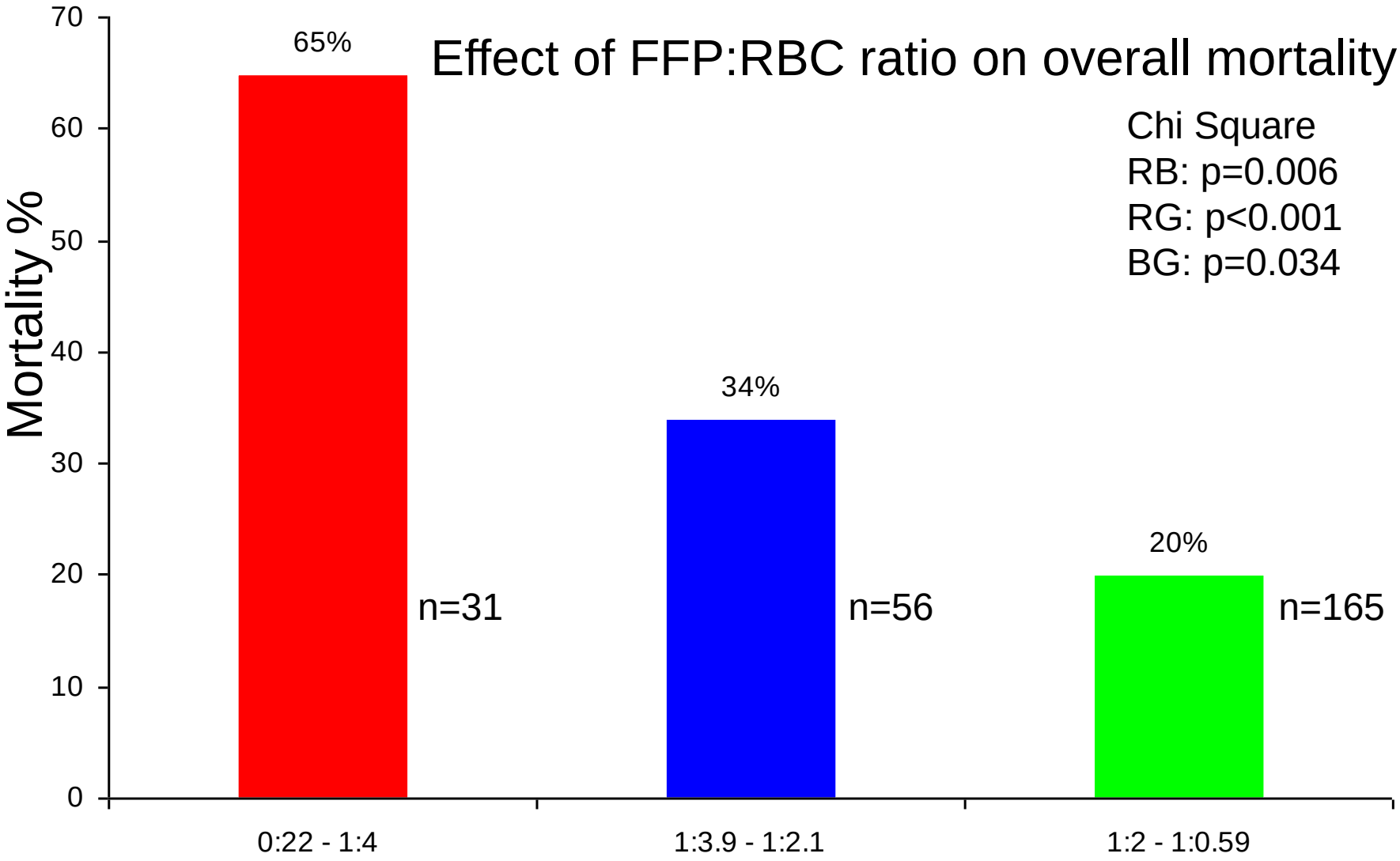
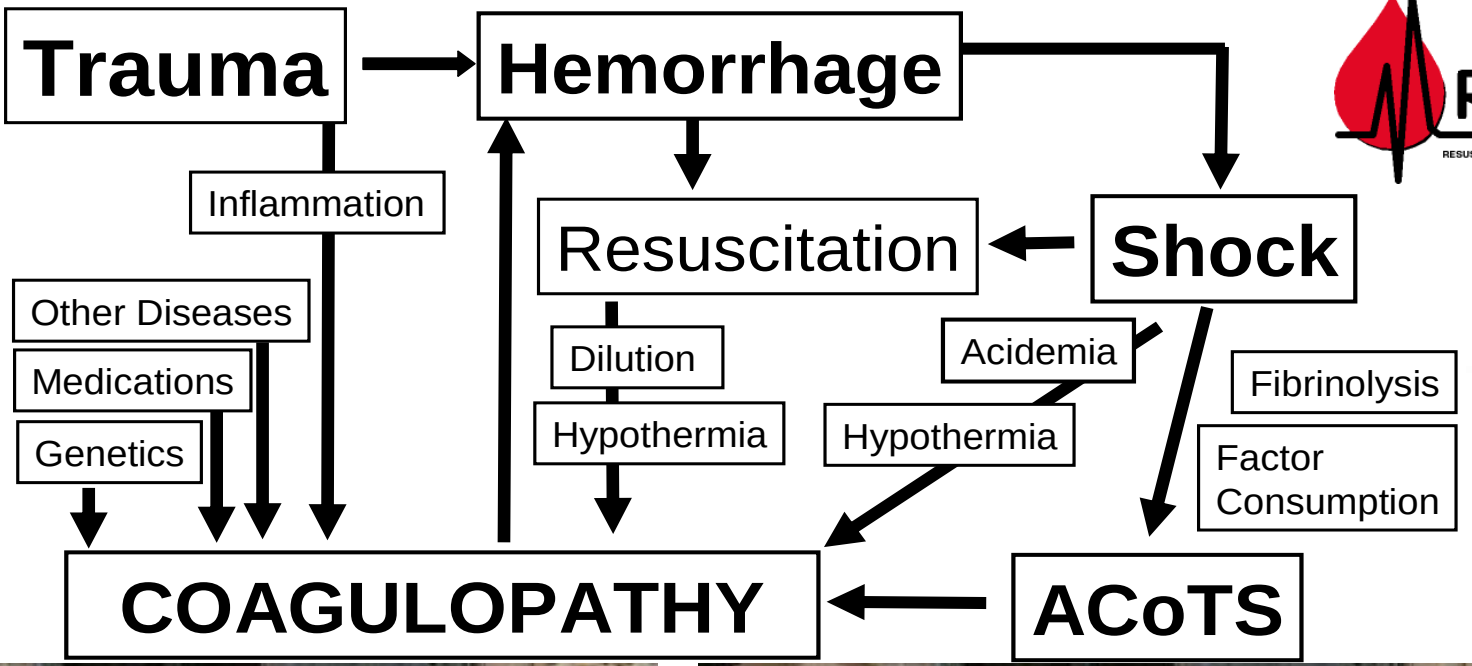
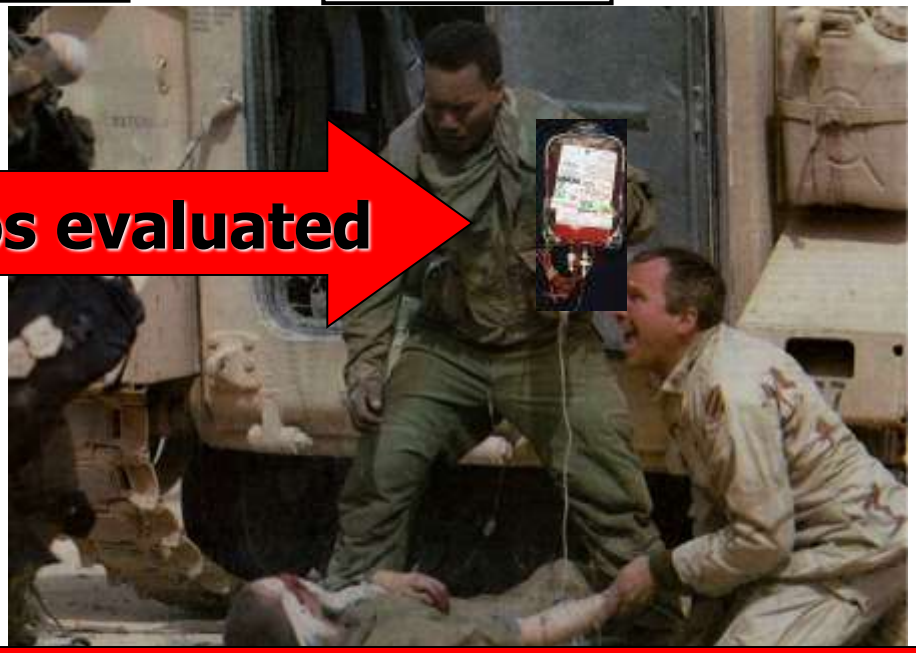
Iraq – Early Aggressive Whole Blood Restoration



Borgman, 2007



Ratios evaluated



PROPER Trial Completed – data May 2014

JAMA Feb 2015

- **Conclusions and Relevance** Among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days. **However, more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours.** Even though there was an increased use of plasma and platelets transfused in the 1:1:1 group, no other safety differences were identified between the 2 groups.

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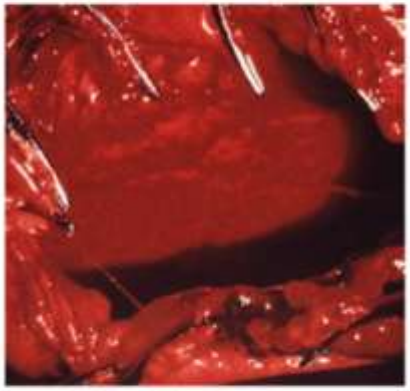
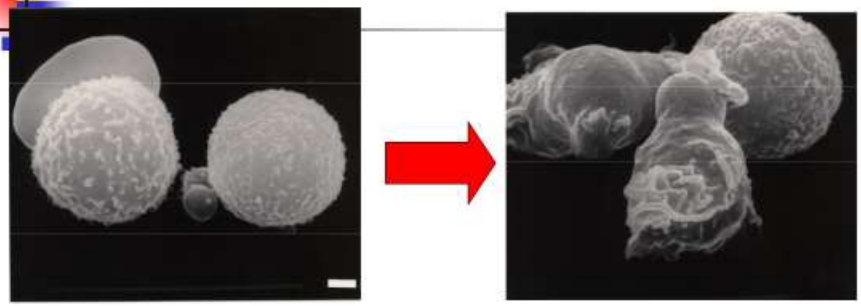
- **Other additives or strategies**

Shock and Gut Ischemia

- Shock - structured hierarchy of ischemia
- Gut first to go down and last to resuscitate
- Often seen as source of systemic activation of inflammation
- Lymph factors postulated



PMN Activation After Shock

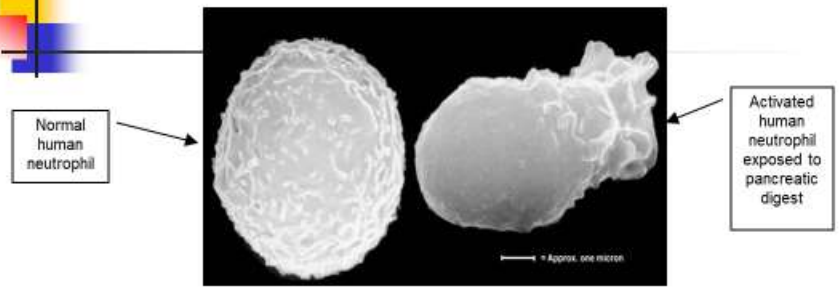


Critical step postulated for MOF

Triggers of Cell Activation

- Inflammatory mediators (bacterial/viral/fungal sources, endotoxins, cytokines, histamine, oxidized products, complement fragments, LTB_4, PAF, etc.)
- Depletion of anti-inflammatory mediators
- Fluid shear stress
- Oxygen Gas Pressure Transitions
- Temperature Transitions

New Hypothesis

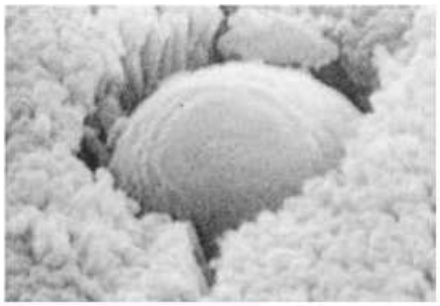


- Gut ischemia allows activated pancreatic proteases in gut lumen to attack intestinal wall producing inflammatory activators

Proc Natl Acad Sci U S A. 2000 Feb 15;97(4):1772-7

Theory 1: Excessive Macrophage Stimulation Liver and Lung

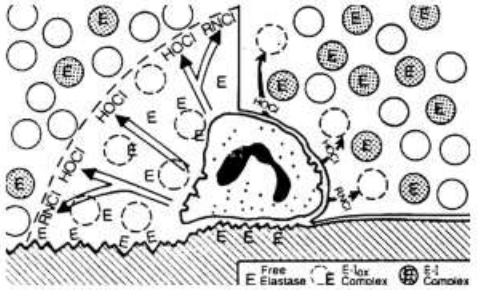
- Translocation - endotoxin
- Direct hepatic macrophage stimulation
- Excessive production
  - TNF
  - IL-1
  - IL-6



Clinical evidence inconsistent

Theory 2: Ischemia, Reperfusion: PMN Activation

- Inflammatory activation
- Gut PMN sequestration and priming: PLA_2
  - Metastatic adhesion to enflamed endothelium
  - Local enzymatic and oxygen free radical destruction



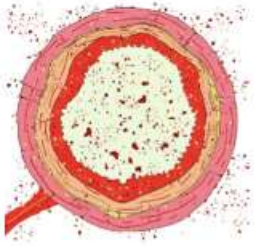
Blocking not clinically effective

Autodigestion hypothesis

Normal intestine

- Containment of activated pancreatic digestive enzymes

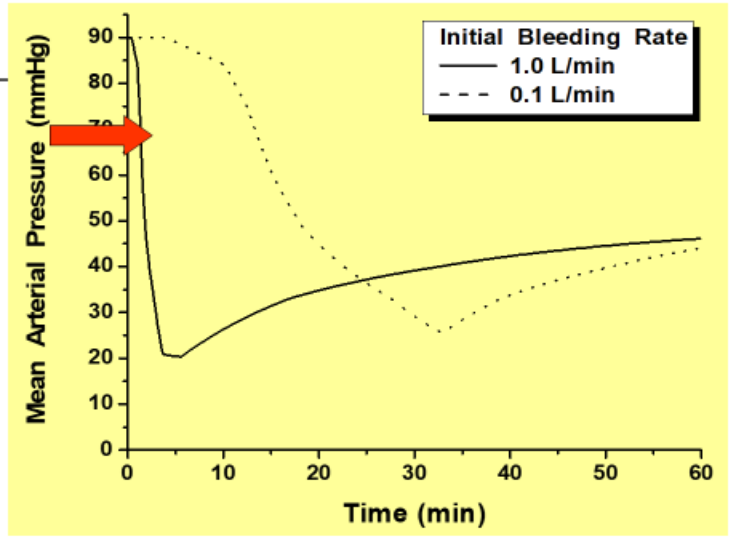
Ischemic intestine



- Breakdown of mucosal barrier
- Leak of pancreatic enzymes

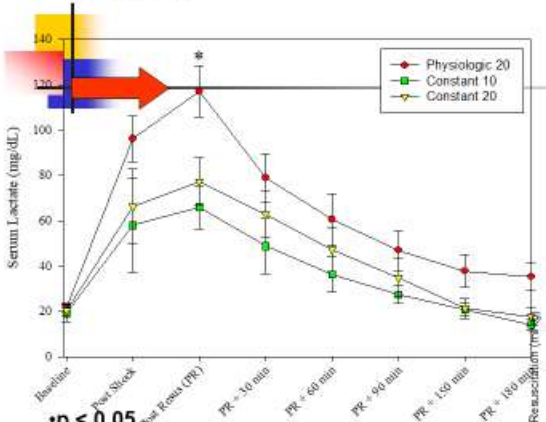
Is there a useful intervention against the destructive action of pancreatic digestive enzymes in the ischemic intestine?

Computer Model

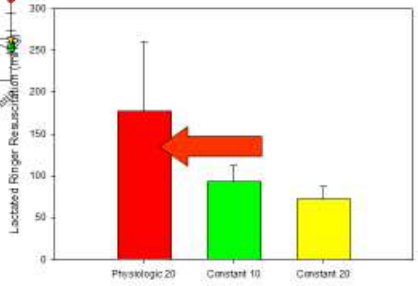


Hirshburg, Hoyt, Mattox, J. of Trauma 60(6) 1221-7, 2006

Lactate

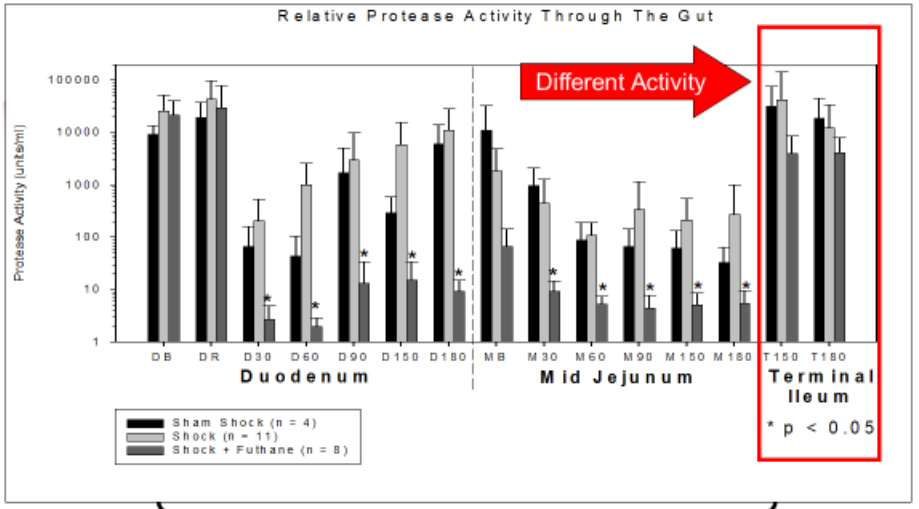


Crystalloid Resus

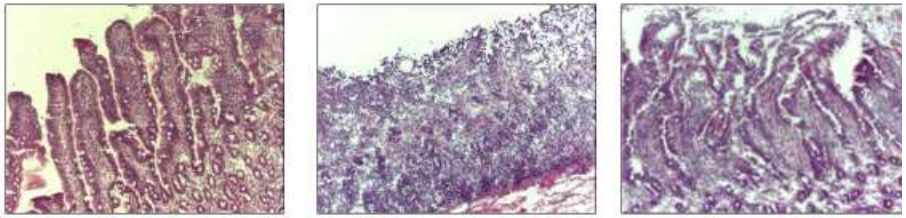


Methods: Classes of Proteinase Inhibitors

- **Serine Proteinases** (pancreatic enzymes)
  - Natural plasma inhibitors:
    - alpha-2-Macroglobulin
    - alpha-1-antichymotrypsin
    - alpha-1-antitrypsin
  - Chemical modifiers:
    - DFP and PMSF are serine group specific, but toxic.
  - Pseudo-substrate enzyme specific inhibitors
    - TPCK (chymotrypsin) and
    - TLCK (trypsin)
  - **Pseudo substrate broad spectrum inhibitor**
    - **Nafamosat**
- **Cystein Proteinases** (cathepsins)
  - alkylating agents
  - peptidyl-fluoromethylketones
  - cystatins
- **Metallo Proteinases** (MMPs)
  - EDTA and TIMPs
- **Aspartyl Proteinases** (phospholipases A2, pepsin)
  - pepstatin, structure specific statine-based analogues



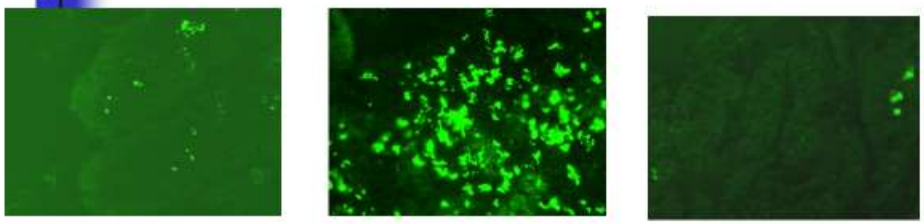
Intestinal H&E Histology



Sham Shock | Shock | Shock - inhibition

Anatomy preserved

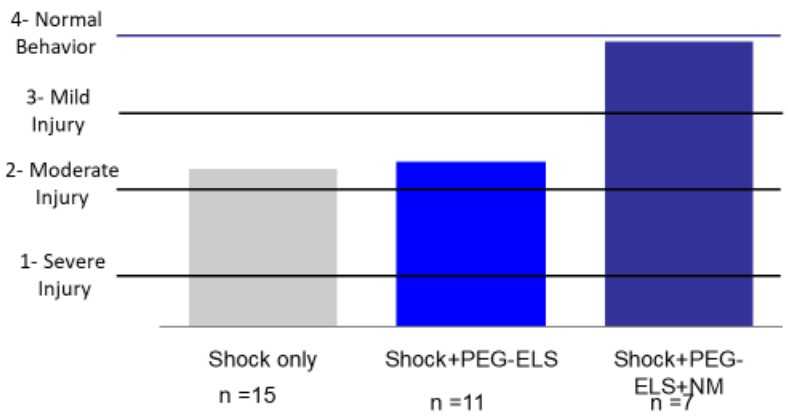
In situ zymography – MMP9



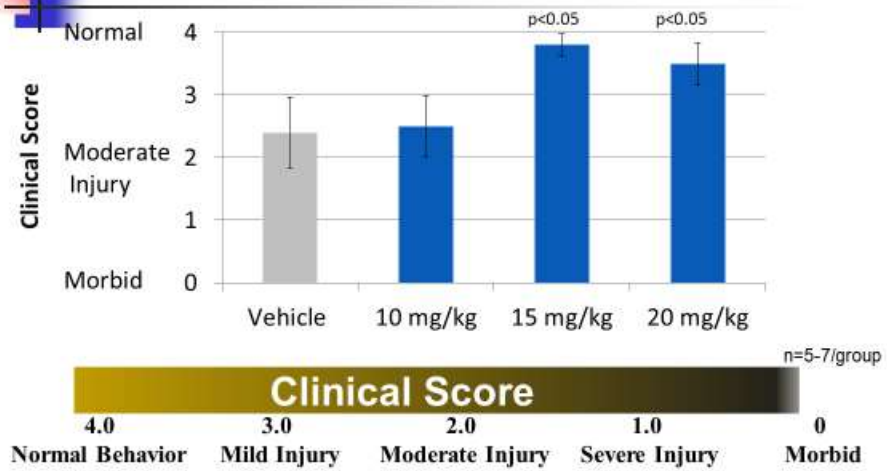
Sham Shock | Shock | Shock - inhibition

Critical Metalloprotease Activation Avoided

Serine Protease Inhibitor in PEG with Electrolytes vehicle Improves Morbidity



In a Mini-Pig Model of Hemorrhagic Shock, Tranexamic Acid Improves Clinical Outcomes



Kong et al 2012

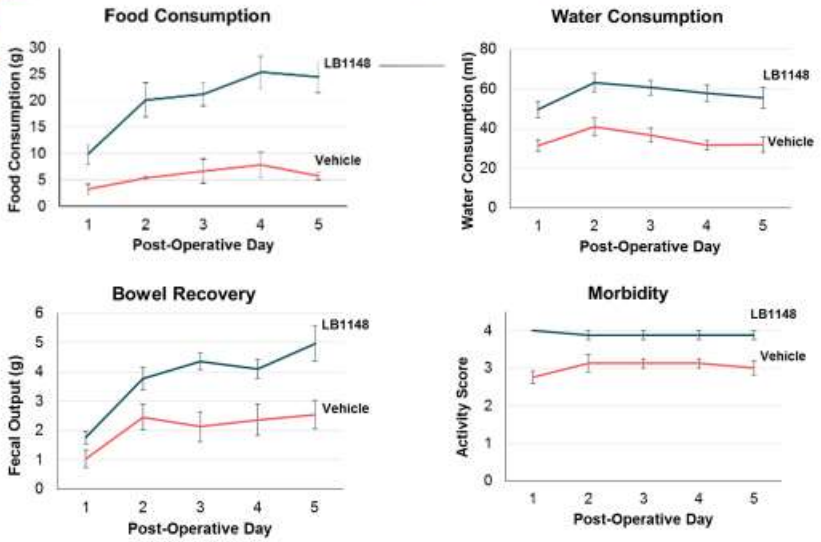

Resuscitation Adjunct
Gut protease inhibitors

A Different Strategy LB1148

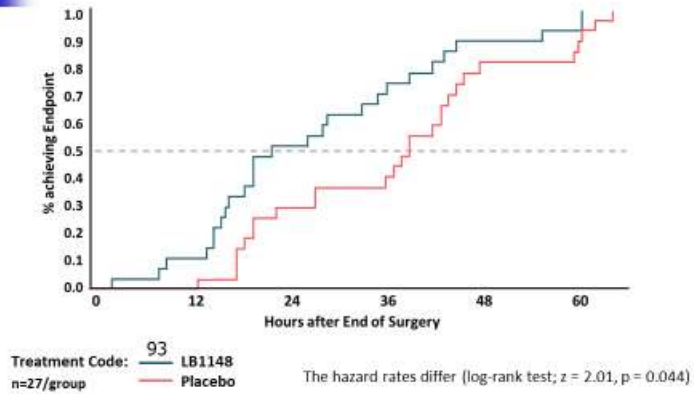
- Oral small-molecule therapeutic
  - Active ingredient: tranexamic acid
  - Used as bowel prep
  - Inhibits 17 digestive enzymes: Prevents damage to the intestine and adhesion formation
  - Preserves bowel function
  - **Reduces hospital stay ,post-op complications**
- Known safety profile
  - FDA-approved components
    - 505(b)2 regulatory pathway
- Patented formulation

Preoperative LB1148 Prevented Abdominal Adhesions in Rat

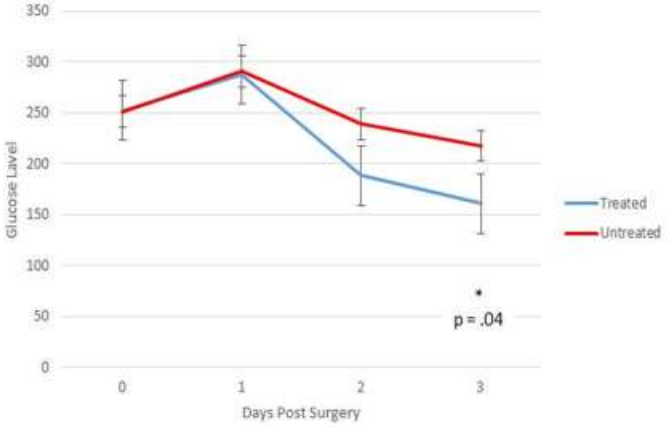
LB1148 Improves postop GI function



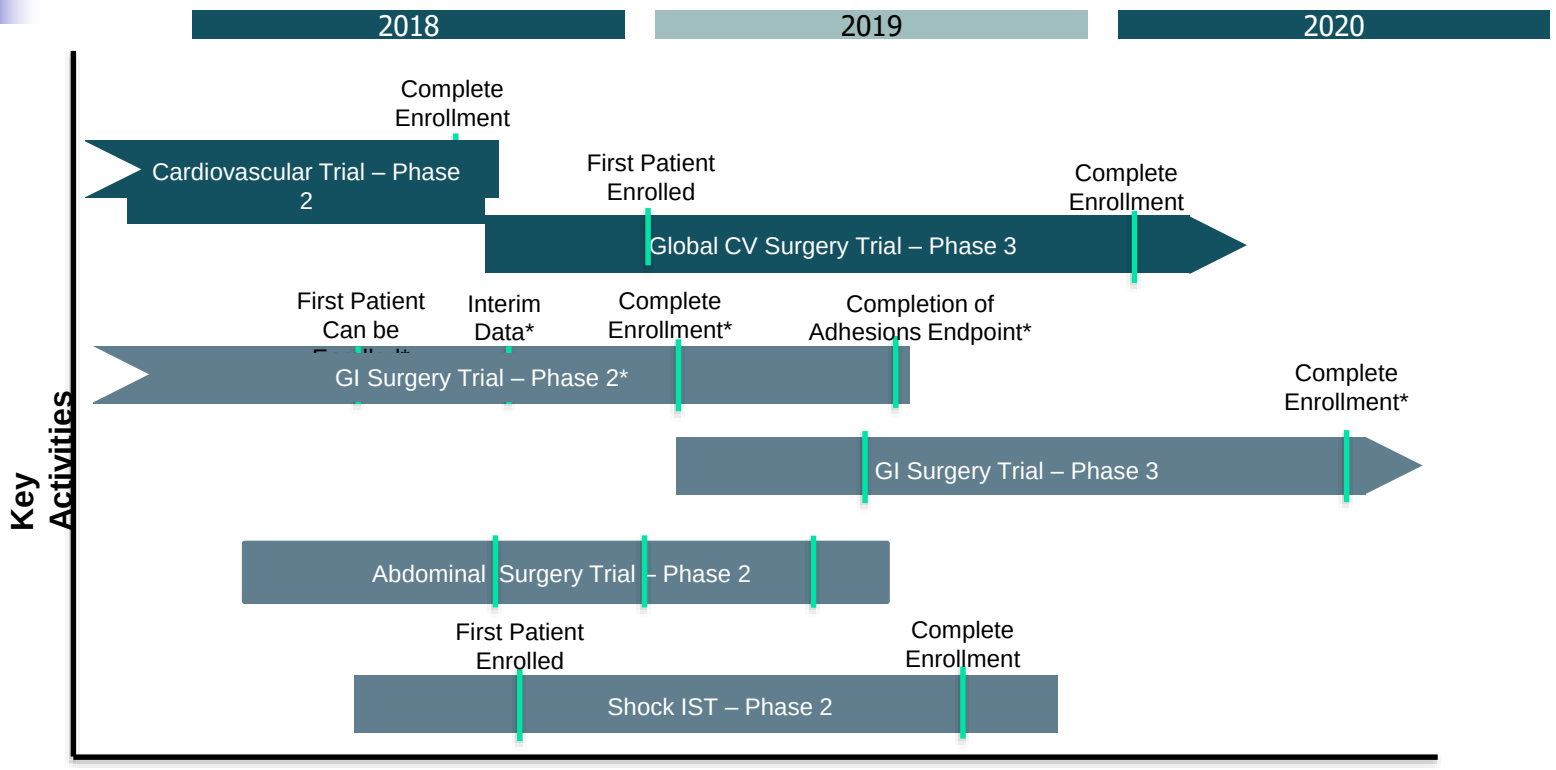
Phase 2: Cardiovascular Surgery - LB1148 –return of function



Improves Glucose Control



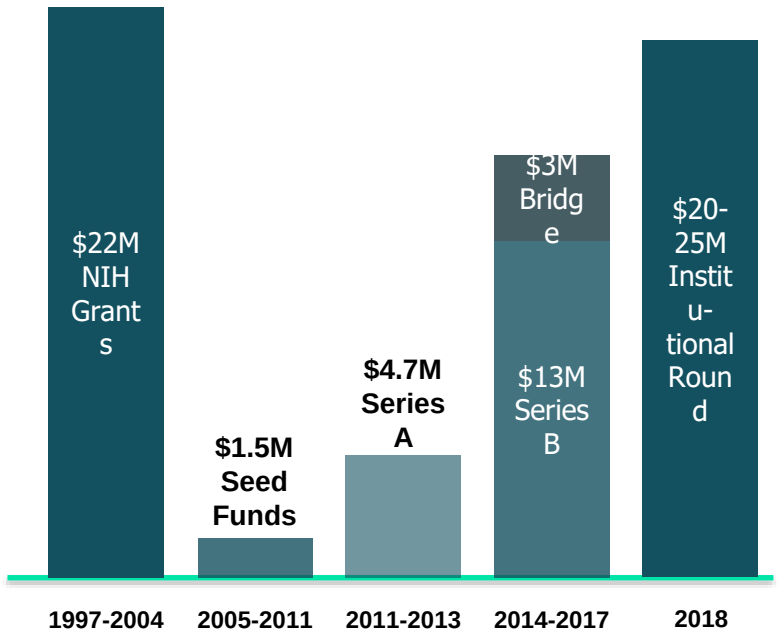
Company Activities and Timelines



** With adequate capital trial can commence enrollment within 2-3 weeks.*

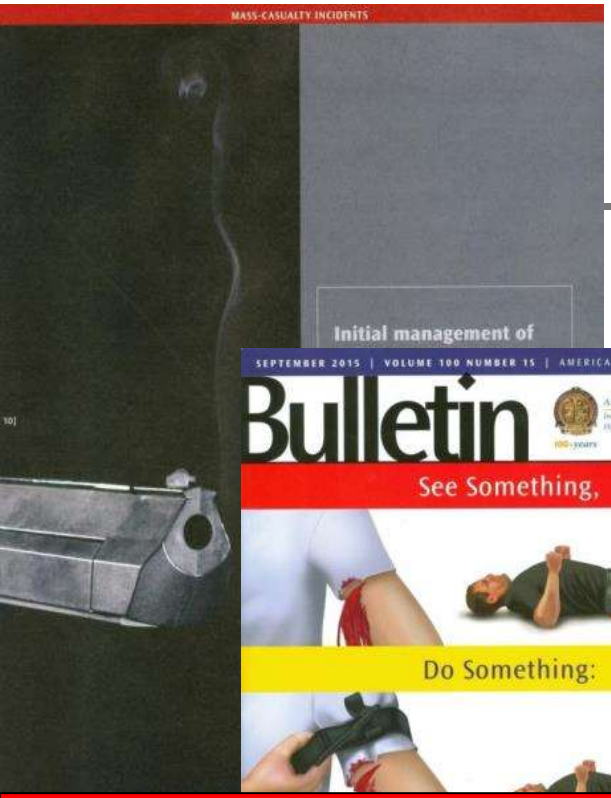
Selected Financial Data

Mix of non-dilutive and private financings



- Raising $20M to $25M intuitional pre-IPO financing round. This funding will carry LBS through multiple phase 2 data readouts.
- With positive phase 2 data readouts in mid-2018 LBS will pursue an IPO in Q3.

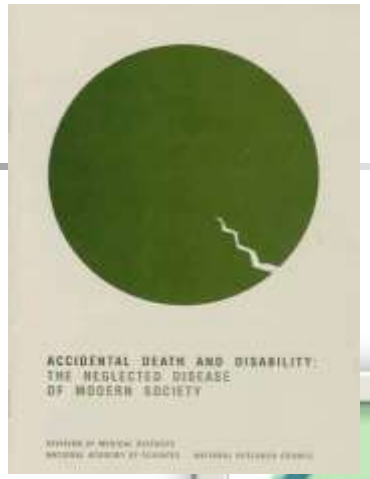
The Hartford Consensus

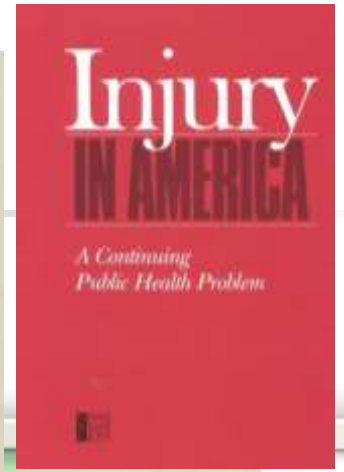


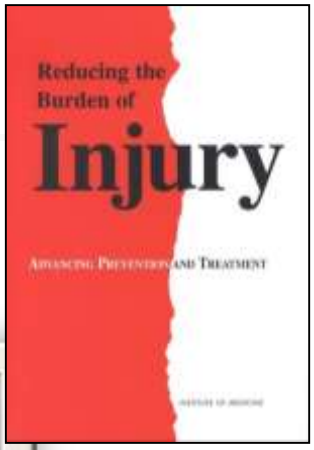
Website:
BLEEDING CONTROL.ORG

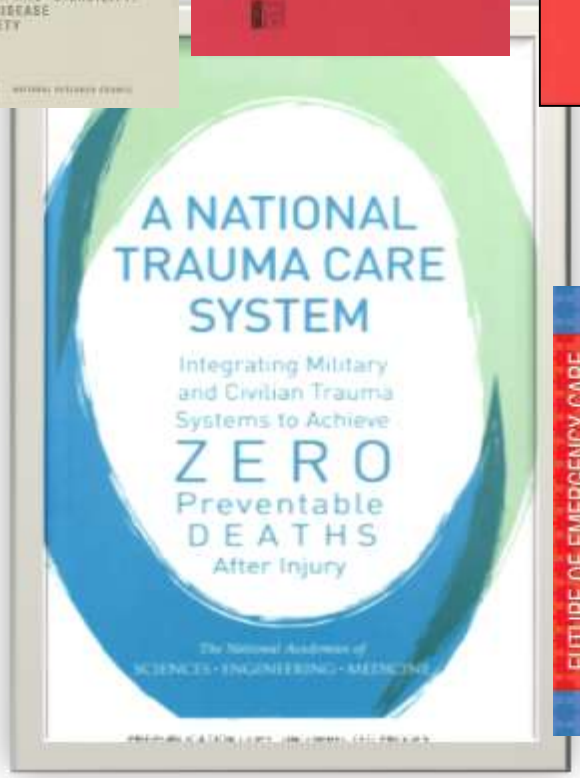
Public Course, National Focus
PSA – OCT 2016

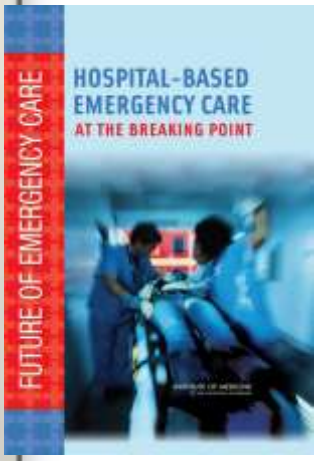
National Academy of Medicine











- 2016 - Calls for Zero Preventable Deaths
  - ACS Sponsor
- National Implementation Strategy
  - Sharing of Civilian and Military Systems Approach
- Nov 1-2, 2016

Conclusions

- We have ambivalence about resuscitation
- Religion, economics, war time logistics and our knowledge of shock have influenced practice
- The study of wartime injuries has changed medical practice repeatedly

Conclusions

- Early coagulopathy is real
  - need early indicators
- The reconstitution of blood is likely to save lives
- Targeting gut end organ response holds promise
- Clinical trials and reevaluation of protocols make this clearer · it is the only way