Resuscitation: Past Beliefs and Current Clinical Trials

David B. Hoyt, MD FACS
Executive Director
American College of Surgeons
Chicago, IL
Resuscitation

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

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

Resuscitation – Greek Medicine

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

This will take 4000 years to overcome
Alexander the Great - 336 BC

Galen – Blood letting

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

Galens’ Theory

Roman Military Care: Organized System

World Changes

- Christianity 400-500
- Latin to Arabic
  - Galen to Avicenna
  - Bled on opposite side
- Islam 700-800

Scientists went along for Aristotle’s Study of Natural History

Spreading Greek Medicine

Research Study During Conflict Established

Far Forward Care Established
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

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

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
Early Gun Shot Wounds

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

Shock still not a priority
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

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

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

1960s - Civilian Use

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

Hx Coagulopathy 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
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 in Trauma Systems**

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

---

**New Concept in Damage Control**

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

---

**Saw sicker patients earlier**

**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

RFA 2004
Resuscitation Research Network
- 264 EMS/fire agencies
- 194 hospitals
- Greater than 100 IRBs
- 36,000 EMS/fire personnel
- Population of 24 million

2005

- Seattle/KingCo RCC
- UWCTC
- Portland ROC
- Milwaukee RCC
- Ottawa/OPALS/B.C.
- Iowa Network
- UCSD-San Diego RCC
- Dallas CRR
- Pittsburgh
- Toronto
- Alabama Resus
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?

2015 - Low vs. Conventional Resuscitation Trial Completed

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

BLAST - 2015

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

<table>
<thead>
<tr>
<th></th>
<th>24-Hour Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Limited</td>
<td>96</td>
</tr>
<tr>
<td>Standard</td>
<td>95</td>
</tr>
</tbody>
</table>
Resuscitation Strategies 2018

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

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

NIH, R01HL73233-01, Bulger et al, Arch Surg 2008
Phase III Trial - 2010

28 day survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>28 day survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSD</td>
<td>74.5%</td>
</tr>
<tr>
<td>HS</td>
<td>73.0%</td>
</tr>
<tr>
<td>NS</td>
<td>74.4%</td>
</tr>
</tbody>
</table>

P value: 0.91
Immune Effects Realized

APOPTOSIS

HSD

CIRCULATING NEUTROPHILS

ACTIVATION
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

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

Historical View

- Measure coagulation and platelet counts
- Give plasma when INR or aPTT > 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

Historical View

- Measure coagulation and platelet counts
- Give plasma when INR or aPTT > 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
Iraq – Early Aggressive Whole Blood Restoration

Effect of FFP:RBC ratio on overall mortality

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

FFP:RBC Ratio

0:22 - 1:4
n=31
65%

1:3.9 - 1:2.1
n=56
34%

1:2 - 1:0.59
n=165
20%

Borgman, 2007
Trauma → Hemorrhage → COAGULOPATHY → ACoTS

Hemorrhage → Resuscitation → Shock

Inflammation
Other Diseases
Medications
Genetics

Resuscitation → Dilution → Acidemia → Hypothermia

Hypothermia
Fibrinolysis
Factor Consumption

Ratios evaluated

PROPER Trial Completed – data May 2014
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.
Resuscitation Strategies 2018

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

Need new 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

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

PMN Activation After Shock

Critical step postulated for MOF

New Hypothesis

- Gut ischemia allows activated pancreatic proteases in gut lumen to attack intestinal wall producing inflammatory activators
Theory 1: Excessive Macrophage Stimulation Liver and Lung

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

Clinical evidence inconsistent

Autodigestion hypothesis

Normal intestine

- Containment of activated pancreatic digestive enzymes

Ischemic intestine

- Breakdown of mucosal barrier
- Leak of pancreatic enzymes

Theory 2: Ischemia, Reperfusion: PMN Activation

- Inflammatory activation
- Gut PMN sequestration and priming: PLA₂
  - Metastatic adhesion to enflamed endothelium
  - Local enzymatic and oxygen free radical destruction

Blocking not clinically effective

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

Hirshburg, Hoyt, Mattox, J. of Trauma 60(6) 1221-7, 2006
Intestinal H&E Histology

Serine Protease Inhibitor in PEG with Electrolytes vehicle Improves Morbidity

In situ zymography – MMP9

Critical Metalloprotease Activation Avoided

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

STOP, PREVENT, HEAL
Preoperative LB1148 Prevented Abdominal Adhesions in Rat

**Mean # of Adhesions**

- Vehicle: p < 0.001
- LB1148 Treated

**Phase 2: Cardiovascular Surgery**

- LB1148 - return of function

**LB1148 Improves postop GI function**

- Food Consumption
- Water Consumption
- Bowel Recovery
- Morbidity
- Fecal Output (g)

**Implements Glucose Control**

- Glucose Levels
  - Treated
  - Untreated

**93**

- Treatment: Code
- n = 27/group
- The hazard rates differ (log-rank test; z = 2.01, p = 0.044)
Company Activities and Timelines

Key Activities

- Cardiovascular Trial – Phase 2
  - Complete Enrollment
  - First Patient Can be Enrolled
  - Interim Data*

- GI Surgery Trial – Phase 2*
  - First Patient Enrolled

- Shock IST – Phase 2
  - Complete Enrollment

- GI Surgery Trial – Phase 3
  - Completion of Adhesions Endpoint*
  - Complete Enrollment

- Global CV Surgery Trial – Phase 3
  - Complete Enrollment

* 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
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