Resuscitation: Past and Present

David B. Hoyt, MD FACS
Executive Director
American College of Surgeons
Chicago, IL
Henry Swan, MD - The Beginning

- SURGERY BY DIRECT VISION IN THE OPEN HEART DURING HYPOTHERMIA
  - Henry Swan, Irvin Zeavin, S. Gilbert Blount, Jr., Robert W. Virtue
Resuscitation

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

Spectrum: Saline to Fresh Whole Blood
Early Surgery

- Ancient
  - Trephination
    - Release spirits that cause headache
  - Trauma
    - Removing arrows
    - Casting fractures
  - General care
    - Blood letting
Blood Letting – Greek Medicine

- Homer – the Iliad 800 BC
  - 147 wounds described
  - 114 died
- Mortality – 77%
  - Treatment
    - Application of herbs
    - Blood letting
Scientists went along for Aristotle's Study of Natural History Spreading Greek Medicine Research Study During Conflict Established

Alexander the Great 336 BC

Scientists went along for Aristotle's Study of Natural History

Spreading Greek Medicine Research Study During Conflict Established
Galen – Blood letting

- Born 131 AD
  - MD training – 149 AD
- Moved to Alexandria
  - Studied animal dissections
- 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
Medicine Returns to Europe

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

Origin of Chairman
Franciscan Roger Bacon: Apology

“De erroribus medicorum” – an 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
1347-Trauma Low Volume

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impolithium</td>
<td>1</td>
</tr>
<tr>
<td>Infants</td>
<td>16</td>
</tr>
<tr>
<td>Killed by a fall from the Belfrey at Alhallow's the Great</td>
<td>5</td>
</tr>
<tr>
<td>Kinglevin</td>
<td>2</td>
</tr>
<tr>
<td>Lethargy</td>
<td>6</td>
</tr>
<tr>
<td>Palsie</td>
<td>1</td>
</tr>
<tr>
<td>Plague</td>
<td>17</td>
</tr>
<tr>
<td>Rickers</td>
<td>7</td>
</tr>
</tbody>
</table>
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
Barber - Surgeons

- 1534- Company-Guild joined
  - Henry VIII
  - Monks prohibited from blood letting
- Given 4 executed criminals/year for dissection

1492- Blood Letting Calendar
Second publication Gutenberg press
Critical Development
Anatomy: Vesalius - Rejected

- Initial drawings – Galen like
- 1543 - De Fabrica Humani Corporis – 300 woodcuts
  - Pupils left him, burned his manuscripts, gave up anatomy
- Could not explain R → L passage of blood.
Critical Development
Physiology: Galileo - 1581

- Medical School @ Pisa
- Watched pendulum
  - Timed pulse
- Imprisoned by Pope for views about earth orbiting sun
Critical Development
Anatomy Meets Physiology

- Harvey – challenged Galen
  - No pores in the heart
  - Demonstrated venous return
  - Calculated ejection volume
    HR x 60cc
  - 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
SHOCK - “A momentary pause in the act of death.”

John Collins Warren
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
Transfusion Popularized

- Surgical procedure - direct transfusion
- Crile technique followed
  - 35% transfusion reaction
- Problems: coagulation, agglutination-hemolysis, technical problems, infection
Agglutination and Hemolysis

- Landsteiner - Vienna
- 1900 Published work
  - Experimented on self
  - He was grouped O
- 1912 – Ottenberg
  - Mt Sinai – simplified test
  - Reduced hemolysis to zero.
Anticoagulation

- 1915 Lewisohn - Mt. Sinai
  - Na citrate

- “The technique of blood transfusion...was suddenly made as simple...as saline infusion...”

- Slow to be adopted
  - Fever and chills - endotoxin
Walter Cannon

- MD physiologist - Harvard
- Studied American Forces
- 1923 - 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."
World War I

- 1918-US adopted citrated blood
- Post war evaluation
  - Better than gum acacia and salt solution
  - No serum reaction if blood grouped

“Slight as my experience has been 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
“But fundamentally we have been ignorant. One reason for our ignorance is the relative irregularity of the appearance of shock in civil life and the consequent difficulty of pursuing consistent studies. The circumstances of warfare, however, are such as to permit, at times, systematic examination of large numbers of shock cases instead of infrequent single cases, as in civil life. With such opportunity theoretic consideration should be set aside.”
Alfred Blalock

- 1925 – Joined Harrison
  - Vanderbilt Chief Residents
  - Vivien Thomas – 1929
- Defined relationship of blood loss to shock
  - 1/3 volume – hypotension
  - 40% - death
- Volume resuscitation critical
1924-5 Hitler and Stalin
Colloid Resuscitation - WW II

- Blood would not survive the transatlantic journey
- Shifted focus to plasma
  - Committee on Transfusion
    - 1940 - Walter B. Cannon
- Albumin first used
  - Pearl Harbor
World War II

- 1943 - Churchill- Harvard
  - “Plasma not a blood substitute”
- Described over zealous shock resuscitation
- Pushed for blood
After leaving the Boston Children's, I became a member of a surgical team in the Fourth Auxiliary Surgical Group and later in the Fifth Surgical Group in the European Theater, and my experience extended from D-plus one on Utah Beach to the Elbe River. We were in mobile platoons of field hospitals operating non-transportable wounded and I had a rather extensive experience in trauma surgery, which stood me in good stead in later years. And, among other incidents, I had the opportunity to operate on a man who had a fragment of a booby trap which had pierced his popliteal artery and had cut about halfway through. And the SOP (or the Standard Operating Procedure) officially required would have been to ligate the artery. But I felt that if I had been that man, I would like to have had someone try to save that artery, as the probability of my losing my foot would have been very grave. So, using some French-eye needles, which I had smuggled from Children's Hospital, and some 4-0 silk, I did a suture anastomosis of the artery. Fortunately, both for me and for the soldier, the anastomosis worked and no clot occurred and he left the hospital with a pink foot. This experience reinforced my Children's Hospital cardiac experience so that when I came back after the war to Denver, I was interested in both the field of congenital heart disease and vascular surgery.
Korea Blood Program

- Military program collapsed
- No blood first 70 days
- First changes in coagulation reported
  - Small transfusion volumes
1960s - Civilian Use

- Blood like oil – wildcatters
- Unregulated
  - Fractionation for drugs
  - Big money
- Inappropriate collection - rampant
- Hepatitis emerged
- AIDS – no clue
Vietnam-Coagulation Disorders

- First description: **coagulopathy**
- Described relation of shock and acidosis
- 9% of massive transfusions
  - Simmons and Collins
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 O₂ del.
- 7 randomized studies - no difference
- Increased Compartment Syndromes
Trends in Resuscitation: 1990s
Pop the Clot

- Animal models 60’s
  - Shaftan
- Clinical trial
  - Mattox
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
First Clinical Trials Network

National Heart, Lung and Blood Institute
Canadian Institutes of Health Research
National Institute of Neurological Disorders and Stroke
Defence Research and Development Canada
United States Army
Heart and Stroke Foundation of Canada
American Heart Association
Resuscitation Strategies 2011

- Should we resuscitate
- Ringer’s lactate and NS
- HTS
- Colloids
- Hemoglobin solutions
- Blood
- Other additives
- Enteral pancreatic inhibition
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.’”
2011 - Low vs. Conventional Resuscitation Trial Planned

- ROC pilot – field and early ED
- 250cc vs. normal
  - Hypotensive pts
- Challenge – get difference in two groups
Resuscitation Strategies 2011

- Should we resuscitate
- Ringer’s lactate and NS
- HTS
- Colloids
- Hemoglobin solutions
- Blood
- Other additives
- Enteral pancreatic inhibition
Trends in Resuscitation: 2000s

Fluid Type

- Concerns with R.L. and NS
  - Pro-inflammatory
  - Hyperchloremic acidosis
- HTS
  - Higher pressure for same volume
  - Immunologic advantage
Three Peaks in Mortality

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
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
Primary Outcome: 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>
<tr>
<td>P value</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Treatment and survival rates for different groups.
## Mortality by Transfusion Group

<table>
<thead>
<tr>
<th></th>
<th>HSD</th>
<th>HS</th>
<th>NS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 units PRBC, first 24 hr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died in Field or ED</td>
<td>6.4%</td>
<td>9.0%</td>
<td>3.5%</td>
<td>0.01</td>
</tr>
<tr>
<td>Died w/in 6 hours</td>
<td>6.8%</td>
<td>9.0%</td>
<td>3.7%</td>
<td>0.02</td>
</tr>
<tr>
<td>Died w/in 28 days</td>
<td>10.0%</td>
<td>12.2%</td>
<td>4.8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1-9 units PRBC, first 24 hr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died in Field or ED</td>
<td>5.0%</td>
<td>3.9%</td>
<td>3.7%</td>
<td>0.73</td>
</tr>
<tr>
<td>Died w/in 6 hours</td>
<td>5.5%</td>
<td>6.7%</td>
<td>6.7%</td>
<td>0.83</td>
</tr>
<tr>
<td>Died w/in 28 days</td>
<td>8.7%</td>
<td>9.4%</td>
<td>12.3%</td>
<td>0.31</td>
</tr>
<tr>
<td>&gt; 10 units PRBC, first 24 hr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died in Field or ED</td>
<td>0</td>
<td>0</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>Died w/in 6 hours</td>
<td>4.1%</td>
<td>3.5%</td>
<td>5.9%</td>
<td>0.35</td>
</tr>
<tr>
<td>Died w/in 28 days</td>
<td>6.8%</td>
<td>5.5%</td>
<td>8.5%</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Immune Effects

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 2011

- Should we resuscitate
- Ringer’s lactate and NS
- HTS
- Colloids
- Hemoglobin solutions
- Blood
- Other additives
- Enteral pancreatic inhibition
Human Polymerized Hemoglobin

1 Unit = 50 Grams

- 500ml, 10g/dl
- $P_{50} = 28-30$ torr
- $T_{1/2} = 1$ day
- Shelf-life > 1 year
Ambulance Infusion
Results: Study Overall

- 714 patients
- 82 patients died

349 Received PolyHeme®
- 46 Deaths (13%)

365 Received Control
- 36 Deaths (10%)

NO Difference
Resuscitation Strategies 2011

- Should we resuscitate
- Ringer’s lactate and NS
- HTS
- Colloids
- Hemoglobin solutions
- **Blood**
- Other additives
- Enteral pancreatic inhibition
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


500 mL

Warm

Hct: 38-44%

Plt: 150-400K

Coags: 100%

1500 mg Fibrinogen
Historical View

- Measure coagulation and platelet counts
- Give plasma when not INR or aPTTTr ≥ 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
Civilian Trends 70s-80s

- Role of FFP
  - “It is **not necessary** to supplement transfusion of stored modified whole blood with fresh blood or fresh frozen plasma”
    - Counts 1979

- Role of platelets
  - “Prophylactic platelet administration is **not warranted** as a routine measure to prevent massive transfusion … microvascular non mechanical bleeding (MVB)”
    - 1985-Reed
Early Suggestion about Ratios

- Major vascular injuries - Denver General 1982

- “Although coagulation studies were often poorly documented, indirect evidence of inadequate factor replacement was obtained by calculating the ratio of bank blood to units of fresh frozen plasma...commonly accepted ratio of 4-5:1 was evident, increasing to 8:1 in non survivors and 9:1...in overt coagulopathy...”
Trauma Associated Coagulopathy

- 1999-Cinat
  - Mortality improved
    - More aggressive coagulation correction
    - More efficient warming
    - Increased component therapy
    - Decreased operation time

- **Ratio of FFP: RBC may be important**
  - University of California, Irvine
Iraq

- Fresh whole blood - massive transfusion
- Virtual fresh whole blood 1:1:1
  - Evolved

**Fresh whole blood - massive transfusion**

**Virtual fresh whole blood 1:1:1**

Evolved

**TIME = 0**
Initial labs drawn  **Type & Cross**

Immediately gets 4 donors from RTD tent Or from CSH to “prime” pump

**Additional Donors**
Called from phone List ~8 at a time

Any gaps in Donors Filled with Additional donors

**Whole Blood Drive**

“Walking Blood Bank”

**DCCS**

**Blood Bank**

**Nursing Supervisor**

**Surgeon**

**Emergency Release pRBCs**

Massive Transfusion Pack:
4 pRBC
4 FFP
10 cryoppt

**Whole Blood Drive**

**4 FWB**

**60 MINUTES**

**30 MINUTES**

**90 MINUTES**

**120 MINUTES**

**PROTOCOL TERMINATED WHEN NO LONGER NEEDED**

**Suspend routine duties**

**Get help**
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

Effect of FFP:RBC ratio on overall mortality

<table>
<thead>
<tr>
<th>FFP:RBC Ratio</th>
<th>Mortality %</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:22 - 1:4</td>
<td>65%</td>
<td>31</td>
</tr>
<tr>
<td>1:3.9 - 1:2.1</td>
<td>34%</td>
<td>56</td>
</tr>
<tr>
<td>1:2 - 1:0.59</td>
<td>20%</td>
<td>165</td>
</tr>
</tbody>
</table>

Borgman, 2007
Education Initiative for Critical Bleeding in Trauma

- Consensus publications
  - Current Practice Profile
  - Animal models
  - Mechanisms

- Multidisciplinary Consensus study
  - July 2008
  - Hemostasis mechanisms
  - Coagulopathy mechanisms
  - Blood Component Therapy

TRIUMA Supplement 2008
I want blood!!!

PROPER Trial Planned
Freeze Dried FFP

- FDA approved product likely
- Great interest in pre-hospital trial
Resuscitation Strategies 2011

- Should we resuscitate
- Ringer’s lactate and NS
- HTS
- Colloids
- Hemoglobin solutions
- Blood
- Other additives
- Enteral pancreatic inhibition
Other Promising Agents

- Pentoxyphyline
- Ethyl pyruvate
- Antioxidants
- Erythropoietin
- Estrogen
  - Current ROC trial
- Tranexamic acid
Autodigestion hypothesis

Normal intestine

• Containment of activated pancreatic digestive enzymes

Ischemic intestine

• Breakdown of mucosal barrier
• Leak of pancreatic enzymes
Pancreatic Enzyme Inhibition: Intestinal H&E Histology

Sham Shock

Shock

Shock - inhibition

Serine Proteinase Inhibition
Post Shock Morbidity

Postoperative score

- 4- Normal Behavior
- 3- Mild Injury
- 2- Moderate Injury
- 1- Severe Injury

Shock only | Shock+GL | Shock+GL+NM
Gut protease inhibitors

Resuscitation
Adjunct
Conclusions

- We have ambivalence over transfusion
- Religion, economics, war time logistics and our knowledge of shock have determined practice
- The study of wartime injuries has changed medical practice repeatedly
Conclusions

- Early coagulopathy is real
  - damage control scenario
  - need early indicators
- Protocols exist
  - inconsistent within and across trauma centers
  - target correction too late do to their incremental nature
Conclusions

- The reconstitution of blood and use of adjuvant therapy is likely to save lives
- Clinical trials and reevaluation of protocols is needed