



**MEMC V**  
**Resuscitation Session:**

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**Resuscitation of Hemorrhagic Shock Patients with Hemoglobin-based Oxygen Carriers (HBOCs)**



Edward P. Sloan, MD, MPH 

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**2009 MEMC V Meeting**



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**Disclosures**

- DCLHb research via UIC contract from Baxter Healthcare and Jackson Foundation (NMRC).
- Consultant to Northfield Laboratories and Biopure.

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**• Hemoglobin-based Oxygen Carriers**



## **HBOCs**

### **Optimal Shock therapy**

- Cellular and tissue hypoxia
- Goal: Enhance cellular perfusion
- Our approach is macro
- Limitations of current Rx
- HBOCs: Can they enhance perfusion and improve resuscitation?

## **Perspectives**

### **Harvey Klein, MD**

- NIH Transfusion Medicine chief
- 8/13 million units urgent
- Allogenic blood has inherent risks
- “An inherently defective raw material”

## **Perspectives**

### **Harvey Klein, MD**

- Infection
- Hemolytic reactions
- Allo Abs
- Immuno-suppression
- Graft vs. host
- Allergic/febrile

## **Perspectives**

### **C. Everett Koop, MD**

- “4/13 million transfusions... absolutely essential”
- “If blood were completely safe, we would use more of it...”
- “Aggregate blood risk is not insignificant”
- Time, storage, shortages, aging pop

## **Human Banked Blood**

### **Limitations**

- Outdated blood: not useful
- 25% of RBC's cleared by 24°
- Reticulo-endothelial system overload
- Immuno-suppression

## **Human Banked Blood**

### **Limitations**

- Up to 50% of RBCs: No O<sub>2</sub> delivery
- 40 torr (MVO<sub>2</sub>): 33% efficiency
- Significant left shift
- 2,3 DPG depleted
- Restoration in 8-12 hours

## **HBOCs**

### **Issues to Consider**

- O2 Carrier type
- Hb sourcing
- Hb configuration
- Clinical properties
- Clinical indications

## **HBOCs**

### **O2 Carrier Type**

- O2 carrying solution
- PFCs
- Hb-based O2 carrier

## **HBOCs**

### **Hb Sourcing**

- Human
- Bovine
- Recombinant
- Transgenic species

## **HBOCs**

### **Hb Configuration**

- Single molecule
- Multiple molecules
- Added moieties
- Packaging

## **HBOCs**

### **Clinical Properties**

- Oxygen carrier
- Colloid volume expander
- Viscosity agent
- Pressor agent
- Perfusion agent

## **HBOCs**

### **Clinical Indications**

- Blood sparing agent
- Blood substitute
- Resuscitation drug

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# HemAssist (Baxter)

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# The US ED THS & the EU Prehospital HOST DCLHb Clinical Trials

Edward P. Sloan, MD, MPH

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# DCLHb Overview

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## DCLHb Overview

- 10% solution of tetrameric Hb
- Proposed characteristics:
  - Oxygen carrier, delivery
  - Pharmacologic effect
  - Enhanced perfusion
  - Effective even with hemorrhage
  - Improved preclinical outcomes
- Safe in phase II THS clinical trial

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# US THS Clinical Trial Design and Results

Edward P. Sloan, MD, MPH

**Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock**  
A Randomized Controlled Efficacy Trial

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Jeffrey Range, MD  
Mary Nan Mallory, MD  
and George Rodman, Jr, MD  
for the DCLHb Traumatic Hemorrhagic Shock Study Group

**Context** Severe, uncompensated, traumatic hemorrhagic shock causes significant morbidity and mortality, but resuscitation with an oxygen-carrying fluid might improve patient outcomes.

**Objective** To determine if the infusion of up to 1000 mL of diaspirin cross-linked hemoglobin (DCLHb) during the initial hospital resuscitation could reduce 28-day mortality in traumatic hemorrhagic shock patients.

**Design and Setting** Multicenter, randomized, controlled, single-blinded efficacy trial conducted between February 1997 and January 1998 at 18 US trauma centers selected for their high volume of critically injured trauma patients, but 1 did not enroll patients.

**Patients** A total of 112 patients with traumatic hemorrhagic shock and unstable vital signs or a critical base deficit, who had a mean (SD) patient age of 39 (20) years. Of the infused patients, 79% were male and 56% were white. An exception to informed consent was used when necessary.

**Intervention** All patients were to be infused with 500 mL of DCLHb or saline solution. Critically ill patients who still met entry criteria could have received up to an additional 500 mL during the 1-hour infusion period.

**Main Outcome Measures** Twenty-eight day mortality, 28-day morbidity, 48-hour mortality, and 24-hour lactate levels.

## Protocol Design

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- Sample size = 850 patients
- Patient population: severe trauma pts
  - Estimated 2 - 4% of all trauma pts
- Persistent hypoperfusion (inadequate tissue oxygenation)

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## Dosing

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- Dose: 500 mL initially, then 2 x 250 mL for a total of 1000 mL, as needed, based on clinical status
- Infusion to begin within 60 minutes after hospital arrival
- Infusion complete within 60 minutes after dosing begins

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## Patient Care

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- All standard therapies and procedures normally used to treat patients with severe traumatic injury to be provided.
- Standard therapy included immediate:
  - Fluid therapy
  - Blood transfusion
  - Surgical intervention

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## Inclusion Criteria

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- Males or females 18 years or older
- Evidence of hemorrhage
- Tissue hypoxia and cellular hypoperfusion

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## Inclusion Criteria

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- Hypoperfusion criteria:
  - SBP  $\leq$ 90 & pulse  $\geq$ 120 or
  - SBP  $\leq$ 90 & pulse <60 with pre-terminal rhythm
  - Base deficit of 15 mmol/L or worse

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## Exclusion Criteria

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- Age <18 years
- Known pregnancy
- Pulseless traumatic arrest during hospitalization
- Imminent death precludes resuscitation efforts
- Known objection to the use of blood, blood products

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### Exclusion Criteria

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- Known injury time >4 hours prior to infusion
- Hospitalization >60 minutes prior to infusion

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### Exclusion Criteria

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- Combined multisystem and head trauma with clinical findings consistent with significant mass effect:
  - Severe coma, lateralizing signs, posturing, or pupil dilatation secondary to uncal herniation
- Isolated head trauma, penetrating or blunt

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### Primary Endpoint: Mortality

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- Reduced 28-day mortality
  - 40% mortality expected in targeted protocol patient population
  - 25% mortality reduction projected with DCLHb therapy
    - Standard therapy: 40%
    - DCLHb therapy: 30%

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### US THS Trial Overview

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- First patient enrolled: Feb 1997
- Last patient enrolled: Jan 1998
- New study sites
  - Feb - Aug 97: 5
  - Sept - Dec 97: 12 (17 total)
- Number of patients: 98 (112 ITT)
- Enrollment hold: Jan 2, 1998
- Recommended end: March 17, 1998

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### Overall US THS Mortality

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- DCLHb mortality: 24/52 (46%)
- Control mortality: 8/46 (17%)
- p<.003
  
- Blunt mortality: 23/55 (42%)
- Penetrating mortality: 9/43 (21%)
- p<.03

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### DMC Recommendation

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March 17, 1998

- “The THS 95.1 Data Monitoring Committee recommends to the Sponsor that the THS 95.1 trial be terminated, because of an observed increase in mortality among patients receiving DCLHb relative to those receiving normal saline.”

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## DMC Recommendation Basis

- 28-day raw mortality
  - Control: 8/46 (17%)
  - DCLHb: 24/52 (46%)  $p=0.006$
- Kaplan-Meier 28-day mortality analysis,  $p=0.003$
- Intent to treat analysis,  $p=0.015$

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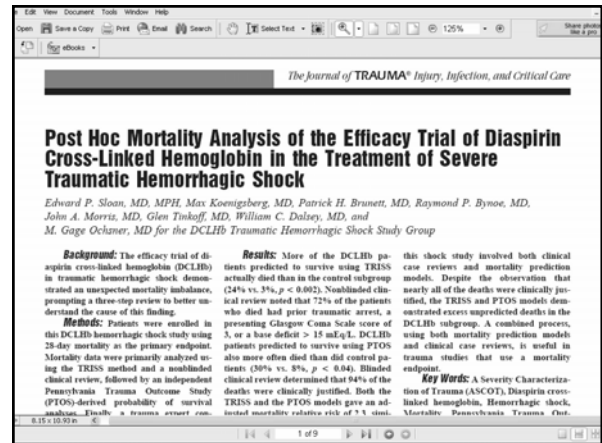
## DMC Recommendation Basis

- Futility Analysis: Extremely low probability of achieving a positive trial result (mortality endpoint)

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## US THS Study Results: Further Observations

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## US THS Mortality Analysis

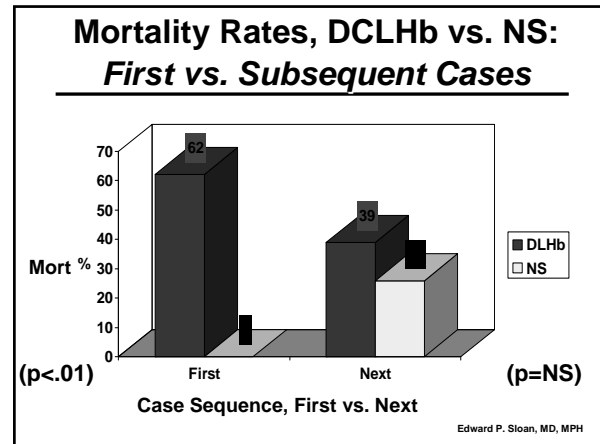
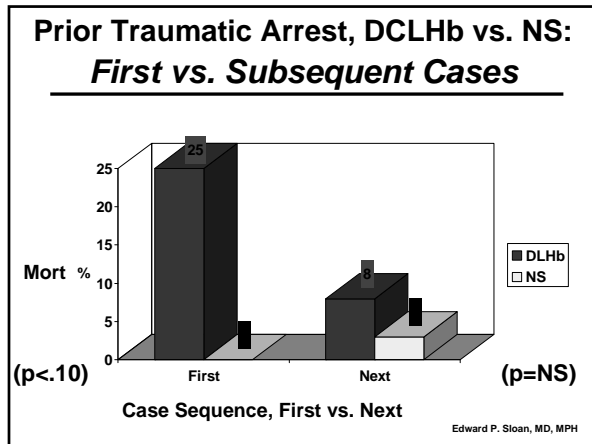
- Post-hoc mortality review
- More DCLHb treated patients predicted to survive did not as compared to control patients
- 94% of deaths clinically justified in blinded clinical review
- 72% of deaths related to prior traumatic arrest, GCS = 3, BD > 15

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## US THS Study Conduct Analysis

- First vs. subsequent analysis
- Patient profiles differ over time
- Unstable mortality rate over time
- Suggests study conduct influenced trial results to some extent
- (Subsequent mortality rates similar to EU HOST trial)

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- ### US THS Intent to Treat
- Non-infused ITT patients sickest
  - Same ITT, infused DCLHB mortality
  - Different ITT control patient mortality
    - Infused control mortality: 8/46 (17%)
    - ITT control mortality: 5/7 (71%)
    - p<.007
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- ### US THS Protocol Violations
- Higher DCLHb mortality patient protocol violation rate trend
  - Hb mortality violations: 9/24 (38%)
  - NS mortality violations: 1/8 (12%)
    - p<.38
  - Suggest study conduct influence
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- ### US THS Prior Cardiac Arrest
- Higher DCLHb prior cardiac arrest rate
  - DCLHb prior arrest: 10/52 (19%)
  - NS prior arrest: 1/46 (0.3%)
    - p<.02
  - Suggests baseline mortality risk difference
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- ### US THS Hemorrhage Analysis
- When a vascular injury was present in DCLHb patients, it was more likely to be the worst injury
  - Vascular injury: higher mortality trend
  - No relationship between any SAE, AE of hemorrhage and DCLHb use
  - No relationship between vascular injury and hemorrhage AE
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## US THS Early Mortality

- Comparable early mortality rates
- DCLHb 48 hr mortality: 20/24 (81%)
- NS 48 hr mortality: 7/8 (88%)
  - P=1.00
- Suggests that early deaths due to comparable baseline mortality risk in both groups

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## US THS Early Fluid Use

- DCLHb patients who died received less fluids than did comparable control patients who died
- DCLHb patients: 5-8 liters in 2 hrs
- Control patients: 12-18 liters in 2 hrs
- No evidence of inadequate fluid use in either group (3:1 rule, 6 liters class IV)
- Markedly higher fluid use in control pts

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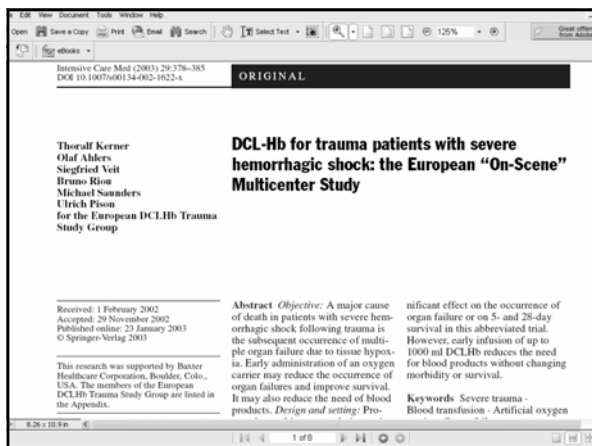
## US THS Early Blood Use

- DCLHb patients who died received less blood than did comparable control patients who died
- DCLHb patients: 6-9 units in 2 hrs
- Control patients: 8-12 units in 2 hrs
- Clinically relevant early difference?
- Greater difference at 3 hrs and beyond

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## EU HOST Clinical Trial Design and Results

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## EU HOST Design

- Prehospital trauma patient study
- Class III, IV hemorrhagic shock
- SBP < 90 mmHg
- No infusions > 1000 cc prior to start
- Study infusions to SBP 90-100 mmHg
- Other exclusions similar
- Different clinical endpoints

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### EU HOST Study Endpoints

- Primary endpoint: Reduced organ failures and deaths at 3-5 days
- Secondary endpoints:
  - Organ failures at 14 days
  - Blood use up to 7 days
  - 28 day mortality

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### EU HOST Trial Overview

- First patient enrolled: July 1997
- Last patient enrolled: June 1998
- Study sites: 27 sites, 3 countries
- Number of patients: 121
- Screened patients: 993
- Enrollment end: June 1998

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### EU HOST Enrollment End

- No reduced organ failures, mortality
- Concerns from US THS study
- Greater need for blood in control pts
- AEs not statistically different
- No mortality in penetrating trauma control patients

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### Overall EU HOST Mortality

- DCLHb mortality: 23/54 (43%)
- Control mortality: 25/67 (37%)
- $p < .12$
- Blunt mortality: 43/84 (51%)
- Penetrating mortality: 5/37 (14%)
- $p < .001$

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## Combined Mortality Data from the US THS & EU HOST Clinical Trials

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### Mortality in US THS, EU HOST

- Some mechanism differences
- Different practice setting
- Restricted fluid infusions in EU prior
- What are the combined results?
- How do the results compare based on mechanism and study solution?

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### Overall Combined Mortality

- DCLHb mortality: 47/106 (44%)
- Control mortality: 33/113 (29%)
- $p < .025$
  
- Blunt mortality: 66/139 (47%)
- Penetrating mortality: 14/80 (18%)
- $p < .01$

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### Mortality Based on MOI, Infusion

- DCLHb blunt: 33/64 (52%)
- Control blunt: 33/75 (44%)
- $p < .37$
  
- DCLHb penetrating: 14/42 (33%)
- Control penetrating: 0/38 (0%)
- $p < .001$

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### Mortality in US THS, EU HOST

- Control penetrating patients fared extremely well
- No penetrating control patient mortality in two studies on two continents
- Noted influence on overall mortality comparisons

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## US and EU Traumatic Hemorrhagic Shock Study Results: *Further Observations*

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### US THS BP Effects

- **BACKGROUND:** Hemoglobin solutions have demonstrated a pressor effect that could adversely affect hemorrhagic shock patient resuscitation through accelerated hemorrhage, diminished perfusion, or inadequate resuscitation.

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### US THS BP Effects

- **CONCLUSIONS:** Neither mean BP readings nor elevated BP readings were correlated with DCLHb treatment of traumatic hemorrhagic shock patients. As such, no clinically demonstrable DCLHb pressor effect could be directly related to the adverse mortality outcome observed in the US study.

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### US THS Perfusion Effects

- **BACKGROUND:** DCLHb has demonstrated a pressor effect that could adversely affect traumatic hemorrhagic shock patients through diminished perfusion to vital organs, causing base deficit (BD) and lactate abnormalities.

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### US THS Perfusion Effects

- **CONCLUSIONS:** Although expired patients had more greatly altered perfusion than those who survived, DCLHb treatment of traumatic hemorrhagic shock patients was not associated with BD or lactate abnormalities indicative of poor perfusion.

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### US THS Shock Index Effects

- **OBJECTIVES:** To determine whether diaspirin cross-linked hemoglobin (DCLHb) use impacts the ability of the shock index (SI) to detect uncompensated shock and the need for resuscitation in traumatic hemorrhagic shock patients.

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### US THS Shock Index Effects

- **CONCLUSIONS:** SI values correlated with outcome in traumatic hemorrhagic shock patients from the DCLHb studies. Because the ability of SI to predict mortality did not vary with DCLHb use, HBOCs tested in future clinical trials should not be expected to alter the ability of the SI to detect uncompensated shock.

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### DCLHb (HemAssist) Status

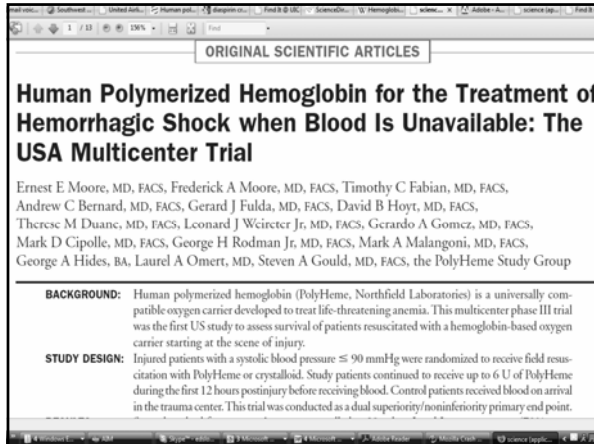
- No FDA submission
- Baxter no longer studying use
- Second generation recombinant technology not successful
- No continued study
- No potential for use

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## PolyHeme (Northfield)

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### US THS PolyHeme Results

- **CONCLUSIONS:** Patients resuscitated with PolyHeme, without stored blood for up to 6U in 12 hours post-injury, had outcomes comparable with those for the standard of care. Although there were more adverse events in the PolyHeme group, the benefit-to-risk ratio of PolyHeme is favorable when blood is needed but not available.

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### PolyHeme Status

- No FDA approval for use
- Northfield Laboratories: bankruptcy
- No continued study
- No potential for use

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### Hemopure (Biopure)

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### US RESUS Protocol

- Naval Medical Research Center (NMRC)
- HBOC-201
- Hemopure (Biopure)
- Pre-hospital resuscitation
- Traumatic hemorrhagic shock
- Exception to informed consent

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### Hemopure Status

- No FDA approval for use
- Approved for use when blood needed in South Africa
- Approved for veterinary use
- No continued study
- No potential for use in trauma
- Biopure in bankruptcy

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## ***Resuscitation of Hemorrhagic Shock Patients with Hemoglobin-based Oxygen Carriers (HBOCs)***



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## **Approving an HBOC**

- It is difficult to:
- Outperform blood, or
- Prove that blood is outperformed, or
- Develop an HBOC that is safe, or
- Enhance the current standard of care in the resuscitation of traumatic hemorrhagic shock patients.

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## **Resuscitation Protocol?**

- Volume resuscitate to some extent
- Support perfusion
- Allow permissive hypotension
- Strive for compensated shock
- Utilize blood products wisely

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## **Blood Product Use**

- Rapid use of O neg blood
- Quickly obtain type specific blood
- Cross match as able
- Utilize platelets
- Utilize fresh frozen plasma
- Auto-transfuse
- Quick operative intervention

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## **HBOC Resuscitation**

- Take Home Points:
  - Optimize the standard of care...
  - Research is hard...
  - Innovations are hard to develop...
  - It is hard to outdo what God has done...
  - But we must keep trying.



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## **Questions?**

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