Plasma Products:  
Thawed, Liquid, Dried and Beyond

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Disclosures

Founder and on the board of Decisio Health

The PROPPR Study was Funded by NIH

DoD funded for prehospital multicenter transfusion study
Bottom Line Up Front

• Hemorrhage is the leading potentially preventable cause of trauma death
• Crystalloid resuscitation increase blood loss, transfusion requirements and death

• Balanced blood product resuscitation decreases blood loss, transfusion requirements and improves survival
  – Plasma as the primary resuscitation fluid
  – Must have thawed/liquid plasma in the ED or prehospital to really do this well

• Time is critical
• Rapid progress in trauma care occurs during a war.

• Damage control resuscitation addresses **diagnosis and treatment of the entire lethal triad** immediately upon admission.
DCR components

- Stop bleeding
- Hypotensive resuscitation
- Minimize crystalloid
- Use plasma to resuscitate patients
- Increased platelet use
- Reverse hypothermia and acidosis
- Hemostatic adjuncts
Optimal Resuscitation Fluids
In the next evolution of transfusion practice, it is exciting to consider the real logistical and clinical benefits of exclusively using dried products such as plasma, platelets, fibrinogen, and RBCs to resuscitate bleeding patients, available at the point of care.

- **Dried Plasma and fibrinogen will replace all time sensitive use of FFP and Cryo**
  - Essentially all transfusions for bleeding
The resuscitation fluids of choice for casualties in hemorrhagic shock are (in priority order):

- whole blood,
- plasma, RBCs and platelets in 1:1:1 ratio;
- plasma and RBCs in 1:1 ratio;
- plasma or RBCs alone;
- Hextend;
- crystalloid (lactated Ringer’s or Plasma-Lyte A).
How do you make early blood products happen?

- Work with the Blood bank and Donor Center
- O- RBCs—in the ED and prehospital
- AB or A plasma—in the ED and prehospital
  – Thawed or Liquid plasma
- Platelets—in the ED and prehospital

- Prehospital and in the ED
Instituting a thawed plasma procedure: it just makes sense and saves cents

Gay Wehrli, Nancy E. Taylor, Annette L. Haines, Thomas W. Brady, and Paul D. Mintz

**TABLE 1. Product utilization**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Total products transfused</td>
<td>38,352</td>
<td>45,482</td>
</tr>
<tr>
<td>Total plasma units transfused</td>
<td>9,726</td>
<td>14,121</td>
</tr>
<tr>
<td>Total products discarded</td>
<td>429</td>
<td>355</td>
</tr>
<tr>
<td>Total plasma units discarded</td>
<td>37</td>
<td>13</td>
</tr>
</tbody>
</table>

1. FFP
2. Thawed
3. Liquid
4. Dried
LIQUID PLASMA (LIQUID PLASMA) is separated no later than 5 days after the expiration date of the Whole Blood and is stored at 1 to 6 C. The profile of plasma proteins in Liquid Plasma is poorly characterized. Levels and activation state of coagulation proteins in Liquid Plasma are dependent upon and change with time in contact with cells, as well as the conditions and duration of storage.

Action
This component serves as a source of plasma proteins. Levels and activation state of coagulation proteins are variable and change over time.

Indications
Initial treatment of patients who are undergoing massive transfusion because of life-threatening trauma/hemorrhages and who have clinically significant coagulation deficiencies.
Plasma Options and Time

• FFP (requires thawing)
  – 4 hours
  – Time and breakage

• Thawed plasma
  – 5 days
  – Degradation

• Liquid plasma
  – 25 days
  – degradation

AB or low titer A
How I treat patients with massive hemorrhage

Pär I. Johansson, Jakob Stensballe, Roberto Oliveri, Charles E. Wade, Sisse R. Ostrowski and John B. Holcomb

Copenhagen and Houston

Diagram:
- Start of Hemorrhage
  - Monitoring: Correct: Temperature, Ca\(^{2+}\), K\(^+\), p\(_{\text{a}}\)O\(_{2}\), p\(_{\text{a}}\)CO\(_{2}\). Shock Reversal: pH, Lactate
  - Anti-fibrinolytics*: Tranexamic acid according to CRASH2 and/or VHA
  - Transfusion therapy: Goal-directed VHA-guided resuscitation
  - Hemorrhage dynamics: Ratio 1:1:1, RBC according to Hb.
- Hemostasis:
  - VTE prophylaxis

Time:
- 30 min
- 60 min
Does it Translate? Impact of Contemporary Military Medicine on Civilian Trauma Care


- Survey of 650 TMDs.
- For DCR, 86% of responding centers reported use of a 1:1:1 PRBC:FFP:PLT ratio.
- “This national survey of TMDs suggests that military data supporting DCR has significantly altered civilian practice.”
Changing Use of Plasma in the US 2008-2011

- The combined total of WBD and apheresis plasma
  - 3,882,000 units transfused in 2011
  - 13.4% less than 2008
    - 4,484,000 units

- However in 2011 there were 1,181,000 units of thawed plasma transfused
  - 30.4% of all plasma transfused.

- Of all plasma transfused 142,000 were Group AB.
Figure 4-3. Percent of plasma transfused as thawed plasma (average = 16.7%).
Figure 4-2. Types of plasma transfused, 2008-2011.
Prehospital and Hospital

• No distinction
• Should be a seamless continuum
• What works in the hospital should be used prehospital

• Not slow down transport
• Basic premise of EMS

5000 Hospitals
1852 trauma centers
50,000 ambulances
Translation

• Large centers with:
  – lots of trauma
  – Lots of big elective surgery
  – Lots of cancer

• For the other 4000 hospitals and their patients… out of luck
The glycocalyx is a ubiquitous barrier that protects the underlying endothelium and prevents injurious neutrophil-endothelial interaction.

A = baseline  
B= shock  
C = LR resus  
C = Plasma resus
The HP and clot forming ability of TP significantly declined with storage.

- FFP-0 TP may have a greater ability to restore hemostasis and correct coagulopathy compared with FFP-5.

The clinical consequences for transfused patients deserve further exploration.
Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma

Nena Matijevic, PharmD, PhD, Yao-Wei Wang, MD, Bryan A. Cotton, MD, MPH, Elizabeth Hartwell, MD, James M. Barbeau, MD, Charles E. Wade, PhD, and John B. Holcomb, MD, New Orleans, Louisiana

Figure 5. Effects of single freeze-thaw cycle on LQP TEG parameters. Aliquots of never-frozen LQP at each time point were frozen and subsequently thawed and analyzed by TEG. After a freeze-thaw cycle, MA was significantly decreased compared with fresh LQP-0 and was equivalent to that of thawed FFP Day 0 (TP-0).
Never-frozen liquid plasma blocks endothelial permeability as effectively as thawed fresh frozen plasma

J Trauma, 2014

Yanna Cao, MD, Anahita Dua, MD, MS, MBA, Nena Matijevic, PhD, Yao-Wei Wang, MD, Shibani Pati, MD, PhD, Charles E. Wade, PhD, Tien C. Ko, MD, and John B. Holcomb, MD, Houston, Texas

- LQP corrected TNF-α induced EC permeability and preserved hemostatic potential after 28 days of storage, similar to TP stored for 5 days.
Thawed and Liquid Plasma

• 5 day vs 23 day storage
• Spreading across trauma centers
  – 80% use the 1:1:1 approach
• Funded DoD trials
  – Many helicopter services
  – Ground EMS systems
• Practice changing despite inadequate products
The evolving role of lyophilized plasma in remote damage control resuscitation in the French Armed Forces Health Service

Trans 2013

Anne Sailliol, Christophe Martinaud, Andrew P. Cap, Corinne Civadier, Benoit Clavier, Anne-Virginie Deshayes, Anne-Christine Mendes, Thomas Pouget, Nicolas Demazeau, Marine Chueca, François-Régis Martelet, and Sylvain Ausset

- Describes their regulatory and substantial clinical experience with dried plasma
- 1945 to current
- Pathogen reduced
Spray-dried plasma and fresh frozen plasma modulate permeability and inflammation in vitro in vascular endothelial cells


Permeability Coefficient at 10%

Fold Change Permeability (cm²/min)

- Control
- LR
- Hextend
- FFP
- SD-FFP
- SDP
WBC Adhesion

A. 30% Concentration

B. 10% Concentration

% Decrease in Endothelial Leukocyte Binding

Legend:
- Control
- LR
- Hextend
- FFP
- FFP-SD
- SDP

N. S.: Not Significant

* Significant difference
The use of lyophilized plasma in a severe multi-injury pig model

Tim H. Lee, Philbert Y. Van, Nicholas J. Spoerke, Gregory J. Hamilton, S. David Cho, Kate Watson, Jerome Differding, and Martin A. Schreiber

![Graph showing volume comparisons for different plasma types and ratios.](image-url)
Adiponectin in Fresh Frozen Plasma Contributes to Restoration of Vascular Barrier Function after Hemorrhagic Shock

Adiponectin Improves Vascular Barrier Function

Shock 2015

Xiyun Deng\textsuperscript{1,*}, Yanna Cao\textsuperscript{1,*}, Maria P. Huby\textsuperscript{2}, Chaojun Duan\textsuperscript{1,3}, Lisa Bae\textsuperscript{2}, Zhanglong Peng\textsuperscript{4}, Rosemary A. Kozar\textsuperscript{4}, Marie-Francoise Doursou\textsuperscript{5}, John B. Holcomb\textsuperscript{1,2}, Charles E. Wade\textsuperscript{1,2} and Tien C. Ko\textsuperscript{1}
Back to the Future
Lyophilized Plasma Resuscitation
German Dried Plasma in the IDF
Freeze Dried Plasma at the Point of Injury- From Concept to Doctrine

Elon Glassberg\textsuperscript{1,2}, Roy Nadler\textsuperscript{1,2}, Sami Gendler\textsuperscript{1,2}, Amir Abramovich\textsuperscript{1,2}, Philip C. Spinella\textsuperscript{3,4}, Robert T. Gerhardt\textsuperscript{4}, John B. Holcomb\textsuperscript{5,6}, Yitshak Kreiss\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Product</th>
<th>LyoPlas\textsuperscript{®} (39)</th>
<th>FLyP\textsuperscript{®} (5,7,10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing country</td>
<td>Germany</td>
<td>French</td>
</tr>
<tr>
<td>Reconstitution time</td>
<td>Up to 10 minutes</td>
<td>Up to 5 minutes</td>
</tr>
<tr>
<td>Storage</td>
<td>Up to 25 c</td>
<td>Up to 25 c</td>
</tr>
<tr>
<td>Compatibility</td>
<td>Blood type specific  *</td>
<td>Universal ABO compatibility</td>
</tr>
<tr>
<td>Donor profile</td>
<td>Single donor (men or nulliparous women)</td>
<td>Up to 11 donors</td>
</tr>
<tr>
<td>Infection prevention</td>
<td>Repeated donor Serologic testing, following a 4 month quarantine</td>
<td>Amotosalen photoactivation</td>
</tr>
<tr>
<td>Container</td>
<td>Glass bottle</td>
<td>Glass bottle</td>
</tr>
<tr>
<td>pH</td>
<td>7-7.2</td>
<td>8</td>
</tr>
<tr>
<td>Reconstitution fluid</td>
<td>ml of sterile water 200</td>
<td>ml of sterile water 200</td>
</tr>
<tr>
<td>Shelf life</td>
<td>15 Months</td>
<td>24 months</td>
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</table>
French Dried Plasma Product carried by some US Special Operations Forces. Approved by FDA and WH.
Different Dried Plasmas

Several US companies working on dried plasma

Other ProCoagulant Products
Very Small, lightweight as a dried product
Plasma Studies

• Excellent baseline standard of care from the many recent studies
  – PROMMTT and PROPPR and PROHS

• New more logistically favorable products need rapid preclinical evaluation and then appropriate human studies

• Must be dried, storage for 2 years at ambient temp, rapid mixing and universal donor
Permeability?

- Reversal of endothelial damage associated with TBI and Shock
  - Decrease edema and MOF
- Liquid Plasma does this very well
  - One of the dried plasma products
- Do the PCC products?
  - 6 proteins?
- Do the fibrinogen products?
- Cost of products?
What do we do - today

• Identify patients who need resuscitation
  – Prehospital and hospital
• Use blood products, not crystalloid or artificial colloids
• Transfuse in a balanced fashion, starting with the first units
  – Platelets and plasma early
• Documented improved outcomes
“The Future”
Dried / Lyophilized Components

• Lyophilized Fibrinogen
  – Used for trauma patients in Austria
  – Approved in US
• Frozen, FD platelets or Lyophilized Platelets
  – human studies and animal trials (LP)
  – European countries in Afghanistan
• Dried plasma
  – animal studies
  – Human trials
  – Approved in many EU countries, used in Afghanistan and Israel
• RBCs
  – Stem cell derived-DARPA
  – lyophilized RBC’s?
• Various individual coagulation proteins
In the next evolution of transfusion practice, it is exciting to consider the real logistical and clinical benefits of exclusively using dried products such as plasma, platelets, fibrinogen, and RBCs to resuscitate bleeding patients, available at the point of care.

- **Dried Plasma and fibrinogen will replace all time sensitive use of FFP and Cryo**
  - Essentially all transfusions for bleeding
Thank You

The entire physician, resident, nursing, administrative, and technical team at MHH and UT

Dr Beth Hartwell

Dr Yu Bai

Ms Rhonda Hobbs