AABB Annual Meeting Education Program 2014

October 25-28, 2014 | Pennsylvania Convention Center | Philadelphia, PA

Presentation Handouts

(9409-TC-PBM) Massive Transfusion: Product Alternatives

October 28, 2014 ✧ 10:30 AM - 12:00 PM

Advancing Transfusion and Cellular Therapies Worldwide

Event Faculty List

Event Title: **(9409-TC-PBM)** Massive Transfusion: Product Alternatives
Event Date: October 28, 2014
Event Time: 10:30 AM - 12:00 PM

Director
Beth Shaz, MD
Chief Medical Officer
New York Blood Center
bshaz@nybloodcenter.org
Disclosure: No

Moderator
John Hess, MD
hessj3@uw.edu
Disclosure: Did not disclose

Speaker
Beth Hartwell, MD
Medical Director
Gulf Coast Regional Blood Center
bhartwell@giveblood.org
Disclosure: No

Speaker
John Holcomb, MD, FACS
Speaker
UT Health
John.Holcomb@uth.tmc.edu
Disclosure: No

Speaker
Richard Kaufman, MD
Medical Director, Adult Transfusion Service
Brigham and Women's Hospital
rmkaufman@partners.org
Disclosure: Yes

Supplying Traditional, Optimal, & Alternative Products

Supporting Massive Transfusion Needs

Beth A. Hartwell, MD
Medical Director

Gulf Coast Regional Blood Center

Commit for Life.

AABB WeeklyReport

Advancing Transfusion and Cellular Therapies Worldwide

Visit aabb.org | Unsubscribe to this Newsletter | October 24, 2014 | Vol. 20 | No. 37

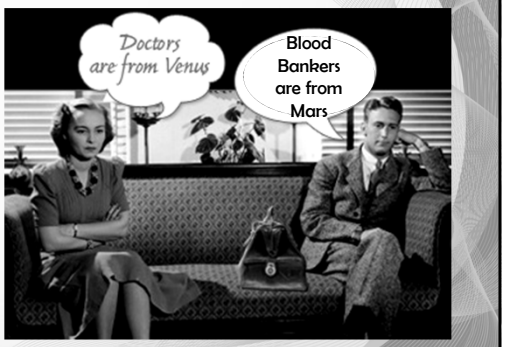
Frozen Products
Nationally, there is increased use of most plasma types. Demand is greatest for AB and B plasma, and filling requests from civilian and military blood centers takes a week for AB and up to two days for B.

Commit for Life.

The Landscape

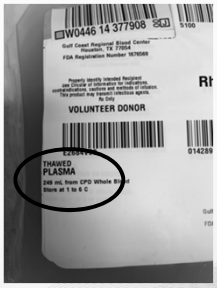
- Early plasma use is critical in trauma resuscitation.
- Plasma use typically protocol driven.
- There will be increased use of plasma products.
- Logistical concerns about meeting the demand.

Commit for Life.



Commit for Life.

Frozen → Thawed Plasma



- FFP/ PF24 / PF24RT24
- Relabel 24 hrs post-thaw
- Stored for 5 days at 1-6C
- Decreases plasma wastage
- Requires constant inventory management

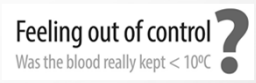
Commit for Life.

Pre-Thawed Plasma

Commit for Life.

Logistical Concerns

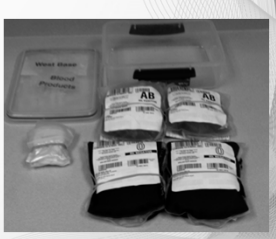
- Where will blood be stored prior to being placed on the helicopter?
- How will blood be transported?



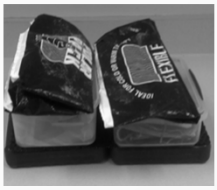
- What if it is not used?
- How to manage inventory in multiple locations?

Commit for Life.

Base Station Refrigerator



Commit for Life. 9



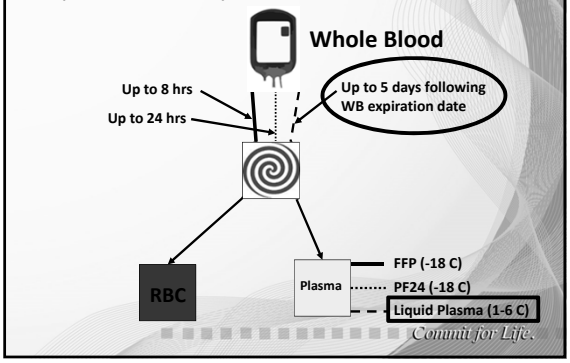
- D4 rotation – deliver D1 thawed AB plasma; pick up D4 trauma plasma & return to hospital BB
- Demand for AB plasma increased

Commit for Life.

Commit for Life.

Commit for Life.

Preparation of Liquid Plasma

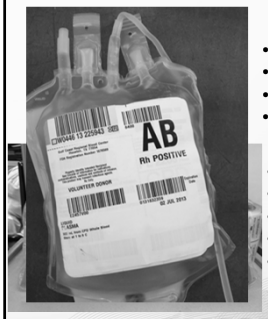


Commit for Life.

Talking with Component Production…

Commit for Life.

Production Issues



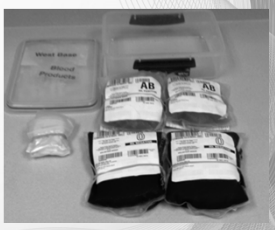
- WB only acceptable starting material
- Separated within 8 hrs of collection
- TRALI compliant
- 26-day expiration (CPD)

- Prepared by special order
- Sent to hospital on D1
- Direct sale, non-returnable
- Not irradiated
- Non-licensed

Commit for Life.

July 2012 – LP replaces TP

- D14 rotation – deliver D2 liquid AB plasma; pick up D14 trauma plasma & return to hospital BB
- Wastage = 1.9%



Commit for Life. 16

AB Plasma Supply & Demand

- Now supply 3 additional hospitals with LP
  - Current production is 20-30 AB LP units/week
- Issues
  - Increased demand for AB plasma products
  - Impact of TRALI mitigation standards (2014)
  - AB donors moved to apheresis collections
  - Minimal need for AB RBCs

Commit for Life.

REPORT

Immunohematology. 2011;27:61-65

Challenging dogma: group A donors as "universal plasma" donors in massive transfusion protocols

E.J. Isaak, K.M. Tchorz, N. Lang, L. Kalal, C. Slapak, G. Khalife, D. Smith, and M.C. McCarthy

- Availability of AB plasma is limited.
- Group A plasma would be an alternative in emergency situations.
- Group A plasma would be compatible with 85% of population.
- Trauma patients concurrently receiving group O RBCs (decreases risk of hemolysis).
- Plasma-incompatible platelets are routinely transfused without AHTR.

Commit for Life.

Institution Experience

Mayo Rochester

- Thawed A plasma used since 2008
  - Male donors; no titers performed
  - Median titer (AHG) 16; 92% had titer ≤64
- 7% of emergent plasma transfusions were ABO-incompatible
- No clinical reports of hemolysis
- No difference in rates of ALI, TRALI, ARDS, ARF, sepsis or death

Commit for Life.

To Titer or Not To Titer?

Dartmouth-Hitchcock Medical Center

- Thawed group A plasma used for initial trauma pack since 2012
- Anti-B titer ≤ 50 (97% of donors)
- No reported cases of hemolysis

University of Massachusetts (2008-2013)

- Thawed group A plasma for trauma resuscitation
- 6% (23 patients) received ABO-incompatible plasma
- No overt evidence of AHTR; 3 patients had w+ DAT post-transfusion

Commit for Life.

Issues for Implementation

- No official standard for "low titer"
  - Most common titer cut-off in range of 50 – 100
  - Use male plasma only?
- Titer methodology varies
  - Tube, gel, solid phase technology
  - Saline titer vs. AHG titer (IgM vs. IgG)
- Donor (and recipient) demographics
- IS configuration and physician acceptance

Commit for Life.


I'm thinking we should look into this "dried plasma" stuff…
Commit for Life.


PIG PROGRESS
Search...
Click here for print magazine or digital magazine
Breeding Growing / Finishing Pork & Processing Health / Diseases Regions Special Focus Whitepapers
Piglet Health Sow Management Alternative Growth Promotion Piglet Feeding
special focus › piglet feeding
Porcine plasma proteins for feed intake and health
Since September 2005 porcine plasma has been re-allowed as a feed ingredient for pigs and poultry in the European Union. Coincidentally this fitted in perfectly with the ban on Antimicrobial Growth Promoters (AMGP), which was imposed on the 1st January 2006, because plasma also improves piglets' growth performance and health without developing antibiotic resistance.
Plasma powder has a positive effect on piglet health and feed intake. The colour of agglomerated (left) and non-agglomerated (right) plasma powder is not dark as many believe.
By Geert van der Velden, MSc, product manager, Sonac
The ban on Antimicrobial Growth Promoters (AMGP) and the reallowance of porcine blood plasma as a feed ingredient for pigs and poultry stimulated the question whether plasma could be a good alternative for AMGP's. In a recently published experiment it was concluded that plasma has more effect on growth and feed intake when using feed without AMGP than it has with feed containing AMGP (Figure 1).
Piglet Feeding Home
Baby piglets go mmmm…
Pig-Omic
New organic mineral concept against diarrhoea
Vitfoss
DSM
BRIGHT SCIENCE. BRIGHTER LIVING.
Commit for Life.


Commit for Life.

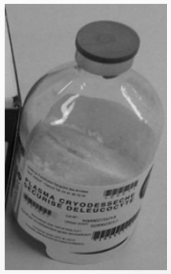
Dried/Lyophilized Plasma (Then)

Commit for Life.

Dried/Lyophilized Plasma (Now)

Commit for Life.

INTERCEPT Lyoplasma (France)*

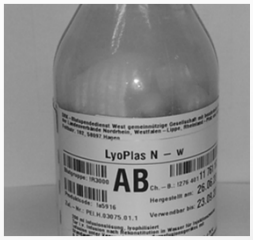


- Pool of up to 11 donors
- Leukoreduced, TRALI compliant
- Pathogen inactivation process
- RT storage for 2 years
- Universal ABO compatibility

*INTERCEPT Lyoplasma is not approved in the U.S.

Commit for Life.

LyoPlas N (Germany)*



- Single donor product
- Male or nulliparous female
- Repeat donor testing
- RT storage for 15 months
- ABO specific

*LyoPlas N is not approved in the U.S.

Commit for Life.

Freeze-Dried Plasma Product Carried by US Special Operations Forces

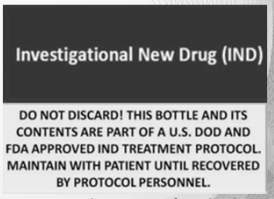


Photo courtesy of JH Holcomb, MD

Commit for Life. 29

Commit for Life.

Commit for Life.

History Lesson

WWI
- Practice of giving fresh Whole Blood to injured soldiers was introduced.

WWII
- By 1945, Whole Blood became agent of choice in battle.

Late 1970s - early 1980s
- Whole Blood not used in civilian settings. No clinical data, but made business sense.

No clinical trials in civilian setting to compare Whole Blood transfusion therapy to component therapy.

Commit for Life.

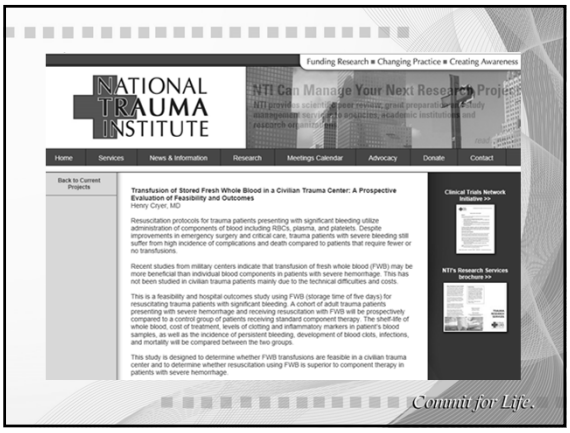
A Randomized Controlled Pilot Trial of Modified Whole Blood Versus Component Therapy in Severely Injured Patients Requiring Large Volume Transfusions

Bryan A. Cotton, MD, MPH,† Jeanette Podbielski, BSN,† Elizabeth Camp, MSPH,† Timothy Welch, NREMT-P,† Deborah del Junco, PhD,‖ Yu Bai, MD, PhD,‖ Rhonda Hobbs, MT (ASCP),‖ Jamie Scroggins, MT (ASCP),§ Beth Hartwell, MD,§ Rosemary A. Kozar, MD, PhD,* Charles E. Wade, PhD,*† and John B. Holcomb, MD*† on behalf of The Early Whole Blood Investigators*

Ann Surg 2013

- Randomized to receive either WB + Plts or RBC + Plasma + Plts
- WB <5 days old
- Conclusion:
  - WB did not reduce transfusion volumes compared with standard component therapy.
  - Excluding patients with severe brain injury, use of WB significantly reduced transfusion volumes.

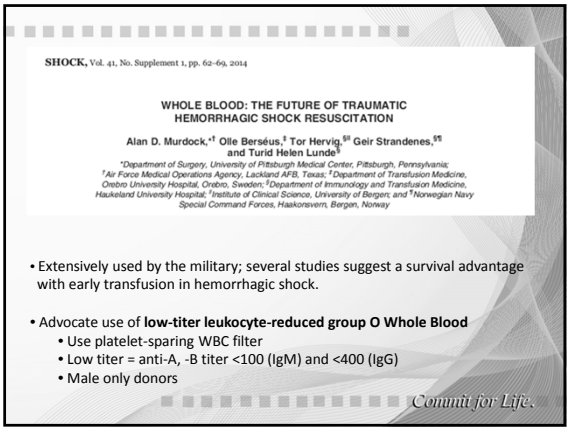
Commit for Life. 33



Does WB Need to Be ABO-Specific?

- Group O WB used as "universal" blood extensively by military
  - Full hemostatic function at 10 days (1-6C)
  - 300,000 WB units transfused; 34 TRXN (RBC incompatibility; 1 due to high titer unit)
- Common practice to transfuse ABO plasma-incompatible platelets
  - 1:10,000 clinical hemolytic rxns (usually group O with high titer anti-A)

Commit for Life.



SHOCK, Vol. 41, No. Supplement 1, pp. 62–69, 2014

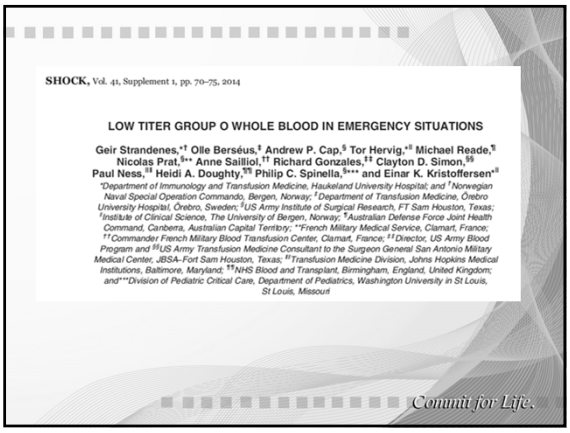
WHOLE BLOOD: THE FUTURE OF TRAUMATIC HEMORRHAGIC SHOCK RESUSCITATION

Alan D. Murdock,*† Olle Berséus,‡ Tor Hervig,§¶ Geir Strandenes,§¶ and Turid Helen Lunde‖

*Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; †Air Force Medical Operations Agency, Lackland AFB, Texas; ‡Department of Transfusion Medicine, Örebro University Hospital, Örebro, Sweden; §Department of Immunology and Transfusion Medicine, Haukeland University Hospital; ¶Institute of Clinical Science, University of Bergen; and ‖Norwegian Navy Special Command Forces, Haakonsvern, Bergen, Norway

- Extensively used by the military; several studies suggest a survival advantage with early transfusion in hemorrhagic shock.
- Advocate use of **low-titer leukocyte-reduced group O Whole Blood**
  - Use platelet-sparing WBC filter
  - Low titer = anti-A, -B titer <100 (IgM) and <400 (IgG)
  - Male only donors

Commit for Life.



SHOCK, Vol. 41, Supplement 1, pp. 70–75, 2014

LOW TITER GROUP O WHOLE BLOOD IN EMERGENCY SITUATIONS

Geir Strandenes,*† Olle Berséus,‡ Andrew P. Cap,§ Tor Hervig,*‖ Michael Reade,¶ Nicolas Prat,‖** Anne Sailliol,†† Richard Gonzales,‡‡ Clayton D. Simon,§§ Paul Ness,‖‖ Heidi A. Doughty,¶¶ Philip C. Spinella,‖*** and Einar K. Kristoffersen*‖

*Department of Immunology and Transfusion Medicine, Haukeland University Hospital; and †Norwegian Naval Special Operation Commando, Bergen, Norway; ‡Department of Transfusion Medicine, Örebro University Hospital, Örebro, Sweden; §US Army Institute of Surgical Research, FT Sam Houston, Texas; ‖Institute of Clinical Science, The University of Bergen, Norway; ¶Australian Defense Force Joint Health Command, Canberra, Australian Capital Territory; **French Military Medical Service, Clamart, France; ††Commander French Military Blood Transfusion Center, Clamart, France; ‡‡Director, US Army Blood Program and §§US Army Transfusion Medicine Consultant to the Surgeon General San Antonio Military Medical Center, JBSA-Fort Sam Houston, Texas; ¶¶Transfusion Medicine Division, Johns Hopkins Medical Institutions, Baltimore, Maryland; ‖‖NHS Blood and Transplant, Birmingham, England, United Kingdom; and***Division of Pediatric Critical Care, Department of Pediatrics, Washington University in St Louis, St Louis, Missouri

Commit for Life.

Hope for Middle-Aged Men

- Group O donors (Brazilian study)
  - Low mean titers of anti-A and anti-B in men older than 50 years of age
  - High mean anti-B titers in young women (19-29 yrs)
- "This study confirms that over 50-year-old Group O men should be selected as blood donors in non-identical ABO transfusion situations."

Commit for Life.

Damage Control Resuscitation:
MT Protocols, Traditional, Optimal and Alternative Products

Oct 2014

John B. Holcomb, MD, FACS
Professor of Surgery
Chief, Division of Acute Care Surgery
Director, Center for Translational Injury Research
University of Texas Health Science Center Houston, TX

Texas Trauma Institute
MEMORIAL HERMANN
UTHealth
Academic Health Center at Houston

Nothing to Disclose

2

Texas Trauma Institute
UTHSC-Houston +MHH
and the TMC

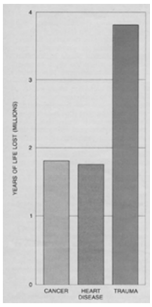
3

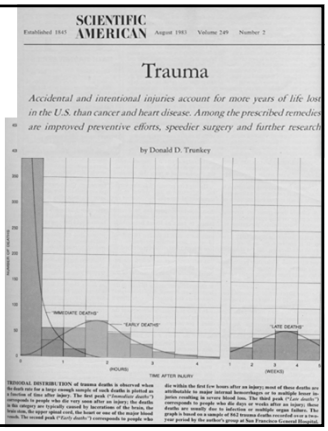
Injury Data

- Combat injury death rates have decreased over the last 10 years.
- Death after injury in the United States and across the world has increased > 20% in the last decade.
  - At the same time cancer, heart disease and HIV related deaths in the US have decreased.
- Worldwide, injury accounts for more deaths than malaria, TB and HIV combined.
- More than 40 million are injured in the US every year.
- Because injury is a largely a disease of young people, death after injury is far and away the leading cause of life years lost between the ages of 1 and 75 and costs the US > 400 billion dollars a year.
- Injury and bleeding is a really big deal

4

Classic Tri-Modal Distribution of Death




SCIENTIFIC AMERICAN

Trauma

Accidental and intentional injuries account for more years of life lost in the U.S. than cancer and heart disease. Among the prescribed remedies are improved preventive efforts, speedier surgery and further research

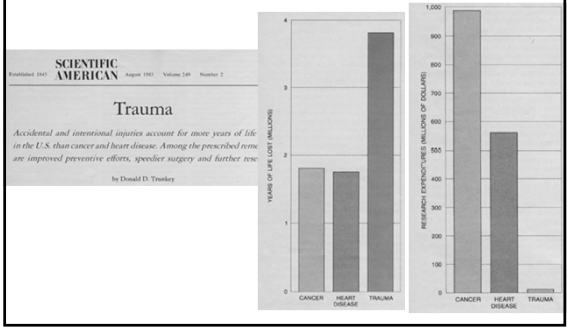
by Donald D. Trunkey

"IMMEDIATE DEATHS" "EARLY DEATHS" "LATE DEATHS"

TIME AFTER INJURY

TRIMODAL DISTRIBUTION of trauma deaths is observed when the death rate for a large enough sample of such deaths is plotted as a function of time after injury. The first peak ("Immediate deaths") in the graph corresponds to people who die very soon after an injury; the deaths in this category are typically caused by lacerations of the brain, the brain stem or the upper spinal cord, the heart or one of the major blood vessels. The second peak ("Early deaths") corresponds to people who die within the first few hours after an injury; most of these deaths are attributable to major internal hemorrhage or to multiple lesser injuries resulting in severe blood loss. The third peak ("Late deaths") corresponds to people who die days or weeks after an injury; these deaths are usually due to infection or multiple organ failure. The graph is based on a sample of 862 trauma deaths recorded over a two-year period by the author's group at San Francisco General Hospital.

Dichotomy between life years lost and funding


SCIENTIFIC AMERICAN

Trauma

Accidental and intentional injuries account for more years of life lost in the U.S. than cancer and heart disease. Among the prescribed remedies are improved preventive efforts, speedier surgery and further research

by Donald D. Trunkey

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

GLOBAL HEALTH

Injuries

May 2, 2013

Robyn Norton, Ph.D., M.P.H., and Olive Kobusingye, M.Med. (Surg), M.P.H.

- In 2010, there were 5.1 million deaths from injuries
  - deaths from injuries was > HIV, tuberculosis and malaria combined (3.8 million).
- Overall, the number of deaths from injuries increased by 24% between 1990 and 2010.

7

Years of Potential Life Lost (YPLL) Before Age 65

Cause of Death	YPLL	Percent	
All Causes	948,426	100.0%	
Unintentional Injury	199,903	21.1%	**31.7%**
Suicide	52,265	5.5%	
Homicide	48,190	5.1%	
Malignant Neoplasms	137,221	14.5%	
Heart Disease	107,009	11.3%	
Perinatal Period	75,496	8.0%	
Congenital Anomalies	43,615	4.6%	
Cerebrovascular	21,817	2.3%	
HIV	21,508	2.3%	
Liver Disease	21,352	2.3%	
All Others	220,050	23.2%	

8

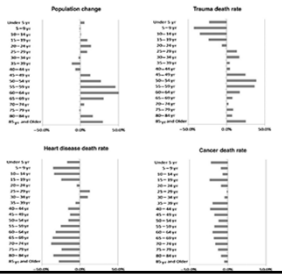
The National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System. US Department of Health and Human Services, CDC; 2008. Available at: http://www.cdc.gov/ncipc/wisqars/. Accessed May 22, 2009.

Increasing Trauma Deaths in the United States

Peter Rhee, MD, MPH, Bellal Joseph, MD, Viraj Pandit, MD, Hassan Aziz, MD, Gary Vercruysse, MD, Narong Kulvatunyou, MD, and Randall S. Friese, MD

Ann Surg 2014

- From 2000 to 2010, the US population increased by 9.7% and the number of trauma deaths increased by 23%.



Why is this?

Increasing Trauma Deaths in the United States

Peter Rhee, MD, MPH, Bellal Joseph, MD, Viraj Pandit, MD, Hassan Aziz, MD, Gary Vercruysse, MD, Narong Kulvatunyou, MD, and Randall S. Friese, MD

Ann Surg 2014

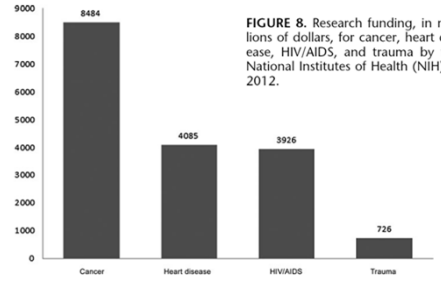
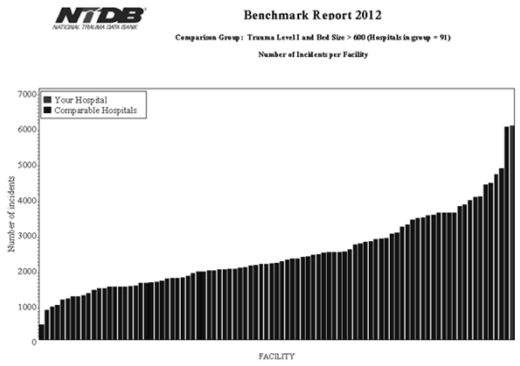


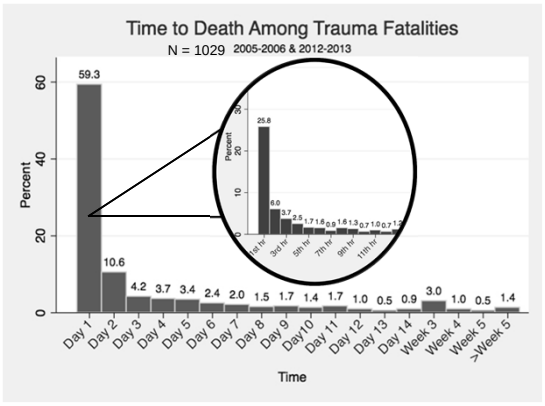
FIGURE 8. Research funding, in millions of dollars, for cancer, heart disease, HIV/AIDS, and trauma by the National Institutes of Health (NIH) in 2012.



ACS tqip TRAUMA QUALITY IMPROVEMENT PROGRAM

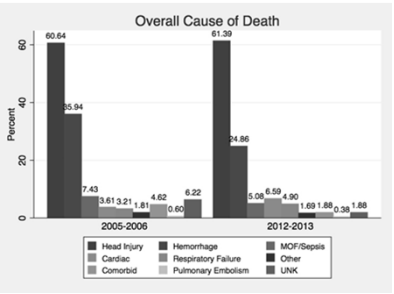
Admissions from 2012 and 2013, includes 160,560 risk adjusted incidents from198 centers.

The odds of trauma related death at TTI is < 90% of all other TQIP hospitals.



1029 Trauma Deaths- Single Center

2005-06 2012-13



Mortality decreased 30%
- 6.6% to 4.7%
- $p < 0.05$

Hemorrhage deaths decreased from 36% to 25% ($p<0.01$).

Traditional Resuscitation

- Used to be a serial resuscitation
  1. Crystalloid / colloids -- many liters
  2. RBCs – many units
  3. Plasma – limited
  4. platelets – very limited

"Kool aid" blood draws
Very bad sign

In 2007, things started changing

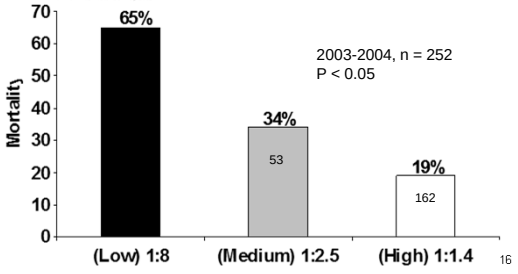
15

The Journal of TRAUMA® Injury, Infection, and Critical Care

J Trauma, 2007

The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beekley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD



2003-2004, n = 252
P < 0.05

16

The blood bank: from provider to partner in treatment of massively bleeding patients

TRANSFUSION 2007;47:176S-181S.

Pär I. Johansson

TRANSFUSION PRACTICE

Proactive administration of platelets and plasma for patients with a ruptured abdominal aortic aneurysm: evaluating a change in transfusion practice

TRANSFUSION 2007;47:593-598.

Pär I. Johansson, Jakob Stensballe, Iben Rosenberg, Tanja L. Hilslov, Lisbeth Jørgensen, and Niels H. Secher

17

Special Commentary The Journal of TRAUMA® Injury, Infection, and Critical Care

J Trauma, 2007.

Damage Control Resuscitation: Directly Addressing the Early Coagulopathy of Trauma

John B. Holcomb, MD, FACS, Don Jenkins, MD, FACS, Peter Rhee, MD, FACS, Jay Johannigman, MD, FS, FACS, Peter Mahoney, FRCA, RAMC, Sumeru Mehta, MD, E. Darrin Cox, MD, FACS, Michael J. Gehrke, MD, Greg J. Beilman, MD, FACS, Martin Schreiber, MD, FACS, Stephen F. Flaherty, MD, FACS, Kurt W. Grathwohl, MD, Phillip C. Spinella, MD, Jeremy G. Perkins, MD, Alec C. Beekley, MD, FACS, Neil R. McMullin, MD, Myung S. Park, MD, FACS, Ernest A. Gonzalez, MD, FACS, Charles E. Wade, PhD, Michael A. Dubick, PhD, C. William Schwab, MD, FACS, Fred A. Moore, MD, FACS, Howard R. Champion, FRCS, David B. Hoyt, MD, FACS, and John R. Hess, MD, MPH, FACP

- Rapid progress in trauma care occurs during a war.
- Damage control resuscitation addresses **diagnosis and treatment of the entire lethal triad** immediately upon admission.

18

DCR components

- Stop bleeding
- Hypotensive resuscitation
- Minimize crystalloid
- Use plasma to resuscitate patients
- Increased platelet use
- Reverse hypothermia and acidosis
- Hemostatic adjuncts

19

Optimal?

- Copenhagen and Houston
  - And many others
- Prehospital RBCs and plasma
- Minimal crystalloid and colloid
- Early balanced and ratio driven in bleeding patients
- When bleeding slows, goal directed with TEG

20

Does it Translate? Impact of Contemporary Military Medicine on Civilian Trauma Care

AH Haider MD, MHS, L Powell BA, CK Zogg, MSPH, EB Schneider PhD, J Orman PhD, F Butler MD, R Gerhardt MD, ER Haut MD, DT Efron, JP Mather MD, EJ MacKenzie PhD, D Schwartz, D Geyer MD, JJ DuBose MD, TE Rasmussen MD, LH Blackbourne MD

- 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.”

21

ACS tqip TRAUMA QUALITY IMPROVEMENT PROGRAM

Based on admissions from 2012 and 2013, includes 160,560 incidents from 198 centers.

AAST 2014 poster 71% of TQIP centers use 1:1:1

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
  - Must have thawed/liquid plasma in the ED or prehospital to really do this well
- Time is critical – minutes count

23

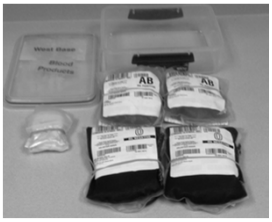
How do you make early blood products happen?

- 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

24

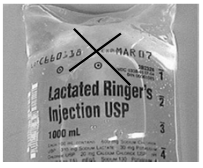
Liquid Plasma and RBCs are the Primary Resuscitation Fluids Pre-Hospital

Base Station (x4) Refrigerator



26

Optimal Resuscitation Fluids



PROP:P:R

Prospective Randomized Optimum Platelet and Plasma Ratios

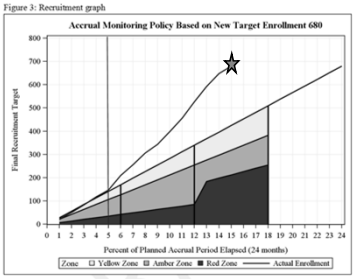
3 Aug 2012 - 3 Dec 2013

12 centers, screened 11,185

Enrolled 680

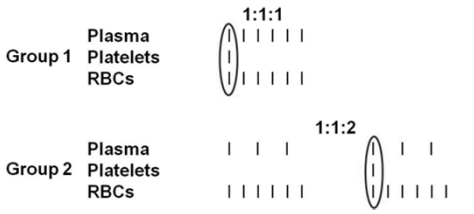
Massive transfusion

Figure 3: Recruitment graph



PROPPR study

PROPPR Cooler Cycles



29

Rapid Delivery of Products

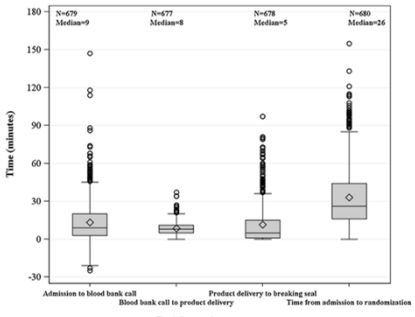
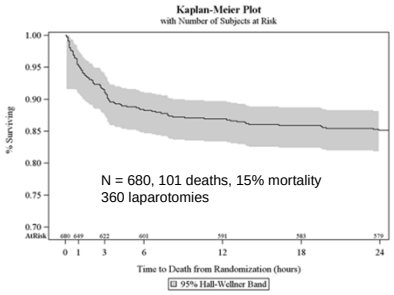


Fig. 4. Process time measures.

30

PROPPR 24 Hour KM



N = 680, 101 deaths, 15% mortality
360 laparotomies

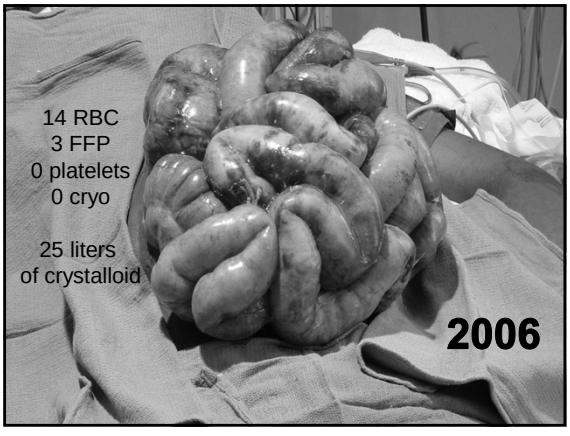
31

Blood Product Resuscitation

Improved survival

- Balanced better than Unbalanced
  - Borgman MA, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007
  - Pidcoke HF, et al. Ten-year analysis of transfusion in Operation Iraqi Freedom and Operation Enduring Freedom: increased plasma and platelet use correlates with improved survival. J Trauma. 2012.
  - Holcomb JB, et al. The PROMMTT study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013.
- Early better than Late
  - Radwan ZA, et al. An emergency department thawed plasma protocol for severely injured patients. JAMA Surg. 2013
  - Cap AP, et al. Timing and location of blood product transfusion and outcomes in massively transfused combat casualties. J Trauma. 2012.
- Earlier and Balanced = Fewer blood products Given
  - Cotton BA, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. Ann Surg. 2011
  - Kautza BC, Glue Grant. Changes in massive transfusion over time: an early shift in the right direction? J Trauma. 2012.

32

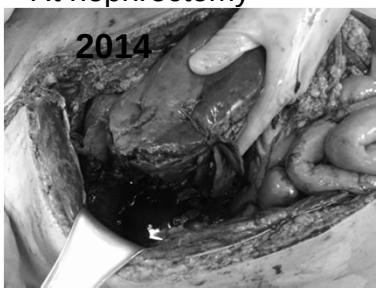


Rt pulmonary lower lobe wedge, Rt hepatic lobectomy, Rt nephrectomy

pH = 7.0

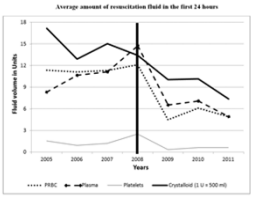
14 RBC
14 FFP
2 platelets
2 cryo

2 liters
of crystalloid



DAMAGE CONTROL RESUSCITATION INCREASES SUCCESSFUL NON-OPERATIVE MANAGEMENT RATES AND SURVIVAL AFTER SEVERE BLUNT LIVER INJURY

Binod Shrestha[1] MD, John B. Holcomb[1,2] MD, Elizabeth Camp[1] MS, Deborah J. Del Junco[1,2] Ph.D., Bryan A. Cotton[1,2]MD, MPH, Rondel Albarado[2] MD, Brijesh S. Gill[2] MD, Rosemary A. Kozar[2] MD, Ph.D., Lillian S. Kao[2] MD, Michelle K. McNutt[2] MD, Laura J. Moore[1,2] MD, Joseph D. Love[2] DO, George H. Tyson[2] III, MD, Charles E. Wade[1,2] Ph.D.

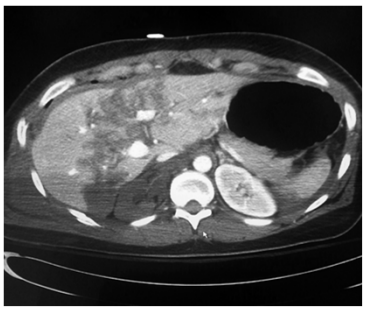


- 2005-2011,
  - 1412 (4.7%) blunt liver injury.
- 244 (17%) Grade IV and V injuries
  - 206 patients survived left the ED.
  - Pre DCR vs DCR
- DCR decreased crystalloid and blood product use
- DCR increased non-operative management
  - 54 to 74%, p<0.01
- DCR treatment improved survival
  - 73% to 94% (p<0.01).

Accepted, J Trauma 2014

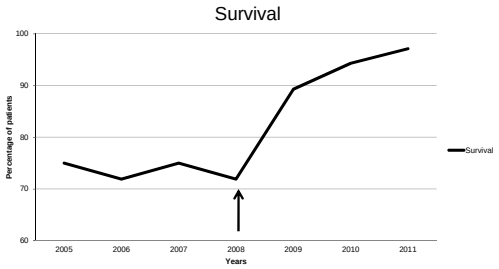
35

Grade V Liver injury



36

Survival of Grade 4 and 5 Liver Injury over 7 years n = 206



37

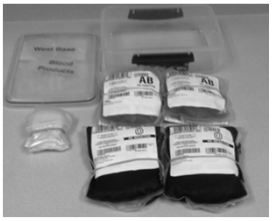
New / Alternative Products

- Looking to the future
- Right around the corner

38

Liquid Plasma and RBCs are the Primary Resuscitation Fluids Pre-Hospital

Base Station (x4) Refrigerator



40

PreHospital Blood Products

PREHOSPITAL TRANSFUSION OF PLASMA AND RED BLOOD CELLS IN TRAUMA PATIENTS

John B. Holcomb, MD, Daryn P. Donathan, BS, Bryan A. Cotton, MD, Deborah J. del Junco, PhD, Georgian Brown, RN, Toni von Wenckstern, RN, Jeanette M. Podbielski, RN, Elizabeth A. Camp, PhD, Rhonda Hobbs, Yu Bai, MD, PhD, Michelle Brito, BS, Elizabeth Hartwell, MD, James Red Duke, MD, Charles E. Wade, PhD

PreHosp Em Care 2014

- Similar to the data published from the ongoing war, improved early outcomes were associated with placing RBCs and plasma prehospital.
- Thousands of units flown, > 300 patients transfused
  - 1.9% wastage

Plasma and RBCs, prehospital, ED and OR

Several centers have platelets in the ED

Balanced blood product resuscitation of bleeding patients is our standard of care

Why not place platelets on helicopters?

42

r-TEG Display in the ED/OR/ICU

- We no longer send PT / PTT / INR, fibrinogen and platelet counts

THE 2011 NATIONAL BLOOD COLLECTION AND UTILIZATION SURVEY REPORT

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.

44

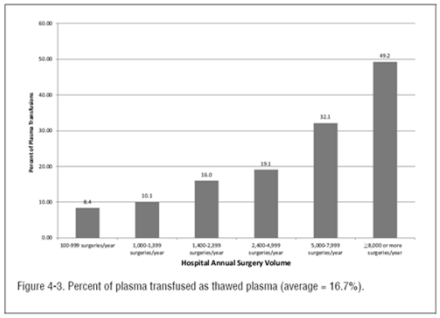


Figure 4-3. Percent of plasma transfused as thawed plasma (average = 16.7%).

20 Blood Transfused in the United States

45

THE 2011 NATIONAL BLOOD COLLECTION AND UTILIZATION SURVEY REPORT

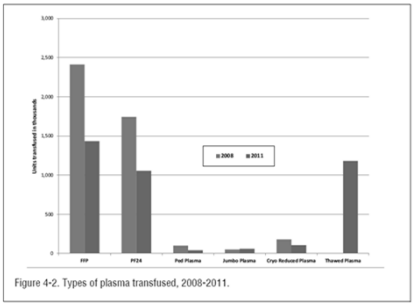


Figure 4-2. Types of plasma transfused, 2008-2011.

46

Blood Transfused in the United States 19

THE 2011 NATIONAL BLOOD COLLECTION AND UTILIZATION SURVEY REPORT

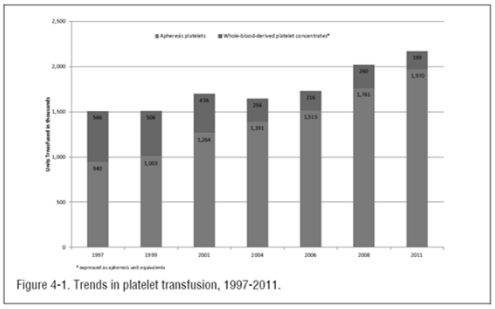


Figure 4-1. Trends in platelet transfusion, 1997-2011.

47

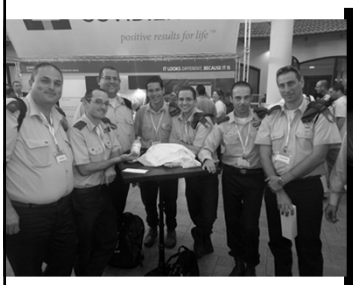
Back to the Future

Lyophilized Plasma Resuscitation

FIGURE 159.—Administration of plasma on beach, only few feet from surf, to survivor of landing craft sunk off coast in first days of invasion of Normandy, June 1944.

48

German Dried Plasma in the IDF

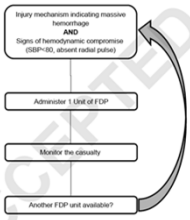


49

Freeze Dried Plasma at the Point of Injury- From Concept to Doctrine

Shock, 2013

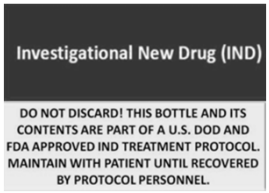
Elon Glassberg[1,2], Roy Nadler[1,2], Sami Gendler[1,2], Amir Abramovich[1,2], Philip C. Spinella[3,4], Robert T. Gerhardt[4], John B. Holcomb[5,6], Yitshak Kreiss [1,2]



	LyoPlas® (39)	FLyP® (5,7,10)
Product		
Manufacturing country	Germany	French
Reconstitution time	Up to 10 minutes	Up to 5 minutes
Storage	Up to 25 c	Up to 25 c
Compatibility	Blood type specific *	Universal ABO compatibility
Donor profile	Single donor (men or nulliparous women)	Up to 11 donors
Infection prevention	Repeated donor Serologic testing, following a 4 month quarantine	Amotosalen photoactivation
Container	Glass bottle	Glass bottle
pH	7-7.2	8
Reconstitution fluid	ml of sterile water 200	ml of sterile water 200
Shelf life	15 Months	24 months

50

French Dried Plasma Product carried by some US Special Operations Forces. Approved by FDA and WH



51

"The Future"
Dried / Lyophilized Components at the Bedside

- 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
- RBCs
  - Stem cell derived-DARPA
  - lyophilized RBC's
- Various individual recombinant coagulation proteins

52

Reconstitution: Reverse Engineering

J Trauma 2011

John B. Holcomb, MD

- In the next evolution of transfusion practice, it is exciting to consider the real logistical and possible clinical benefits of exclusively using dried products such as plasma, platelets, fibrinogen, and RBCs to resuscitate bleeding patients
- Dried Plasma will replace all time sensitive use of FFP
  - Eliminate frozen plasma
  - Essentially all plasma transfusions for bleeding

53

Fluid Resuscitation for Hemorrhagic Shock in Tactical Combat Casualty Care

TCCC Guidelines Change 14-01 – 2 June 2014

JSOM 2014

Frank K. Butler, MD; John B. Holcomb, MD; Martin A. Schreiber, MD; Russ S. Kotwal, MD; Donald A. Jenkins, MD; Howard R. Champion, MD, FACS, FRCS; F. Bowling; Andrew P. Cap, MD; Joseph J. Dubose, MD; Warren C. Dorlac, MD; Gina R. Dorlac, MD; Norman E. McSwain, MD, FACS; Jeffrey W. Timby, MD; Lorne H. Blackbourne, MD; Zsolt T. Stockinger, MD; Geir Strandenes, MD; Richard B, Weiskopf, MD; Kirby R. Gross, MD; Jeffrey A. Bailey, MD

- The resuscitation fluids of choice for casualties in hemorrhagic shock are (in priority order):
  1. whole blood
  2. plasma, RBCs and platelets in 1:1:1 ratio
  3. plasma and RBCs in 1:1 ratio
  4. plasma alone
  5. RBCs alone
  6. Hextend
  7. crystalloid (lactated Ringer's or Plasma-Lyte)

54

Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective

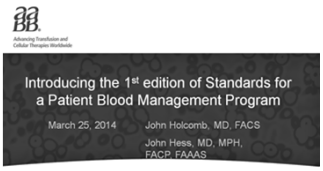
John B. Holcomb[1] and Shibani Pati[2]

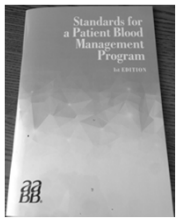
Hematology 2013

[1]Center for Translational Injury Research, Department of Surgery, and Texas Trauma Institute, University of Texas Medical School, Houston, TX; and [2]Blood Systems Research Institute and Department of Laboratory Medicine, University of California, San Francisco, San Francisco, CA

- Repair the endothelium
- Restore the glycocalyx
- Decrease inflammatory response
- Decrease permeability and edema

55





- PBM?
  - Right blood products to the right patient at the right time
    - Stop bleeding
  - Credentialed to transfuse
  - PBM Hospital levels of care

56

Summary

- Uncontrolled Hemorrhage is a major problem
  - Massive Hemorrhage is only 2% of all civilian trauma admissions
  - Limit crystalloid
- Predictive models are here
  - Rapid dx of MH patients who are in shock and coagulopathic
  - Must start plasma and platelets much earlier
  - Decrease crystalloid
- Understand mechanisms
- New products?

57

Summary

- Use physiology (not tradition) to drive diagnosis and interventions
- Don’t make the presenting problems worse with iatrogenic resuscitation injury.
- Accept known risks and benefits
- Go and talk with your blood banker, work collaboratively

58

Hemostatic agents in postpartum hemorrhage

Richard Kaufman MD

Disclosures

- None

Postpartum hemorrhage (PPH)

- A key cause of maternal morbidity/mortality
- Overall fatality rate is 1%

Abdul-Kadir R 2014, Transfusion in press

PPH: causes

- Uterine atony (80%)
- Placental problems
- Genital tract trauma
- Systemic disorders e.g. coagulopathy

PPH: management

- 1st line: uterine massage/uterotonic agents
- 2nd line: intrauterine balloon tamponade, uterine brace sutures, uterine artery ligation or embolization
- 3rd line: hysterectomy

Abdul-Kadir R 2014, Transfusion in press

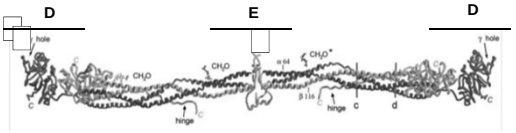
PPH: hemostatic agents

- Fibrinogen replacement
- Antifibrinolytics
- rFVIIa

PPH: hemostatic agents

- **Fibrinogen replacement**
- Antifibrinolytics
- rFVIIa

Fibrinogen structure



Brown JH 2000, PNAS 97:85

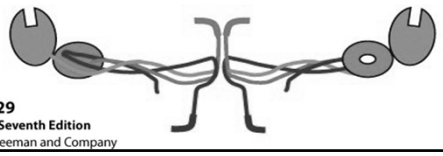


Figure 10.29
***Biochemistry,* Seventh Edition**

Fibrin polymerization

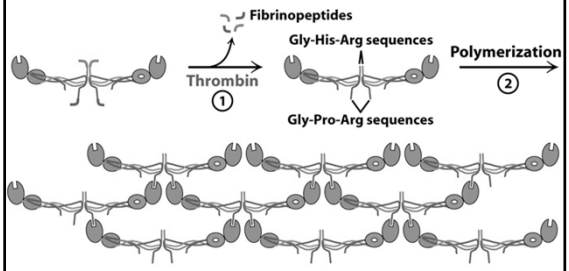
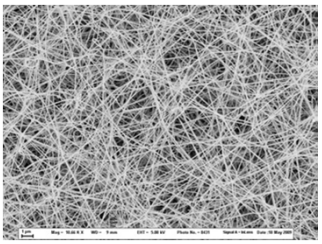


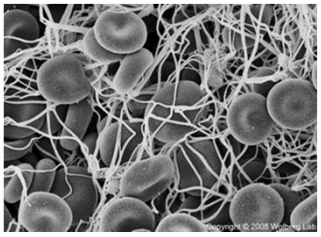
Figure 10.29
Biochemistry, Seventh Edition

Polymerized fibrin (acellular)



www.med.unc.edu

Polymerized fibrin (cellular)



www.med.unc.edu

Fibrinogen replacement options

Product	Amount to ↑ fibrinogen by 100 mg/dL	Approximate volume (mL)	Time to issue (min.)
Plasma	4 units	1000	5 - 30
Cryo	1 pool = 10 units	150	30
Fibrinogen concentrate	2 vials	100	N/A (Omnicell)

Fibrinogen replacement options

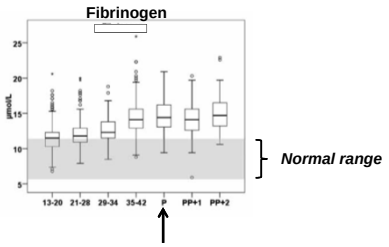
Product	Amount to ↑ fibrinogen by 100 mg/dL	Approximate volume (mL)	Time to issue (min.)
Plasma	4 units	1000	5 - 30
Cryo	1 pool = 10 units	150	30
Fibrinogen concentrate	2 vials	100	**N/A (Omnicell)**

Fibrinogen concentrate

- Heat-treated, lyophilized powder derived from pooled human plasma
- 1 vial: 900-1300 mg fibrinogen
- Labeled indication: congenital fibrinogen deficiency
- Risks: allergic reactions, thromboses

What data suggest that fibrinogen replacement is important in PPH?

Fibrinogen is normally elevated in pregnancy



Szeci 2010;Throm Haemost 103:718

Low fibrinogen predicts severe PPH

The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage

B. CHARBIT,*† L. MANDELBROT,‡ E. SAMAIN,§ G. BARON,¶ B. HADDAOUI,‡‡‡ H. KEITA,‡¶ O. SIBONY,** D. MAHIEU-CAPUTO,¶ M. F. HURTAUD-ROUX,** M. G. HUISSE,*‡‡ M. H. DENNINGER,†‡‡ and D. DE PROST‡†††‡‡ FOR THE PPH STUDY GROUP

*AP-HP, Hôpital Saint-Antoine, Clinical Investigation Center, Paris; †AP-HP, Hôpital Beaujon, Clichy; ‡AP-HP, Hôpital Louis Mourier, Colombes; §Hôpital Jean Minjoz, Besançon; ¶AP-HP, Hôpital Bichat, Paris; **AP-HP, Hôpital Robert Debré, Paris; ††INSERM U698, Paris; and ‡‡AP-HP, CIB PhenoGen, Paris, France

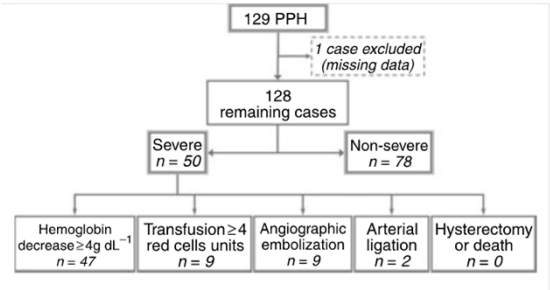
J Throm Haemost 2007; 5: 266

Low fibrinogen predicts severe PPH

- Prospective observational study
- Inclusion: PPH requiring IV prostaglandin
- PPH managed by standard protocol
  - RBCs for Hb < 7 g/dL
  - PLTs/plasma: MD discretion
- Blood samples collected at 0, 1, 2, 4, 24 hrs

Charbit, J Throm Haemost 2007; 5: 266

Low fibrinogen predicts severe PPH



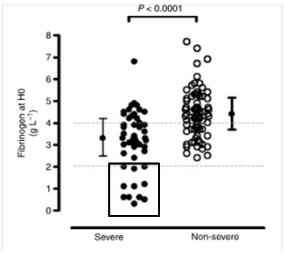
Charbit, J Throm Haemost 2007; 5: 266

Low fibrinogen predicts severe PPH

Characteristic	Severe PPH (n=50)	Non-severe PPH (n=78)	*P*
Maternal age (yrs)	28	30	0.34
Maternal weight (kg)	56	62	0.01
Gestational age (wks)	40	40	0.29
Parity	2	2	0.2
Twin deliveries	4	11	0.06
Length of labor (hrs)	6	6	0.94
C-section (%)	20	17	--

Charbit, J Throm Haemost 2007; 5: 266

Low fibrinogen predicts severe PPH



Charbit, J Throm Haemost 2007; 5: 266

Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial

M. Cortet[1,2,3,4*], C. Deneux-Tharaux[5], C. Dupont[6,7], C. Colin[8], R.-C. Rudigoz[9], M.-H. Bouvier-Colle[5] and C. Huissoud[2,9,10]

2012; Br J Anaesth 108:984

Low fibrinogen is associated with severe PPH

146,876 deliveries

↓

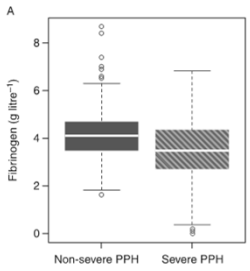
9365 PPH

↓

738 PPH
+ fibrinogen levels

Cortet 2012; Br J Anaesth 108:984

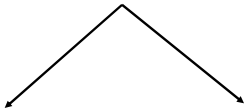
Low fibrinogen is associated with severe PPH



Cortet 2012; Br J Anaesth 108:984

FIB-PPH Study

245 adult women with PPH



Fibrinogen concentrate 2 g

Placebo

Wikkelsoe AJ 2012; Trials 13:110

FIB-PPH Study

- **Inclusion:**
  - Perioperative blood loss ≥ 1000 mL
  - Hysterectomy and blood loss ≥ 500 mL
  - Exploration of the uterus & blood loss ≥ 1000 mL
- **Exclusion:**
  - Unable to provide consent
  - Known inherited coagulopathy
  - Anticoagulation therapy prepartum
  - Pre-pregnancy weight <45 kg

Wikkelsoe AJ 2012; Trials 13:110

FIB-PPH Study

- **Primary outcome:**
  - Need for transfusion with allogeneic blood products
- **Secondary outcomes:**
  - Severe PPH
    - Hb decrease > 4 g/dL
    - ≥ 4 RBCs
    - Embolization, arterial ligation, or hysterectomy
    - Death
  - Total blood loss; safety end points: DVT, PE, MI

Wikkelsoe AJ 2012; Trials 13:110

FIB-PPH Study

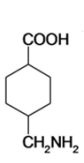
- **Power calculation**

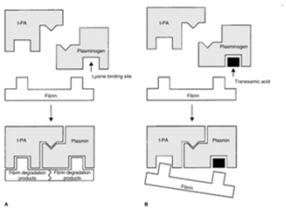
80% power to detect a 33% reduction in the need for any blood transfusion.

Wikkelsoe AJ 2012; Trials 13:110

Are antifibrinolytics helpful in treating PPH?

Antifibrinolytics

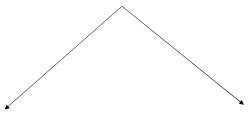




- Epsilon aminocaproic acid (Amicar)
- Tranexamic acid (TXA)

CRASH-2 Trial

20,211 adult trauma pts



Tranexamic acid
2g

Placebo

Primary end-point: in-hospital death within 4 weeks

Lancet 2010;376:23

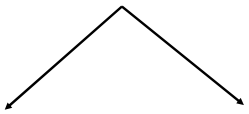
CRASH-2 Trial

Cause of death	Tranexamic acid n = 10,093	Placebo n = 10,114	p
Any cause	1,463 **(14.5%)**	1,613 **(16.0%)**	**0.0035**
Bleeding	489 (4.9%)	574 (5.7%)	0.0077
Vascular occlusion	33 (0.3%)	48 (0.5%)	0.096
Multiorgan failure	209 (2.1%)	233 (2.3%)	0.25
Head injury	603 (6.0%)	621 (6.2%)	0.60
Other causes	129 (1.3%)	137 (1.4%)	0.63

Lancet 2010;376:23

EXADELI Study

144 Women with PPH > 800 mL

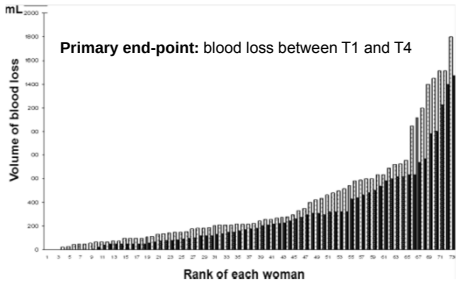


Tranexamic acid
2g

Placebo

Ducloy-Bouthers, Critical Care 2011; 15: R117

EXADELI Study



Primary end-point: blood loss between T1 and T4

Ducloy-Bouthers, Critical Care 2011; 15: R117

WOMAN Trial

World **M**aternal **An**tifibrinolytic Trial

Shakur H 2010; Trials 11:40

WOMAN Trial

15,000 adult women

Tranexamic acid
1g
+
1g for cont. bleeding

Placebo

Shakur H 2010; Trials 11:40

WOMAN Trial

- **Inclusion:**
  - Adult women with PPH
  - Blood loss after vaginal delivery ≥ 500 mL OR
  - Blood loss after C-section ≥ 1000 mL OR
  - Enough blood loss to cause hemodynamic compromise
- **Exclusion:**
  - MD believes clear indication for TXA
  - MD believes clear contraindication for TXA

WOMAN Trial

- **Primary outcome:**
  - Proportion of women who die or undergo hysterectomy
- **Secondary outcomes:**
  - Death
  - Surgical interventions
  - Blood transfusion
  - Health-related quality of life
  - Thrombotic events
  - Cost-effectiveness

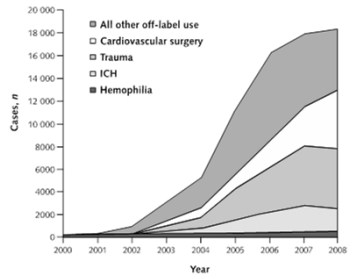
WOMAN Trial

- **Power calculation**

90% power to detect a 25% reduction from 4% to 3% in the primary endpoint of mortality or hysterectomy.

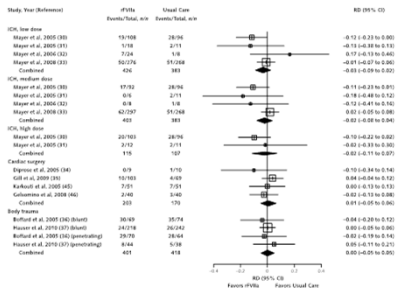
What about rFVIIa in PPH?

Off-label rFVIIa use



Logan 2011, Ann Int Med 154:516

rFVIIa off-label: meta-analysis



Yank 2011, Ann Int Med 154-529

rFVIIa: thromboembolic risk

	rFVIIa (n = 2583)	Placebo (n = 1536)		
TE event	**n (%)**	**n (%)**	**OR (95%CI)**	**P**
All events	264 (10.2)	134 (8.7)	1.17 (0.94-1.47)	0.16
Arterial events	141 (5.5)	49 (3.2)	1.68 (1.20-2.36)	0.003
Venous events	137 (5.3)	88 (5.7)	0.93 (0.70-1.23)	0.61

Levi, NEJM 2010; 363:1791

rFVIIa in PPH

Cases (n)	**Dose** (µg/kg)	**Doses** median (range)	**Clinical response** (%)	**Adverse events** (%)
272	10-137	1.1 (1-3)	85	2.5

Franchini M 2008. Sem Throm Hemost 34:104

Conclusions

- PPH remains an important cause of morbidity and mortality around the world.
- Fibrinogen replacement may be particularly important in treating PPH, although high-quality evidence is still pending.
- Options for replacing fibrinogen are: cryoprecipitate versus fibrinogen concentrate. These have not been directly compared in prospective clinical studies.