(R) Damage Control Resuscitation: treatment of acute blood failure

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Disclaimer:
The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Disclosures:
I have no relevant conflicts of interest.
I am an active duty officer in the U.S. Army.
Non-compressible hemorrhage:

- Massive injury: **PA transection**
- Blood loss: 2.5+ liters
- Shock
- Coagulopathy


24 y.o. Soldier: 2x 7.62mm GSWs
LT chest... *Lethal injury?*
24 y.o. Soldier: 2x 7.62mm GSWs
LT chest… *Is this a lethal injury?*

- At night
- On an assault target
- Troops in contact
- In the mountains of AFG
- In January (ambient temperature <20°F plus wind chill)
- No ER or CT scan or blood bank, nearest surgical facility is >1hr away by helicopter plus fixed wing transport
- 37min from POI to 6-person surgical team

*Who thinks this patient is going to make it?*
He made it! One month later, discharged from hospital, RTD

- On objective: TCCC (27 min)
  - Removed from line of fire
  - BP 60/P
  - Chest seals, needle decompression
  - IV access
  - 1gm TXA
  - 1U FDP
  - Litter carry to HLZ
- On helo: en route care (12 min)
  - P 180, SpO2 91%
  - IO access
  - 1U FDP, 1U RBC
  - HPMK
- At FOB: surgical team
  - L Chest tube (500ml blood, air), R Chest tube (2000ml blood)
  - Traumatic arrest → thoracotomy → PA injury repaired → cardiac massage → ROSC after 4min
  - 2U FFP, 2U RBC
- Evac to Bagram Air Field (hospital)
Preventable trauma deaths due to *non-compressible bleeding* (mil or civ)

**US Military Death Distribution**
4,569 Combat Deaths (2001-2011)

**Died of Wounds** (Level II and above)  
506 deaths

<table>
<thead>
<tr>
<th>Killed in Action (Level I)</th>
<th>4,090 deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Pre-MTF Combat Deaths</td>
<td>4,090</td>
</tr>
<tr>
<td><em>Potentially Survivable Deaths</em></td>
<td>1,075 (26%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>984 (91.5)</td>
</tr>
<tr>
<td>Airway</td>
<td>69 (6.4)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (2.0)</td>
</tr>
<tr>
<td><em>Potentially Survivable Hemorrhage</em></td>
<td>984 (24%)</td>
</tr>
<tr>
<td>Truncal</td>
<td>675 (17%)</td>
</tr>
<tr>
<td>Junctional</td>
<td>170 (4%)</td>
</tr>
<tr>
<td>Extremity</td>
<td>139 (3%)</td>
</tr>
</tbody>
</table>

Damage Control: the key to saving lives and keeping the ship afloat.

Damage Control for Combat Trauma

• Stop the bleeding!  
  – Don’t try to fix everything at once, just stabilize

• Treat shock!  
  – Lack of tissue perfusion = death; need oxygen

• Treat coagulopathy!  
  – Blood that doesn’t clot will leak out (see above)

How do you do this?

Surgical control of hemorrhage + blood!
Who should get DCR?

• Active bleeding $\Rightarrow$ at risk for or exhibiting signs of hemorrhagic shock

• About 40-50% of combat casualties receiving transfusion or 10-20% overall
  – SBP < 110mm Hg, HR > 105, HCT < 32%, pH <7.25
    • 3 of 4 above $\Rightarrow$ 70% risk of MT, all 4 $\Rightarrow$ 85%
  – Can also consider INR > 1.4, StO2 < 75%, lactate>2.5
  – Truncal, axillary, neck, groin bleeding
  – Large soft tissue injury, proximal amputation, mangled extremity
  – Coagulopathy, hypothermia

• This is **clinical**: eyeball test, mental status, radial pulse
The balancing act of DCR

• **Must treat shock** (hypovolemia → hypoxia) without worsening…

• **Acute coagulopathy of trauma**
  - (ACOT, TIC, ATC,…): “INR>1.2” -- 25% of major trauma patients

• **ACOT associated w/ increased mortality** (22.7% vs. 7.0 %), blood product requirements, MOF
  - Mortality in OIF/OEF patients w/ ACOT 30% vs. w/o ACOT 6%

• **Complex process**: fibrinolysis, platelet dysfunction, fibrinogen consumption, hemodilution, auto-heparinization, protein C
  - Occurs in first 30 minutes post-traumatic injury, Independent of iatrogenic hemodilution
  - Not necessarily a thrombin deficiency (hyper → hypocoagulable)
  - Hypoperfusion and tissue injury required (acidosis, tissue factor)

• **Optimal treatment unknown.** Current approach is empirical. Give **functionality of WHOLE BLOOD; don’t make things worse.**


Damage Control Resuscitation vs. ATLS

• Advanced Trauma Life Support (ATLS) Guidelines* & Combat Casualty Care Course (C4) in 2003:
  – 2 liters lactated Ringers or saline first, then RBCs, then plasma and platelets if coagulation labs are abnormal, plus more saline…
• ATLS c/w DCR, ATLS is associated with more…
  • Abdominal compartment syndrome (16% vs. 8%)
  • MOF (22% vs. 9%)
  • Death (27% vs. 11%)

DCR = Hemostatic Resuscitation

- Minimize crystalloid, **DO NOT USE HEXTEND**
  - Or, BETTER, use **WHOLE BLOOD**
- Permissive hypotension
  - Do not chase “120/80” – do not “pop the clot”
  - Target should be about SBP = 90 until surgical hemostasis ensured
- Tranexamic acid

**THIS, not that!**
• Caveat: *empiric* method based largely on retrospective data (except for TXA – CRASH-2 trial)


DCR foundations

Borgman, Spinella

Fig. 1. Percentage mortality associated with low, medium, and high plasma to RBC ratios transfused at admission. Ratios are median ratios per group and include units of fresh whole blood counted both as plasma and RBCs.

DoD WB studies show ? equivalency between WB and 1:1:1

Perkins, Cap

Holcomb, Wade

Perkins Transfusion 2011
Spinella J Trauma 2009
Limitations of Retrospective Data

• Survival bias?
  – Do patients survive because they get a 1:1:1 ratio, or do patients who would have survived anyway live to receive the blood products?
  – Dead people do not receive transfusions; most trauma mortality is in first 2-3 hours
  – Takes time to prepare FFP, so dead “low ratio” patients may be those who died waiting for FFP

• Need RCTs: PROPPR!
  – 1:1:1 vs. 1:1:2 [not vs. ATLS!]
  – Funded by DoD and NHLBI/NIH

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma

The PROPPR Randomized Clinical Trial

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baranuk, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Brails, MD, MPH; Eleven M. Bulger, MD, Rachael A. Callison, MD, MSPH; Mitchell Jay Cohen, MD; Bryan A. Cotton, MD, MPH; Timothy C. Faber, MD; Keshil Saha, MD; Jeffrey D. Kerby, MD, PhD; Peter Mudali, MD; Terrence Okoro, MBCHB, MS; Sandra Podbielski, MD; PhD; Bryce R. H. Robinson, MD; Thomas M. Scalza, MD; Martin A. Schreiber, MS; Deborah M. Stein, MD; Jordan A. Weirberg, MD; Jeanette L. Callum, MD; John R. Hess, MD, MPH; Neha Mitajevic, PhD; Christopher N. Miller, MD; Jean-Francois Pittet, MD; David E. Hoyt, MD; Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPPR Study Group

CONCLUSIONS AND RELEVANCE Among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1:1:2 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days. However, more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours. Even though there was an increased use of plasma and platelets transfused in the 1:1:1 group, no other safety differences were identified between the 2 groups.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01545232


Figure 2. Kaplan-Meier Failure Curves for Mortality at 24 Hours and 30 Days

The colored areas indicate 95% confidence bands, which were calculated using the Hall-Wellner method. The Hall-Wellner bands extend to the last event (death) in each group. For 24-hour mortality, the Cox proportional hazards regression model, adjusted for site as a random effect, produced a hazard ratio (HR) of 0.72 (95% CI, 0.49-1.07). There were no patients lost to follow up during the first 24 hours from randomization. For 30-day mortality, the Cox proportional hazards regression model, adjusted for site as a random effect, produced an HR of 0.82 (95% CI, 0.61-1.12). Between 24 hours and 30 days, 4 patients were lost to follow-up and were censored when they withdrew consent or were last known to be alive (3 in the 1:1:1 group and 1 in the 1:1:2 group).
Time to Death: KIA/DOW
Golden Hour is too late to start DCR…

Number of KIA and DOW Deaths by Time Increment (AFG)
N=457

- KIA
- DOW

Must start resuscitation pre-hospital: Remote DCR (RDCR)!
Pre-Hospital Transfusion Saves!

Table 2. Medevac Study Population Post-treatment Characteristics & Outcomes

<table>
<thead>
<tr>
<th>Unadjusted Post-treatment Between-Group Differences</th>
<th>Transfused Pre-hospital</th>
<th>Not Transfused Pre-hospital</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>*KIA (%)</td>
<td>2 (3.8%)</td>
<td>58 (20.3%)</td>
<td>0.003*</td>
</tr>
<tr>
<td>*Died (KIA + DOW) within 24 hours of MEDEVAC take-off from POI (%)</td>
<td>2 (3.8%)</td>
<td>64 (22.4%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>*Died (KIA + DOW) within 30 days (%)</td>
<td>5 (9.4%)</td>
<td>77 (26.9%)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Tranexamic Acid [TXA] (%)</td>
<td>48 (90.6%)</td>
<td>144 (50.3%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Documented shock [SBP&lt;90, HR&gt;120 or shock index &gt;0.9] upon ED arrival (%)</td>
<td>N=52</td>
<td>N=233</td>
<td>0.110</td>
</tr>
<tr>
<td>*Massive Transfusion [&gt;10 units/24hrs] (%)</td>
<td>40 (75%)</td>
<td>119 (42%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>ISS: Median (IQR)</td>
<td>29 (17, 36)</td>
<td>24 (17, 36)</td>
<td>0.179</td>
</tr>
<tr>
<td>AIS Score indicating torso hemorrhage (%)</td>
<td>22 (41.5%)</td>
<td>108 (37.8%)</td>
<td>0.646</td>
</tr>
</tbody>
</table>

*Statistically significant at <0.05 level by Fisher’s exact test.
Pre-hospital transfusion saves lives, even during short evacs.
RDCR: immediately if not sooner!

Rapid Pre- or In-Hospital Transfusion
Adjusted Cox Models for 24 hour Survival

Transfusion started within 13* vs. >13 minutes after MEDEVAC take-off from POI

*34 min from injury

Among survivors past minute 13, transfusion started >13-20 vs. >20 minutes after take-off

Increasing duration of shock is not helpful.

Think BLS. How many minutes before myocardium and brain die?
DCR timing key in hospital too: don’t wait!

- Hemostatic resuscitation starting in the ED is associated with decreased mortality.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LOW</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>24-h survival</td>
<td>268/344 (78)</td>
<td>*63/70 (90)</td>
</tr>
<tr>
<td>30-d survival</td>
<td>245/344 (71)</td>
<td>†57/70 (81)</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS injury</td>
<td>16/97 (16.5)</td>
<td>2/13 (15.4)</td>
</tr>
<tr>
<td>Truncal hemorrhage</td>
<td>59/97 (60.8)</td>
<td>†3/13 (23.1)</td>
</tr>
<tr>
<td>Airway</td>
<td>3/97 (3.1)</td>
<td>†2/13 (15.4)</td>
</tr>
<tr>
<td>MOFS</td>
<td>16/97 (16.5)</td>
<td>†6/13 (46.2)</td>
</tr>
<tr>
<td>VTE</td>
<td>1/97 (1.0)</td>
<td>0/13 (0.0)</td>
</tr>
<tr>
<td>Air embolism</td>
<td>2/97 (2.1)</td>
<td>0/13 (0.0)</td>
</tr>
</tbody>
</table>

\( \chi^2: *p = 0.02, †p = 0.08, ‡p < 0.05. \)
Total deaths = 112: LOW = 99 (2 with cause of death undetermined), HIGH = 13.

- Hour-by-hour plasma deficit (RBC-plasma) associated w/ higher mortality

The story so far...

- #1 cause of preventable death in trauma = bleeding
- DCR works to reduce bleeding mortality in trauma
- DCR delivers functionality of whole blood
- There is no golden hour
- The sooner you start DCR, the better (move to pre-hospital: RDCR)
- Treat physiology, don’t worry about “massive transfusion”
  - MT protocol activation is just code for “give DCR”

-- What have we learned about the pathophysiology of shock and ACOT?
-- What products are best?
-- Can we tailor therapy or is an empiric approach better?
Fick’s Equation (short version):

\[ D_{02} = 1.34 \times Hgb \times SaO2 \times CO \]

What are your options? Assume patient is breathing… Hgb is your lever.

- Hypotensive resuscitation means CO fixed

- SBP 80-90 means CO 2-3 L/min vs. 6 L/min in healthy 80 kg Soldier
Transfusing 1:1:1
CO 3, Hb 9

Transfusing WB
CO 3, Hb 14

Normal
CO 6, Hb 14

Delivery Dependent

VO₂

378
CO 6, Hb 4.8

SVO₂

OER

Lactate

NADH

Reduced CtOx

Delivery Independent

VO₂

551

SVO₂

OER

Lactate

NADH

Reduced CtOx

DO₂crit

DO₂
Pitfalls of resuscitation…

- Volume resuscitation: key $\uparrow$CO
- Oxygen delivery vital: $\uparrow$VO$_2$

**ATLS:** crystalloids/colloids, then RBCs

**WARNING**

Repayment of O$_2$D is not enough!

Dilution of clotting factors and platelets causes coagulopathy, continued bleeding, death.
Blood as an organ?

- Classic studies treat blood as “volume” or “oxygen delivery”
- Outcomes: LD50, metabolic parameters (BD, lactate, pH, etc.), cardiovascular (CO)

Blood & endothelium:
- Mesodermal origin, 3d week embryonic development
- Organ with multiple functions:
  - Metabolic support
  - Immune system
  - Coagulation
  - Trophic regulation

“Blood Organ Failure” as an element of Shock & Trauma?
- Acute Traumatic Coagulopathy (ATC)
- Immunosuppression combined with dysregulated inflammation

New trauma models: shock & coagulopathy

- Clinical studies demonstrate coagulopathy prior to iatrogenic hemodilution (ATC)
- *Beyond pure hemorrhage* → *include tissue trauma*

Models explore coagulation & immune function:
- V1.0 → observe prolonged PT, aPTT
- V2.0 → mechanism: aPC? *Probably not*…
- V3.0 → observe platelet dysfunction
- V4.0 → TEG/ROTEM fibrinogen dynamics
- V5.0 → observe cytokine changes, immune cell activation…

Endothelial & tissue effects inadequately understood

- Technologically challenging
- Immune and trophic function → need better link to $O_2D$ and ATC

Brohi *Ann Surg* 2007
Darlington *Shock* 2013
Kutcher *J Trauma* 2012
Better understanding of platelet dysfunction

USAISR rat model. Similar findings in clinical studies.
Platelets can’t maintain aggregation response!

![Graph showing aggregation over time](image-url)
Platelets stick to leukocytes: a lot!
How effective is current resuscitation with respect to PLT function?

*PLT CT (x10^3/μL)*

- Subject (R-TX)
- Algorithm (RF-TX)
- RFP-TX

*TRAP*

- Subject
- PLT CONC
- RFP-TX
- RFP-PUR

* p≤0.001
* p=NS

Pidcoke J Trauma 2015
How hemostatic is current resuscitation?

ROTEM analysis of transfused Products...

Definitely need the PLT, but they’re not great.
Need a platelet product that really works!

Which platelets would you want if you were bleeding?

- 5d RT clots are weak
- 4C storage maintains clot strength

* Compared to Fresh; n=4, p < 0.05

Nair BJH 2017 in press
Aggregation response well preserved in PAS at 4°C

Getz Transfusion 2016
Why would you use RT platelets in patients needing DCR?

Collagen 2.5 μg/mL + EPI 2 μM

ADP 5 μM + EPI 2 μM

Getz Transfusion 2016
Mitochondrial respiration conserved in 4C storage
(Also, mitochondrial gene expression…)

A

B

RT PLT: zombies

4C PLT: primed and ready
Apoptosis in RT storage
PAS is better than plasma
Mitochondrial gene expression preserved during 4C storage
PAS is better than plasma for 4C storage

PAS dilutes fibrinogen.
Fibrinogen binding drives activation, metabolic exhaustion.
PAS is better than plasma for 4C storage

Fibrinogen binding drives aggregate formation. PAS prevents this.
Platelet aggregation & count after platelet transfusion in cardiac surgery

MANOVA model comparing 22 °C vs 4 °C included changes in ADP, ASPI, COL, RISTOH, and TRAP: Wilk's Lambda p-value = 0.057

*Results reported as mean ± SEM. Results include first transfusion episode. Storage to 7 days.
Blood product utilization

*Results reported as mean ± SEM. Observation time: from start of surgery until 7 o’clock day 1 after surgery.

- SAG
- Octaplas
- PLT
- Fibrinogen

22 C
4 C
*Results reported as mean ± SEM. Observation time: from chest closure until 7 o’clock day 1 after surgery.
Hypoxia and Hemostasis

Drowning = perfect hypoxia model

Hypoxia → endothelial tPA release → massive Fibrinolysis (& auto-heparinization)

Treat this with:
-- TXA
-- Fibrinogen

If the hypoxia is due to Blood loss, will need:
-- RBC
-- volume
-- coag factors
-- platelets
i.e, whole blood

Figure 1. Tissue factor activates extrinsic hemostasis (EXTEM) traces from admission to 6 hr after arrival of a drowning victim. A reference rotational thrombelastometric analysis trace (25% opacity) is used as overlay to visualize differences from normal clotting. Parameters analyzed are clotting time (CT, s: time from adding starting reagent until clot begins to form; range, EXTEM [35–80 s], kaolin activates contact phase [INTEM, 100–240 s]), clot formation time (CFT, s: time from CT until a trace amplitude of 20 mm is reached; range: EXTEM [36–160 s], INTEM [35–110 s]), alpha angle (α, °: angle of tangent at 2-mm amplitude; kinetic of clot formation), maximum clot firmness (MCF, mm: maximum trace amplitude, range: EXTEM, INTEM: [53–72 mm]) and maximum lysis (ML, %: difference between MCF and lowest trace amplitude in %; range: EXTEM, INTEM: [≤15%]). A, Admission, (B) 100 min, (C) 180 min, and (D) 360 min after first presentation. Hyperfibrinolysis progressively resolved and MCF increased over time, after tranexamic acid (1,000 mg) and fibrinogen (4,000 mg) had been given IV.

Schwameis CCM 2015.
Fibrinolysis is a major driver of ACOT

Note that fibrinogen is also being consumed!
Plasmin also generates bradykinin...

This is why tranexamic acid (TXA) reduces mortality in trauma.

Plasminogen

\[
\begin{align*}
\text{Plasminogen} & \\
\mu g/ml & \\
0 & 1 & 2 & 3 & 4 & 5 \\
90 & 100 & 110 & 120 & 130
\end{align*}
\]

Plasmin

\[
\begin{align*}
\text{Plasmin} & \\
\mu g/ml & \\
0 & 1 & 2 & 3 & 4 & 5 \\
0.5 & 1.0 & 1.5 & 2.0 & 2.5 & 3.0 & 3.5
\end{align*}
\]

CRASH-2 *Lancet* 2010
Wu *AJP* 2015
Cap *Blood* 2017
Marcos-Contreras *Blood* 2017

This is why **tranexamic acid (TXA)** reduces mortality in trauma.
**TXA Mechanism**

- **Tranexamic Acid (TXA)** is a derivative of the amino acid lysine.
  - It has a very high affinity for the lysine binding sites of plasminogen.
  - It blocks these sites and prevents binding of plasmin to the fibrin surface, thus exerting its anti-fibrinolytic effect (described in 1966).

*Also reduces lung & gut edema...*
Should we try to boost thrombin?

What about thrombin generation?

Severe trauma/shock model with elevated INR (coagulopathic), No resuscitation:

-- Prothrombin drops by maybe 20%.
-- Thrombin up 1.5x over first 4 hours.

Remember that plasmin up 2.5x…

Role of rFVIIa or PCC? Maybe in some?

Wu AJP 2015
Recognize complexity →
Identify key nodes → Develop biomarkers → Tailor therapies

Precision Medicine… →
Genetics/ Expression analysis → Personalized Trauma Care?
**Does ROTEM (or TEG) help?**

**Table 1: Demographics**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>pre-ROTEM</th>
<th>post-ROTEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfused patients % (n)</td>
<td>21% (134)</td>
<td>26% (85)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>24 [21-29] (131)</td>
<td>25 [21-29] (84)</td>
<td>0.29</td>
</tr>
<tr>
<td>Gender % of males % (n)</td>
<td>93% (124)</td>
<td>95% (81)</td>
<td>0.57</td>
</tr>
<tr>
<td>Penetrating trauma</td>
<td>81% (109/134)</td>
<td>91% (77/85)</td>
<td>0.08</td>
</tr>
<tr>
<td>Blunt Trauma</td>
<td>16% (21/134)</td>
<td>8% (7/85)</td>
<td>0.14</td>
</tr>
<tr>
<td>ISS</td>
<td>21 [14-29] (134)</td>
<td>24 [17-35] (85)</td>
<td>0.01</td>
</tr>
<tr>
<td>ISS&gt;=15 % (n)</td>
<td>75% (100)</td>
<td>79% (67)</td>
<td>0.52</td>
</tr>
<tr>
<td>Shocked patients BD&gt;=5 % (n)</td>
<td>27% (40/117)</td>
<td>17% (16/70)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean BD in shocked patient</td>
<td>7.0 [6-8.8]</td>
<td>8.0 [5.3-11.8]</td>
<td>0.45</td>
</tr>
<tr>
<td>Mean INR (n)</td>
<td>1.2 [1-1.3] (107)</td>
<td>1.2 [1-1.4] (46)</td>
<td>0.40</td>
</tr>
<tr>
<td>CoT patients INR&gt;=1.2 % (n)</td>
<td>50% (54/107)</td>
<td>61% (28/46)</td>
<td>0.74</td>
</tr>
<tr>
<td>Mean INR in CoT Patients</td>
<td>1.3 [1.2-1.6]</td>
<td>1.4 [1.2-1.5]</td>
<td>0.74</td>
</tr>
<tr>
<td>Admit Hematocrit % (n)</td>
<td>36.4 [31-41.3] (110)</td>
<td>37.5 [34-43.2] (49)</td>
<td>0.09</td>
</tr>
<tr>
<td>Admit Platelet Count x10^3 (n)</td>
<td>203 [145-272] (107)</td>
<td>160 [132-229] (46)</td>
<td>0.10</td>
</tr>
<tr>
<td>Massive transfusions % (n)</td>
<td>5% (7/134)</td>
<td>6% (5/85)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

All values documented are MEDIAN [IQR] (n of observations) unless otherwise specified. ISS is injury severity score, BD is base deficit, CoT is Coagulopathy of Trauma as defined as admission INR>1.2, INR is International Normalization Ratio, ED is emergency department or arrival information.

**DoD pre-/post-ROTEM at Bagram AB, AFG**

Prat *J Trauma* 2017 in press
Table 2: Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>pre-ROTEM</th>
<th>post-ROTEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital days (n)</td>
<td>2 [1-7] (134)</td>
<td>2 [1-3] (85)</td>
<td>0.07</td>
</tr>
<tr>
<td>ICU days (n)</td>
<td>1 [1-3] (134)</td>
<td>1 [1-3] (85)</td>
<td>0.70</td>
</tr>
<tr>
<td>Ventilation-free days (n)</td>
<td>1 [0-4] (134)</td>
<td>0 [0-2] (85)</td>
<td>0.16</td>
</tr>
<tr>
<td>Overall Mortality % (n)</td>
<td>5.2% (7/134)</td>
<td>4.7% (4/85)</td>
<td>1.00</td>
</tr>
<tr>
<td>Blunt Injury Mortality % (n)</td>
<td>4.8% (1/21)</td>
<td>14% (1/7)</td>
<td>0.44</td>
</tr>
<tr>
<td>TRISS Predicted Blunt Mortality % (n)</td>
<td>1.7 (81)</td>
<td>4.5 (52)</td>
<td>0.56</td>
</tr>
<tr>
<td>Penetrating Injury Mortality % (n)</td>
<td>4.6% (5/109)</td>
<td>3.9% (3/77)</td>
<td>1.00</td>
</tr>
<tr>
<td>TRISS Predicted Penetrating Mortality % (n)</td>
<td>2.1 (81)</td>
<td>4.6 (52)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

All values documented as MEDIAN [IQR] (n of observations) unless otherwise specified. ICU is intensive care unit; TRISS is Trauma-Related Injury Severity Score. n is the number of patients in which data was available.

Prat J Trauma 2017 in press
Table 3: Transfusions within 24 hours from admission

<table>
<thead>
<tr>
<th>Product</th>
<th>pre-ROTEM</th>
<th>post-ROTEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusions (All patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed Red Blood Cells</td>
<td>2 [1-3]</td>
<td>2 [1-4]</td>
<td>0.32</td>
</tr>
<tr>
<td>Fresh Frozen Plasma</td>
<td>1 [0-2]</td>
<td>2 [0-3.5]</td>
<td>0.13</td>
</tr>
<tr>
<td>Apheresis Platelets</td>
<td>0 [0-0]</td>
<td>0 [0-1.6]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>0 [0-0]</td>
<td>0 [0-0.5]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Crystalloid (L)</td>
<td>2 [1.3-4.0]</td>
<td>3.5 [1.2-5.3]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Colloids (L)</td>
<td>0 [0-0.3]</td>
<td>0 [0-0.5]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Transfusions (Patients who received the specific blood product)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed Red Blood Cells</td>
<td>2 [1-4]</td>
<td>3 [2-4.5]</td>
<td>0.06</td>
</tr>
<tr>
<td>Fresh Frozen Plasma</td>
<td>2 [1-4]</td>
<td>2 [1-5]</td>
<td>0.23</td>
</tr>
<tr>
<td>Apheresis Platelets</td>
<td>2 [1-6]</td>
<td>2 [1.6.5]</td>
<td>0.51</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>7.5 [1.7-10]</td>
<td>10 [1.5-20]</td>
<td>0.15</td>
</tr>
</tbody>
</table>

All values documented as MEDIAN [IQR]. L represents liters.

Prat J Trauma 2017 in press
ROTEM: more PLT, CRYO

Figure 1:

Proportion of patients transfused (%)

- pRBC
- FFP
- PLT
- Cryo

pre-ROTEM
post-ROTEM

Prat J Trauma 2017 in press
Figure 3:

A. Received all 4 products

- FFP
- PLT
- CRYO

B. Received any transfusion

Pre-ROTEM (n=7) | Post-ROTEM (n=14)
---|---
FFP | 1.0 | 1.1
PLT | 0.3 | 1.3
CRYO | 0.8 | 1.6

Pre-ROTEM (n=134) | Post-ROTEM (n=85)
---|---
FFP | 0.6 | 0.6
PLT | 0.3 | 0.1
CRYO | 0.8 | 0.4

Prat J Trauma 2017 in press
What did the tests show?

Around 1/3 of patients had ROTEM abnormalities in clot formation, strength.

Only 6% had delayed clotting (long CT).

INTEM (contact activation) more sensitive?

Prat J Trauma 2017 in press
(R) DCR: Treating Acute Blood Failure due to blood loss & tissue damage

- Oxygen debt
- Coagulopathy
- Platelet dysfunction
- Endothelial dysfunction
- Innate immune activation

Acute Blood Failure or Hemovascular Dysfunction

Empiric 1:1:1 or WB to replace functionality of lost/dysfunctional blood. But...

SBP>90, higher risk of “popping the clot”… prior to surgical control of bleeding!

Balance replacement of function with risk of re-bleeding → “permissive hypotension”
Golden Hour is too late...
NEED BLOOD at POI

Number of KIA and DOW Deaths by Time Increment
N=457

- KIA
- DOW

JTS 2016.
EVALUATION OF PREHOSPITAL BLOOD PRODUCTS TO ATTENUATE ACUTE COAGULOPATHY OF TRAUMA IN A MODEL OF SEVERE INJURY AND SHOCK IN ANESTHETIZED PIGS

Sarah Watts,* Giles Nordmann,* Karim Brohi,† Mark Midwinter,‡ Tom Woolley,* Robert Gwyther,* Callie Wilson,* Henrietta Poon,* and Emrys Kirkman*

*CBR Division, Defence Science and Technology Laboratory, Defence Science and Technology Laboratory, Porton Down, Salisbury; †Centre for Trauma Sciences, Bizard Institute, Queen Mary University of London, London; and ‡University of Birmingham, Birmingham, United Kingdom

CRISTALLOID IS BAD!

Fig. 3. Effects of tissue injury, hemorrhagic shock, and resuscitation on TEG R time (clot initiation), K time (clot dynamics), and MA (clot strength) in three treatment groups. For more details, see legend to Figures 1 and 2. Mean values ± SEM.
Depends on resuscitation fluid… which would you choose?

Dubick et al. ISR
In preparation
2016

Uncontrolled torso hemorrhage (swine):
50% hemorrhage
Aortotomy

Resuscitation:
SBP 80mmHg maintained
Turns out that RBCs are important…

Dubick et al. ISR
In preparation
2016
What we are doing now that is associated with improved outcomes?

• Aggressive hemorrhage control
  – Hemostatic dressings, tourniquets
• TXA
• Early resuscitation that delivers functionality of WB (WB or 1:1:1)
  – Increasing use of plt & cryo (1:1:1:1)
  – ROTEM-guided DCR?
  – Permissive hypotension?
• Reduced crystalloid/colloid
• Minimize time to surgery
History of Pre-Hospital Shock Resuscitation

Whole Blood is King!

60 years of Blood

Components are cool!

30 years of Clear Fluids

Back to the future???

WW I  WW II  Korea  Vietnam  OIF/OEF  → WB
Component Therapy:
1U PRBC + 1U PLT + 1U FFP + 1 U cryo
680 mL
• Hct 29%
• Plt 80K
• Coag factors 65% of initial concentration

Whole Blood:
500 mL
• Hct: 38-50%
• Plt: 150-400K
• Coag concentration 100%

Anti-coagulants and Additives

1:1:1 Component Therapy:

- 6 x RBC (AS-5)  6 x 120 ml = 720ml
- 6 x FFP       6 x 50 ml  = 300ml
- 1 x aPLT      1 x 35 ml  = 35ml

Total = 1055ml

Whole Blood x 6 Units:

- 6 x 63ml = 378ml

3 times the volume of anticoagulant & additives in reconstituted whole blood from components (1:1:1) compared to whole blood!

Spinella PC, J Trauma. 2009;66:S69-76
Whole Blood Hemostatic Function: 4C>RT, +/- Mirasol PRT

Fig. 4. Multiple electrode PLT aggregometry. A repeated measures analysis demon-

Fig. 5. TEG. Storage at 4°C preserved TEG R time, K, α-angle, MA, clot strength, and
Whole Blood Recent Combat Data

Fresh whole blood use by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets


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

Warm Fresh Whole Blood Is Independently Associated With Improved Survival for Patients With Combat-Related Traumatic Injuries

Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Alec C. Beekley, MD, and John B. Holcomb, MD

Comparison of platelet transfusion as fresh whole blood versus apheresis platelets for massively transfused combat trauma patients

Pre-hospital resuscitation must be simple to be feasible.

→ UNIVERSAL PRODUCT: LTOWB

Type-specific WB is too slow and is unsupportable.

Doctrine must change to reflect risk/benefit trade-offs. *Need blood fast.*
• ABO incompatible platelets ok?

• Why not LTOWB?
  – Similar risk of Group O RBCs
  – Similar risk of Platelet Transfusions
  – Potential MINOR mismatch of plasma
  – Dilution of antibodies, soluble A & B antigens minimize risk
Risk Comparison

- Plasma Incompatible ABO from UK SHOT database for platelet transfusions
  - 1:120,000 risk of MODERATE hemolytic reaction

- Type specific ABO blood products
  - 1:80,000 risk of SEVERE hemolytic reaction
    - Human error
  - Risk is elevated in austere environments!
Group O WB Experience

- **WW I**
  - 15 adverse events reported, all mild reactions
  - High ABO titers measured from donors, IgM > 256

- **WW II**
  - Practically all blood transfused was Group O whole blood
  - Of 256 ABO incompatible Group O transfusions, 3 mild hemolytic reactions reported
    - All ABO IgM titers > 500
  - One report of severe reaction from ABO IgM titer of 8000
    - Army policy that ABO titer must be < 250 for Group O whole blood to be universal donor.
Group O WB Experience

• Korea
  – 400,000 low titer Group O whole blood transfusions with no severe hemolytic reactions when low titer defined as < 250

• Vietnam
    • 1 severe hemolytic transfusion reaction
    • High titer (> 256) Group O whole blood used accidentally in non-O patient
No standard international definition
  – US Korean War and Vietnam standard
    • IgM < 256
  – Norwegian and UK definitions
    • IgM < 100 or IgG < 400

*Hemolysis events rare (case reports)*

*Difficult to optimize standard with current technology*
Whole blood donor program: pre-deployment TTD testing, anti-A/anti-B titers, universal donor identification.

Transfusion plan: **Group A to A, O/low titer to all others.**

Frigate has constant store **10 U WB stored at 4°C, 7 days** (tested, Gulf of Aden 2013).

Norwegian Navy SOF currently carry **GHB with stored WB on each mission.**
2/3 Group O Rangers are low titer (<1:256)

First to implement: 75th Rangers
→ 160th SOAR → SFGs… all SOCOM
→ Pre-collected, cold-stored WB & fresh

US civilian trauma programs:
-- U Pittsburgh
-- Cooper U Hosp (NJ)
-- U Kentucky
-- Mayo
-- U Texas (Houston, San Antonio)
EAST 2016 PLENARY PAPER

Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients

Mark H. Yazer, MD, Byron Jackson, MD, Jason L. Sperry, MD, Louis Alarcon, MD, Darrell J. Triulzi, MD, and Alan D. Murdock, MD, Pittsburgh, Pennsylvania


TRANSFUSION MEDICINE Official Journal of the British Blood Transfusion Society

Measurement of haemolysis markers following transfusion of uncrossmatched, low-titer, group O+ whole blood in civilian trauma patients: initial experience at a level 1 trauma centre

J. N. Seheult,1 D. J. Triulzi,1,2 L. H. Alarcon,2 J. L. Sperry,2 A. Murdock2 & M. H. Yazer1,2

1Department of Pathology, 2The Institute for Transfusion Medicine, and 3Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Received 22 July 2016; accepted for publication 23 September 2016
Fig. 2. Trends in the serum biochemical markers of haemolysis following cWB transfusion in non-group O and group O recipients. Shown are the median and the interquartile range for (a) haptoglobin, (b) total bilirubin, (c) lactate dehydrogenase (LDH), (d) creatinine and (e) serum potassium. The grey shaded areas represent the reference ranges for each analyte. The only significant difference (*) between the non-group O and group O cWB recipients in any of these analytes was the median serum total bilirubin on day 0.
<table>
<thead>
<tr>
<th>OPTION SUMMARY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WB 4°C</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Hgb</strong></td>
</tr>
<tr>
<td><strong>HCT</strong></td>
</tr>
<tr>
<td><strong>PLT</strong></td>
</tr>
<tr>
<td><strong>Fibrinogen, Factors</strong></td>
</tr>
<tr>
<td><strong>TEG</strong></td>
</tr>
<tr>
<td><strong>PLT aggregation</strong></td>
</tr>
<tr>
<td><strong>Volume/product mix (4L)</strong></td>
</tr>
</tbody>
</table>
-- Platelets critical to hemostasis
-- Platelets in short supply & suffer storage lesion due to RT storage *(reduced hemostatic function)*
-- RT platelets optimized for prophylaxis, not bleeding
-- Platelets unavailable outside of major centers
-- Bacterial contamination

USE PLATELETS THAT WORK!
STOP BLEEDING COLD!
• Hemorrhage and injury cause **acute blood failure** or hemovascular dysfunction.

• DCR treats drivers of blood failure simultaneously with blood (and TXA).

• DCR is most effective if **started immediately**: RDCR.

• Risk-benefit of products should be considered in light of exsanguination mortality.

• Simplicity is a virtue: **LTOWB**.

• Use **cold platelets***: longer shelf life, stop bleeding.

* **cold platelets from apheresis or**… in **WB**
Questions?

LTOWB

Cold Platelets