Whole Blood at Point of Injury: *a new treatment paradigm for NATO*

U.S. Army Institute of Surgical Research

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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.

Outline:

1. Overview of combat trauma epidemiology: cause of death and time to death

2. Pathophysiology of hemorrhagic shock and *Blood Failure*

3. State-of-the-art combat casualty care: Remote Damage Control Resuscitation (RDCR)

4. Implications for NATO

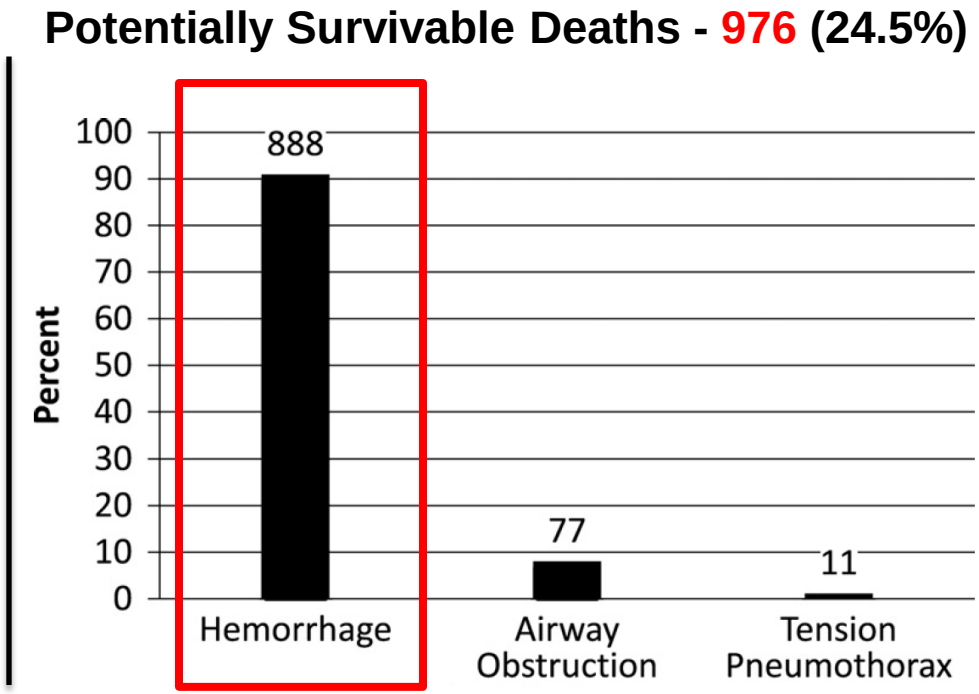
5. Conclusions

US Military Death Distribution (2001-2011)

4,596 Combat Deaths

Died of Wounds (≥ Role II)
580 deaths

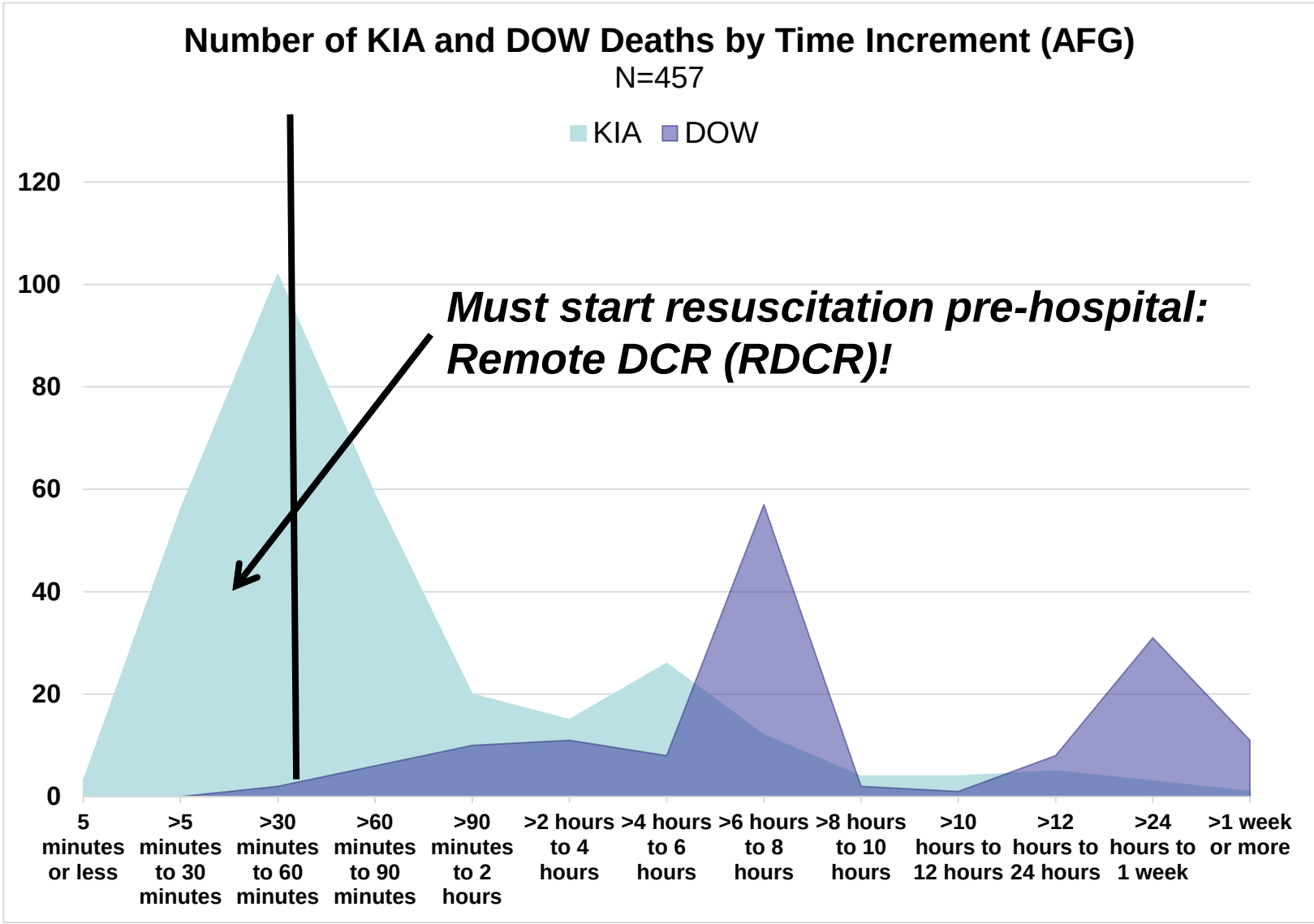
Killed in Action (Role I)
4,016 deaths
- 3,040 nonsurvivable
- **976 potentially survivable**



Eastridge. J Trauma Acute Care Surg. 2012

BLEEDING IS THE PROBLEM

Time to Death: KIA/DOW
"Golden Hour" is too late to start DCR…



Shackelford, et al.
JTS 2016.

Pre-hospital blood transfusion → Large reduction in risk of death

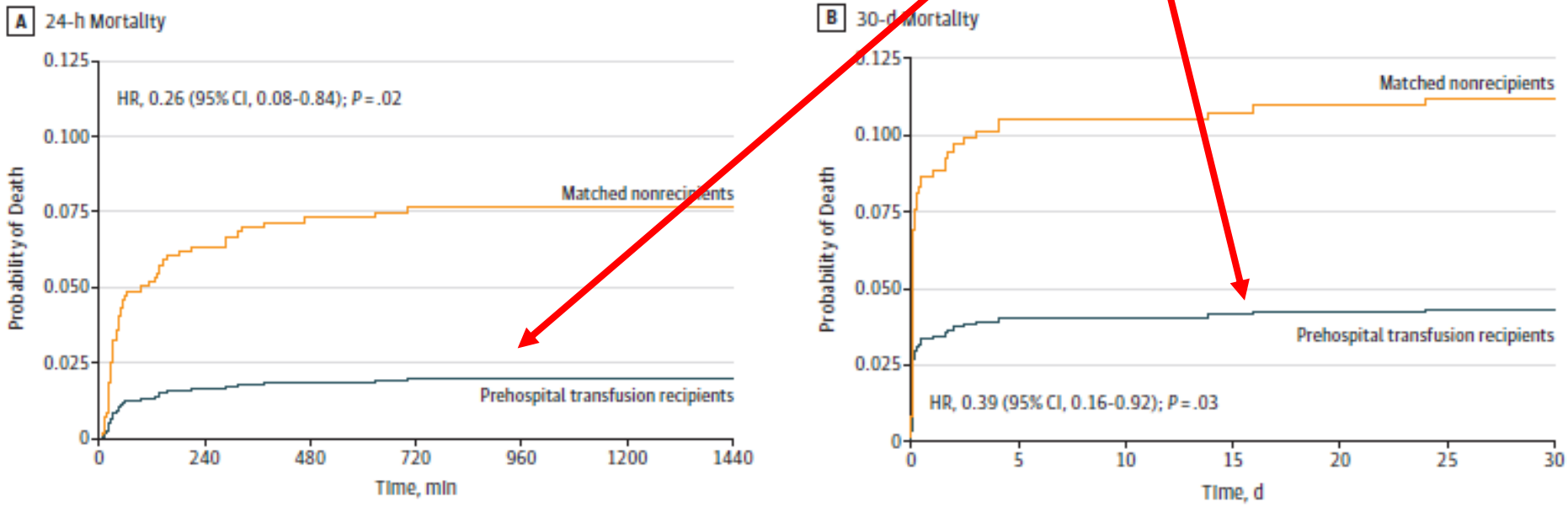
JAMA | Original Investigation

Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan With Acute and 30-Day Survival

Stacy A. Shackelford, MD; Deborah J. del Junco, PhD; Nicole Powell-Dunford, MD; Edward L. Mazuchowski, MD, PhD; Jeffrey T. Howard, PhD; Russ S. Kotwal, MD, MPH; Jennifer Gurney, MD; Frank K. Butler Jr, MD; Kirby Gross, MD; Zsolt T. Stockinger, MD

Which curve do you want to be on?
-- I'll take lower probability of death!

Figure 3. Mortality of Prehospital Transfusion Recipients vs Matched Nonrecipients



Timing is everything→ Transfusion must start 15min from MEDEVAC rescue (36min from POI)

JAMA | Original Investigation

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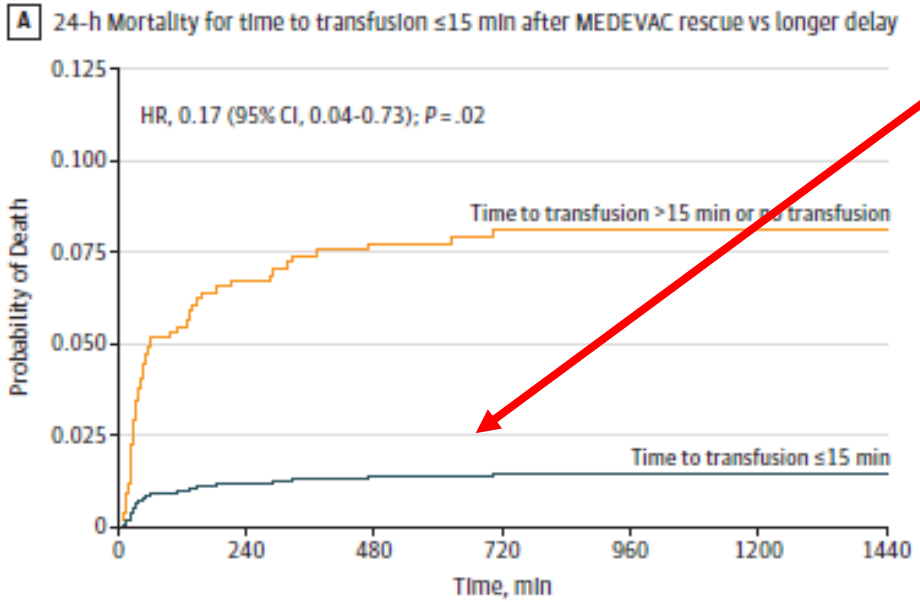
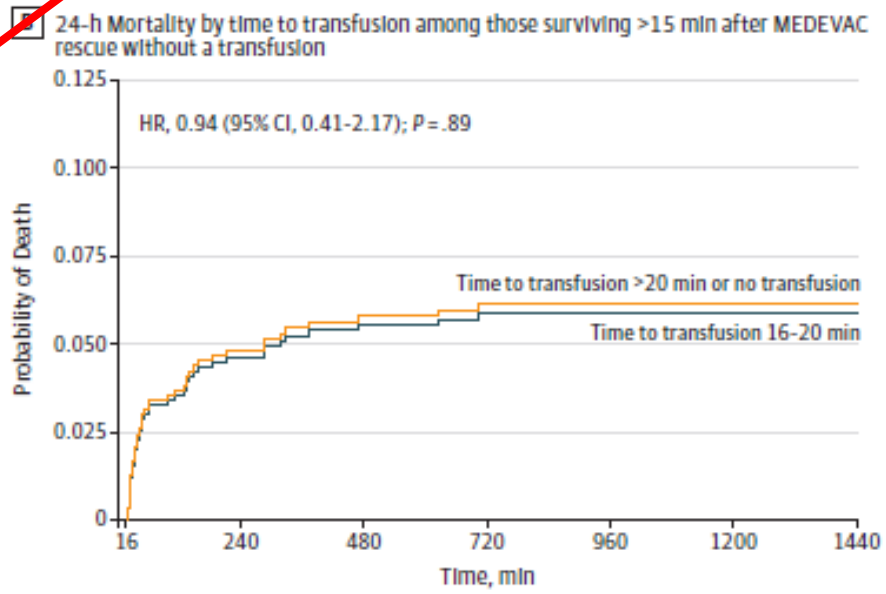
Best results: transfusion within 15min of MEDEVAC (36min of POI)

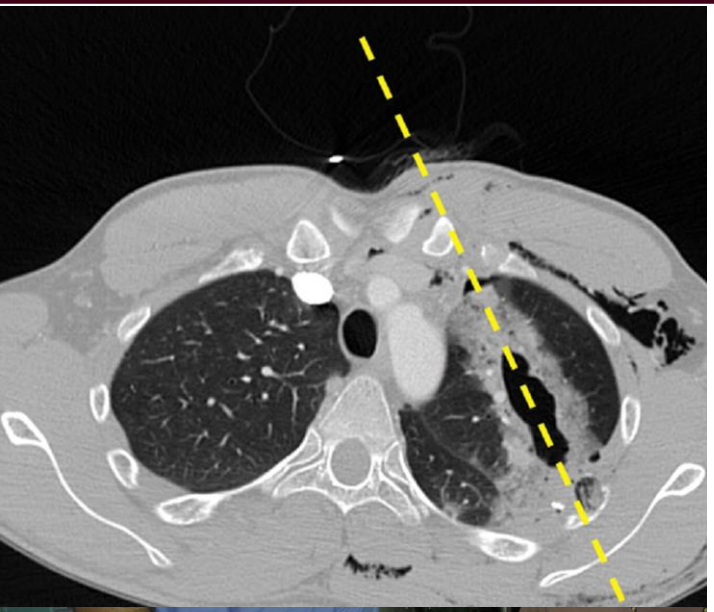
Figure 4. Mortality by Time From Medical Evacuation (MEDEVAC) Rescue to Start of Transfusion





Start transfusion here if not sooner!

Trauma + Hemorrhagic Shock: *Blood Failure*



HEMORRHAGIC SHOCK:

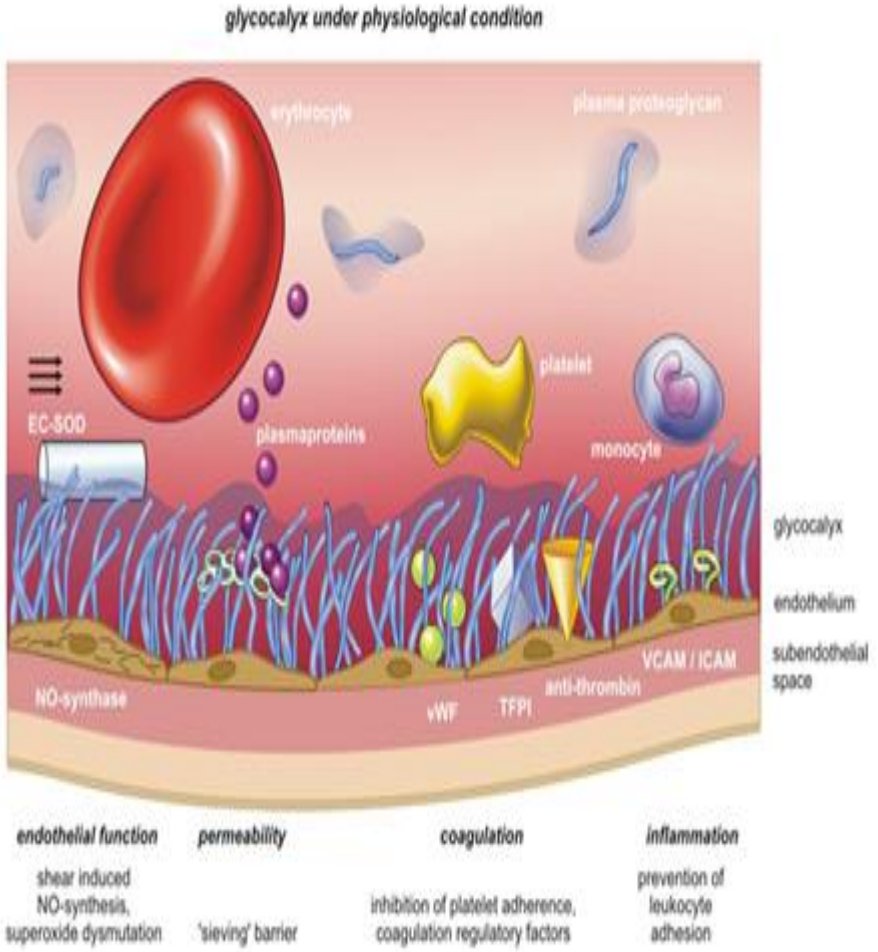
Low cardiac output →
Poor tissue perfusion →
Oxygen debt →
Acidosis →
Fibrinolysis/
Coagulopathy/
Platelet dysfunction →
More bleeding →

Requires aggressive, immediate intervention

DEATH… <u>IN MINUTES</u>

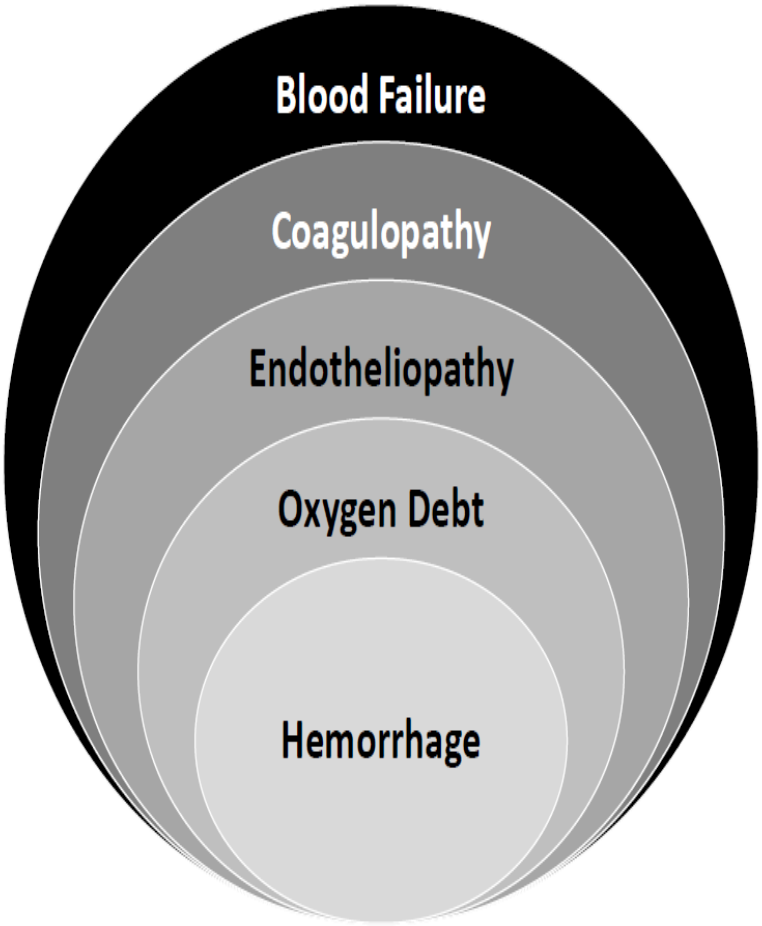
Need to restore <u>functionality</u> of WB!

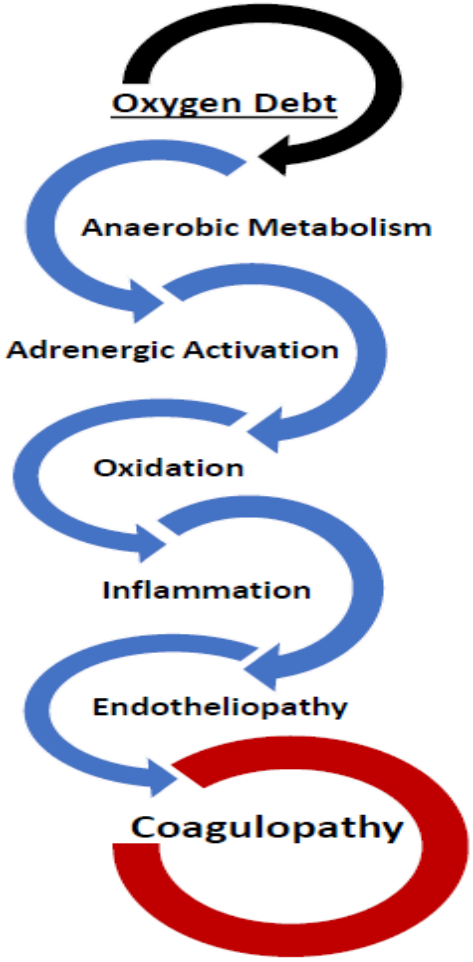
Blood + Endothelium = *Blood as an Organ*



- Embryonic mesoderm → hemogenic endothelium → HSC → blood: 3d week embryo
- Blood = RBCs, WBCs, Platelets, Plasma, *and…* Endothelium (10^{13} cells)
- Microcirculation estimated to cover an area of up to 7000 m^2
- Largest organ system, highest turnover rate.

Loss of Blood + Damaged Endothelium → *Blood Failure*





Must replace the full functionality of blood. Give WHOLE BLOOD.

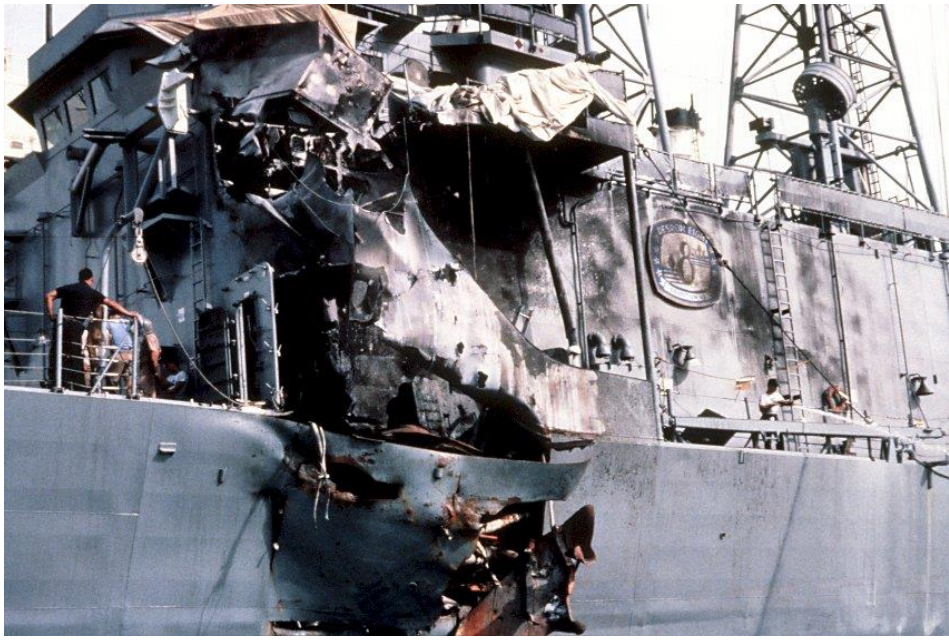
Remote

No R2 or R3 within 1 hour?

Move DCR out of hospital to keep patient alive!

RDCR

+ Damage Control



Damage Control:

First, only do the things essential to keeping the ship afloat. Plug holes & stop bleeding.

Rotondo MF, Schwab CW, et al. *J Trauma*. 1993;35(3):375-82.

+ Resuscitation

Emergency treatment to restore:

Circulating blood volume
Aid oxygen delivery
Replace hemostatic potential

Treat Blood Failure…

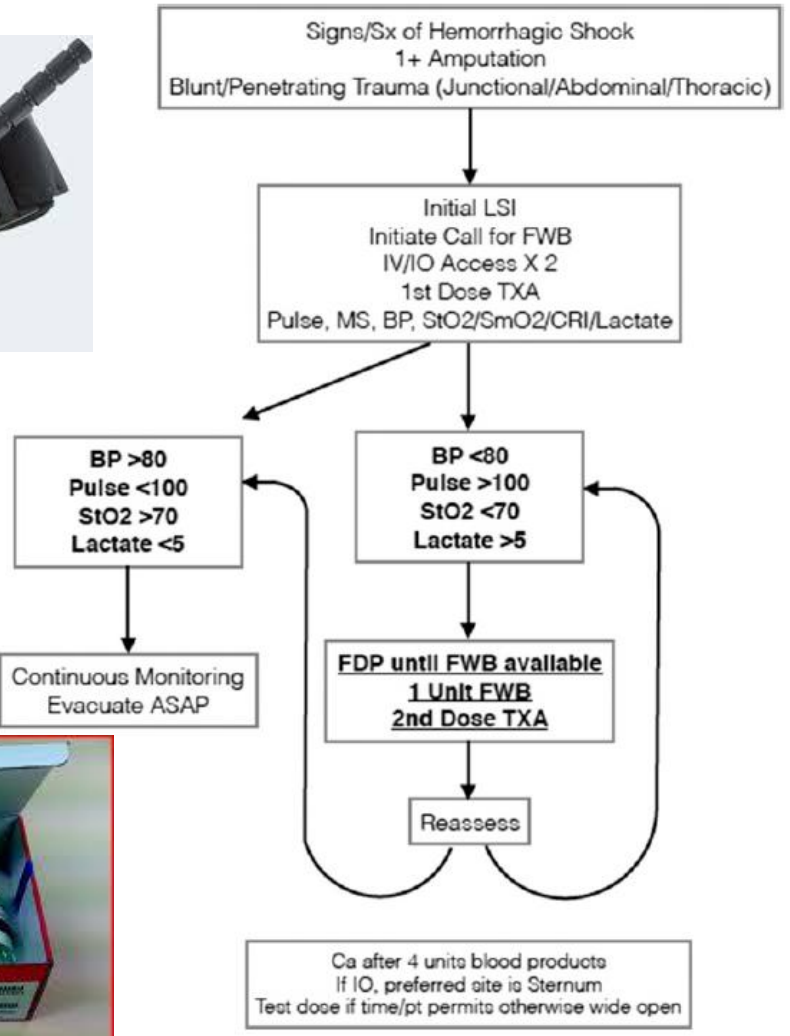
by giving what the patient is losing:

BLOOD!

= RDCR (today)

The essentials:

- ***Hemorrhage control***
- ***Resuscitation***
  - **TXA**
  - ***WHOLE BLOOD***
  - **Plasma (FDP) as a bridge to WB**
  - ***Avoid clear fluids***



75th Hemorrhagic shock.

ROLO!

DCR = Hemostatic Resuscitation

➢***Blood must be able to deliver oxygen & form clots!***

- Minimize crystalloid, ***DO NOT USE HEXTEND***
- RBC:FFP:PLT:cryo = “1:1:1:1” or better: **WHOLE BLOOD**
- **Treat loss of RBC, fibrinogen, platelet function, etc.**
- **Tranexamic acid for fibrinolysis**

THIS, not that!

Need all parts of blood to replace lost organ function

Start with plasma until you can get WB or DCR with components (1:1:1)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 26, 2018 VOL. 379 NO. 4

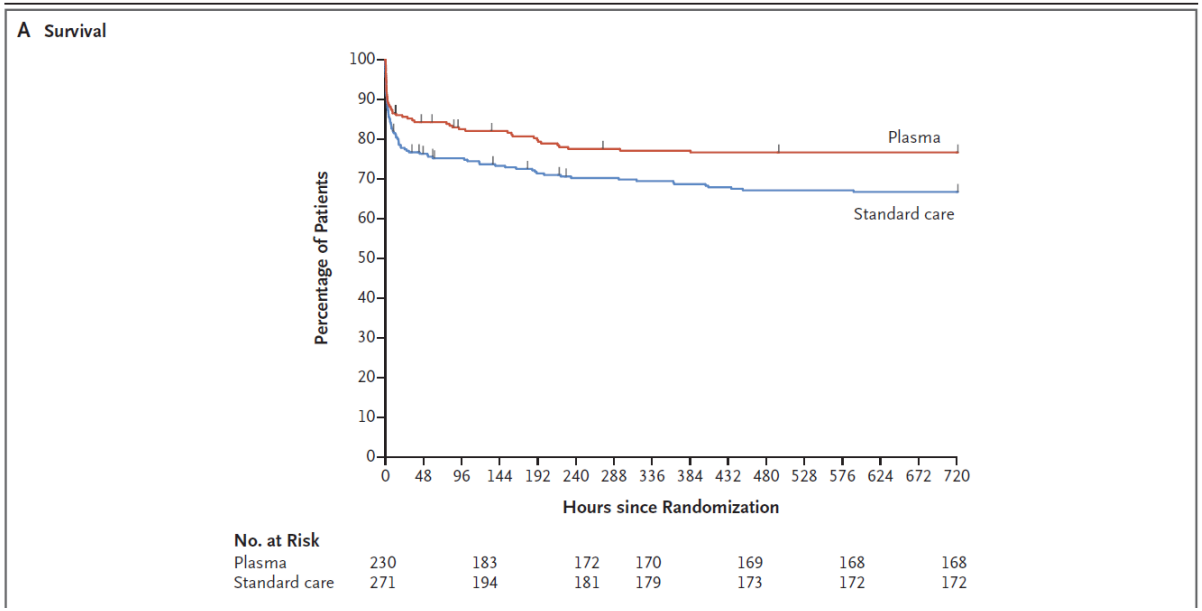
Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock

J.L. Sperry, F.X. Guyette, J.B. Brown, M.H. Yazer, D.J. Triulzi, B.J. Early-Young, P.W. Adams, B.J. Daley, R.S. Miller, B.G. Harbrecht, J.A. Claridge, H.A. Phelan, W.R. Witham, A.T. Putnam, T.M. Duane, L.H. Alarcon, C.W. Callaway, B.S. Zuckerbraun, M.D. Neal, M.R. Rosengart, R.M. Forsythe, T.R. Billiar, D.M. Yealy, A.B. Peitzman, and M.S. Zenati, for the PAMPer Study Group*

Plasma given pre-hospital as a bridge to full DCR reduces mortality by 1/3 (23% vs. 33%)!

Proof of concept for FDP as a bridge to WB in RDCR...

Note: outcomes even better with plasma+RBC



NATO COMEDS/MHCWG: Focus on Pre-Hospital Care

- **<u>Must reduce mortality pre-hospital (R2 or R3 too late)</u>**

- Pre-Hospital Care Improvement Initiative (PHCII) – key events:
  - **March 2016: Landstuhl workshop sponsored by MILMEDCOE**
  - June 2016: 45th COMEDS plenary, Dublin: FRA volunteers to lead PHCII
  - September 2016: 22nd MHCWG meeting in Landstuhl
  - **June 2017: Budapest MILMEDCOE workshop**
  - March 2018: Brussels MHCWG review of PHCII progress
  - April 2018: TIDESPRINT/Genoa: NATO Futures adopts BFF

Output of MILMEDCOE 2016 Landstuhl workshop: BFF

- **TCCC as basis of pre-hospital care**
  - Imperative to extend training throughout the force
- 10-1-2 (current NATO standard) should be refined
  - **Need to push hemorrhage control to self/buddy aide level**
  - 1 hour to resuscitation – miss opportunity to **prevent early hemorrhage deaths**
  - 2 hours to surgery is too late (unless blood provided far forward)
- New goals: **0-30-60 – with Blood Far Forward (BFF)**
  - Immediate self/buddy hemorrhage control
  - **30 minutes to resuscitation with blood**
  - 60 minutes to surgery ideally (perhaps 2 hrs with BFF)
- **BFF key to reducing battlefield mortality**
- Pediatric trauma care not doctrinal but needs to be
  - ethical imperative in view of injuries to non-combatant children

Output of MILMEDCOE 2017 Budapest workshop: BFF is key!

- **TCCC** as basis of pre-hospital care
- Early hemorrhage deaths can be avoided by:
  - Training all personnel in **hemorrhage control** (tourniquets, hemostatic dressings) for self/buddy aid
  - **Transfusing blood** at point-of-injury (POI) and *en route* to surgical care (and give TXA)
- **Must begin implementation of BFF!**

TXA

Low Titer O Whole Blood (LTOWB)

All blood products start as WB

WB collection kit

Donor

Whole Blood

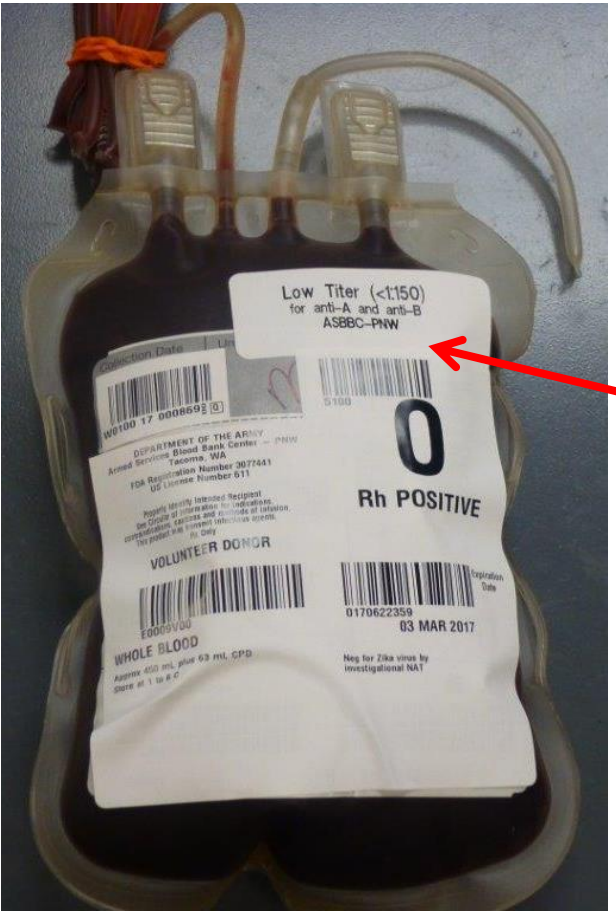
RBC

FFP

aPLT

We separate WB into components by <u>centrifugation</u> to treat isolated blood deficiencies like anemia. In bleeding, we need ALL the components (WB)!

Why give WB?
It's simple!



Don't make things worse (clear fluids)!

Give the patient what he or she is losing!

Keep it simple (one product)!

Can be "universal" (O Low Titer anti-A&B in plasma, RBCs compatible with all)

- New AABB standard
- No need to match blood types in emergency

LTOWB: get it in QUICKLY, because people DIE quickly!

WB is more concentrated

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:

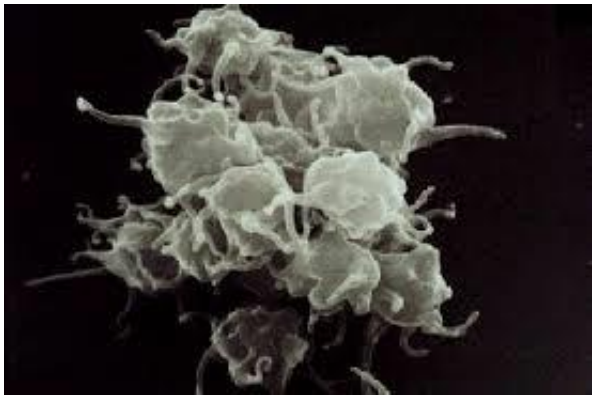
6 x 63ml = 378ml

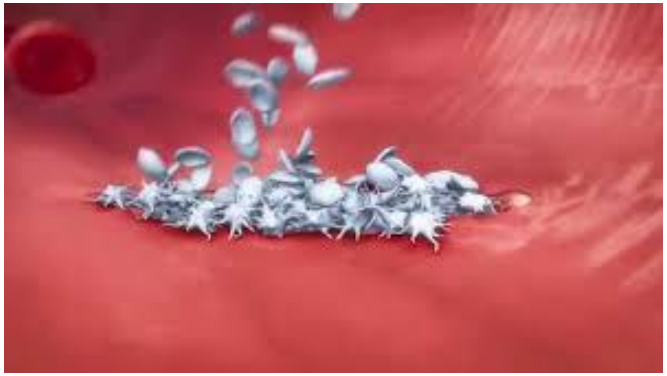
Total: 378ml

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

WB contains platelets: *the* critical effectors of hemostasis.





1. Primary hemostatic plug: PLT + VWF adhesion on exposed collagen

2. PLT surface (& microparticle) phosphatidyl serine + FVa → catalytic surface for thrombin generation (cell-based model of coagulation)

3. PLT aggregation → organization of fibrin into bundles, clot retraction (mechanical hemostasis)

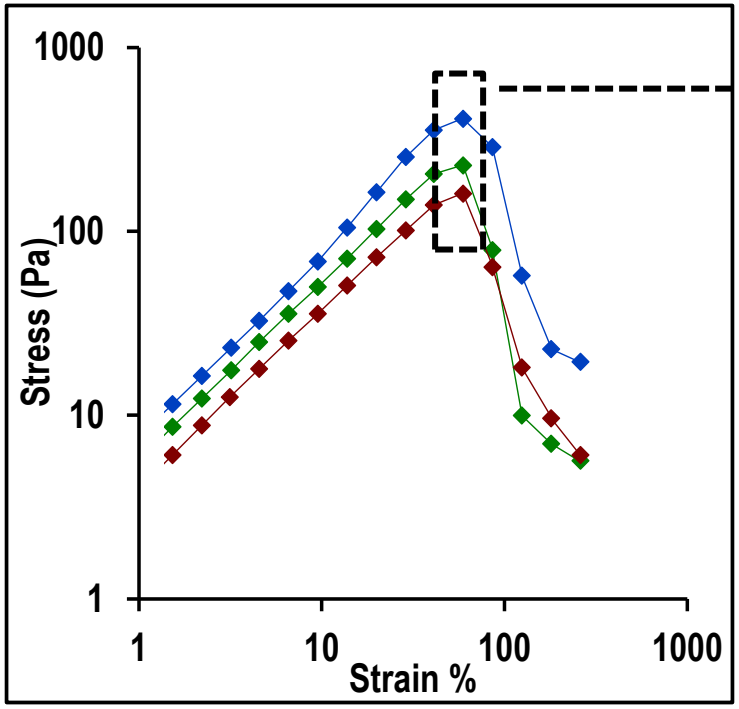
4. PLT secretion → PLT recruitment, PAI-1/A2AP (anti-fibrinolysis), sCD40L (immune activation), serotonin (vasoconstriction)

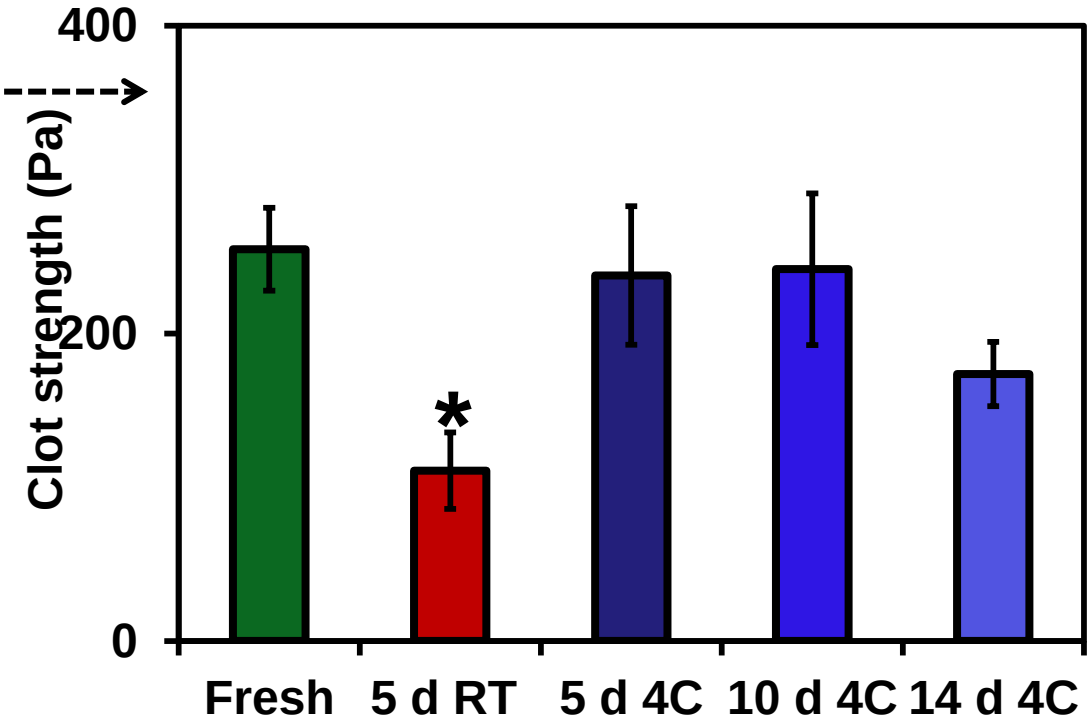
5. Maintenance of vascular endothelial integrity via CLEC-2, GPVI receptors

Need a platelet product that really works!

Which platelets would you want if you were bleeding?

- **Current standard of care 5day 22C-stored platelets make weak clots**
- **4C storage (cold) maintains clot strength → WB has cold platelets!**





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

Nair *BJH* 2017 *in press*

4C-stored WB Hemostatic Function Over Time: *drop in PLT aggregation but preserved clotting*

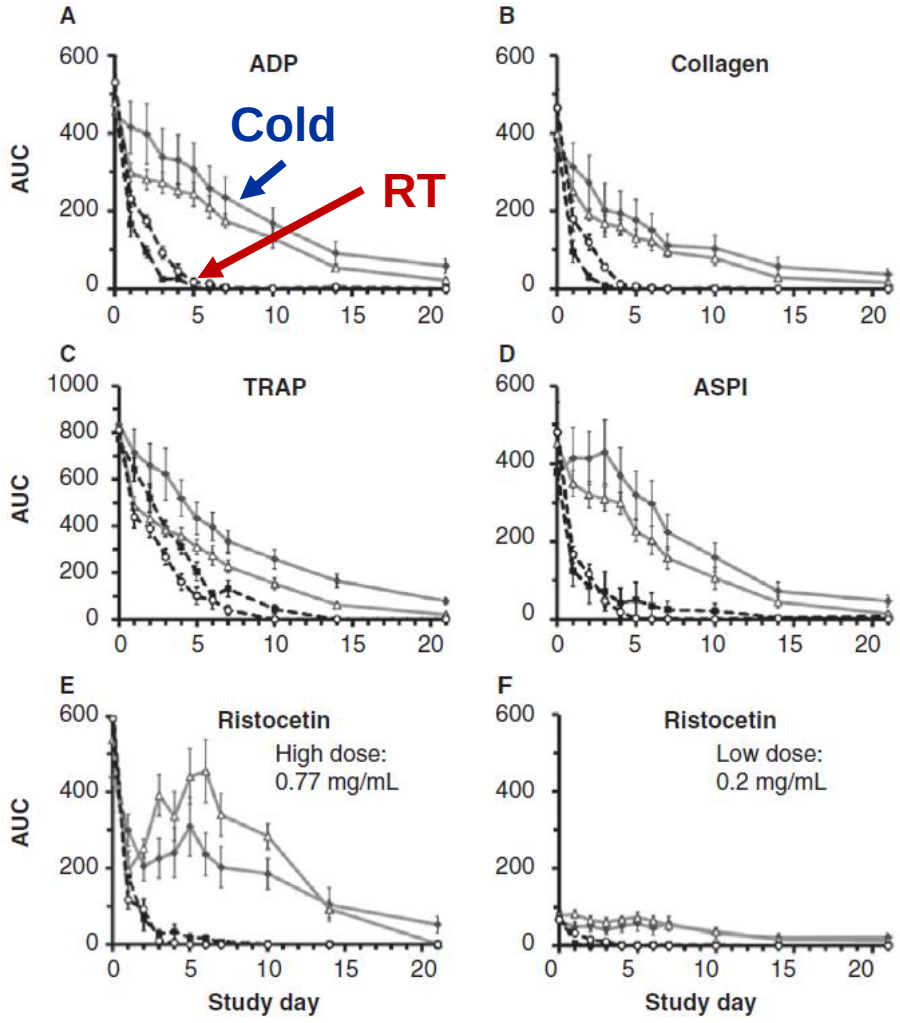


Fig. 4. Multiple electrode PLT aggregometry. A repeated measures analysis demon-

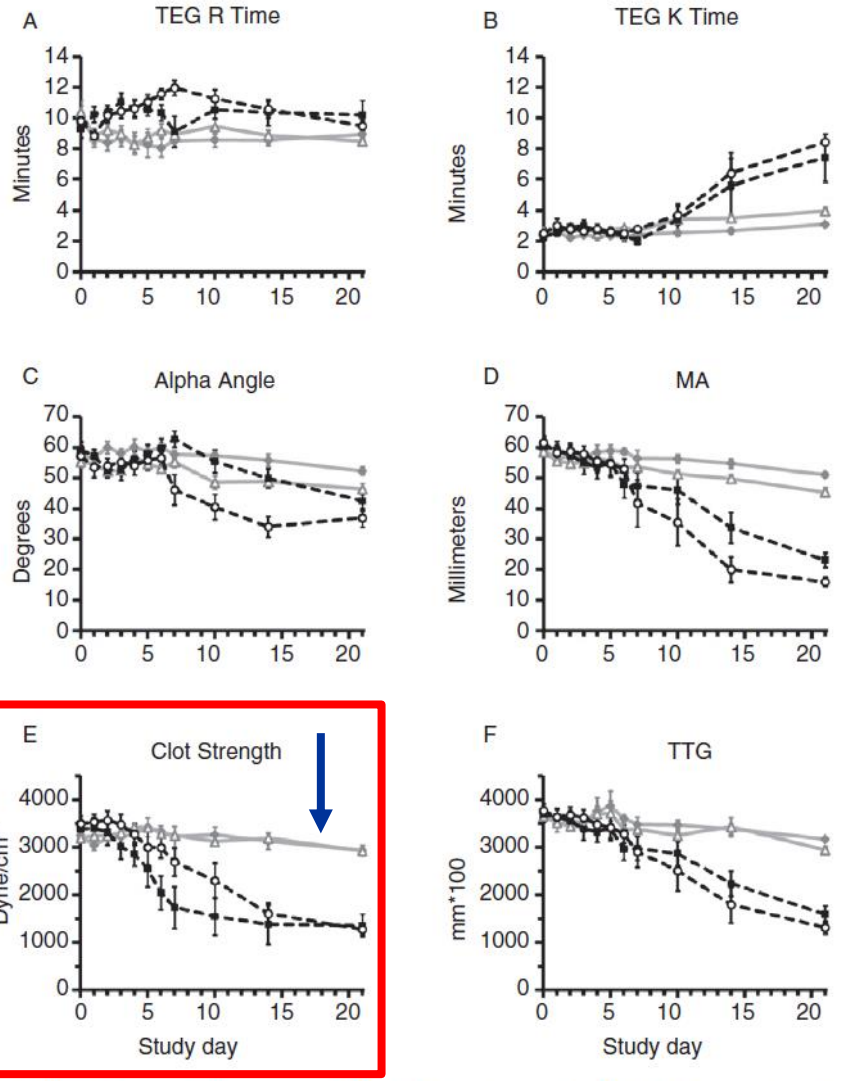
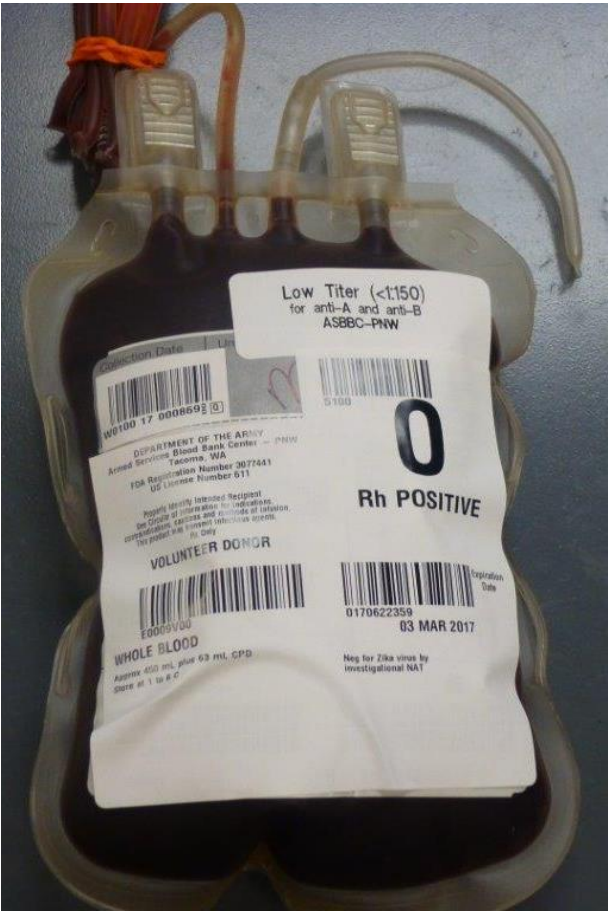


Fig. 5. TEG. Storage at 4°C preserved TEG R time, K, α-angle, MA, clot strength, and

WB vs. Components:
More concentrated, simpler



	WB 4°C	Components (1:1:1)
Hgb HCT	12-13 35-37	9 28
PLT	138-165	90-120
Fibrinogen, Factors	Normal @ baseline, FVIII ≥ 50% d7	All 62% dilution @ baseline, plus loss FVIII
TEG clot strength	Nearly normal d21	Reduced vs. WB
PLT aggregation	≥ 50% baseline d7-10 at 4C	Nearly complete loss d5 in 22C-PLT
Practical aspects (4L)	8 bags, one storage mode (8 U, 4000 ml)	13 bags, three storage modes (6:6:1, 4150 ml)

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

Shawn C. Nessen, Brian J. Eastridge, Daniel Cronk, Robert M. Craig, Olle Berséus, Richard Ellison, Kyle Remick, Jason Seery, Avani Shah, and Philip C. Spinella

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

Jeremy G. Perkins, Andrew P. Cap, Philip C. Spinella, Andrew F. Shorr, Alec C. Beekley, Kurt W. Grathwohl, Francisco J. Rentas, Charles E. Wade, John B. Holcomb, and the 31st Combat Support Hospital Research Group

Fresh Whole Blood is Better than CT

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

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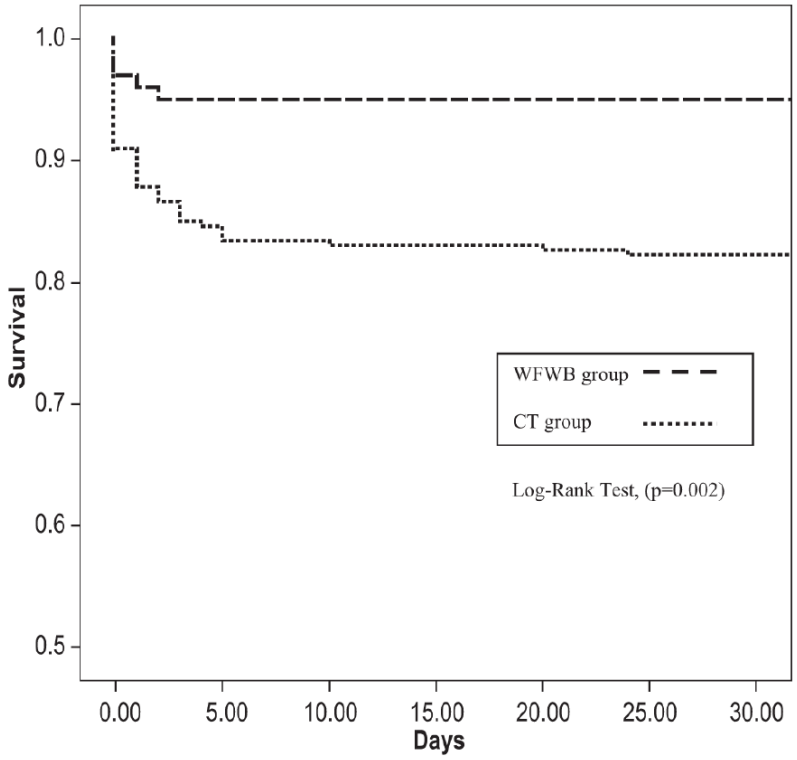
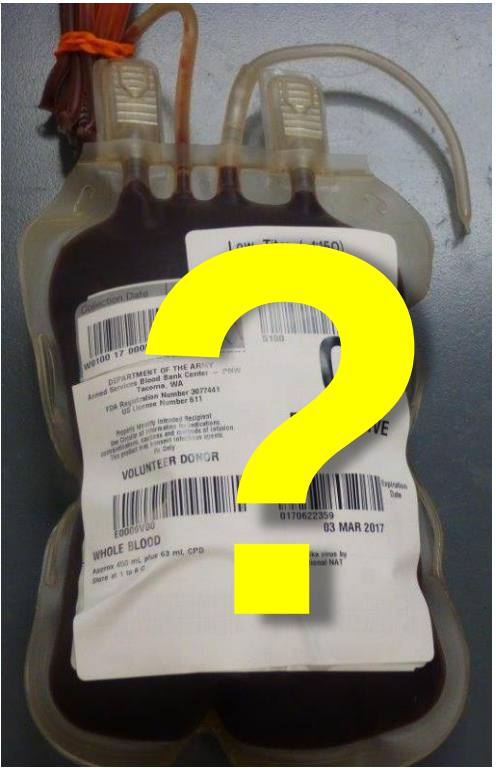


Variable	WFWB (n = 100)	CT (n = 254)	*p* Value
Stored RBC (U)	9 (7–14)	16 (10–22)	<0.001
Plasma (U)	4 (3–8)	10 (6–16)	<0.001
Apheresis platelets (U)	0	2 (1–4)	<0.001
WFWB (U)	5 (3–9)	0 (0–0)	<0.001
Cryoprecipitate (U)	0 (0–0)	0 (0–1)	0.007
Total RBC (U)	16 (11–22)	16 (10–22)	0.44
Total blood volume (L)	7.4 (5.4–10.4)	9.3 (6.2–13.3)	0.006
Anticoagulant/ additives (L)	1.7 (1.3–2.5)	2.5 (1.6–3.6)	<0.001
Actual blood volume (L)	5.7 (4.1–8.)	6.8 (4.5–10)	0.03
PLT:RBC ratio	0.33 (0.2–0.5)	0.86 (0.6–1.3)	0.001
Plasma:RBC ratio	0.74 (0.55–0.9)	0.73 (0.53–1)	0.73
Massive transfusion (%)	89/100 (89%)	198/254 (78%)	0.017
rFVIIa use (%)	42/100 (42%)	101/353 (40%)	0.72

Data presented as Median (IQR) or as percentages.

rFVIIa, recombinant factor VIIa.

WB options: walking BB (fresh but untested) vs. stored



*Assuming RT-PLT

WFWB (WBB)	CPD WB 4°C	CPDA-1 WB 4°C
Best hemostasis (100%)	< WFWB w/ decrease in PLT function after d14 At least equivalent to components* @ 1:1:1	< WFWB w/ decrease in PLT function after d14 At least equivalent to components* @ 1:1:1
Highest infectious risk	Low infectious risk (standard)	Low infectious risk (standard)
Use as WFWB w/in 8 hrs or refrigerate	21d shelf life	35d shelf life
Need pre-titered O donors to get universal; *OTW* type-specific	LTOWB or type-specific	LTOWB or type-specific

Priorities for Action

- NATO standards for:
  - **WB Production, Storage/Shipping**
  - WB Use
    - ***EU Regulatory relief to allow "trained personnel" to collect/transfuse WB in pre-hospital setting***
    - NATO "RDCR" Clinical Practice Guideline (CPG) on pre-hospital blood use (consistent with JTS/TCCC)
- NATO-wide adoption of **FDP** (↑production)
- NATO standards for all blood interoperability, traceability

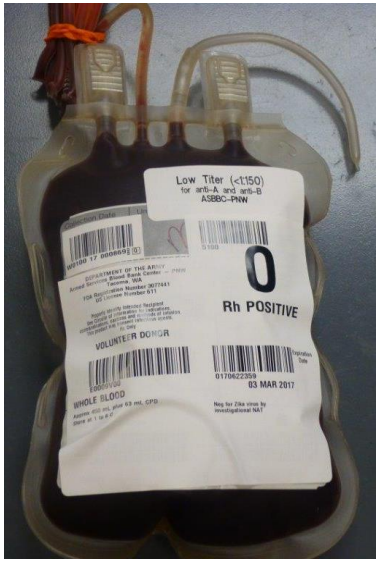
NATO Policy Needs

- NATO standard setting critical:
  - **Think of WB and BFF as a:**

    “common (human) fuel policy”

Low Titer O Whole Blood (LTOWB)

Give BLOOD for (R)DCR



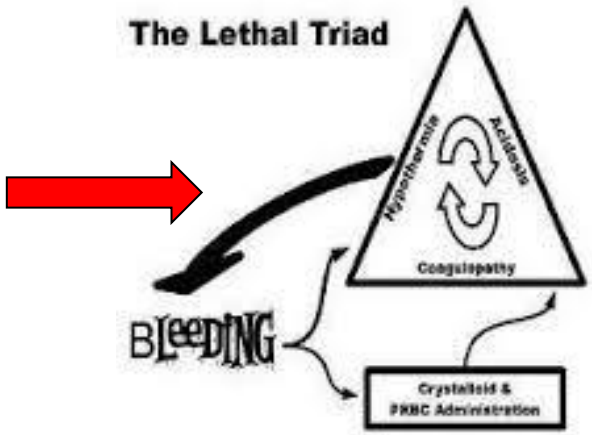
LTOWB is the simplest way to deliver the functionality of lost patient blood.

The freshest WB is the most functional.

BUT: most available data on improved outcomes with pre-hospital transfusion based on COMPONENTS!

ANY mix of WB or components is better than clear fluid.

4°C



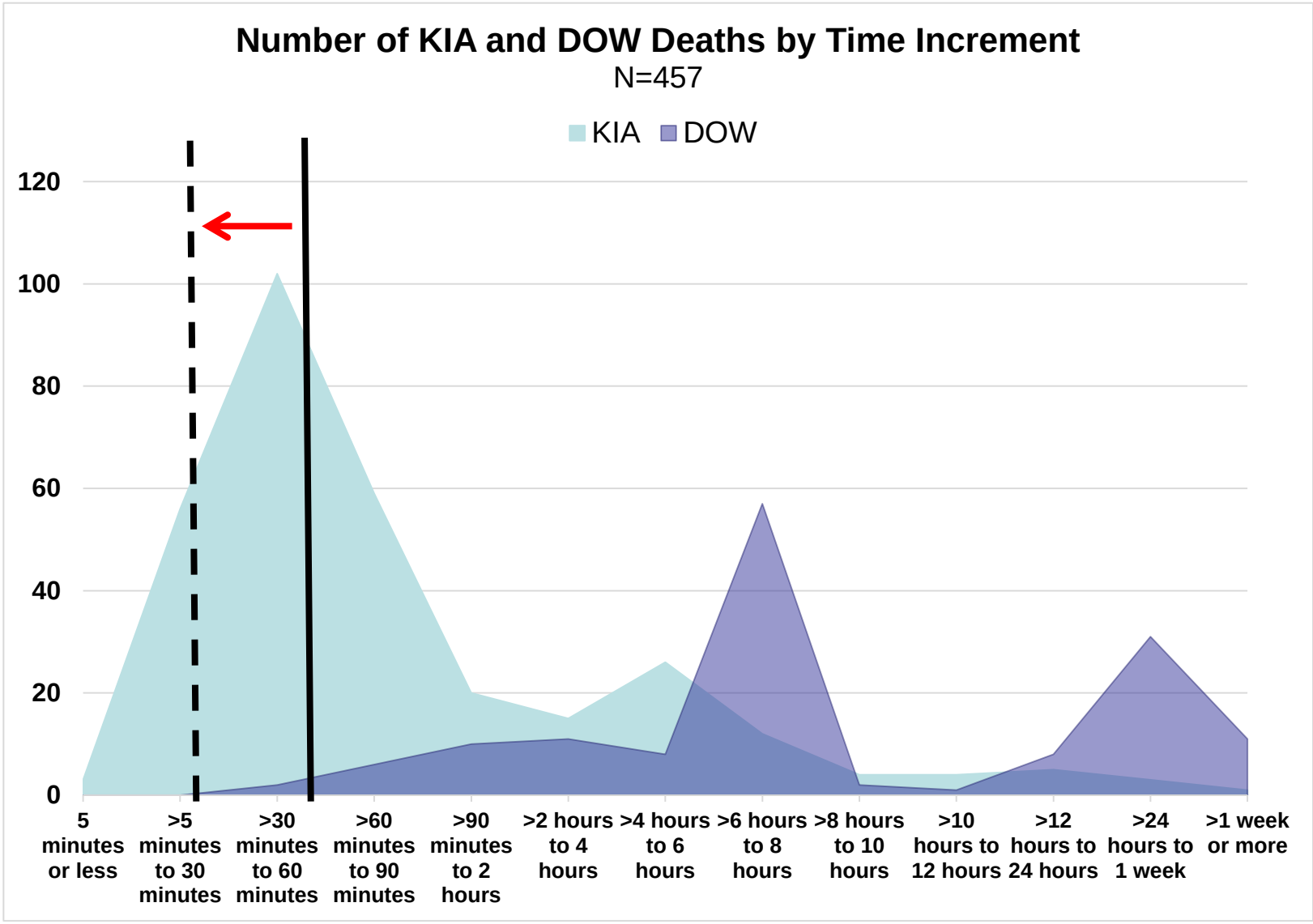
History of Pre-Hospital Shock Resuscitation

Whole Blood is King! *Components are cool!*

WW I **WW II** **Korea** **Vietnam** **OIF/OEF**

60 years of Blood **30 years of Clear Fluids** **Back to the future???** → *WB*

Golden Hour is too late…
NEED BLOOD at POI



JTS 2016.

LTOWB

Cold Platelets

Questions?

TXA

FDP