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2026 MILITARY HEALTH SYSTEM RESEARCH SYMPOSIUM

How Much Fluid is Too Much? Endothelial Signals After TBI

A Secondary Analysis of the Prehospital TXA for TBI Trial

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Trauma

OHSU

Non-Disclosure

- Tanya Anand MD, MPH, MT(ASCP) FACS has no conflicts to report

Acknowledgements

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2

The Prehospital TXA for TBI trial investigators and participants

3

BACKGROUND

Injury injures the endothelium, not just the patient

1

The Impact of Tissue Injury

Hemorrhage and trauma injure the endothelium and glycocalyx, releasing its components into circulation and breaking down the vascular barrier.

2

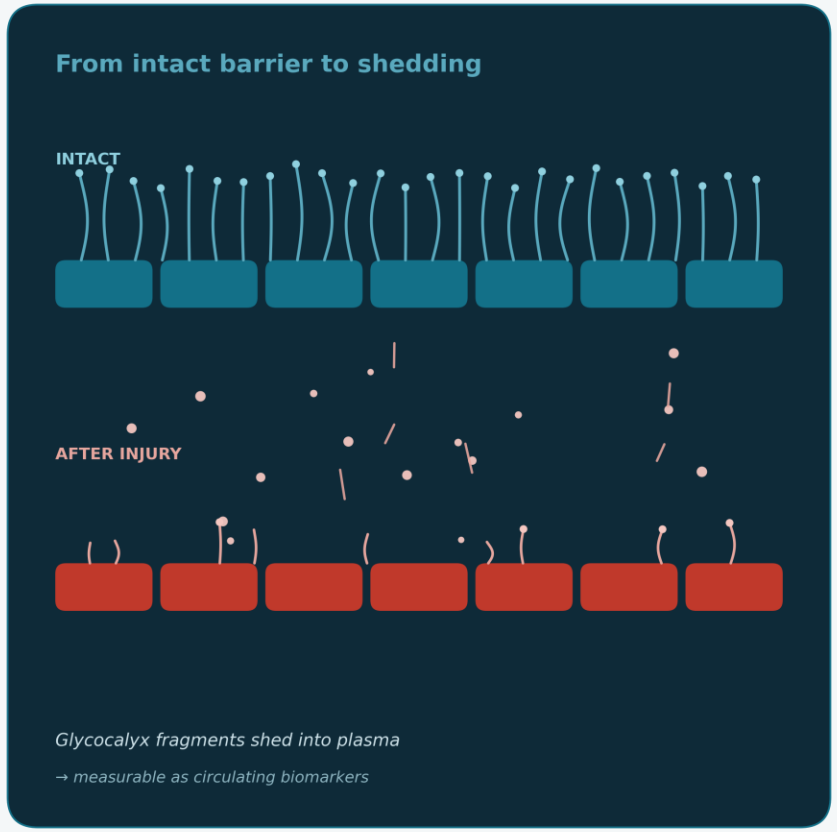
Endotheliopathy of trauma

Shedding of Glycocalyx components → systemic response

3

Measurable biomarkers

Syndecan-1 proxies glycocalyx shedding; thrombomodulin, ICAM-1, VCAM-1, and angiopoietin-2 mark endothelial injury and activation.



ENDOTHELIOPATHY OF TRAUMA AND RESUSCITATION: INTEGRATED BIOMARKER NETWORK

TRAUMA / HEMORRHAGE / SHOCK / CRYSTALLOID RESUSCITATION

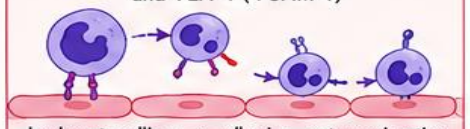
INFLAMMATORY CYTOKINE ACTIVATION
TNF-α, IL-1β, IL-6, HMGB1, DAMPs

TNF-α

1. LEUKOCYTE ADHESION & ENDOTHELIAL ACTIVATION

- ICAM-1 ↑ (sICAM-1)
- VCAM-1 ↑ (sVCAM-1)

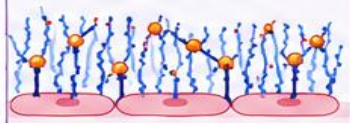
Upregulated by cytokines (TNF-α, IL-1) via NF-κB signaling
Promotes leukocyte adhesion via LFA-1 / Mac-1 (ICAM-1) and VLA-4 (VCAM-1)



2. GLYCOCALYX INJURY

- Syndecan-1 ↑ (SDC-1)

Shedding of glycocalyx proteoglycans
Loss of mechanotransduction and barrier integrity
Increased vascular leak



3. VASCULAR STABILITY (Tie2 SIGNALING)

- Angiopoietin-1 ↑ (Ang-1)
- Angiopoietin-2 ↑ (Ang-2)

Activates Tie2
Stabilizes endothelium
Reduces permeability
Anti-inflammatory

Antagonizes Tie2
Destabilizes endothelium
Increases permeability
Pro-inflammatory

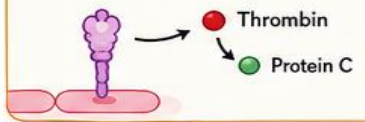
PROTECTIVE — DESTABILIZING

Endothelial quiescence ⟷ Endothelial activation

4. ENDOTHELIAL COAGULATION & ANTICOAGULANT DYSFUNCTION

- Thrombomodulin ↑ (sTM)

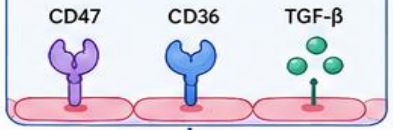
Shedding of TM reflects endothelial injury
Reduced thrombin–TM complex formation
↓ Protein C activation



MATRIX REMODELING & NITRIC OXIDE REGULATION

- Thrombospondin-1 ↑ (TSP-1)

Released with endothelial stress
Activates CD47/CD36
Inhibits NO signaling
Activates TGF-β / ECM remodeling



A. LEUKOCYTE RECRUITMENT & TRANSMIGRATION

Inflammatory mediator release
Microvascular inflammation
Amplified endothelial injury

B. GLYCOCALYX DEGRADATION

Barrier dysfunction
Increased permeability
Platelet & leukocyte adhesion

C. ENDOTHELIAL DESTABILIZATION

Increased permeability
Intercellular junction disruption
Endothelial activation

D. COAGULOPATHY / ENDOTHELIOPATHY

Impaired anticoagulant signaling
Thrombin generation
Microthrombosis

E. ECM REMODELING & VASOMOTOR DYSFUNCTION

Reduced nitric oxide bioavailability
Endothelial dysfunction
Impaired repair

LEGEND

- Red: Inflammatory Activation
- Pink: Leukocyte Adhesion
- Purple: Glycocalyx Integrity
- Green: Vascular Stability (Tie2 Axis)
- Orange: Coagulation & Anticoagulant Signaling
- Blue: Matrix Remodeling / NO Regulation
- → Direct activation / effect
- ⇢ Cross-talk / indirect interaction

MICROVASCULAR DYSFUNCTION

Capillary leak • Edema • Impaired perfusion • Microthrombosis

ORGAN DYSFUNCTION & POOR OUTCOMES

KEY CONCEPT

Endotheliopathy in trauma is driven by interconnected pathways of inflammation, glycocalyx injury, endothelial activation, dysregulated coagulation, and impaired vascular stability.

These biomarkers reflect distinct but interacting mechanistic nodes that converge to cause microvascular dysfunction and organ injury.

BACKGROUND

Crystalloid resuscitation: A second hit?

Endothelial and Glycocalyx Biomarkers in Children With Sepsis After One Bolus of Unbalanced or Balanced Crystalloids*

Jaime Fernández-Sarmiento, MD, PhD, Lina María Salazar-Peláez, BSc, MSc, PhD, Lorena Acevedo, MD, Laura Fernanda Niño-Serna, MD, MSc, Steffanie Flórez, MD, Laura Alarcón-Forero, MD, Hernando Mulett, MD, Laura Gómez, BSc, Juan Carlos Villar, MD, MSc, PhD

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Low-volume resuscitation with normal saline is associated with microvascular endothelial dysfunction after hemorrhage in rats, compared to colloids and balanced crystalloids

Luciana N. Torres[1*], Kevin K. Chung[2,3], Christi L. Salgado[1], Michael A. Dubick[1] and Ivo P. Torres Filho[1]

Normal Saline solutions cause endothelial dysfunction through loss of membrane integrity, ATP release, and inflammatory responses mediated by P2X7R/p38 MAPK/MK2 signaling pathways

Joyce Cheung-Flynn[1], Bret D. Alvis[2], Kyle M. Hocking[1], Christy M. Guth[1], Weifeng Luo[1], Reid McCallister[1], Kalyan Chadalavada[1], Monica Polcz[1], Padmini Komalavilas[1,3]*, Colleen M. Brophy[1,3]

BACKGROUND

Does age matter during crystalloid resuscitation?

Redefining geriatric trauma: 55 is the new 65

Samir M. Fakhry, MD, FACS, Jennifer L. Morse, MS, Jeneva M. Garland, PharmD, Nina Y. Wilson, MSN, Yan Shen, PhD, Ransom J. Wyse, MPH, *and* Dorraine D. Watts, PhD, *Nashville, Tennessee*

Endothelial Glycocalyx in Aging and Age-related Diseases

Lina Sun[1, 2#], Lingyan Wang[1#], Kaisy Xinhong Ye[3], Shoushi Wang[1], Rui Zhang[1], Zhaodong Juan[1], Lei Feng[3*], Su Min[2*]

Decreased Glycocalyx Shedding on Presentation in Hemorrhaging Geriatric Trauma Patients

Tanya Anand, M.D., M.P.H.[a], Anna E. Crawford, B.S.[b], Michael Sjoquist, B.S.[c], Zain G. Hashmi, M.D.[d,e], Robert P. Richter, M.D.[e,f], Bellal Joseph, M.D.[a], Jillian R. Richter, Ph.D.[d,e]

Age matters: A Secondary Analysis of Endothelial Biomarkers in the Prehospital Tranexamic Acid for Traumatic Brain Injury Trial

Tanya Anand, MD, MPH, MT(ASCP), FACS, Scott Mcloud, MS, Lindsay Loss, MD, Karen Minoza, MD, Phillip Jenkins, MD, Susan Rowell, MD, Jack McLean, BS, Bellal Joseph, MD, *and* Martin Schreiber, MD, *Tucson, Arizona*

AIM

To determine whether endothelial and glycocalyx injury demonstrate a dose-dependent relationship with crystalloid volume and whether this biologic response differs by age.

METHODS

Secondary analysis - Prehospital TXA for TBI Trial (2015–2017)

Cohort - Age ≥15 y with biomarkers at baseline and/or 6 h.

Exposure - Total crystalloid (NS, LR, ± HTS) from admission to 6 h.

Outcomes - ICAM-1, VCAM-1, thrombomodulin, syndecan-1, thrombospondin, Ang-1, Ang-2, TNF-α at 6 h and change from baseline (Δ).

Analysis - Group comparison, Spearman correlation, and prespecified dosing groups (0, 1–999, 1000–1999, ≥2000 mL).

Age stratification: Top quartile older adults (OA, ≥55 y); the rest are younger adults (YA, <55y)

RESULTS

Baseline Demographics

Characteristics	Total N=403	YA n=301	OA n=102	p-value
Age, years	36.0 (25.0–53.0)	31.0 (24.0–43.5)	65.0 (58.0–74.0)	**<0.001**
Male	315 (78.1)	238 (79.1)	77 (75.5)	0.061
White	281 (69.7%)	206 (68.4%)	75 (73.5%)	0.383
Black	13 (3.2%)	8 (2.7%)	5 (4.9%)	0.328
Fluid exposure, n (%)				
No fluids	8 (2.0%)	7 (2.3%)	1 (1.0%)	0.685
Crystalloid only	321 (79.7%)	248 (82.4%)	73 (71.6%)	**0.028**
Crystalloid + Blood	74 (18.4%)	46 (15.3%)	28 (27.5%)	0.009
Injury characteristics				
Blunt mechanism	403 (100.0%)	301 (100.0%)	102 (100.0%)	–
ISS	17.0 (9.0–26.0)	17.0 (9.0–25.2)	17.0 (10.0–27.0)	0.736
GCS	8.0 (5.0–10.0)	7.0 (5.0–10.0)	9.0 (5.0–10.8)	0.114

RESULTS

Baseline Demographics – Laboratory Values

Characteristics	Total N=403	YA n=301	OA n=102	p-value
TXA 2g n(%)	220 (54.5%)	160 (53.2)	60 (58.8%)	0.36
Admission Physiology & Laboratory Values				
SBP (mmHg)	135.5 (121.8–151.0)	133.0 (120.5–147.5)	146.0 (126.0–158.0)	**0.016**
HR (bpm)	91.0 (79.0–105.0)	93.0 (79.5–105.5)	85.0 (76.5–95.2)	**0.027**
Lactate (mmol/L)	2.7 (1.9–3.6)	2.6 (1.9–3.4)	2.9 (2.4–3.8)	0.083
INR	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.1)	0.614
Hematocrit (%)	41.0 (37.4–43.4)	41.0 (37.6–43.3)	40.7 (36.1–43.8)	0.664
Hemoglobin (g/dL)	14.0 (12.6–15.2)	14.0 (12.8–15.2)	14.2 (12.2–15.2)	0.358
Platelets ($10^3/\mu L$)	231.0 (187.0–277.5)	228.0 (184.0–271.0)	245.0 (196.5–284.5)	0.161

RESULTS

Baseline equal, but by 6 hours crystalloid diverges

- At admission, biomarkers did not differ between crystalloid and no-fluid patients; trauma itself drives the first hit.
- By 6 hours, ICAM-1 was higher with crystalloid (48,487 vs 37,612 pg/mL; p=0.03).
- Thrombospondin rose with crystalloid but fell without it (Δ +608 vs −270 pg/mL; p=0.04).

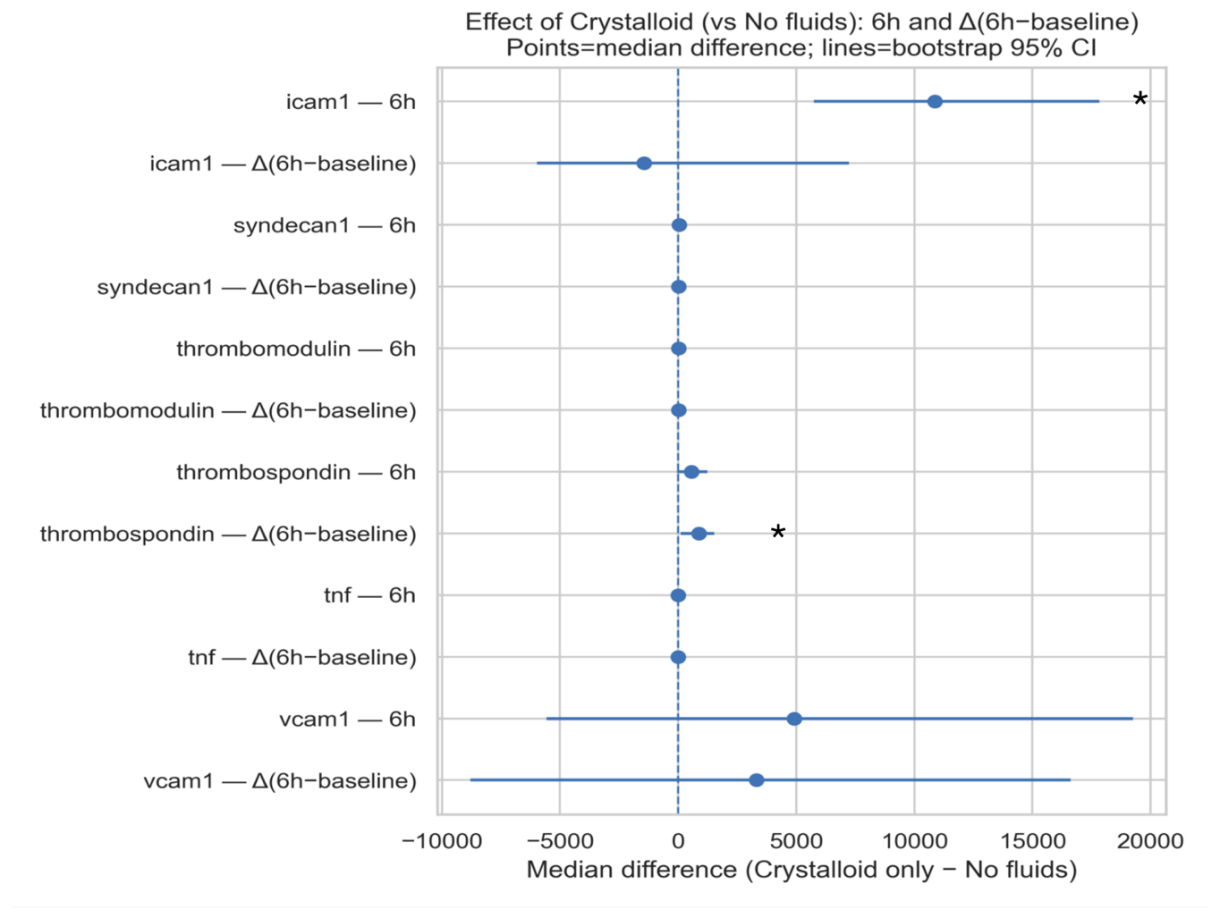
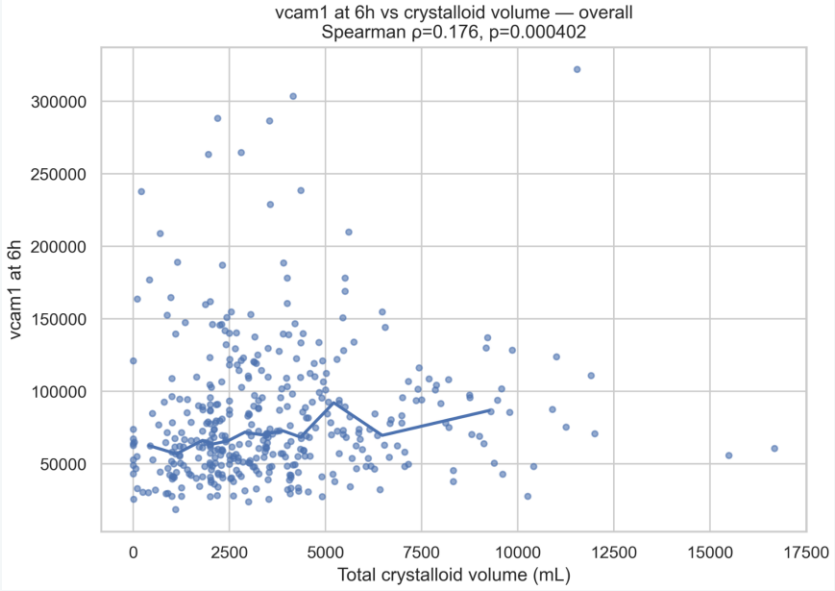


Figure 1 · Crystalloid vs no fluids: median differences at 6 h and Δ (bootstrap 95% CI).

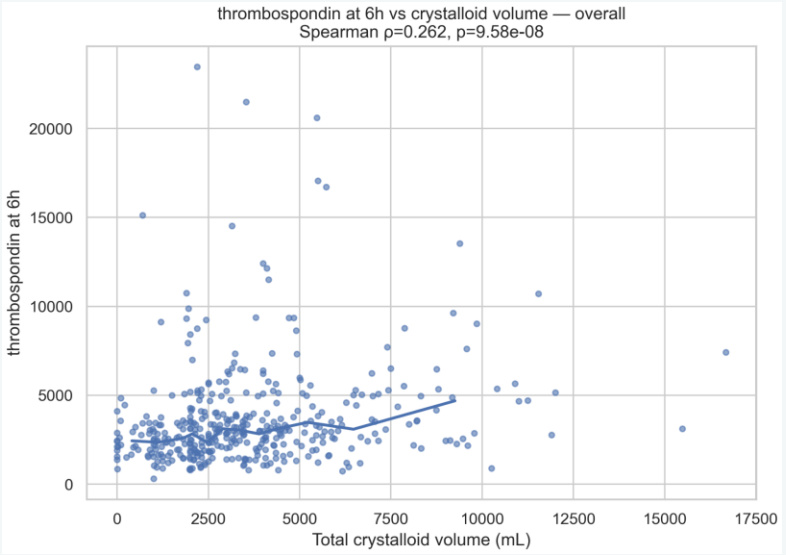
RESULTS

More crystalloid, higher biomarker levels at 6 hours

VCAM-1



Thrombospondin



Syndecan-1

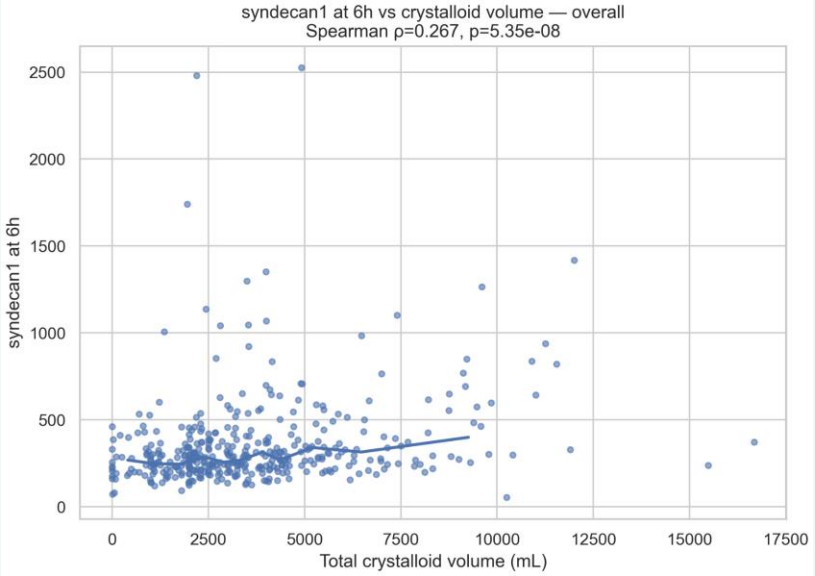


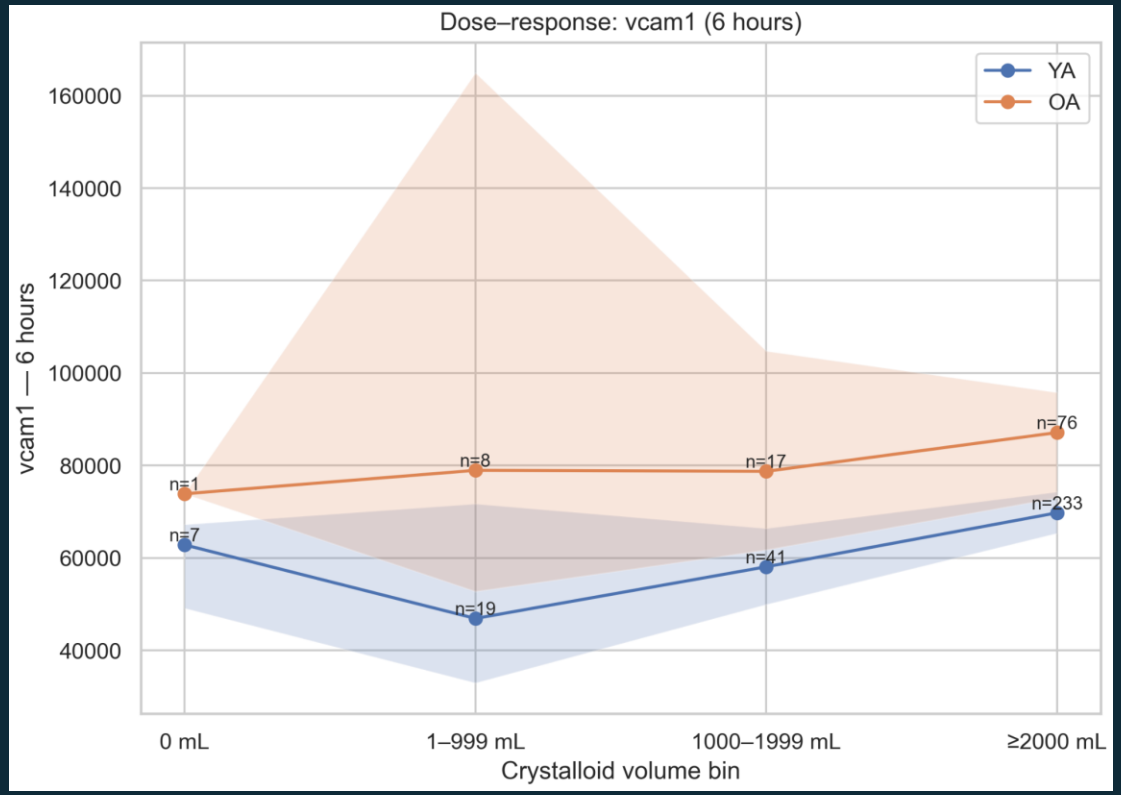
Figure 2 · Crystalloid volume vs 6-hour biomarker concentration (overall cohort), with Spearman ρ and volume-binned median trend.

POSITIVE, DOSE-RELATED CORRELATIONS

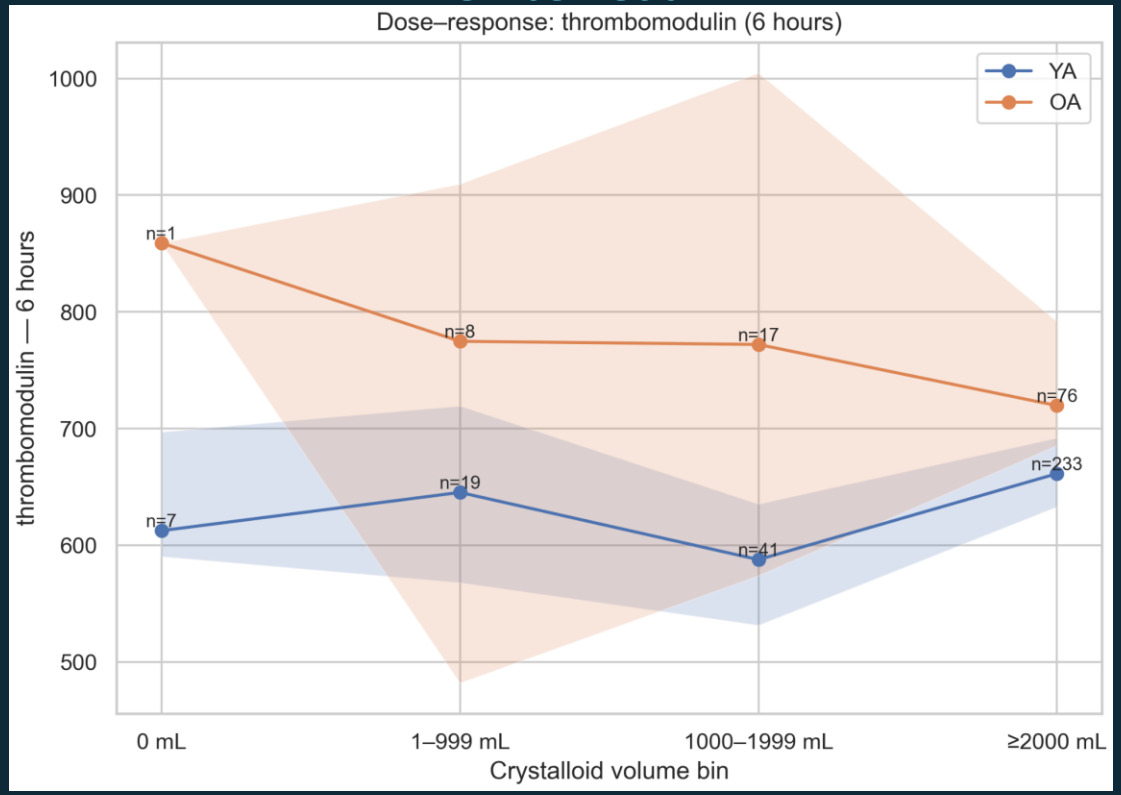
Higher crystalloid volume tracks with higher VCAM-1, thrombospondin, and syndecan-1 at 6 h; thrombomodulin follows the same direction. Effect sizes are modest but consistent across markers and persist after excluding hypertonic saline.

The dose–response splits by age

VCAM-1



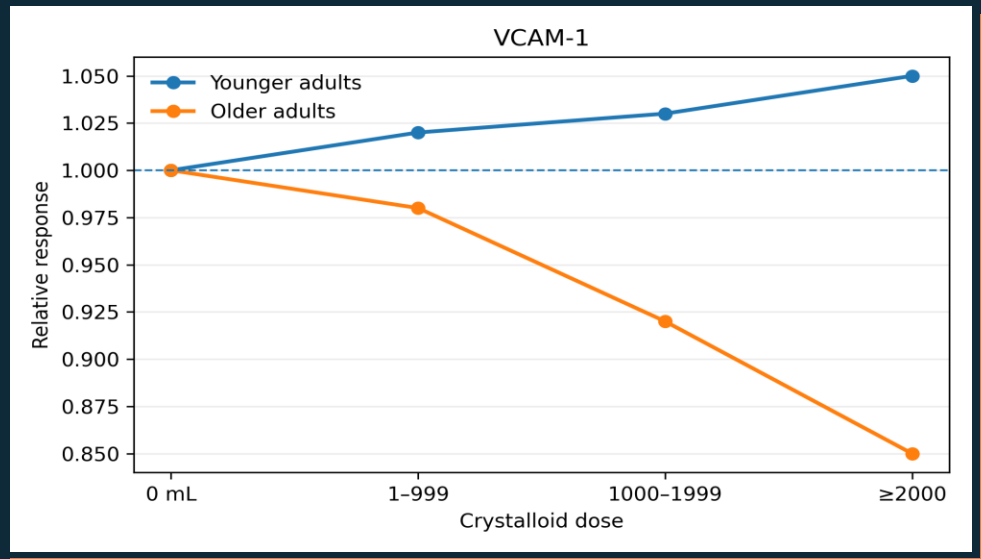
Thrombomodulin

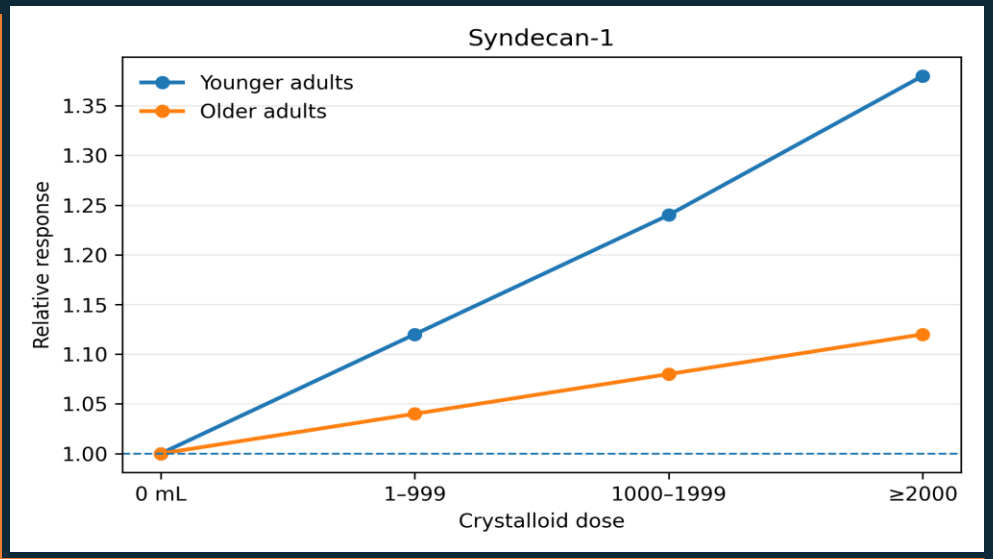


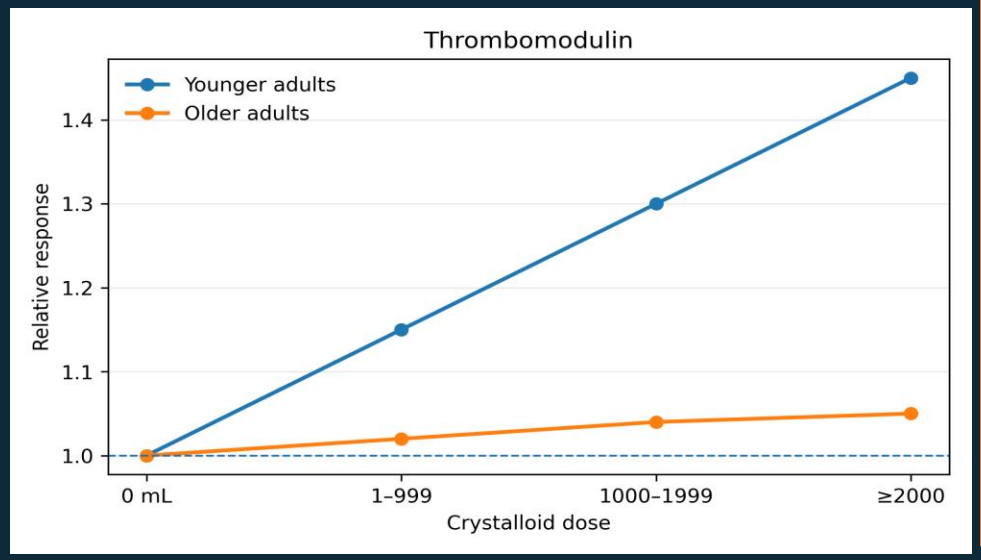
Younger adults: biomarkers climb with dose (thrombomodulin Δ ρ=0.14, p=0.03).
Older adults: blunted or inverse (VCAM-1 Δ ρ=−0.27, p=0.018 across bins).

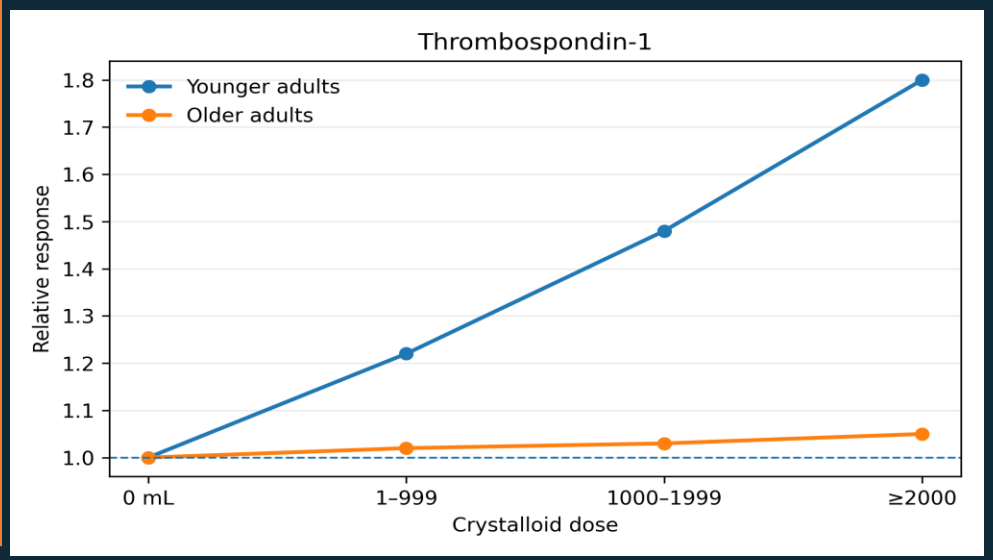
RESULTS

The dose-response splits by age



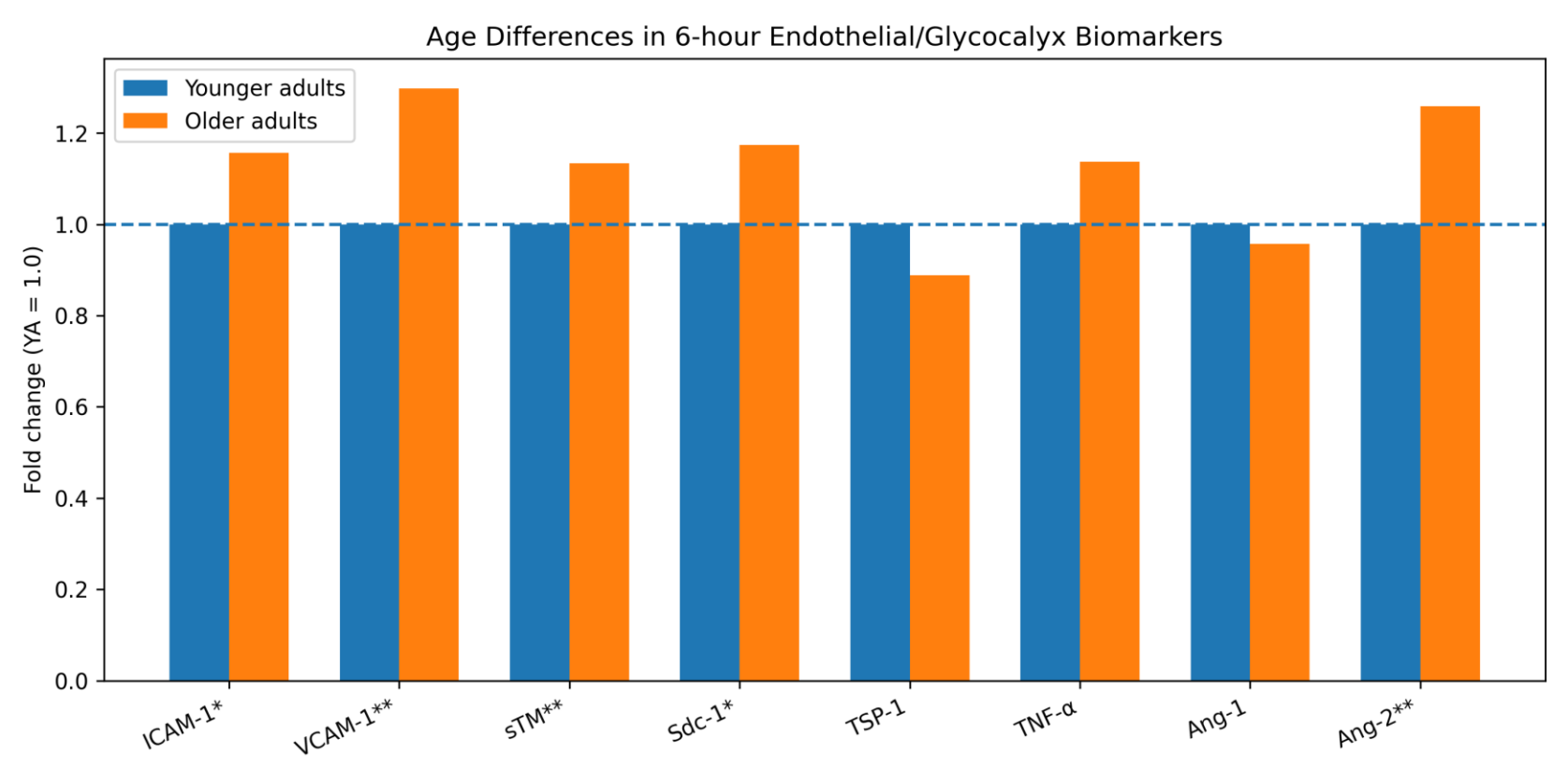






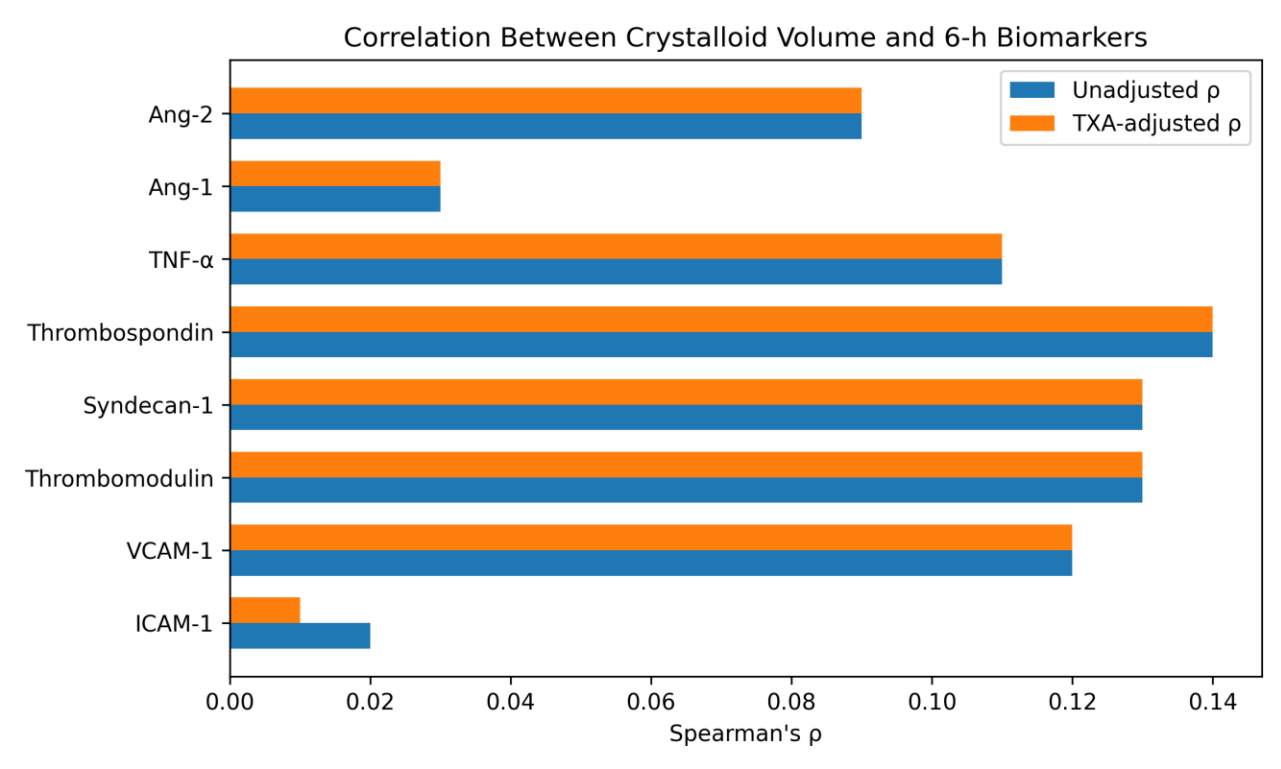
RESULTS

Age-related differences at 6 hours



RESULTS

Associations persist after adjustment for TXA



The association between increasing crystalloid volume and endothelial/glycocalyx biomarkers is robust and independent of TXA treatment

RESULTS

Volume and Outcomes

Outcome	≤500 mL (n=42)	>500 mL (n=361)	p-value
Mortality, n (%)			
In-hospital mortality	6 (14.3)	41 (11.4)	0.61
28-day mortality	7 (16.7)	42 (11.6)	0.32
6-month mortality	7 (16.7)	46 (12.7)	0.47
Morbidity, n (%)			
Any thromboembolic event	3 (7.1)	44 (12.2)	0.45
Myocardial infarction	0 (0.0)	2 (0.6)	1.00
Acute kidney injury	2 (4.8)	13 (3.6)	0.66
Sepsis	2 (4.8)	6 (1.7)	0.20
Pneumonia	4 (9.5)	48 (13.3)	0.63
ICU-free days	25 (12–28)	23 (14–26)	0.07
Ventilator-free days	26 (14–28)	26 (18–27)	0.22
Hospital-free days	21 (0–26)	16 (0–22)	**0.03**
ISS	15 (5–25)	18 (11–29)	**0.03**
GCS	9 (6–11)	7 (4–10)	0.06

INTERPRETATION

Take home message

- Crystalloid resuscitation is associated with measurable endothelial activation and glycocalyx shedding after TBI.
- Increasing crystalloid volume demonstrates dose-dependent relationships with endothelial biomarkers.
- Age fundamentally modifies the endothelial response → OA exhibit attenuated or divergent biomarker trajectories despite similar injury severity.
- Biomarker trajectories may provide a biologic signature of endothelial injury beyond traditional clinical measures.

INTERPRETATION

Biomarker Response Patterns

Increasing crystalloid volume → coordinated endothelial responses rather than isolated biomarker changes.

Multiple biomarkers changed together with increasing crystalloid exposure, suggesting activation of an integrated endothelial program

Younger adults mount a dynamic endothelial response to increasing crystalloid exposure.

Progressive increases in thrombomodulin, thrombospondin-1, and syndecan-1 with greater fluid exposure. The monotonic trajectories suggest preserved endothelial reserve capable of responding to injury and resuscitation.

Older adults demonstrate a fundamentally different endothelial phenotype.

Biomarker trajectories were attenuated or divergent. VCAM-1 showed an inverse relationship with crystalloid dose. The flatter response may be consistent with diminished endothelial reserve, chronic vascular dysfunction, or altered glycocalyx biology rather than absence of injury.

Biomarker trajectories may be more informative than individual biomarker concentrations.

our data suggests we should ask "How do VCAM-1, syndecan-1, thrombomodulin, and thrombospondin change together over time?" The coordinated pattern likely reflects activation of distinct endothelial signaling pathways.

LIMITATIONS

What this analysis can and cannot say

1	**Secondary analysis**	Confounding by indication is possible; we describe association, not causation.
2	**Small no-fluids group**	Only eight patients received no fluids, one older adult, limiting age-stratified contrasts.
3	**Two time points**	Biomarkers at 0 and 6 h only; longer trajectories are unknown.
4	**Surrogate endpoints**	Biomarkers are mechanistic proxies, not clinical outcomes.
5	**Exploratory**	No correction for multiple comparisons; weak effect sizes warrant validation.

CONCLUSIONS

Future Directions

1. Define how differential endothelial responses alter downstream signaling and the microcirculation

2. Determine whether biomarker trajectories can guide personalized fluid type, dose, and timing at the bedside.

3. Use these human response patterns to direct mechanistic bench studies of endothelial and glycocalyx pathways.

4. Validate endothelial phenotypes and determine whether early biomarker trajectories can predict and help us modify the slope of recovery, not simply mortality.

The biology of resuscitation matters. The amount and type of fluid and the patient receiving it, shape the endothelial response after trauma

CONCLUSIONS

Why it matters for military care

- Crystalloid is still part of far-forward and prolonged field care.
- A biologic rationale for limiting crystalloid where blood is scarce.
- Understanding biologic responses to crystalloid administration has potential to improve battlefield resuscitation, prolonged casualty care, and survival by moving from protocolized care to precision care.

Thank you

Questions & Discussion

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