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Brain Matters and Blood Splatters: Drug Therapy in the Emergency Trauma Patient

Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.

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Blood Splatters

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Rochester, NY

Objective

- Determine the appropriateness of pharmacologic agents used for traumatic hemorrhage

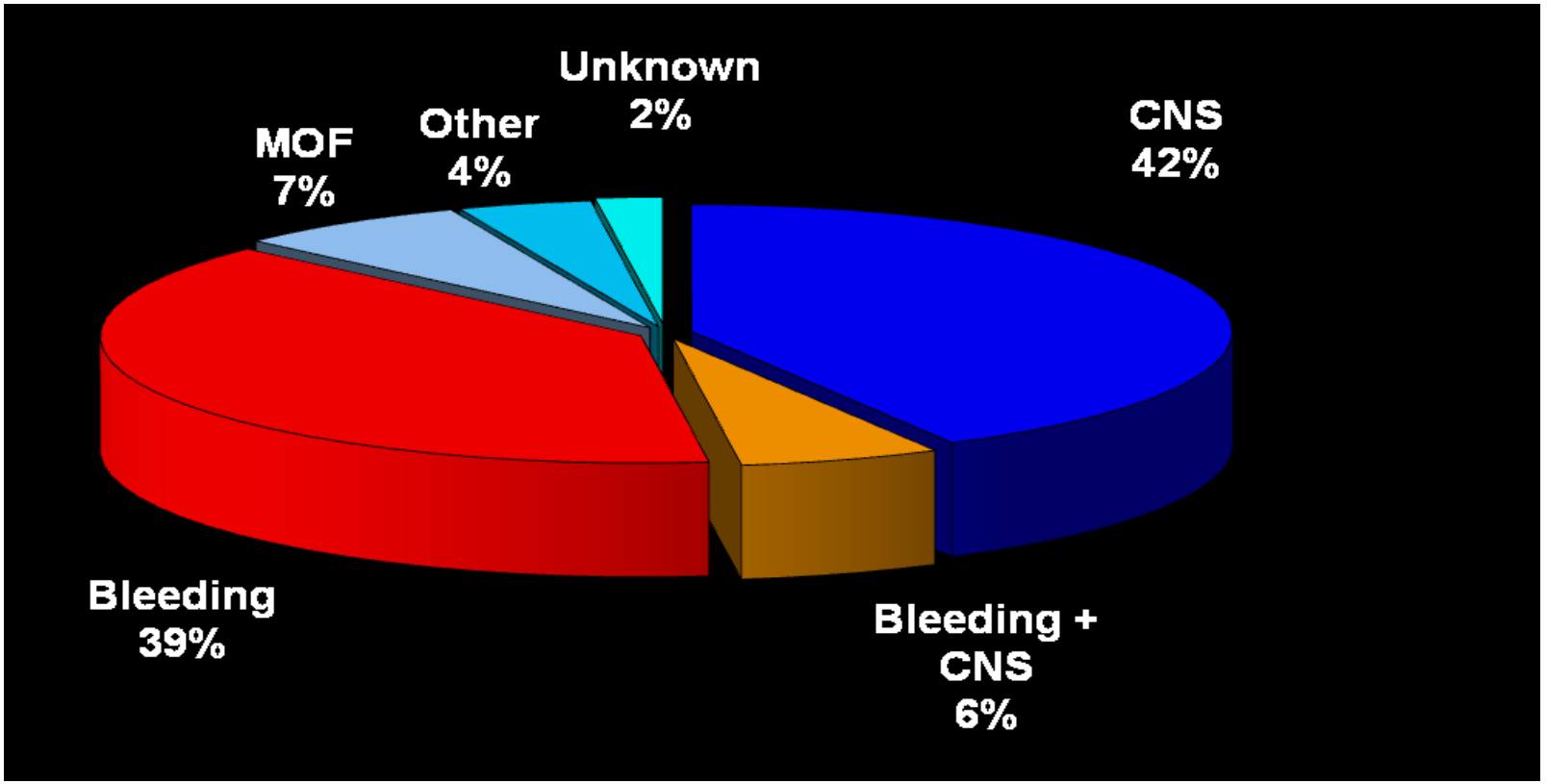
Photo credit: Kate Kokanovich

- 19 yo male MCC vs. car, level 1 trauma
- SBP reported as 85 and repeat 79
- Bilateral lower extremity bone and soft tissue injuries, concern for pulses on R leg, early compartment syndrome on R leg
- R wrist open fracture, pneumothorax L chest, positive FAST

Which management is the most appropriate for resuscitation?

- A Administer crystalloid fluids
- B Administer blood products alone
- C Administer blood products and tranexamic acid (TXA)
- D Administer blood products and prothrombin complex concentrates (PCC)

Bleeding is the Major Cause of Death in Trauma



Sauaia A et al. *J Trauma* 1995;38:185-93

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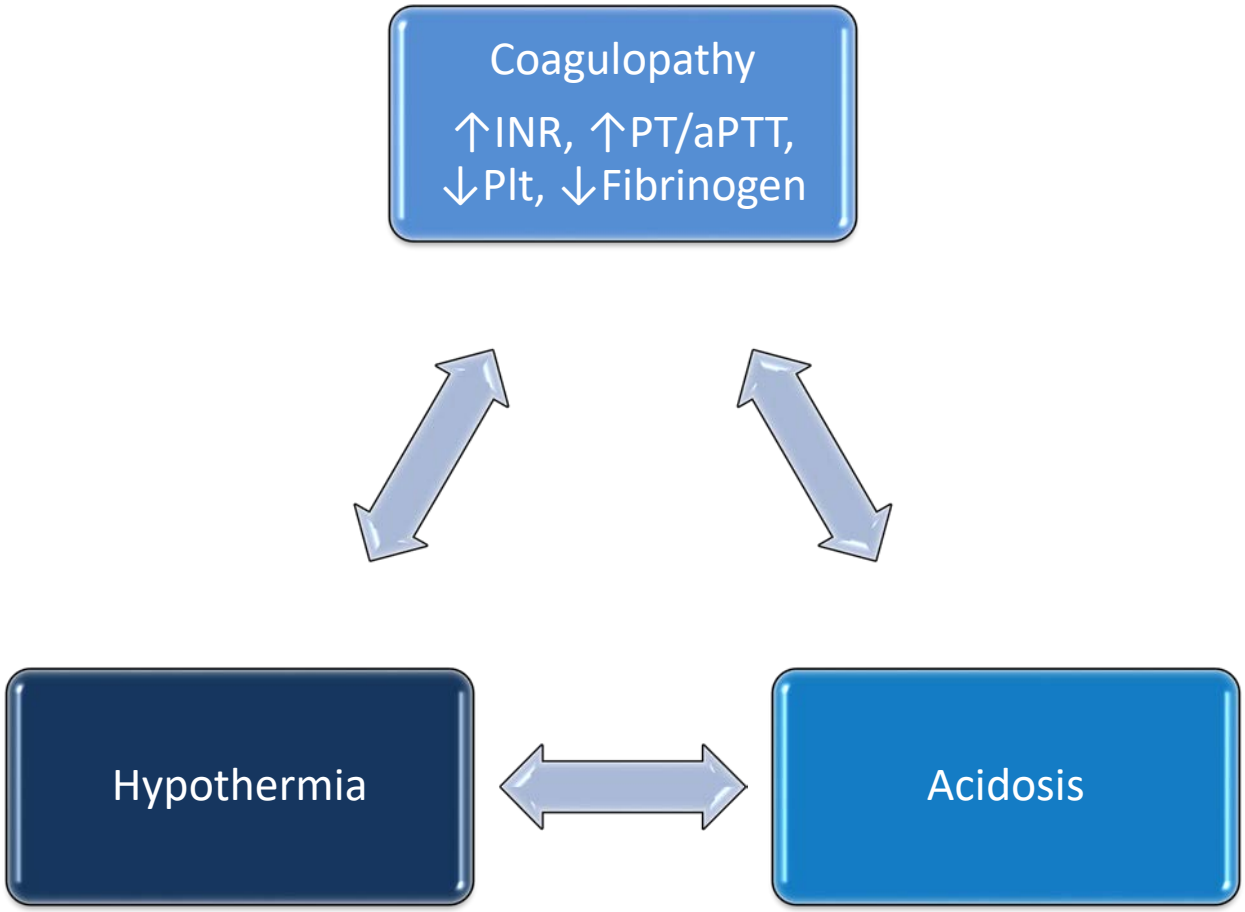
Lethal Triad → High Mortality Rate



Holcomb J, et al. *J Trauma* 2005; 58: 1298-1303
Vincent JL, et al. *Crit Care* 2006; 10:R120
Mohr A, et al. *Crit Care* 2005; 9:S37-S42.

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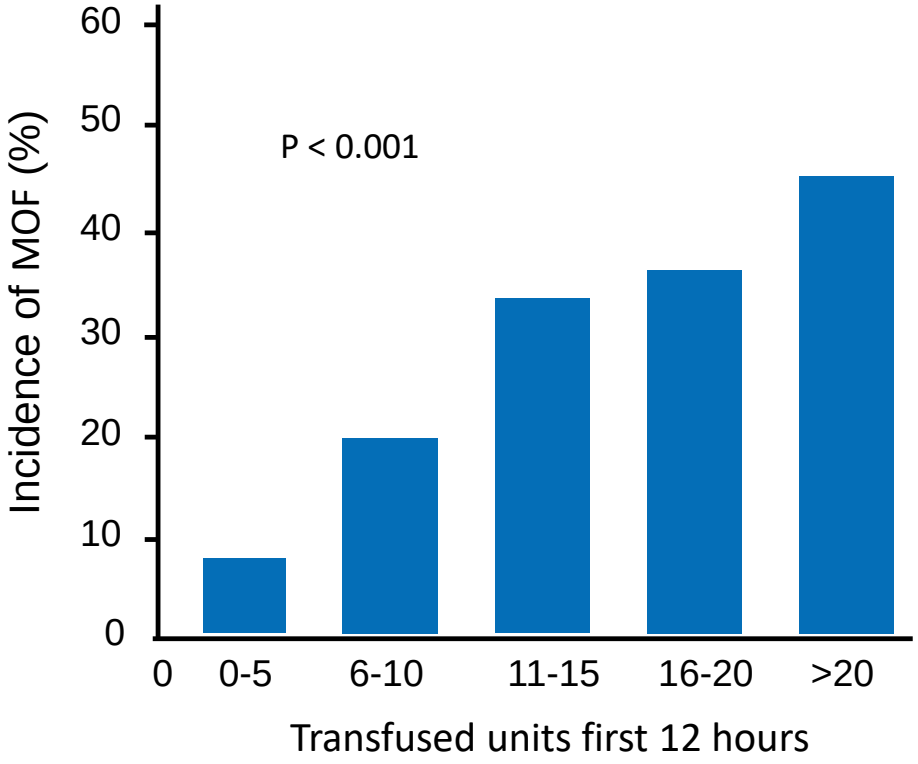
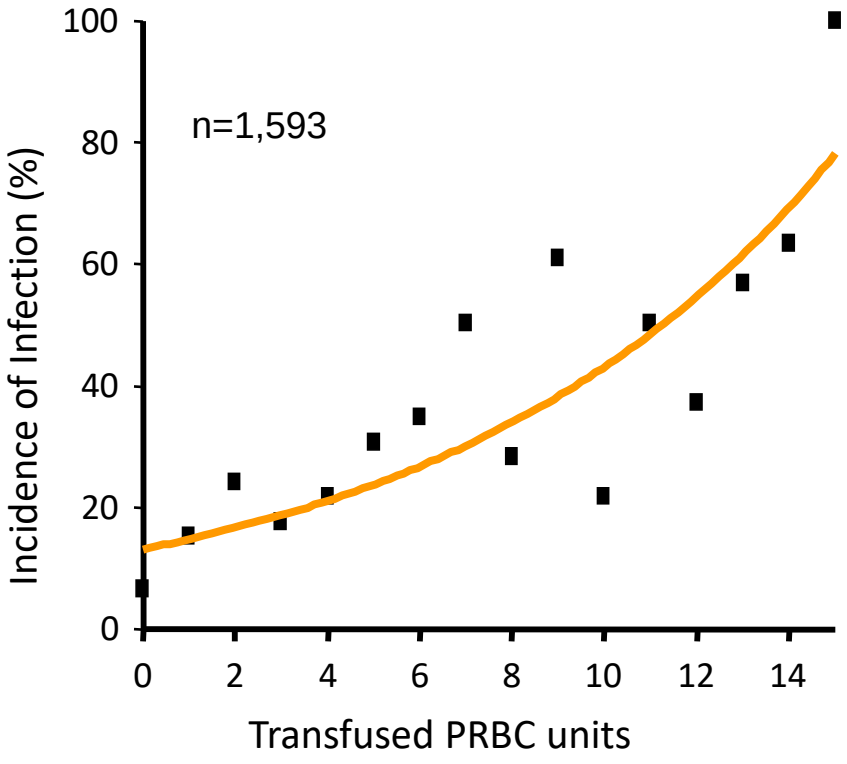
More Blood, More Problems





Moore FA, et al. *Arch Surg* 1997;132:620-4
Claridg JA, et al. *Am Surg* 2000;68:566-72

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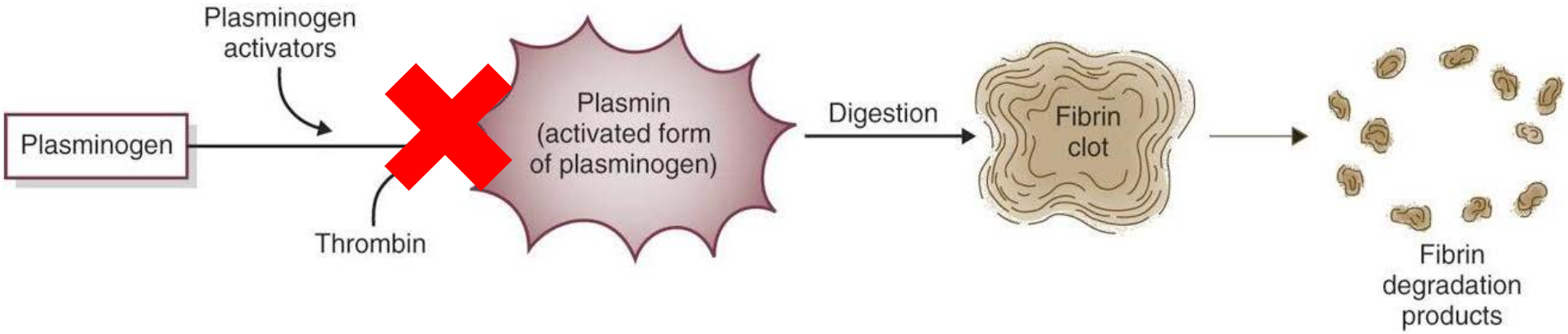
Tranexamic Acid (TXA)

- Hyperfibrinolysis in trauma
  - Dysfunction from severe shock and major tissue trauma
  - Present 2.5-7% of all trauma patients



Schochl H, et al. *Hamostaseologie* 2012;32:22-7

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CRASH-2 Trial

- Randomized, placebo controlled trial
- 40 countries, 274 hospitals, n = 20,211 with or at risk for bleeding
- Randomization – uncertainty principle
- SBP < 90 mm Hg or HR > 110 bpm or thought to be at risk of significant hemorrhage
- 1 g over 10 minutes, then 1 g over 8 hours or placebo

Crash-2 trial collaborators. Lancet 2010;376:23-32

CRASH-2 Trial Results

- Death in the hospital within 4 weeks of injury

	TXA (n=10,060)	Placebo (n=10,067)	RR (95% CI)	p-value
Any cause of death	1463 (14.5%)	1613 (16.0%)	0.91 (0.85–0.97)	0.0035
Bleeding	489 (4.9%)	574 (5.7%)	0.85 (0.76–0.96)	0.0077
Vascular occlusion	33 (0.3%)	48 (0.5%)	0.69 (0.44–1.07)	0.096
Multi-organ failure	209 (2.1%)	233 (2.3%)	0.90 (0.75–1.08)	0.25
Head injury	603 (6.0%)	621 (6.2%)	0.97 (0.87–1.08)	0.60
Other causes	129 (1.3%)	137 (1.4%)	0.94 (0.74–1.20)	0.63

Crash-2 trial collaborators. Lancet 2010;376:23-32

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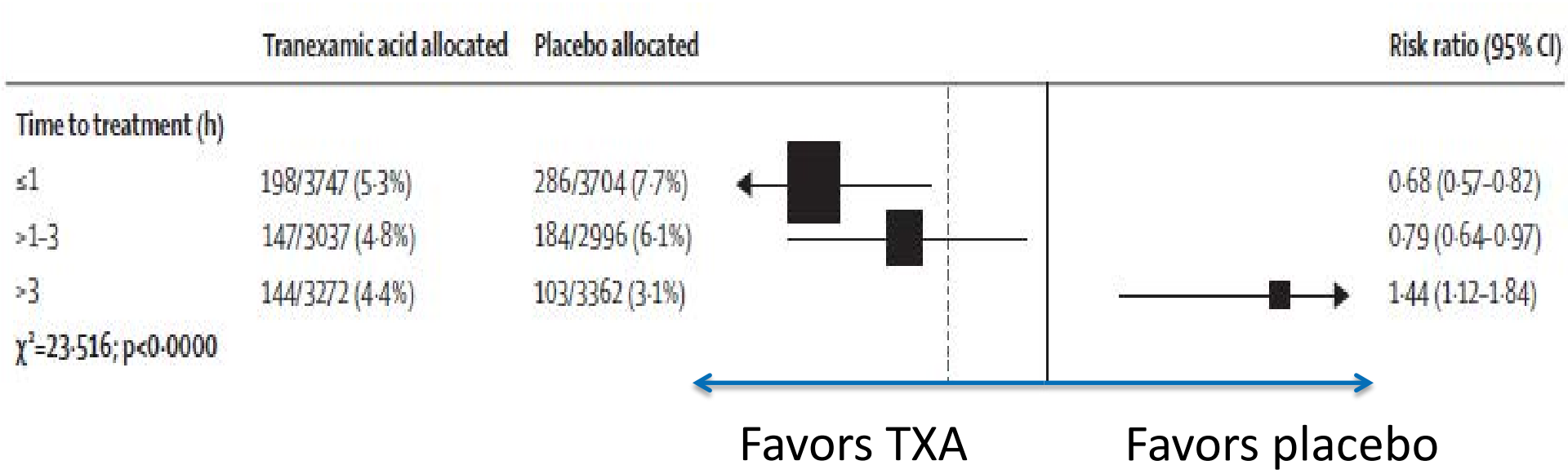
Mortality Subgroup Analysis



Crash-2 trial collaborators. Lancet 2010;376:23-32

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Limitations

	TXA (n=10,060)	Placebo (n=10,067)
Blood products transfused	5067 (50.4%)	5160 (51.3%)
Mean units transfused	6.06 (SD ± 9.98)	6.29 (SD ±10.31)
Systolic blood pressure (mm Hg)		
≤ 75	15.5%	15.9%
76-89	16%	16.8%
≥ 90	68.4%	67.1%
Heart rate (bpm)		
< 77	8.7%	8.6%
77-91	17.1%	17.5%
92-107	25.3%	25.2%
> 107	48.3%	48%

Crash-2 trial collaborators. Lancet 2010;376:23-32

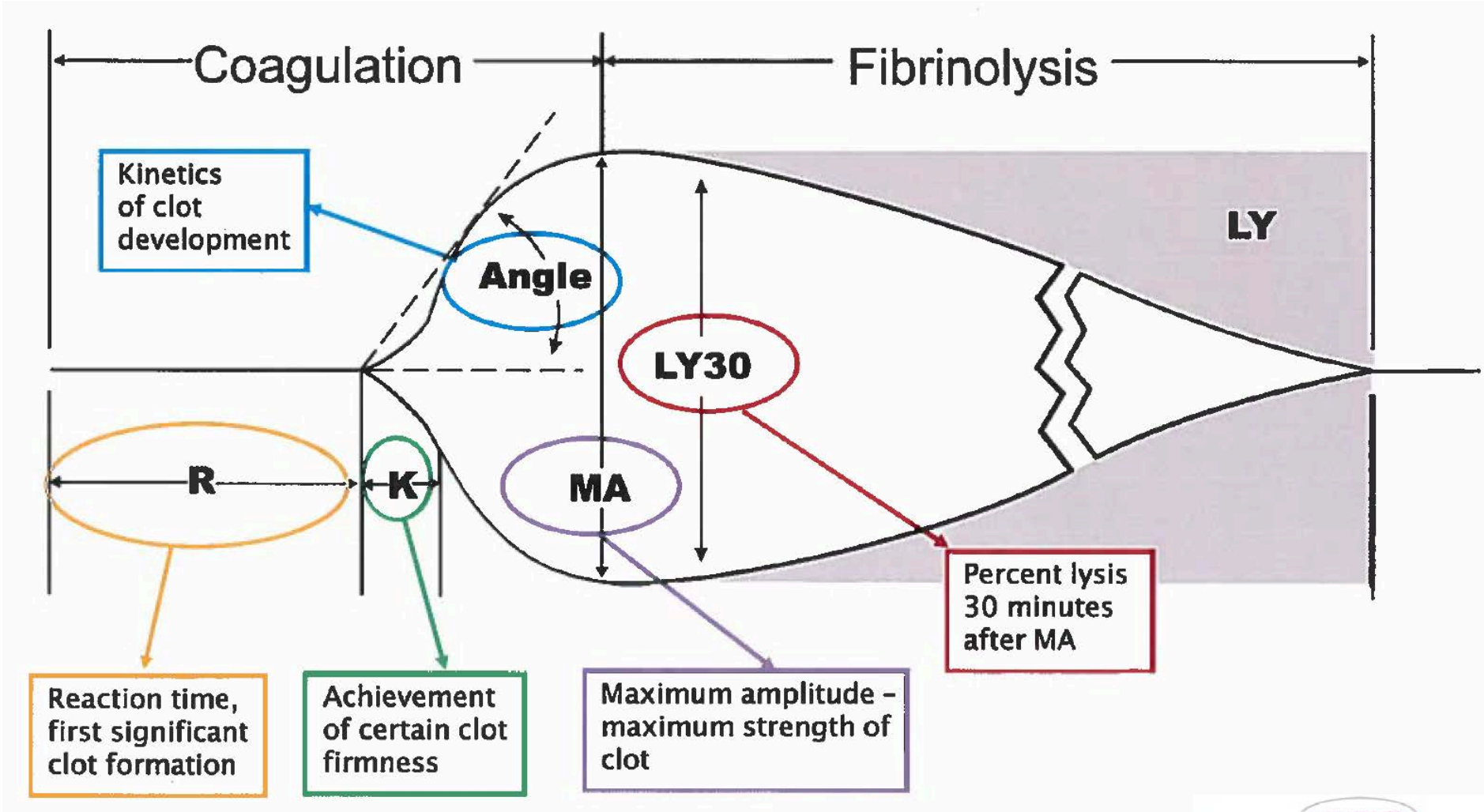
Controversy with CRASH-2

- Design
- Lack of modern trauma systems
- Lack of laboratory monitoring of coagulation function
- No Injury severity scores
- Need for an antifibrinolytic agent since only half required blood transfusion
- NNT 67

- New York Times Article "Cheap drug is found to save lives"
- Death avoidance paper
- WHO essential medications list

Binz S, et al. *J Blood Transfus* 2015;DOI:10.1155/2015/874920
CRASH-2 Collaborators. *Lancet* 11;377:1096-1101
Ker K et al. *BMC Emerg Med* 2012;12:3.
McNeil DG. The New York Times. March 20, 2012
World Health Organization. Geneva: 2013

Thromboelastometry (TEG, ROTEM)



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(t) 020 8371 9908

Normal Hemostasis

Hemorrhagic

Low clotting factors

Low platelet function

Low fibrinogen level

Primary fibrinolysis

Hypocoagulable state

Normal Hemostasis

Thrombotic

Platelet hypercoagulability

Enzymatic hypercoagulability

Platelet & enzymatic hypercoagulability

Secondary fibrinolysis

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MATTERs

- Retrospective, consecutive patients Jan 2009-Dec 2012
- Received at least 1 unit of RBC within 24 hours of injury
- 2009
  - TXA administered at discretion
- 2010 and after
  - TXA administered to those requiring emergent transfusion or based on thromboelastogram data (documented hyperfibrinolysis)
- Loading dose was given, continuation was at discretion

Morrison JJ, et al. *Arch Surg* 2012;147(2):113-9.

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MATTERs Results

- In-hospital mortality
- TXA lower unadjusted mortality
  - 17.4% (n = 293) vs. 23.9% (n = 603), p = 0.03
- Massive transfusion unadjusted mortality
  - 14.4% (n = 125) vs. 28.1% (n = 196), p = 0.004
  - TXA independently associated with survival
    - Odds Ratio 7.228 (95% CI 3-17)
    - NNT 7

Morrison JJ, et al. *Arch Surg* 2012;147(2):113-9.

Thromboembolism Risk

Study	TXA	Placebo
CRASH-2 (any vasoocclusive event)	1.7%	2%
MATTERs		
PE	2.7%	0.3%*
DVT	2.4%	0.2%*
Massive transfusion + PE	3.2%	0%*
Massive transfusion + DVT	1.6%	0.5%
Swendsen, et al. (PE/DVT)	11.5%	0%*
Cole, et al. (Shock patients: PE/DVT)	8%	2%*

*Statistically significant

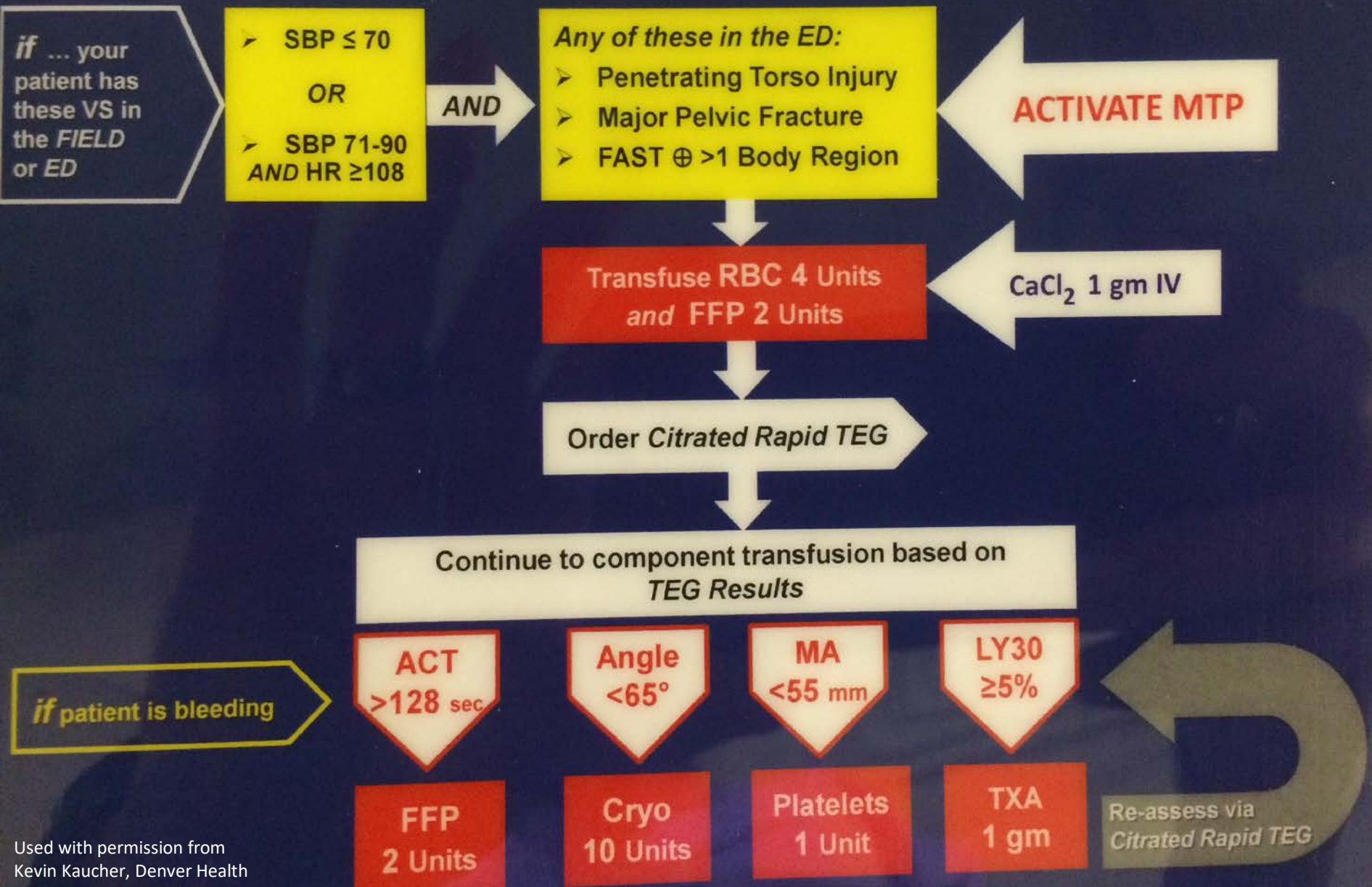
Shakur H et al. *Lancet* 2010;376(9734):23-32.
Morrison JJ, et al. *Arch Surg* 2012;147(2):113-9.
Swendsen H, et al. *J Trauma Treat* 2013;doi:10.4172/2167-1222.1000179
Cole E, et al. *Ann Surg* 2015;261:390-4.

TXA Questions

- Unknown mechanism
  - Anti-fibrinolysis vs. anti-inflammatory
- Is there more to the pathophysiology of trauma induced coagulopathy
- Hyperfibrinolysis determination
  - LY30 3% or greater predicts requirement for massive transfusion/risk of mortality
  - Hyperfibrinolysis (18%), physiologic (18%), shutdown (64%)
- Correct dose
- Pre-hospital use (STAAMP trial, The PATCH study, ….)

Roberts I, et al. *Crit Care* 2014;18:685
Binz S, et al. *J Blood Transfus* 2015;874920
Chapman MP, et al. *J Trauma Acute Care Surg* 2013;75:961-7
Moore HB, et al. *J Trauma Acute Care Surg* 2013;77:811-7
Brown JB, et al. *Prehosp Emerg Care* 2015;19:79-86
Clinicaltrials.gov

MASSIVE TRANSFUSION PROTOCOL (MTP)



Used with permission from
Kevin Kaucher, Denver Health

Prothrombin Complex Concentrate (PCC)

- Contain factors IX, II, X, ± VII
- Reversal of trauma induced dilutional coagulopathy

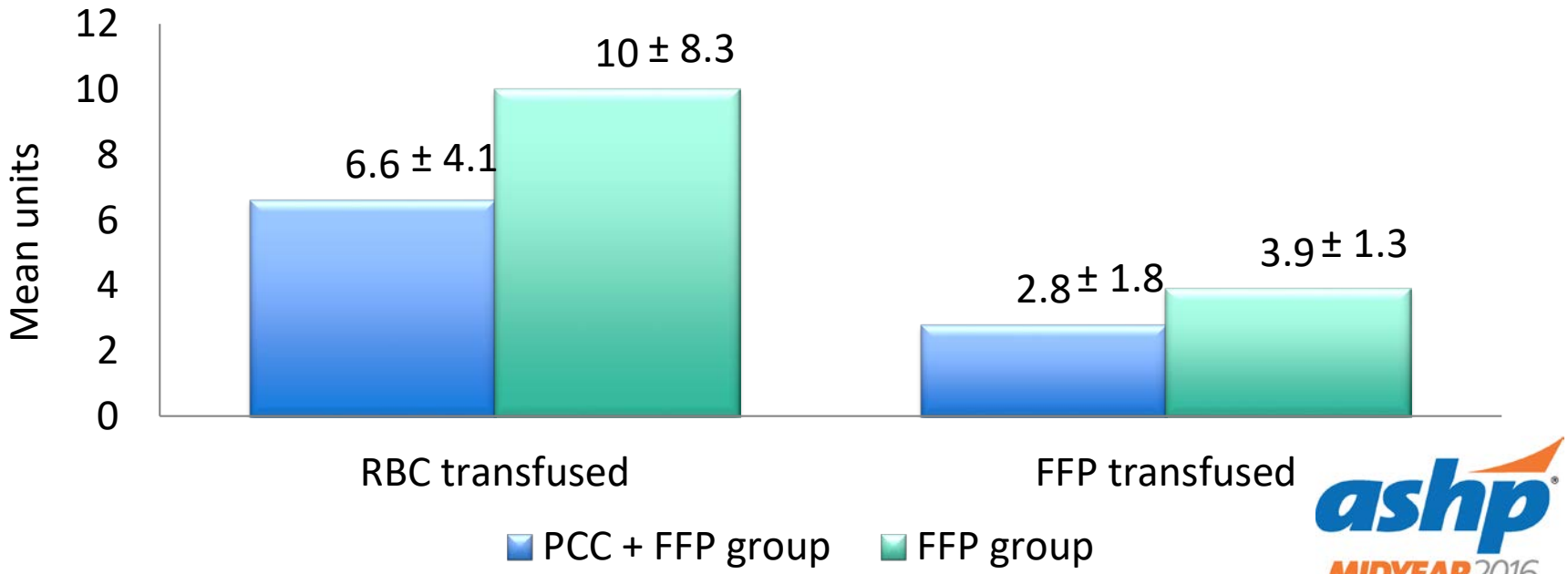
- Retrospective, n = 20 non-warfarin patients (8 TBI)
- Median ISS: 29 (21-44)
- Base deficient > 4: 80%
- 3F-PCC dose: 1,760 ± 576 units (25 units/kg)

	Before PCC	After PCC	p-value
INR	2 ± 0.6	1.4 ± 0.4	0.001
RBC (mean units ± SD)	9.8 ± 6.8	3.8 ± 4.8	0.002
FFP (mean units ± SD)	6 ± 6	3 ± 3.2	0.077
Thromboembolic events = 2 (10%)			

Joseph B, et al. J Trauma 2012;72:828-34

PCC vs. FFP and Reversal of Coagulopathy

- Retrospective, propensity matched, n = 252 coagulopathic (INR ≥ 1.5) trauma patients, 3F-PCC 25 units/kg
- Median ISS: 27 (16-38)
- Correction of INR: 394 vs. 1,050 min, p= 0.001
- Mortality 23 vs. 28%, p = 0.04



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Joseph B, et al. World J Surg 2014;38:1875-81

PCC Administration Guided by Thromboelastography

No. Patients	Criteria for PCC	No. PCC (%)	Dose	Mortality/Transfusion	Safety
128 (≥ 5 units RBC, fibrinogen concentrate)	EXTEM clotting time > 1.5 x normal	98 (75%)	1800	Mortality 24 vs. 34% (predicted by ISS)	
681 (ISS ≥ 16, fibrinogen concentrate ± PCC vs. FFP)	EXTEM clotting time > 1.5 x normal	43 (54%)	1200	Avoidance of RBCs in 29% combination gp vs. 3% FFP gp)	
144 (ISS ≥ 15, fibrinogen concentrate ± PCC vs. FFP)	PT < 50% or INR > 1.5 or EXTEM clotting time > 90 s	66		RBC 2 vs. 9 units Platelets 0 vs. 1 unit Fewer MOF or sepsis than FFP gp	9%

Schochl H, et al. *Crit Care* 2010;14:R55
Schochl H, et al. *Crit Care* 2011;15:R83
Innerhofer P, et al. *Injury* 2013;44:209-16

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Photo credit: Kate Kokanovich

- 19 yo male MCC vs. car, level 1 trauma
- SBP reported as 85 and repeat 79
- Bilateral lower extremity bone and soft tissue injuries, concern for pulses on R leg, early compartment syndrome on R leg
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Combat Gauze

- Impregnated with kaolin
- Kaolin is a negatively charged inert material
- Does not contain animal or human proteins
- Promotes activation of FXII → activates FXI → initiation of clotting cascade → promotes formation of fibrin

Kessler Trauma Center 2013

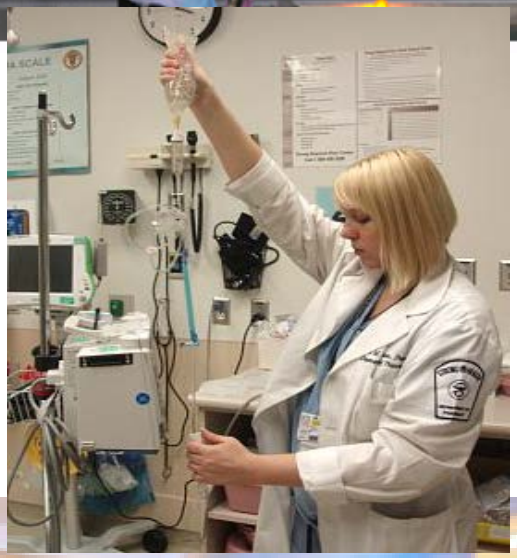
Quickclot.com

Key Takeaways

- Key Takeaway #1
  - Trauma induced coagulopathy is complicated and multifactorial
- Key Takeaway #2
  - Use of tranexamic acid (TXA) remains controversial but may be guided by thromboelastography
- Key Takeaway #3
  - 4F-PCC may decrease overall blood product use but may increase thromboembolic events

Thank You!

UNIVERSITY of ROCHESTER MEDICAL CENTER



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Brain Matters

Sid Patanwala, Pharm.D., BCPS, FCCP, FASHP
Associate Professor
The University of Arizona

Objectives

- Select appropriate pharmacological therapy for the traumatic brain injury patient

- Evaluate the pharmacists role during traumatic resuscitation in the brain injury patient

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The Scenario

Which agent would you choose?

A Rocuronium

B Succinylcholine

Intubation Success

Analysis of 327 adult patients who received RSI

	Succinylcholine	Rocuronium	P value
First attempt success rate	72.6%	72.9%	0.95
Median number of attempts (IQR)	1 (1-2)	1 (1-2)	0.87
Median dose	1.6 mg/kg	1.2 mg/kg	

Multivariate regression: Association of NMBA with intubation success (OR 1.02, 95% CI 0.61-1.7, p=0.95)

Patanwala et al. *Acad Emerg Med* 2011; 18:11-14

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ICP Basic Science - Cats

	Before SUX	After SUX	P Value
ICP-Normotensive (n=9)	8.2 ± 1.1	16.3 ± 2.7	0.01
ICP-Hypertensive (n=8)	27 ± 1.3	47 ± 4.0	0.01

Cottrell et al. Anesth Analg 1983;62:1006-9

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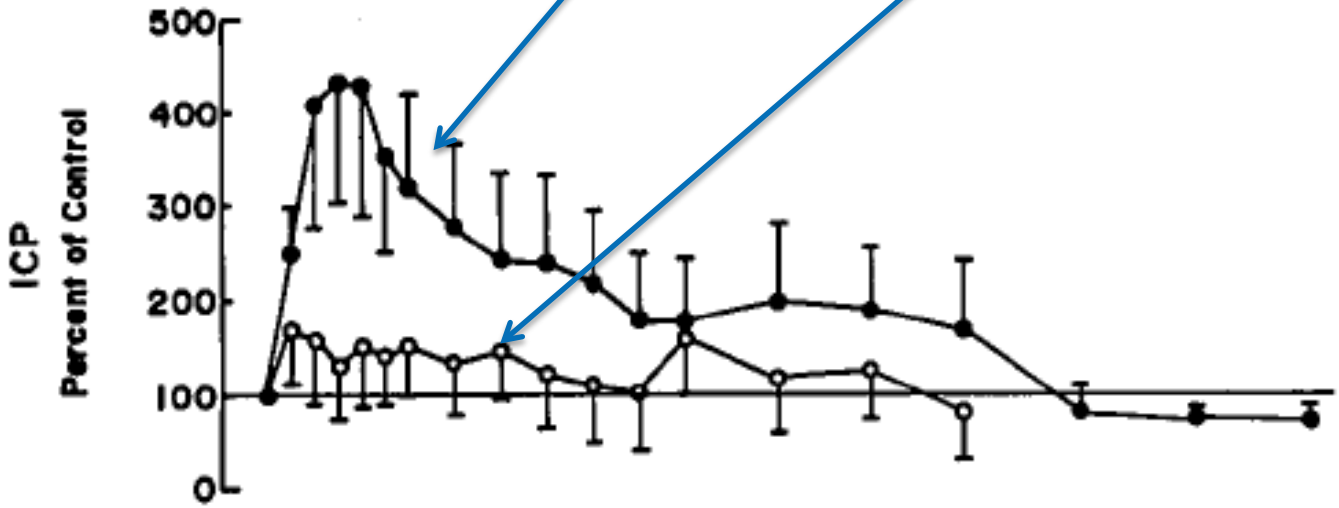
ICP Basic Science - Dogs

Time	SUX (N=6)	Placebo (N=2)	SUX + Pancuronium (N=2)
0-15 min (% Control)	291 ± 89	138 ± 46	118 ± 39
15-30 min (% Control)	189 ± 70	127 ± 54	98 ± 48



Lanier et al. Anesthesiology 1986;64:551-9

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Succinylcholine: ↑ICP?

Study	N	Design	Population	ICP
Brown et al. 1996	11	RCT	<48 hrs s/p TBI	No Δ
Kovarik et al. 1994	6	Case Series	1-5 days s/p TBI	No Δ
Lam et al. 1984	24	Case Series (abstract only)	Aneurism clipping	No Δ (CSF-P)
McLesky et al. 1974	4	Case Series	Neurosurgery	↑ICP (2/4)
Marsh et al. 1980	8	Case Series (abstract only)	Neurosurgery	↑ICP (mean Δ 5.2)

Clancy et al. *Emerg Med J* 2001;18;373-375

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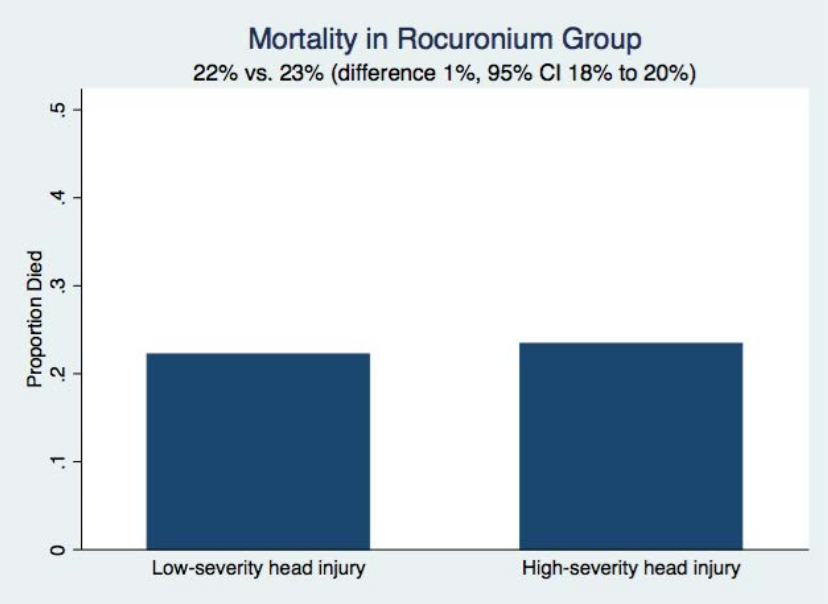
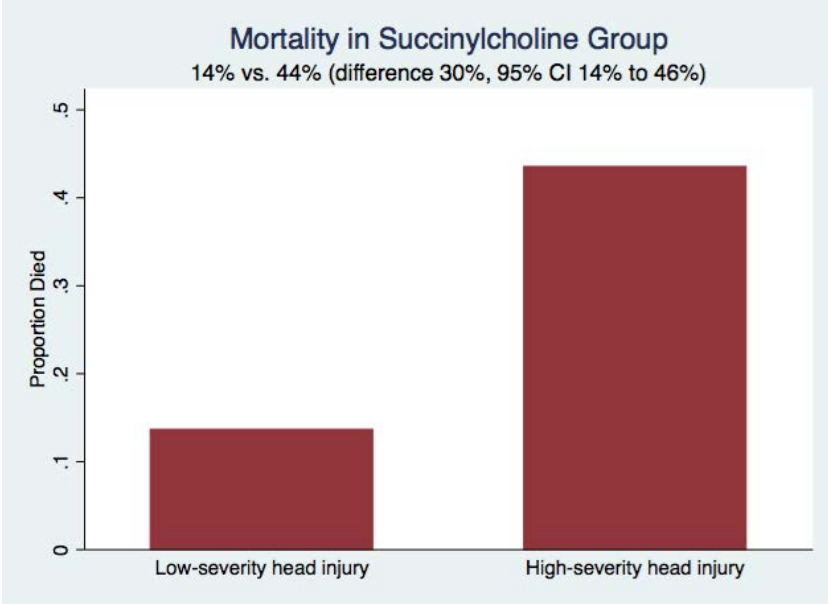
Traumatic Brain Injury

Analysis of 233 adult TBI patients who received RSI





Patanwala AE, et al. Pharmacotherapy 2016;36(1):57-63

Mortality

Severe or critical head injury patients[a]			
Variable	Odds Ratio	95% CI	P-value
Paralytic			
Rocuronium	[Reference]		
Succinylcholine	4.08	1.18 to 14.13	0.026
Glasgow Coma Score[c]	0.36	0.20 to 0.68	0.001
Age[d]	1.04	1.00 to 1.08	0.045
Less than severe head injury patients[b]			
Paralytic			
Rocuronium	[Reference]		
Succinylcholine	0.75	0.29 to 1.92	0.548
Glasgow Coma Scale[c]	0.48	0.31 to 0.74	0.001
Age[d]	1.03	1.00 to 1.06	0.026

Patanwala AE, et al. Pharmacotherapy 2016;36(1):57-63

Due to the potential for transtentorial herniation the team would like to initiate a hyperosmolar agent. Which would you recommend?

A Mannitol

B Hypertonic saline (NaCl 5%)

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EXPERIMENTAL ALTERATION OF BRAIN BULK

LEWIS H. WEED, *Capt., Med. Corps*

AND

PAUL S. McKIBBEN, *1st Lt., San. Corps*

From The Army Neuro-Surgical Laboratory, Johns Hopkins Medical School, Baltimore, Maryland

Received for publication March 22, 1919

- Hy**PER**tonic Solution ----> ↑Size of the brain
- Hy**PO**tonic Solution ----> ↓Size of the brain

Weed L, McKibben PS. 1919;48:531-558

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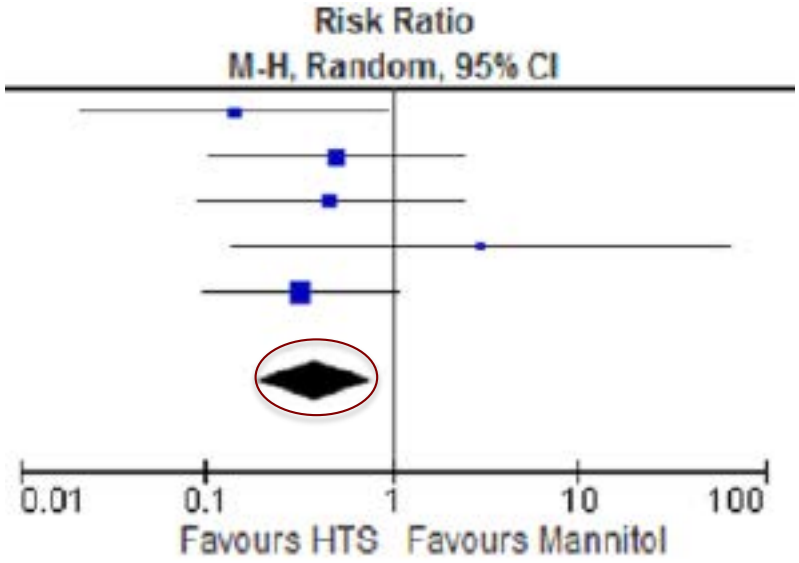
Mannitol Versus Hypertonic Saline

- Systematic Review (n=7 RCTs)
  - No difference in mortality, neurological outcome, or ICP reduction
  - Hypertonic saline may lead to fewer treatment failures



Burgess et al. Ann Pharmacother. 2016 Apr;50(4):291-300

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Guideline Recommendations

- "Although hyperosmolar therapy may lower intracranial pressure, there was insufficient evidence about effects on clinical outcomes to support a specific recommendation, or to support use of any specific hyperosmolar agent, for patients with severe traumatic brain injury"

Carney et al. Neurosurgery 0:1–10, 2016 [Ahead of Print]

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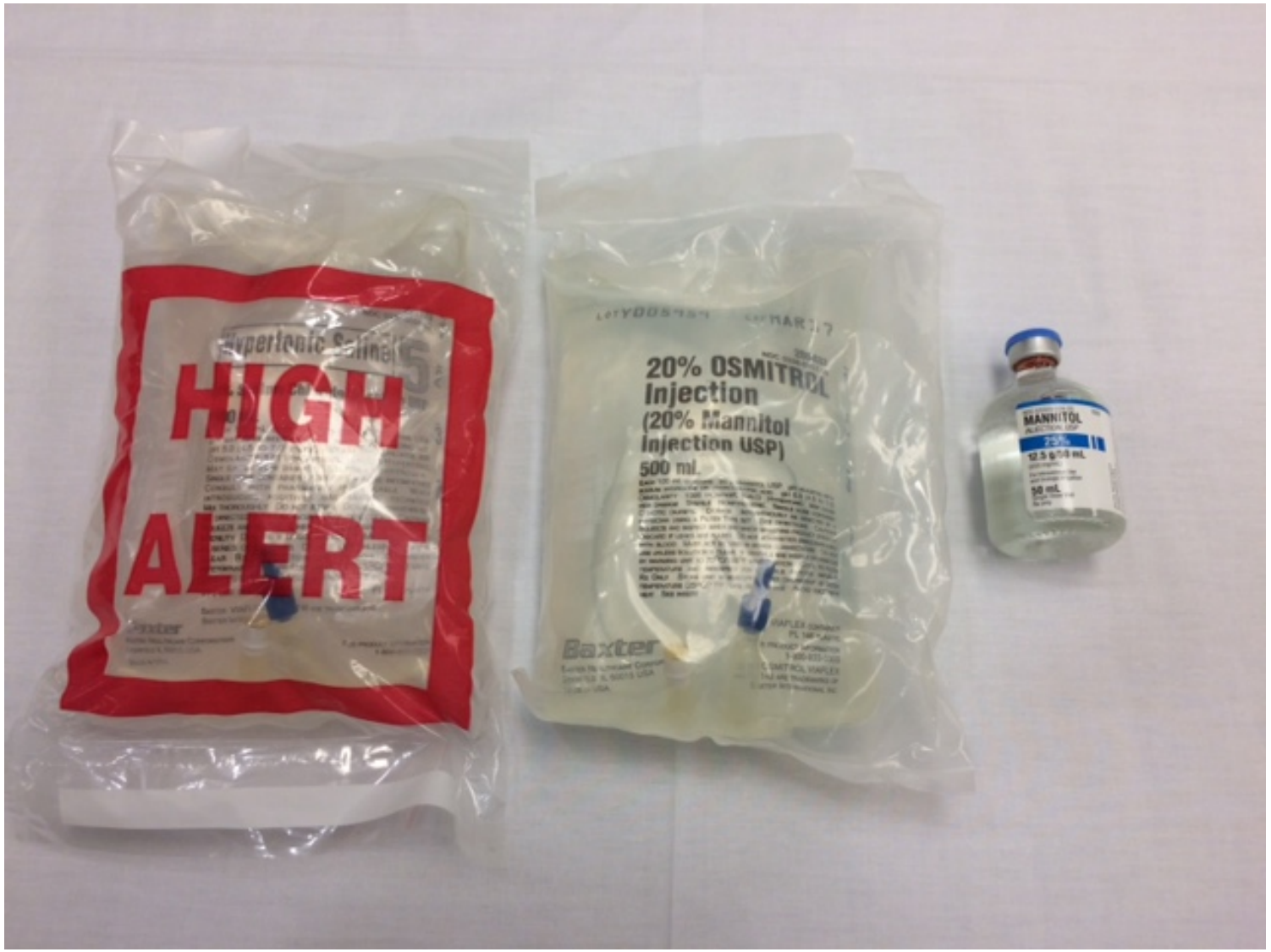
Mannitol Versus Hypertonic Saline



Quick Lesson About Filters

Quick Lesson About Filters

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Seizure prophylaxis is indicated. Which would you choose?

A Phenytoin

B Levetiracetam

Levetiracetam Versus Phenytoin

Prospective Observational Study in Blunt Head Trauma

	Levetiracetam (n=406)	Phenytoin (n=407	P value
Seizures	1.5%	1.5%	0.997
Adverse drug reaction	7.9%	10.3%	0.227
Mortality	5.4%	3.7%	0.236

1000 mg IV q12 hours

Inaba et al. *J Trauma Acute Care Surg*. 2013;74:766-773.

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Guideline Recommendations

- Phenytoin recommended to decrease early post-traumatic seizures (within 7 days), when benefit outweighs risk for treatment
- Prophylaxis with phenytoin or valproate not indicated for late seizures
- Insufficient evidence to recommend levetiracetam compared to phenytoin

Carney et al. Neurosurgery 0:1–10, 2016 [Ahead of Print]

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You plan to use levetiracetam. What dose would you recommend?

A 1000 mg IV q12

B 500 mg IV q12

Product Labeling

2 DOSAGE AND ADMINISTRATION

2.1 Dosing for Partial Onset Seizures

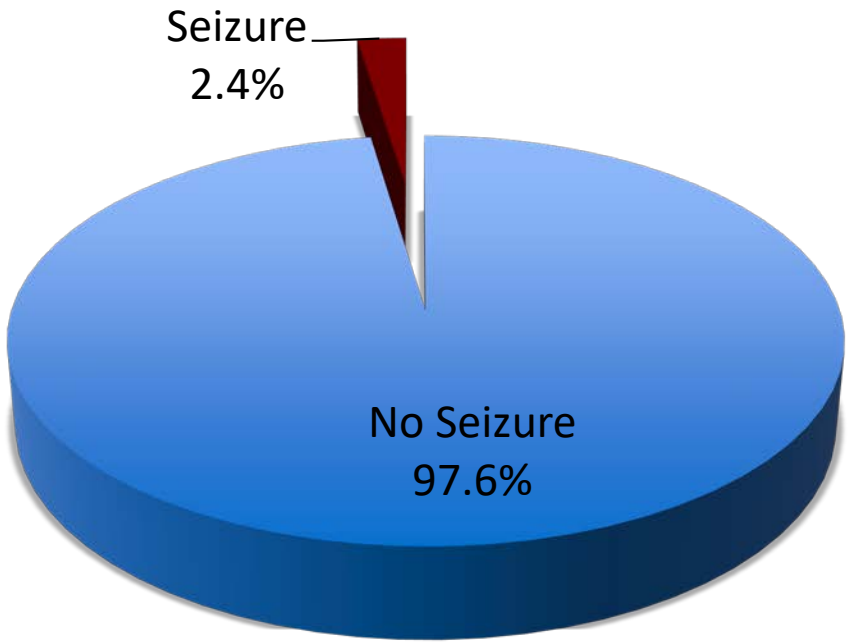
Adults 16 Years and Older

Initiate treatment with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

Package Insert. Levetiracetam injection. UCB, Inc. (Accessed 9/1/16)

Low Dose Effective?

Retrospective cohort of patients with TBI (n=169)
All patients given levetiracetam 500 mg IV q12



Patanwala et al, Brain Inj. 2016;30(2):156-8

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Key Takeaways

- Key Takeaway #1
  - Consider rocuronium for RSI (Note: my data is only hypothesis generating)
- Key Takeaway #2
  - Insufficient evidence to support mannitol versus hypertonic saline. Consider logistical issues.
- Key Takeaway #3
  - Observational studies show levetiracetam equally effective to phenytoin. Adequately powered RCT needed.