Blood Failure Pathophysiology Controversies?
(or)
Some observations regarding coagulation disorders in a unique patient population

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THOR

Bergen, Norway

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Children's
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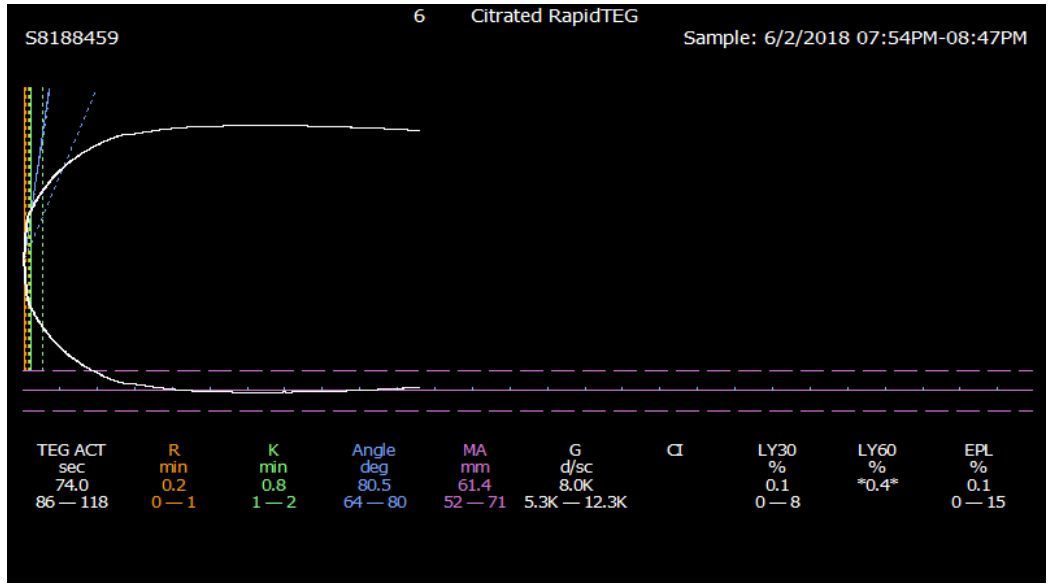
A case…

TRIB LIVE

Toddler's death in Sharpsburg apartment window fall ruled an accident



Initial Labs: H/H 10.2/29.6, plts 224, PT 20.9, PTT 68, INR 1.8
TEG: ACT 74, K 0.8, angle 80.5, MA 61.4, LY30 0.1
Resuscitation: Factor VIIa, FFP (23cc/kg), PRBC, 10cc/kg, NS 20cc/kg
Hospital course: clinically herniated 3 hours post-arrival; brain death confirmed, parents elected to donate organs

Controversies…

- Pediatrics
- Coagulopathy ?
- Traumatic brain injury
- Fibrinolysis
- Plasma
- (whole blood)

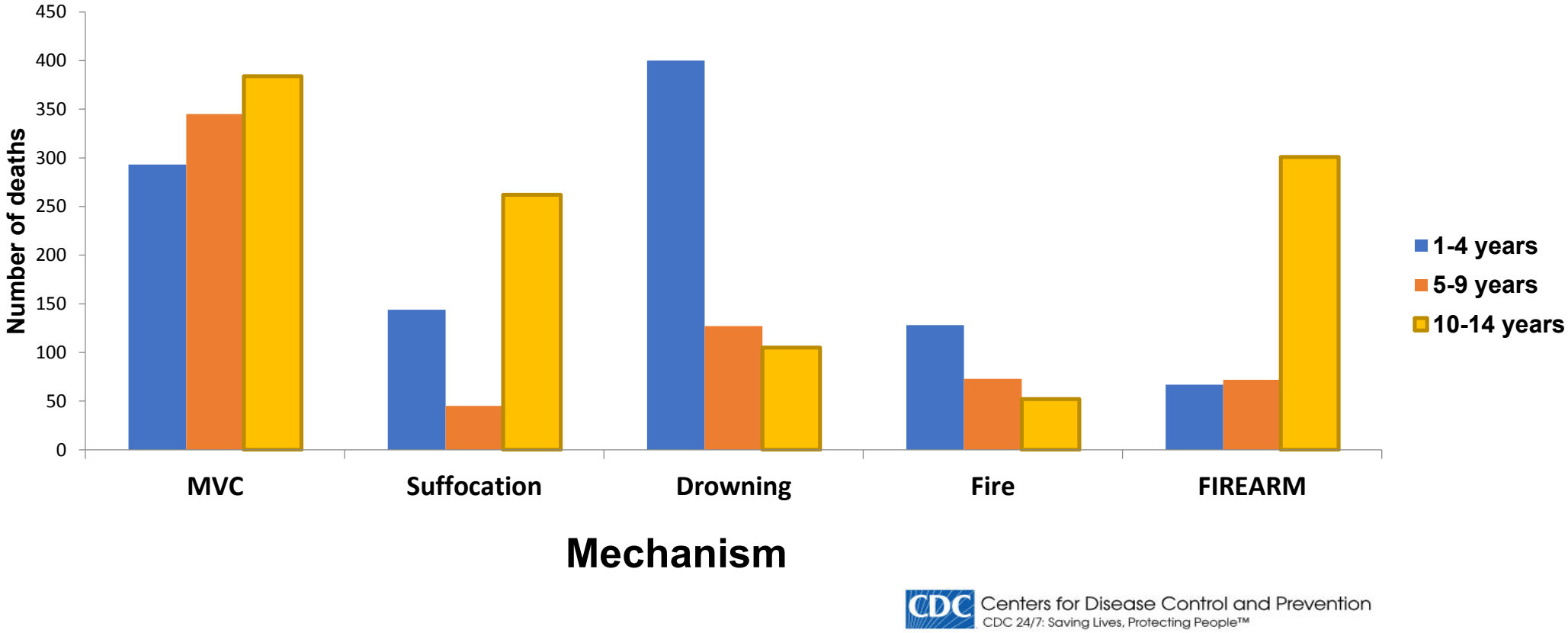
Leading cause of death, United States

Rank	<1	1-4	5-9	10-14	15-24
1	Congenital Anomalies 5,107	Unintentional Injury 1,394	Unintentional Injury 758	Unintentional Injury 885	Unintentional Injury 12,341
2	Short Gestation 4,148	Congenital Anomalies 507	Malignant Neoplasms 439	Malignant Neoplasms 477	Homicide 4,678
3	SIDS 2,063	Homicide 385	Congenital Anomalies 163	Suicide 267	Suicide 4,600
4	Maternal Pregnancy Comp. 1,561	Malignant Neoplasms 346	Homicide 111	Homicide 150	Malignant Neoplasms 1,604
5	Unintentional Injury 1,110	Heart Disease 159	Heart Disease 68	Congenital Anomalies 135	Heart Disease 1,028

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

2010

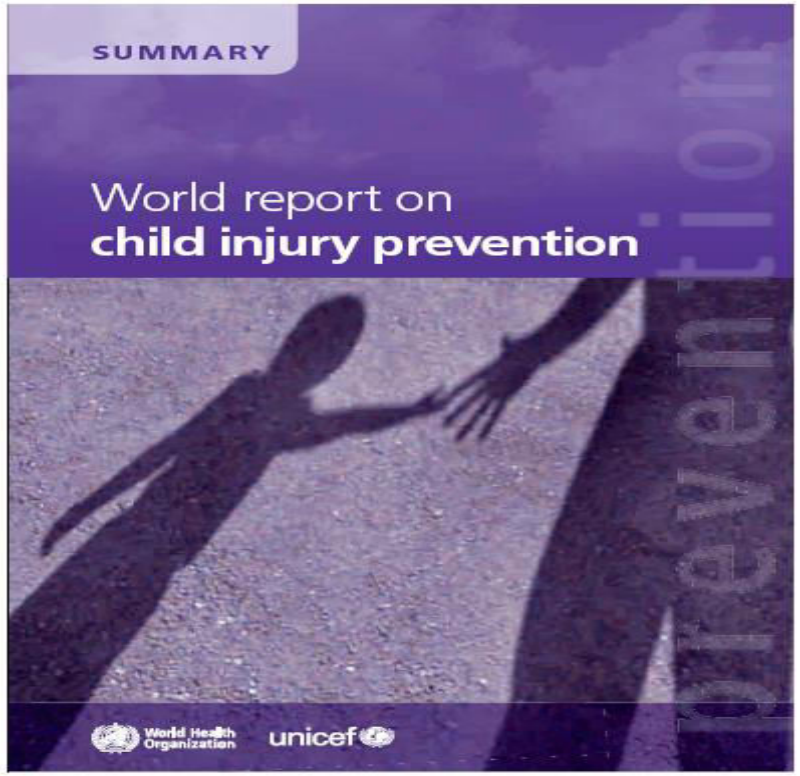
Intentional and unintentional deaths in children ages 1-14 years (US), 2014



World report on child injury prevention

- World Health Organization and UNICEF
- Published December 10, 2008

  - 830,00 die yearly as a result of unintentional injuries
  - Road traffic injuries are leading cause of death for children over 9 years
  - Road traffic injuries and falls are the main causes of injury-related child disabilities
  - Injury prevention initiatives work and are cost effective



Child injuries have been neglected for many years, and are largely absent from child survival initiatives presently on the global agenda. Through this *World report on child injury prevention*, the World Health Organization, the United Nations Children's Fund and many partners have set out to elevate child injury to a priority for the global public health and development communities. The knowledge and experience of nearly two hundred experts from all continents and various sectors were invaluable in grounding the report in the realities faced in many countries.

Why should kids be different?

- Physiology
  - Inflammatory and coagulation systems mature as children age
  - Low levels of underlying co-morbidity
- Injury Patterns
  - Less bleeding
  - Low levels of mortality
  - High levels of traumatic brain injury (the leading cause of traumatic death)
  - Inflicted injury
- Systemic response to injury
  - Low levels of sepsis, multi-system organ failure

Question

- Does acute traumatic coagulopathy occur in children AND what is it's association with outcome?
- 10 year retrospective review of our level 1 pediatric trauma center (2005–2014)
- INR as a "marker" of coagulopathy
- Inclusion Criteria
  - Level 1 trauma activation
  - ICU admission
- Exclusion Criteria
  - No labs drawn within 2 hour of arrival
  - Blood product transfusion prior to arrival
  - Pre-existing coagulation disorder
  - Isolated hanging/drowning
  - Dead on arrival

Results

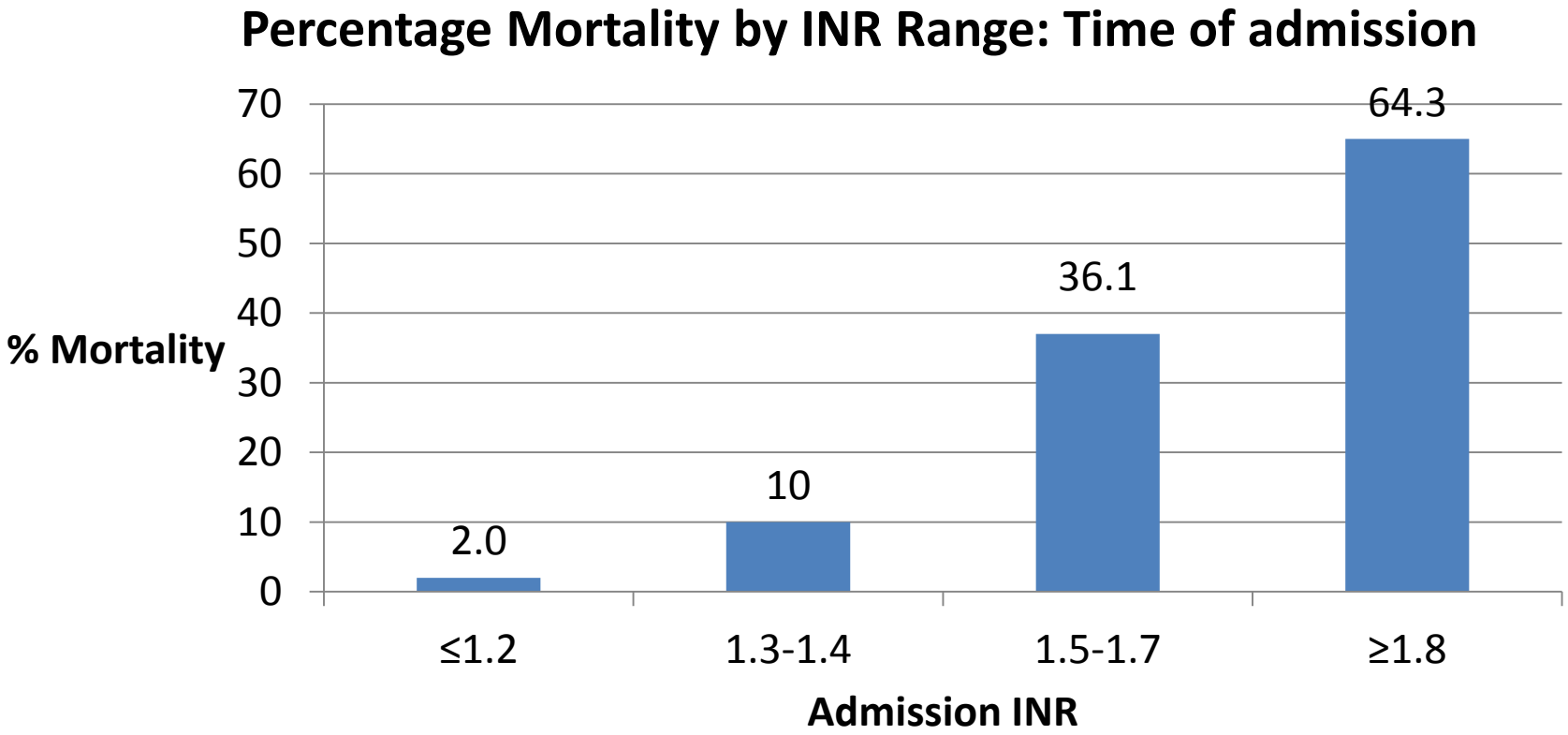
# subjects =776	
Age	8.35 ± 5.51 years
Male	65.7 %
Race	
White	80.0%
Black	14.2%
Other	5.8%
Injury Severity Scale	
Q1	10
Median	18
Q3	27
Glascow Coma Scale	
Q1	3
Median	5
Q3	14
Mechanism	
Blunt	84.8%
Penetrating	6.5%
Abusive head trauma	8.7%
Hemorrhagic Injury	7.0% (n=54)
Coagulopathy	
INR ≥1.3	29.2% (n=227)
INR ≥1.5	13.3% (n=103)
Mortality	11.1% (n=86)

Predictors of Mortality

	INR ≥ 1.3		INR ≥ 1.5	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Elevated INR	3.77 (1.95 – 7.32)	<0.001	4.78 (2.47 – 9.26)	<0.001
Hypotension	3.45 (1.33 – 9.02)	0.011	3.54 (1.33 – 9.40)	0.011
Hypothermia	3.73 (1.96 – 7.07)	<0.001	3.70 (1.93 – 7.11)	<0.001
Acidosis	2.38 (1.29 - 4.39)	0.005	2.15 (1.14 – 4.03)	0.017
Injury Severity Score	1.06 (1.03 - 1.08)	<0.001	1.06 (1.03 - 1.09)	<0.001
Head AIS ≥ 3	3.34 (1.45 – 7.66)	<0.001	3.70 (1.57 – 8.69)	0.003
Hemorrhagic injury	3.03 (1.16 - 7.93)	0.024	2.62 (0.93 - 7.37)	0.068

- Elevated admission INR is common in severely injured kids
- It is associated with poor outcome

Leeper, *J Trauma Acute Care Surgery*, 2016

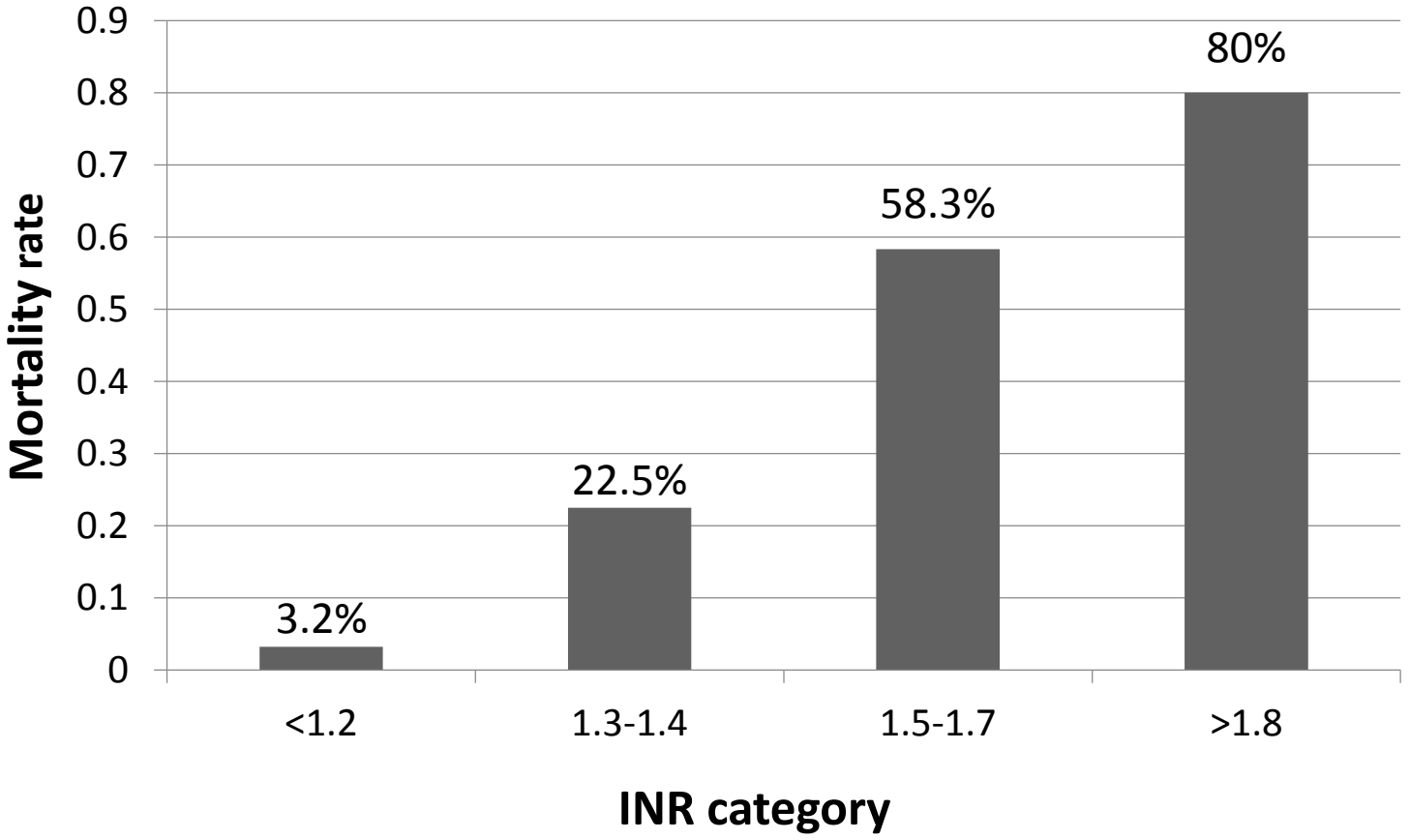


Even a mildly elevated INR at admission is associated with an increased risk of death

Cotton, et al, demonstrated 100% mortality in a pediatric cohort with an admission INR>3 (J Am Coll Surg, 2017)

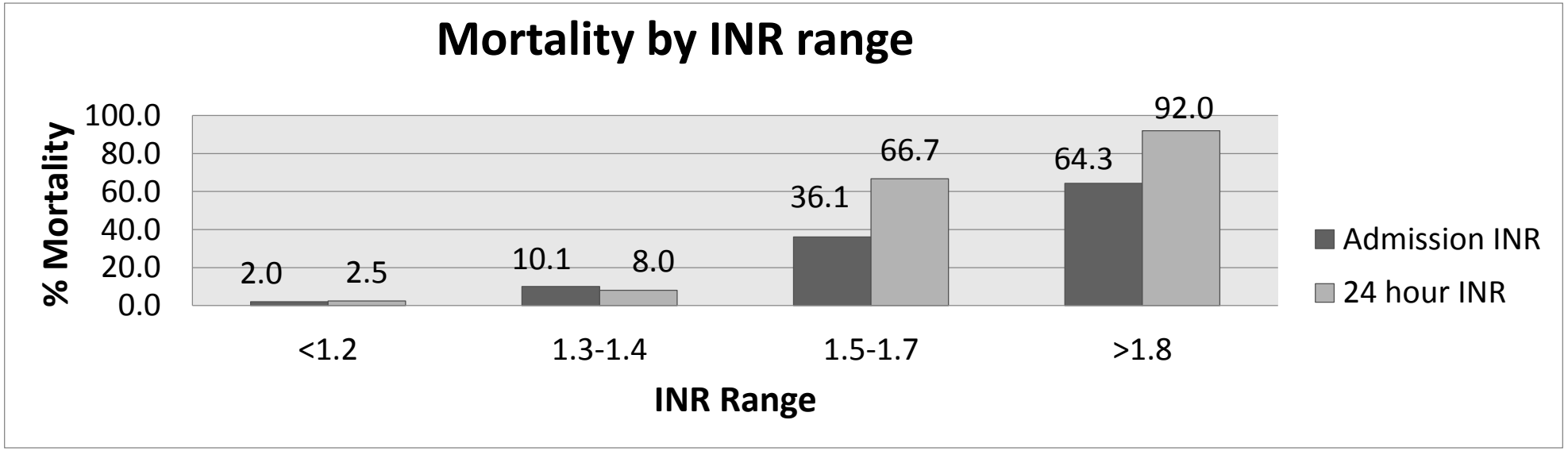
Cannon, et al, in a pediatric military cohort, demonstrated that an INR≥1.5 was associated with an OR of 4.8 for 24hr and hospital mortality (JTACS, 2018)

INR in Inflicted injury patients



Leeper, JTACS, 2016

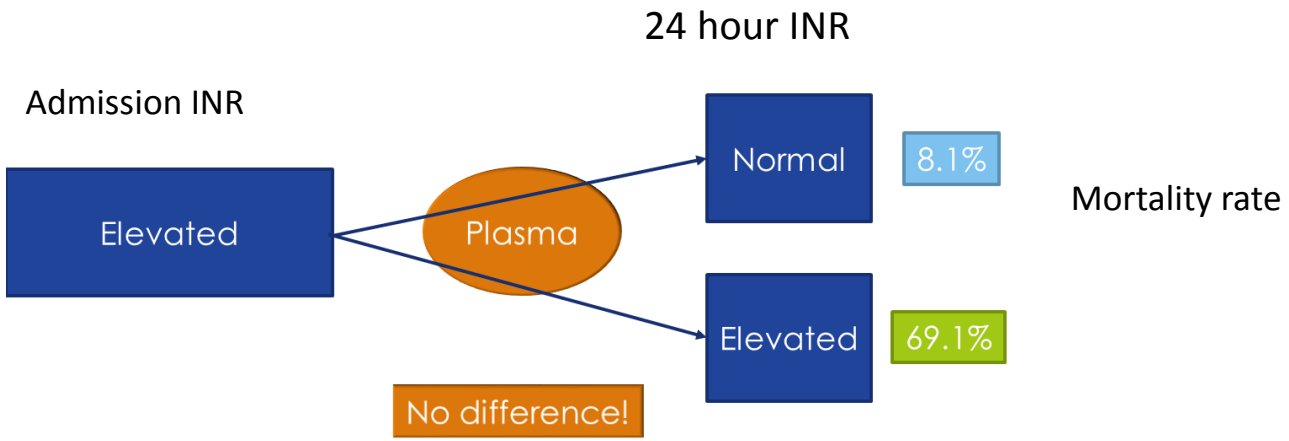
What happens after 24 hrs?



Group	INR Trend: Admission to 24 hours	Frequency % (n)	Mortality Rate % (n)	Group Comparisons
1	Remained normal	65.3 (290)	3.5 (10)	1 vs. 2 p=NS 1 vs. 3 p<0.001 1 vs. 4 p<0.001 2 vs. 3 p<0.001 2 vs. 4 p<0.001 3 vs. 4 p=NS
2	Initially elevated then normalized	14.0 (62)	8.1 (5)	
3	Initially normal then elevated	8.3 (37)	43.2 (16)	
4	Remained abnormal	12.4 (55)	69.1 (38)	

Findings INDEPENDENT of blood product transfusion

- Plasma transfusion meant to “fix” coagulopathy often fails to normalize the INR



Summary

- INR ≥ 1.3 represents a clinically significant inflection point that reflects increased risk of mortality
- Admission INR, INR at 24 hours, and trend in INR are strong predictors of mortality in injured pediatric patients
- Blood product transfusion is not associated with normalization of INR or reduction in mortality in this cohort.
- INR does not represent a treatment target in most patients, but rather serves as a marker of systemic dysregulation, overall injury severity, and a predictor of poor outcome.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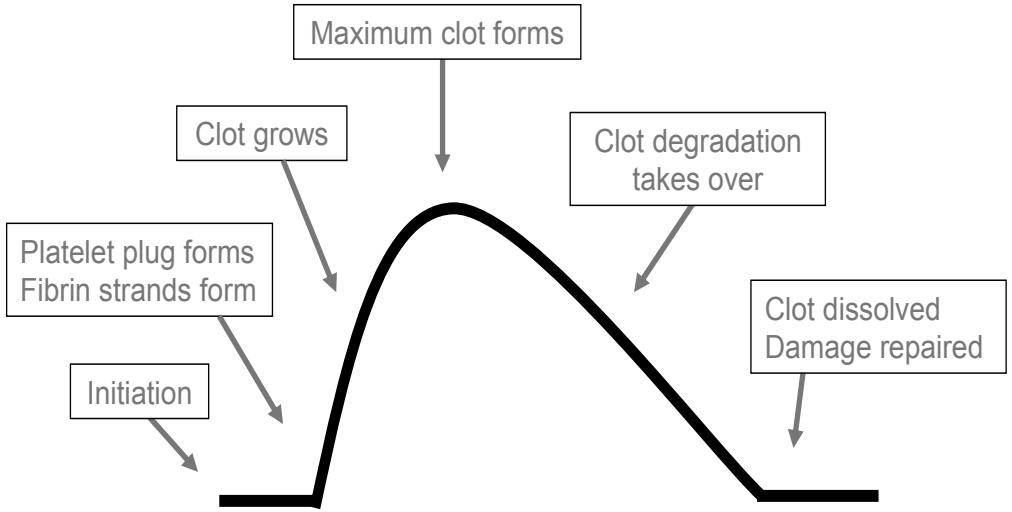
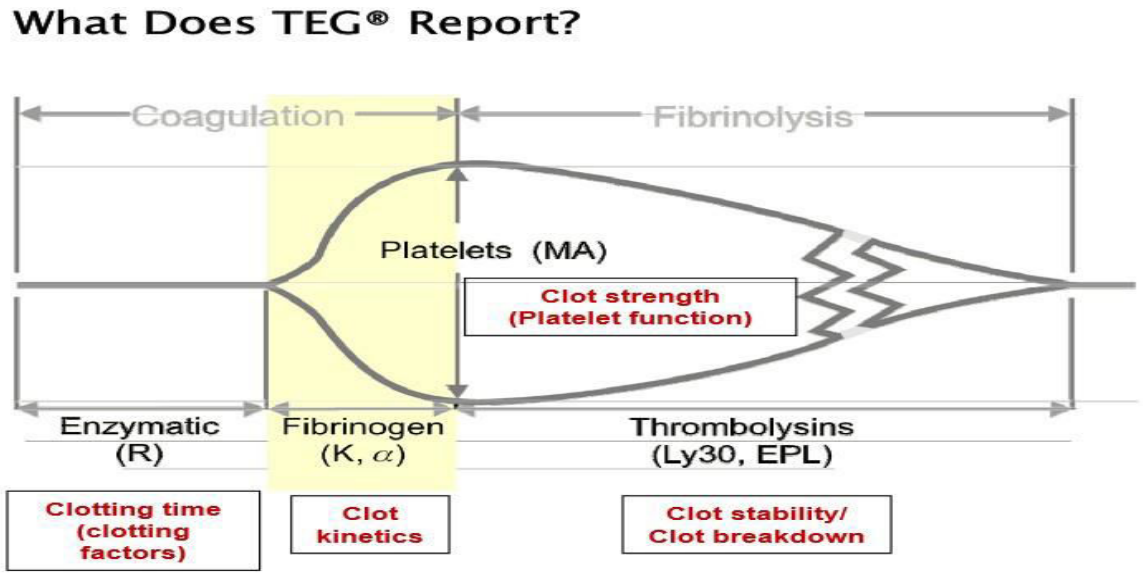
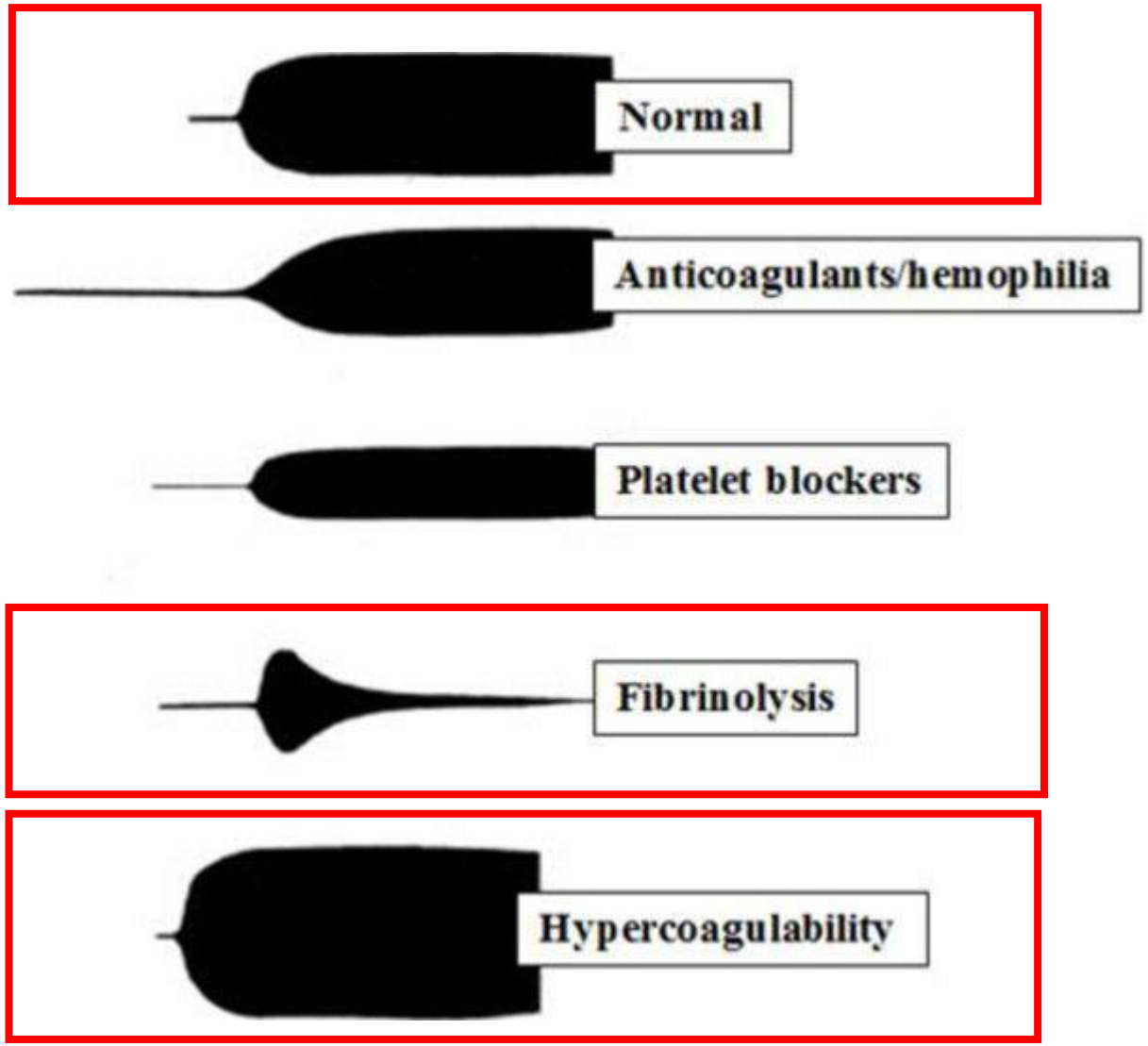
Viscoelastic testing





- Thromboelastography (TEG) and thromboelastometry (TEM) are real time evaluation of clot development and degradation
  - Clotting factors
  - Platelets
  - Fibrinolysis



Teodoro da Luz, et al, *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2013 **21**:29

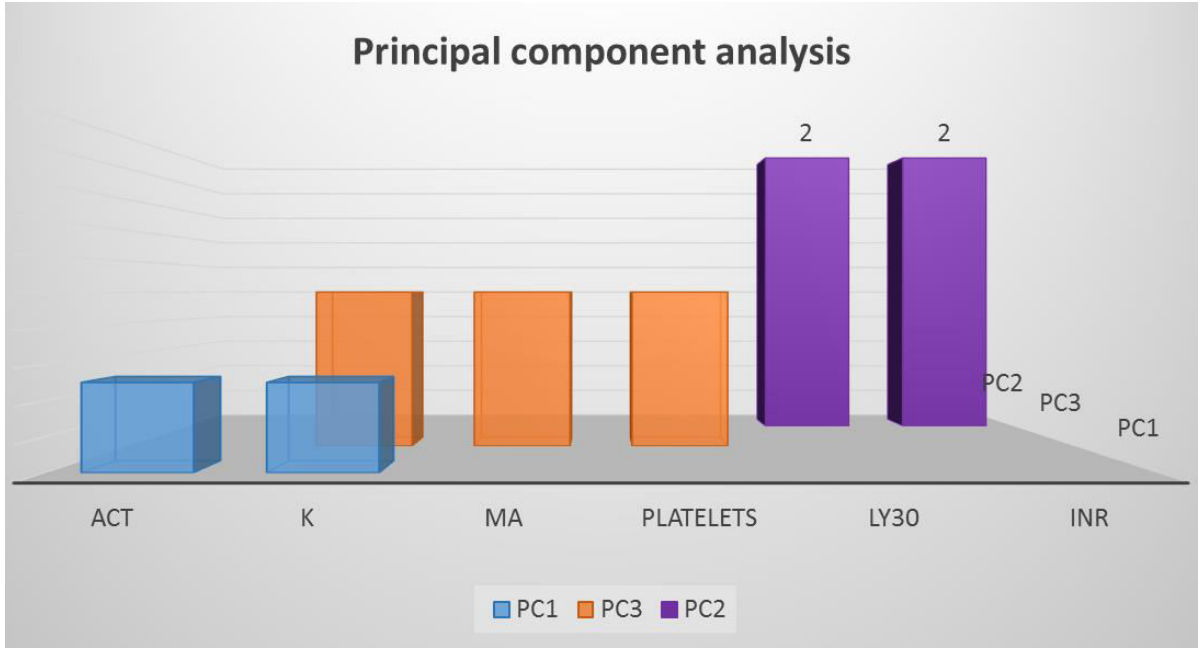
Questions

- What can TEG tell us about trauma induced coagulopathy in children?
- What aspect of the clotting process is most significant in injured children?
- What about hypercoagulopathy?

Principle Component Analysis

- Three distinct patterns of abnormality: clot strength (platelets), fibrinolysis, and global clotting factor depletion
- Abnormal fibrinolysis was associated with the most severely injured patients and all poor outcomes including mortality, transfusion, DVT and disability.

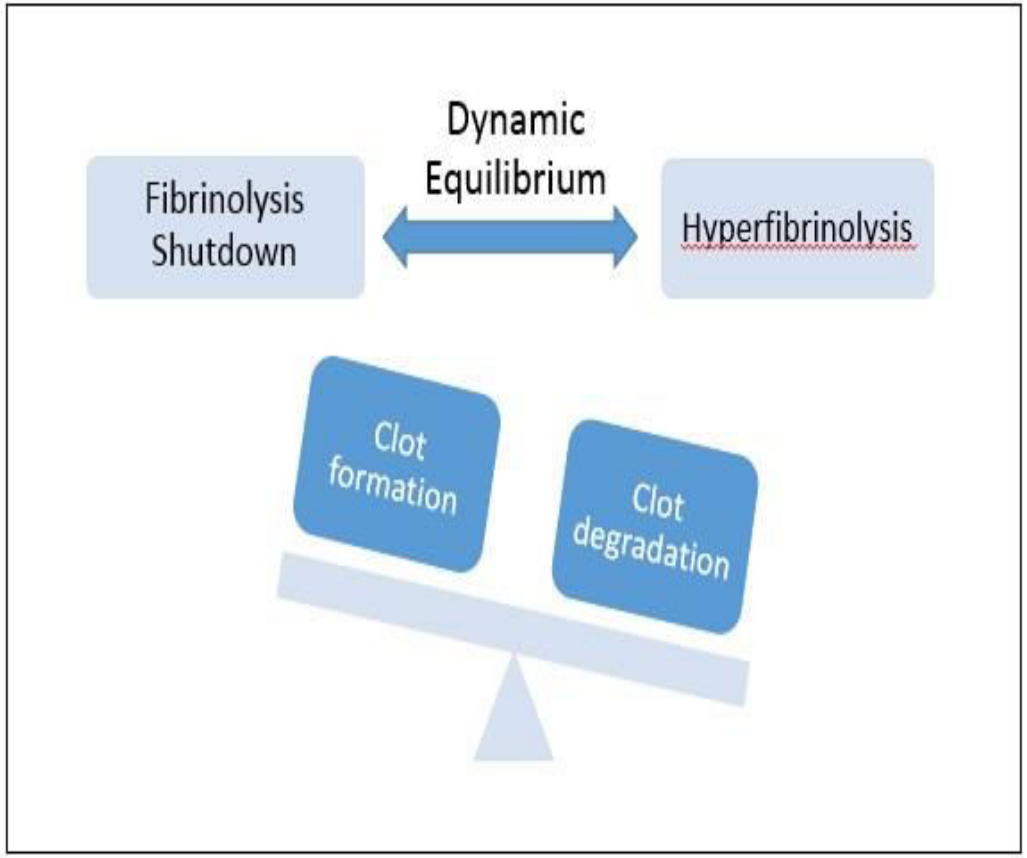
Leeper, *Surgery*, 2018



PC2 score		
	Mortality	OR = 2.07
	Blood transfusion	OR = 2.79
	Injury Severity Score	rho = 0.4
	Deep vein thrombosis	OR = 1.84
	Functional disability	OR = 1.66

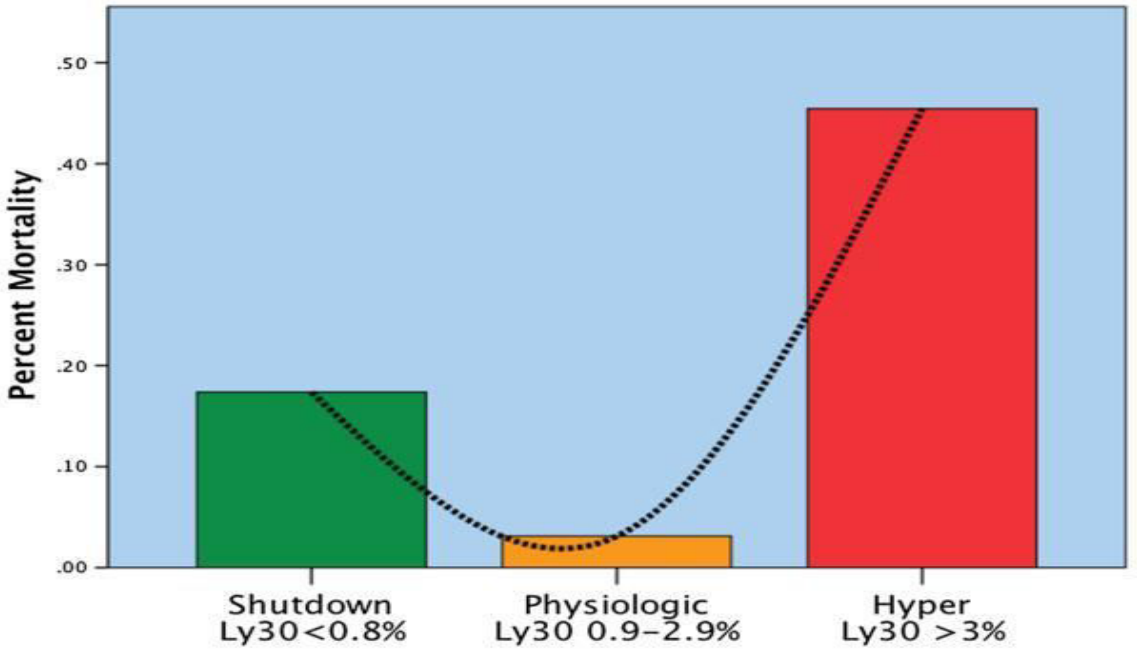
Fibrinolysis

- Clot breakdown
- Physiologic: Part of the process of wound remodeling and healing
- Pathophysiologic
  - Excess (hyperfibrinolysis) can promote bleedinig
  - Deficiency (fibrinolysis shutdown) can promote thrombotic complications



Adult literature

- Hyperfibrinolysis and fibrinolysis shutdown are potential prognostic indicators and treatment targets in adults
- Mortality risk is increased by an odds ratio of 1.6 for shutdown and 3.3 for hyperfibrinolysis
- CRASH 2 – patients given empiric antifibrinolytics (TXA) soon after injury had increased survival → suggests fibrinolysis contributes to bleeding and death



Moore, J Trauma Acute Care Surg, 2014; JACS, 2016

What (if any) is the impact of fibrinolytic abnormalities in injured children?

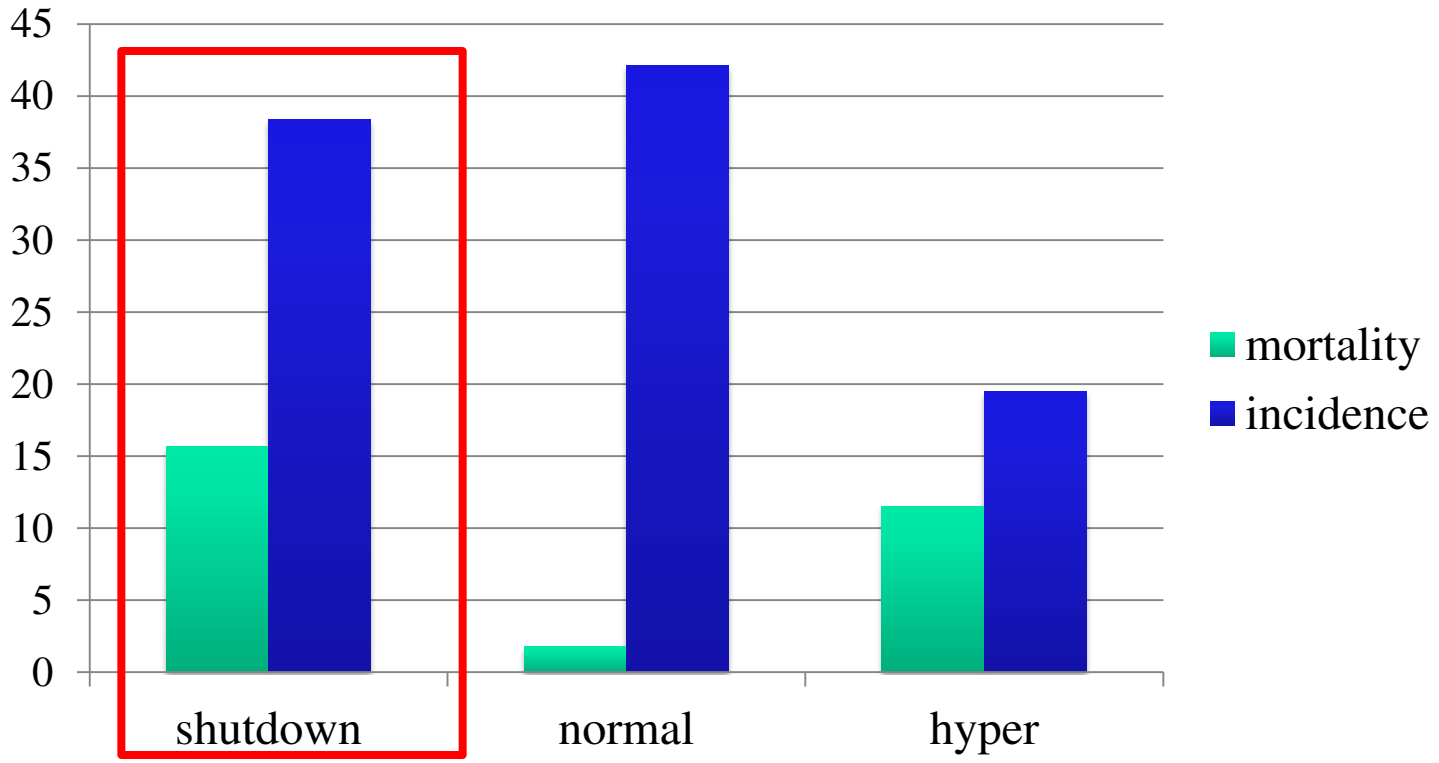
- Prospective cohort of severely injured children with TEG drawn on admission and daily (research) when admitted to the ICU
  - standard of care that a TEG is obtained on all “highest level” trauma alerts in the ED
- Primary outcome: death and disability
- Secondary outcome: need for transfusion, development of venous thromboembolism

Patient Demographics N=101	Median(IQR) or %(n)
Number of TEGs	3(3-5)
Age (years)	8 (4-12)
Female sex	32% (32)
Race	
White	71% (71)
Black	17% (17)
Other	12% (13)
Injury Characteristics	
Mechanism	
Blunt	73% (74)
Penetrating	14% (14)
Abuse	9% (9)
Drowning/Hanging	5% (5)
Body region injured	
Isolated Head	42% (43)
Isolated Trunk/Extremity	31% (31)
Polytrauma	27% (27)
Admission Glascow Coma Scale (GCS) Score	3 (3-15)
Injury Severity Score	25 (16-30)
Severe Traumatic Brain Injury	47.0% (47)

Outcomes	
Mortality	16% (16)
Time to death (days)	4 (3-5)
Cause of death	
Head injury	88% (14)
Hemorrhage	6% (1)
Multisystem Organ Failure	6% (1)
Disability	45% (38/85)
Deep Vein Thrombosis	10.5% (9/85)

- Severely injured
- High incidence of severe TBI (AIS≥3)

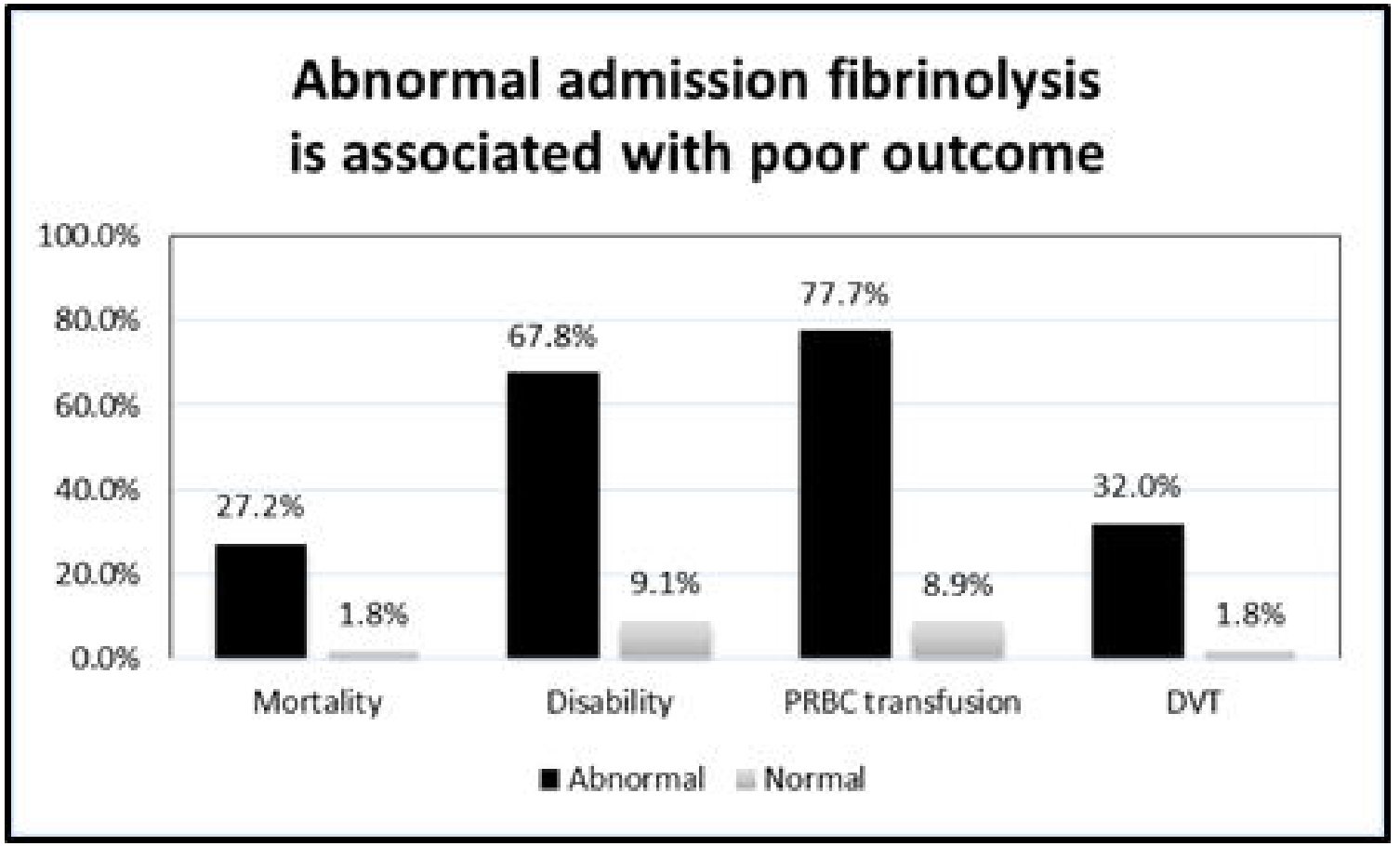
Distribution of fibrinolysis phenotype in injured kids



Most kids have a “normal” level of fibrinolysis and shutdown was more common and associated with a higher mortality than hyperfibrinolysis

Abnormalities in fibrinolysis at the time of admission are associated with deep vein thrombosis, mortality, and disability in a pediatric trauma population

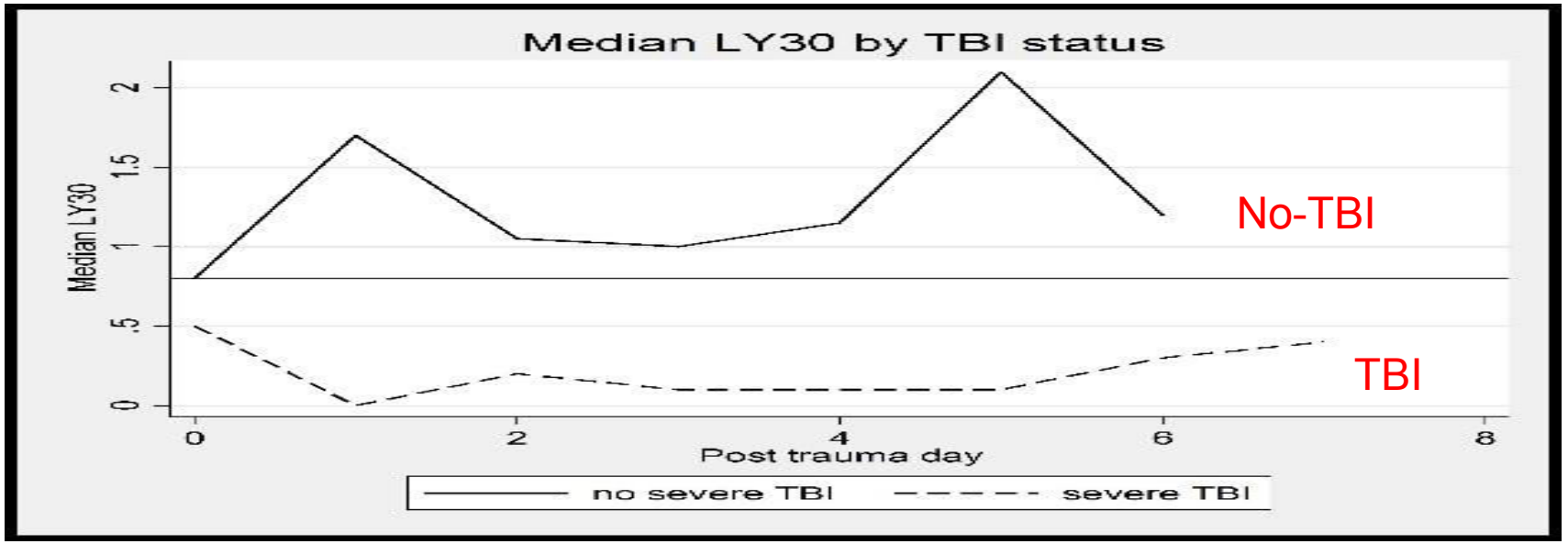
Christine M. Leeper, MD, MS, Matthew D. Neal, MD, Christine McKenna, MSN, CRNP, Jason L. Sperry, MD, MPH, *and* Barbara A. Gaines, MD, *Pittsburgh, Pennsylvania*



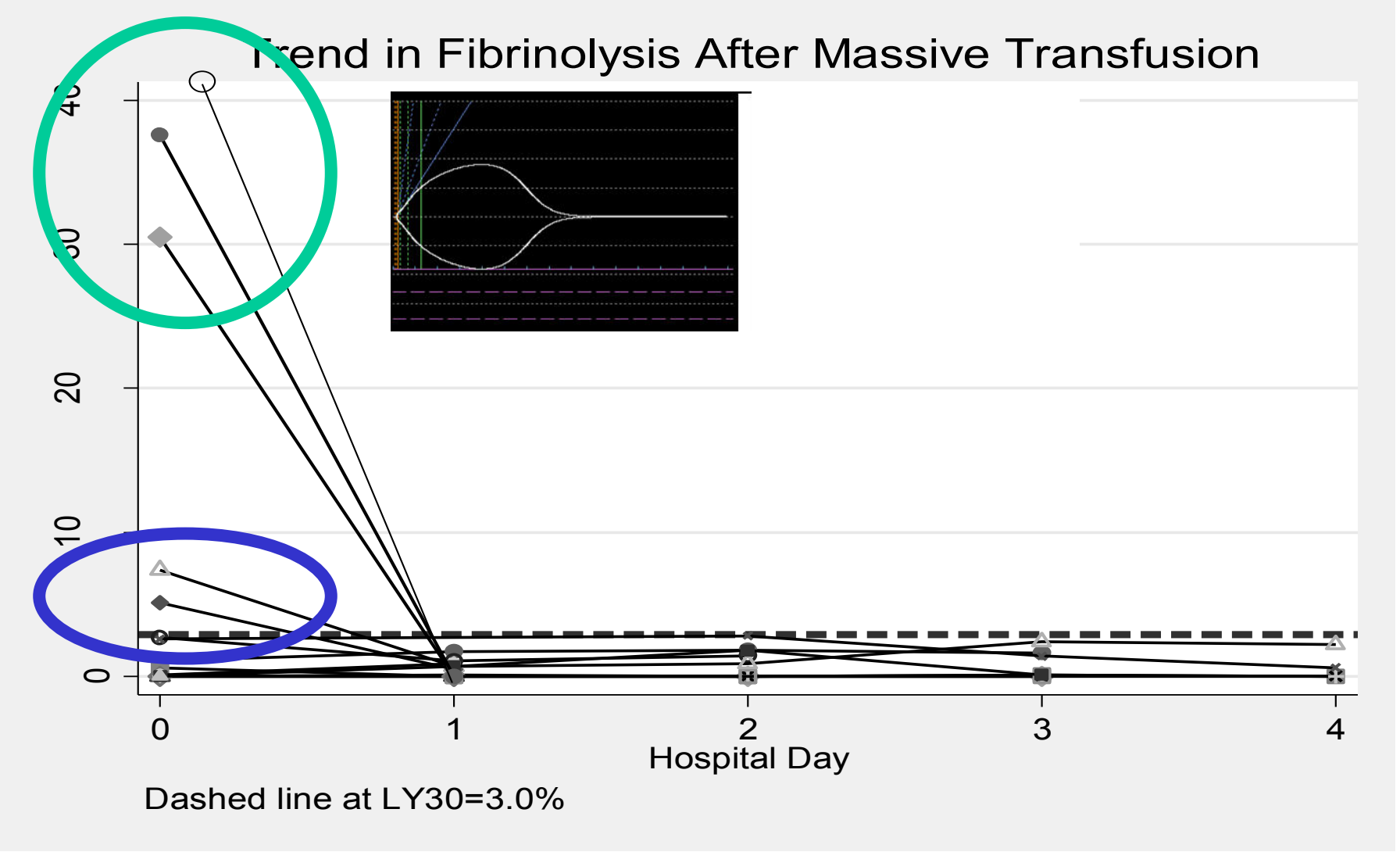
Limitation: single time point, no longitudinal data

“Late” shutdown is associated with poor outcome

- Prospective study of patients admitted to the PICU with daily TEG’s
- Remaining in shutdown OR trending to shutdown was associated with death, disability, and DVT
- Severe TBI was associated with shutdown at all times beyond admission



Hyperfibrinolysis & MTP

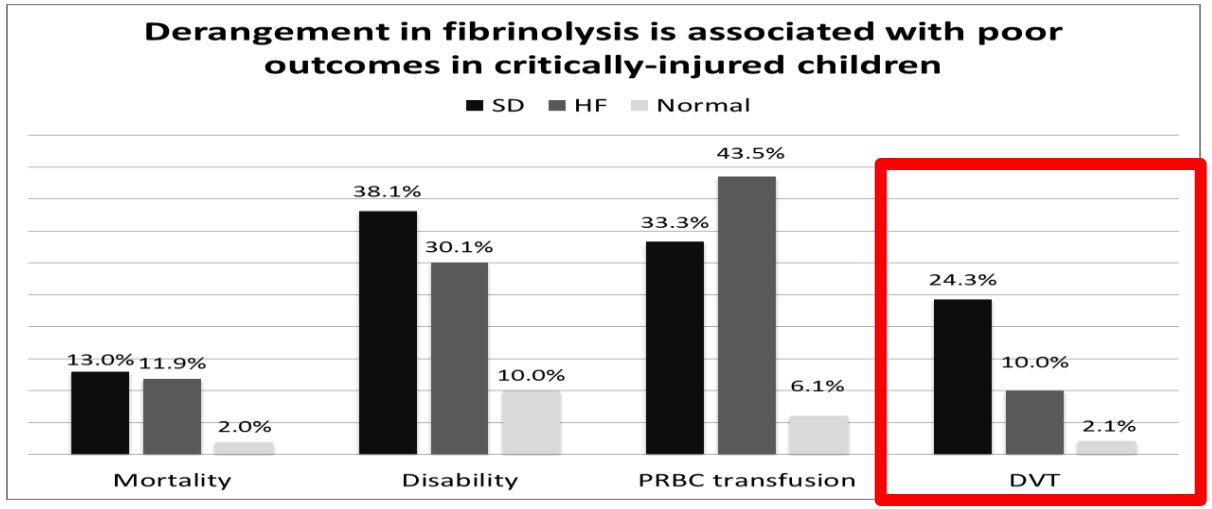


What about hypercoagulopathy???

Regression Model for Predictors of Deep Vein Thrombosis				
	Odds Ratio	95% Confidence Interval		P value
Coagulopathy	2.11	1.08	4.15	*P=0.029
Central Line	4.07	1.88	8.79	*P<0.001
Chemical paralysis	2.28	1.18	4.40	*P=0.014
Ventilator days	1.04	1.02	1.07	*P=0.003
ISS	1.03	1.01	1.06	*P=0.021
NAT	2.37	1.09	5.15	*P=0.030
Age>13	1.47	0.65	3.30	P=NS
Female sex	1.10	0.57	2.12	P=NS

Coagulopathy= INR>1.2

- Elevated admission INR associated with DVT
- Patients who ultimately develop DVT have abnormal fibrinolysis
- Shutdown is associated with DVT



Leeper, Pediatr Blood and Cancer, 2017; JTACS, 2016

Summary

- Disorders of fibrinolysis are common in injured children at time of hospital admission with a high incidence of shutdown
- Fibrinolysis shutdown is associated with poor outcome and TBI
- Extreme hyperfibrinolysis is lethal; less severe is correctable with source control and goal-directed transfusion
- Shutdown is associated with a hypercoagable state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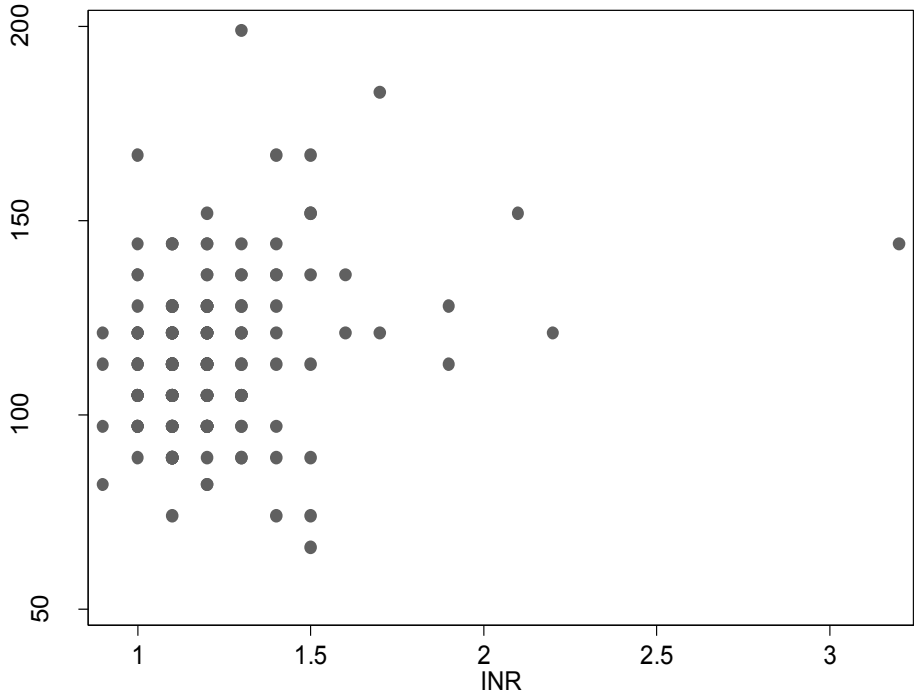
Are INR and rTEG measuring the same thing?

- INR measures the extrinsic pathway of the coagulation cascade in PLASMA. Tissue factor and calcium are added to the specimen.
- rTEG ACT measures the initiation of clotting in WHOLE BLOOD with the addition of Kaolin and tissue factor
- Prolongation of both are interpreted as representing depletion of coagulation factors

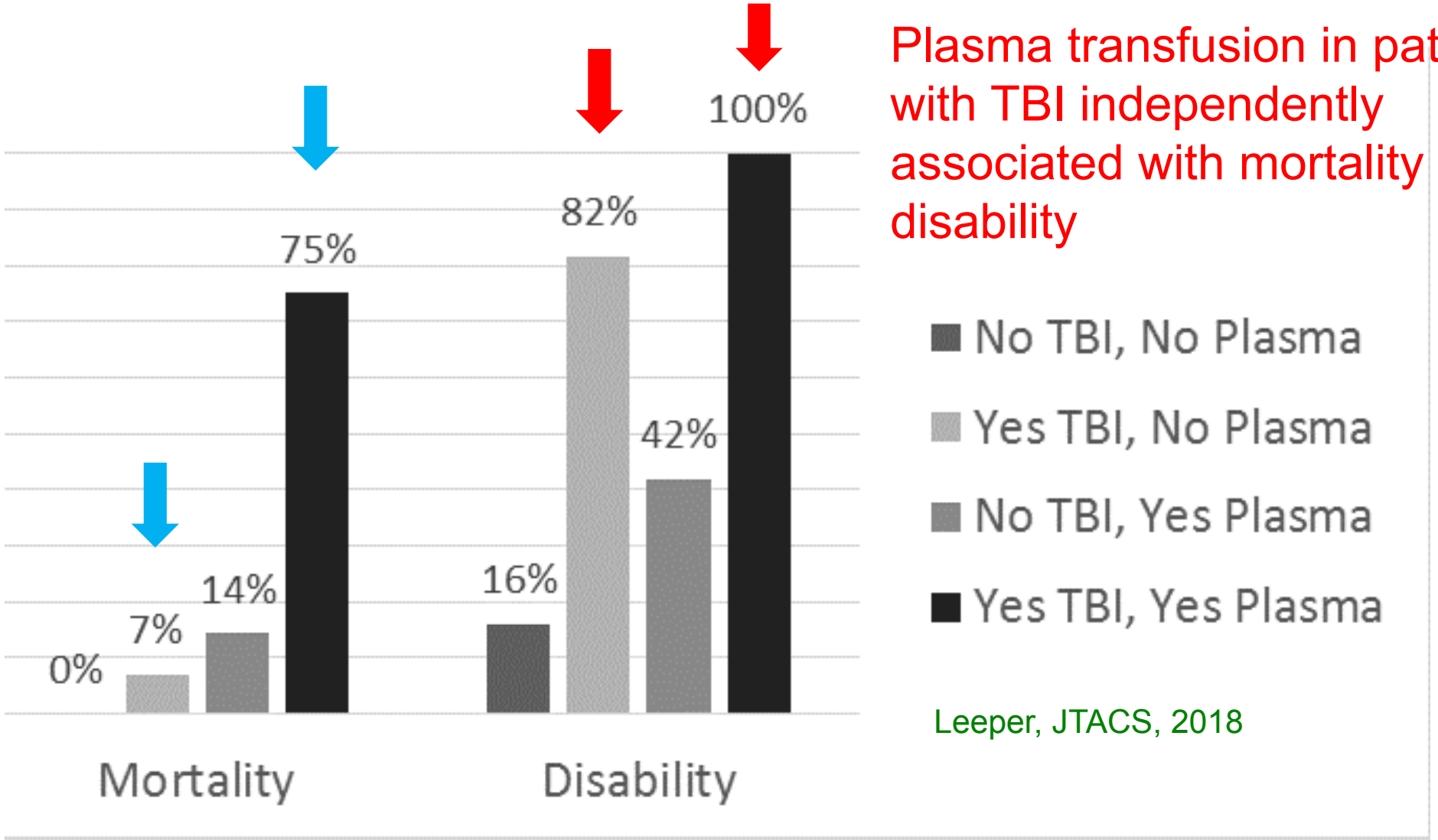
- **So maybe "FIXING" an abnormal INR with factor replacement is NOT helpful**



NO CORRELATION!!!!!

Leeper, JTACS, 2018

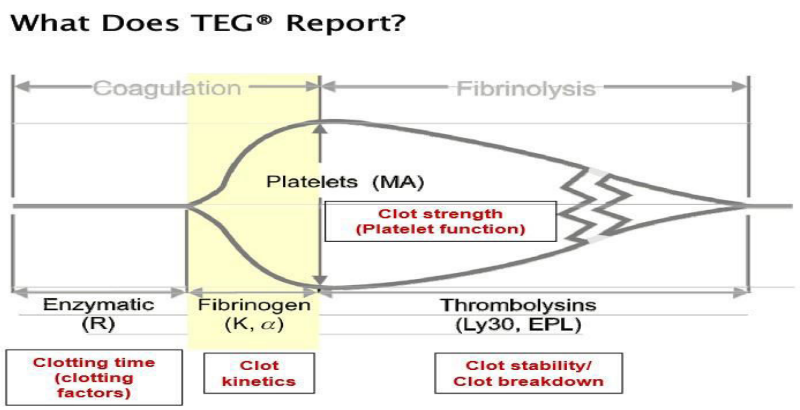
What's so bad about "fixing" the INR?Impact of plasma transfusion in TBI

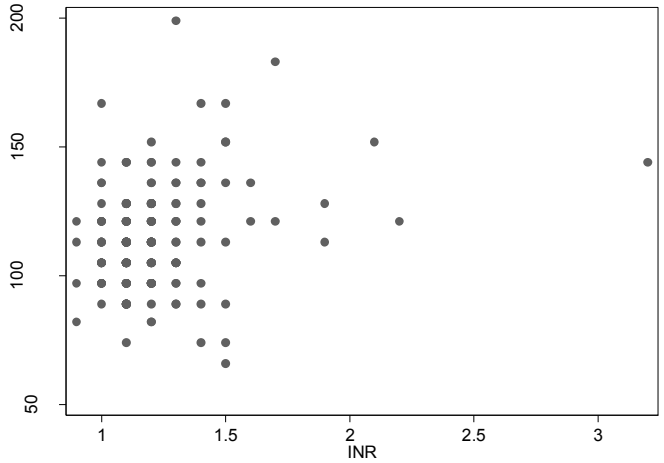


Plasma transfusion in patients with TBI independently associated with mortality and disability

Leeper, JTACS, 2018

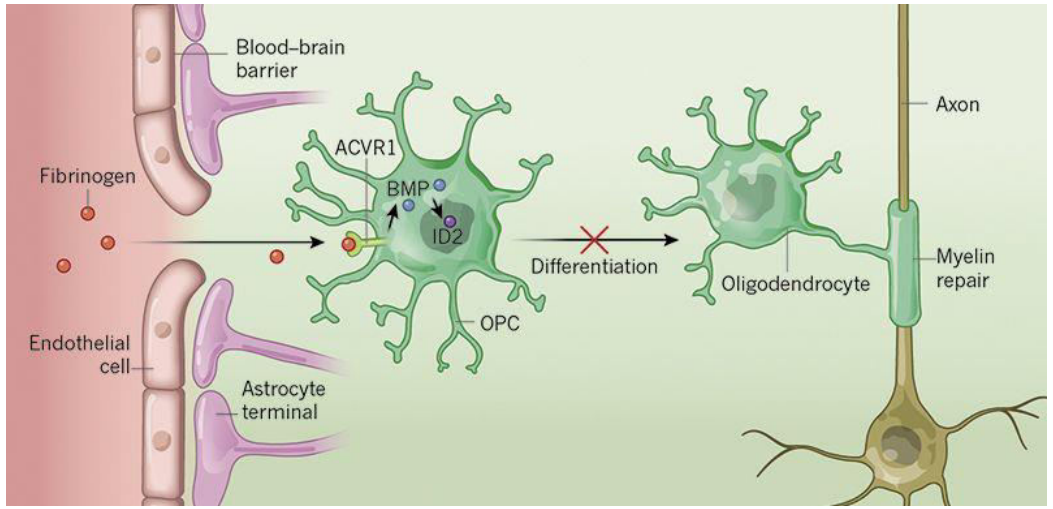
- TEG and INR are measuring different things
- Most injured children are not clinically bleeding and likely have normal levels of clotting factors, but still have laboratory abnormalities
- Elevated INR is a marker of injury severity, particularly in TBI, but not necessarily of bleeding risk or a treatment target
- Fibrinolytic shutdown is COMMON in children with TBI and correlates with poor outcome.
- Over-resuscitation is potentially harmful





Could we be HARMING patients?

- Fibrinogen has DIRECT effects on the brain
- MS literature: Fibrinogen binds to oligodendrocytes, resulting in INHIBITION of differentiation and remyelination (injury repair) Peterson, *Neuron*, 2017)
- Fibrin induces inflammation, degradation, and repair inhibition (Bardehle, *Frontiers in Cellular Neuroscience*, 2015)
- Damage to blood brain barrier (ie INJURY) allow these soluble components entry into the brain parenchyma



Nave, Ehrenreich, Nature, 2017

So maybe...fibrinolytic shutdown is an adaptive *response to disruption of the blood brain barrier designed to decrease entry of neurotoxic substances…*

The future…

- Investigation of the “endotheliopathy” of trauma in a cohort of severely injured children
- Examination of CSF
- Development of an animal model

- Overall: develop a better understanding of the links between “coagulation,” “inflammation,” and the injured brain.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Whole Blood Use for Trauma Resuscitation in Children

- Group O negative whole blood from male donors
- Low titer anti A and anti B antibodies (<50)
- Cold stored in ED refrigerator
- After 14 days, whole blood unit preprocessed to pRBC
- Limited to children ≥3years and 15kg
- Initial experience 20cc/kg, now can administer 30cc/kg
- Patients monitored closely for evidence of hemolysis

Initial WB experience

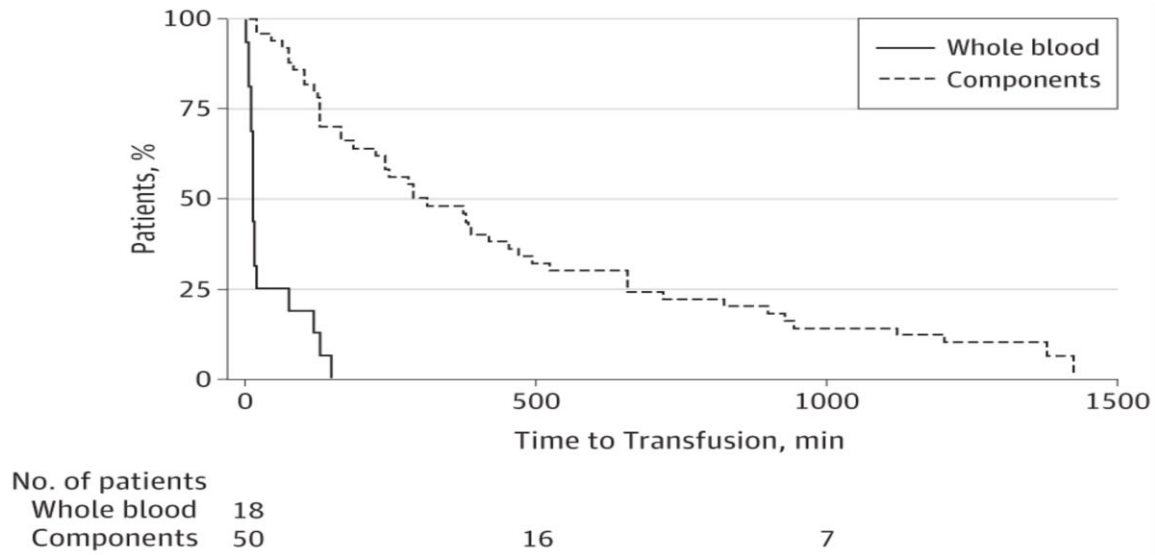
Table. Demographic and Injury Characteristics of Children Receiving Whole-Blood Transfusion[a]

Variable	All Patients (N = 18)
Patient and injury	
Age, y, median (IQR)	11 (5-14)
Sex, No. (%)	
Female	7 (39)
Male	11 (61)
Race, No. (%)	
White	15 (83)
Black	3 (17)
Mechanism of injury, %	
Blunt	14 (78)
Penetrating	2 (11)
Abusive	2 (11)
Admission GCS[7]	3 (3-15)
Injury severity score[8]	34 (26-38)
Outcome	
Mortality, No. (%)	8 (44)
Hospital length of stay, d, median (IQR)	
All patients	7.5 (3-13)
Survivors	13 (9-14)
ICU Length of stay, d, median (IQR)	3.5 (2-6)
Time receiving mechanical ventilation, d, median (IQR)	2 (1-5)

Abbreviations: GCS, Glasgow coma scale; ICU, intensive care unit; IQR, interquartile range.

[a] Use of whole blood is restricted to patients aged ≥3 years and weighing ≥15 kg.

Leeper, *JAMAPeds*, 2018



- Severely injured cohort
- Significantly shortened time to administration of all three blood products (compared to historical controls)
- No evidence of hemolysis

Acknowledgement

Christine Leeper, MD, MS