THE UNIVERSITY OF NEW MEXICO

HEALTH SCIENCES

Therapeutic Plasma Exchange for Trauma-Induced Coagulopathy

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Disclaimers

Consultant/Speaker

- Sanofi Genzyme

Board of Directors

- American Society for Apheresis

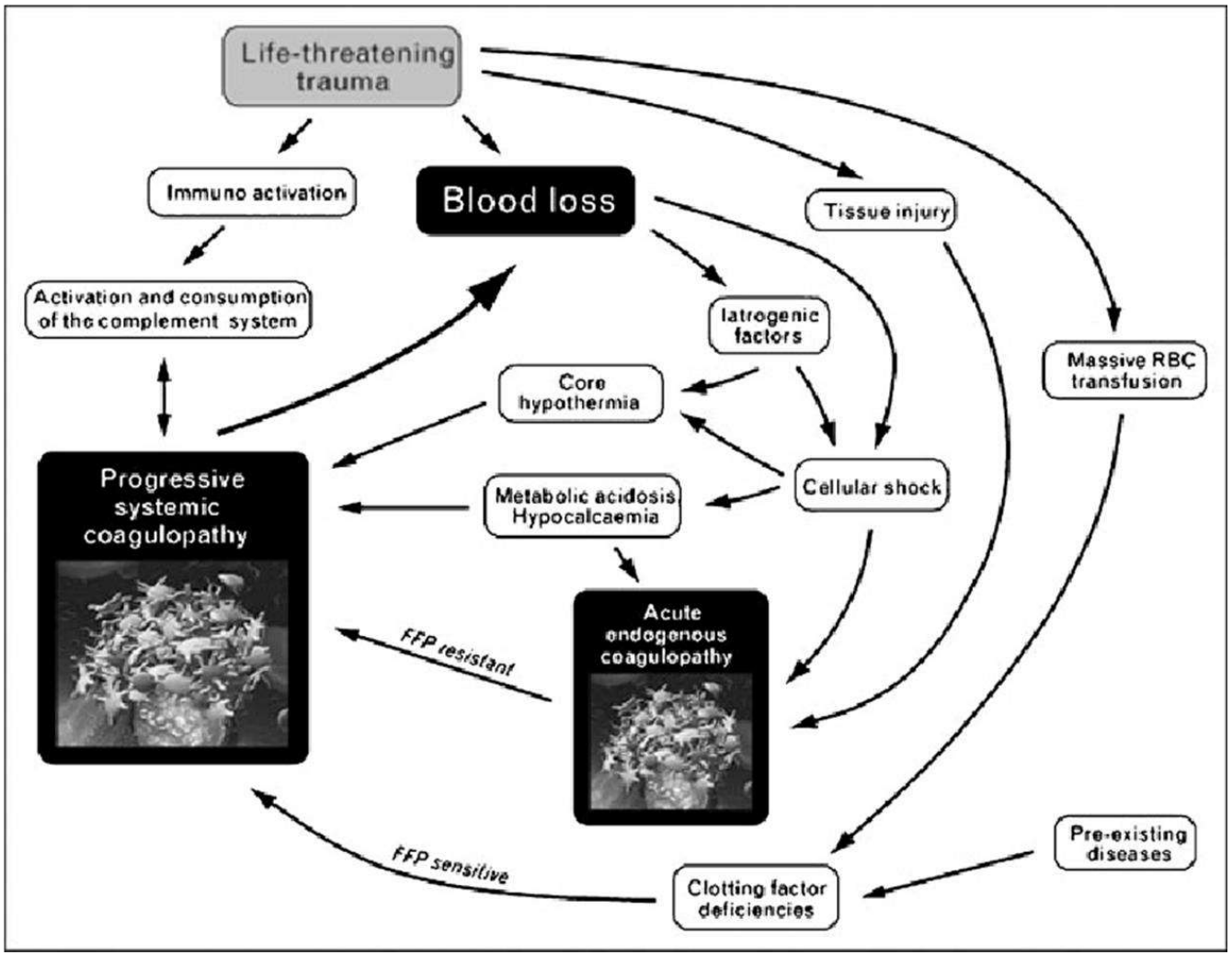
Trauma-Induced Coagulopathy

No standard definition of TIC

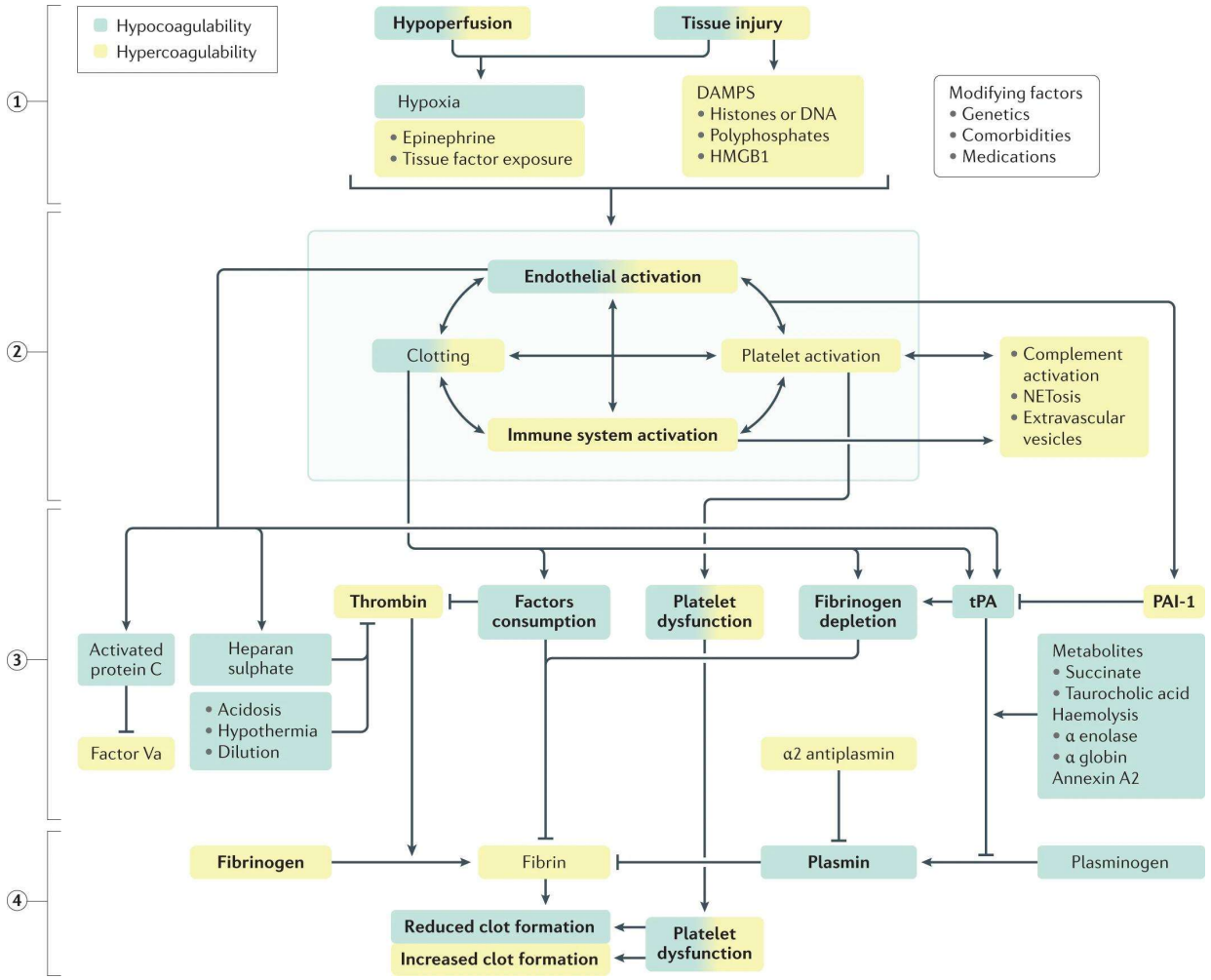
- Refers to abnormal coagulation capacity attributable to trauma

Multiple contributing factors

- Hemorrhagic shock
- Tissue injury
- Endothelial dysfunction
- Platelet dysfunction
- Inappropriate thrombin generation
- Fibrinogen depletion
- Dysregulated fibrinolysis



Gonzalez E et al, Semin Thromb Hemost 2010



Moore EE et al, Nat Rev Dis Primers 2021

Challenge in Treating TIC: It's a classic complex system

"A system that is intrinsically difficult to model due to the dependencies, competitions, relationships, or other types of interactions between its parts and/or between a given system and its environment"

- Complicated, multi-step pathophysiology
- Polyfactorial
- Contributions of different pathologic elements variable
- Relationships range from independent to highly inter-dependent
- Clinical effects are severe
- Spans full spectrum of hemostatic phenotypes: bleeding, thrombotic, or mixed
- Treatment protocols heterogeneous
- Influence of pre-trauma state: comorbidities, medications, genetics
- Modifying any single pathologic element unlikely to reverse TIC

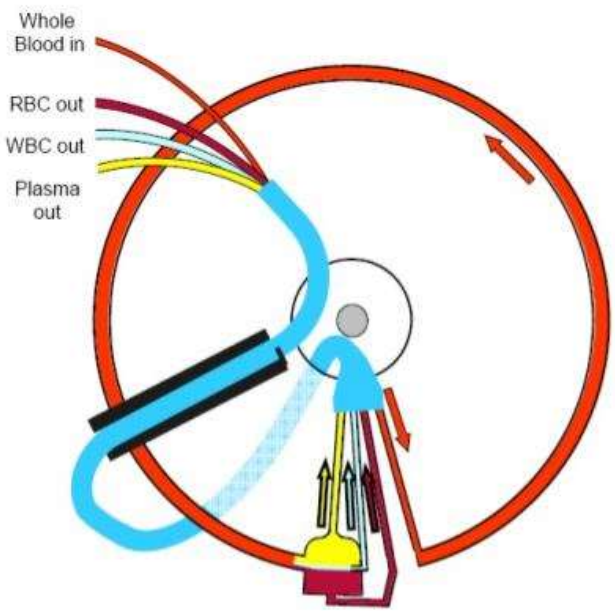
Therapeutic Plasma Exchange (TPE)

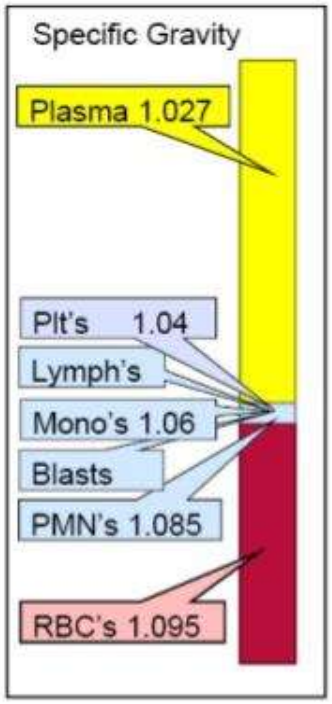
Extracorporeal technology to efficiently and euvolemically remove/replace plasma

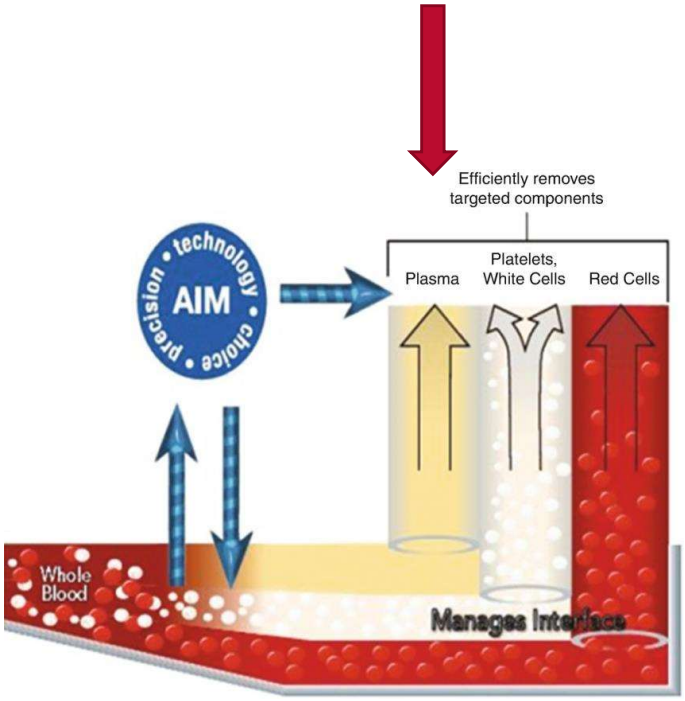
Donor plasma as a replacement fluid selected intentionally has benefits
- Normal concentrations of all pro- and anti-coagulation factors and enzymes
- No abnormal compounds (DAMPs, metabolites, hormones, or other pathologic substances)
- Routinely used in treating conditions w/ coagulopathies (TTP, CAPS, TAMOF a/w sepsis, etc)

Exquisite safety profile in a variety of settings
- Critical illness
- Pregnancy
- Pediatrics and adults
- Medical
- Surgical

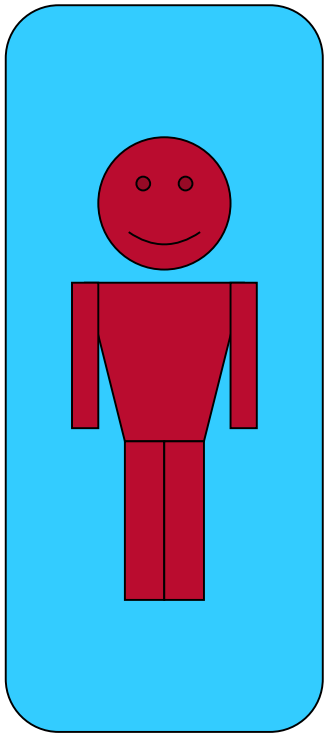
Highly non-specific technology
- All elements within plasma removed



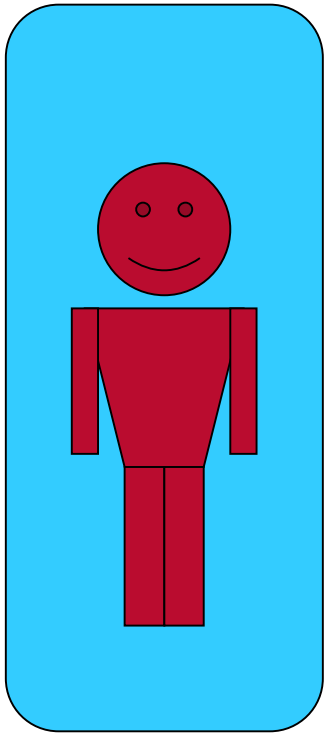


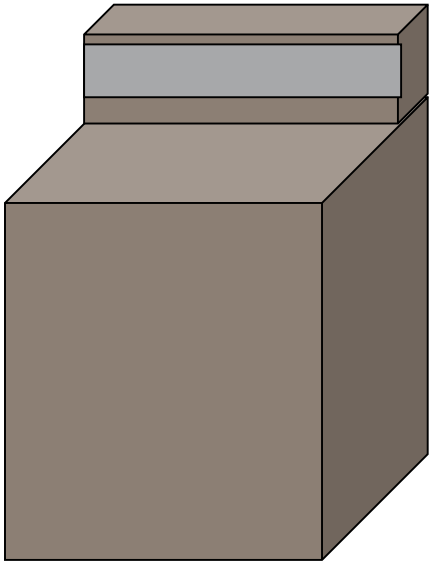


Courtesy Drs. Sergio Torloni and David Ward

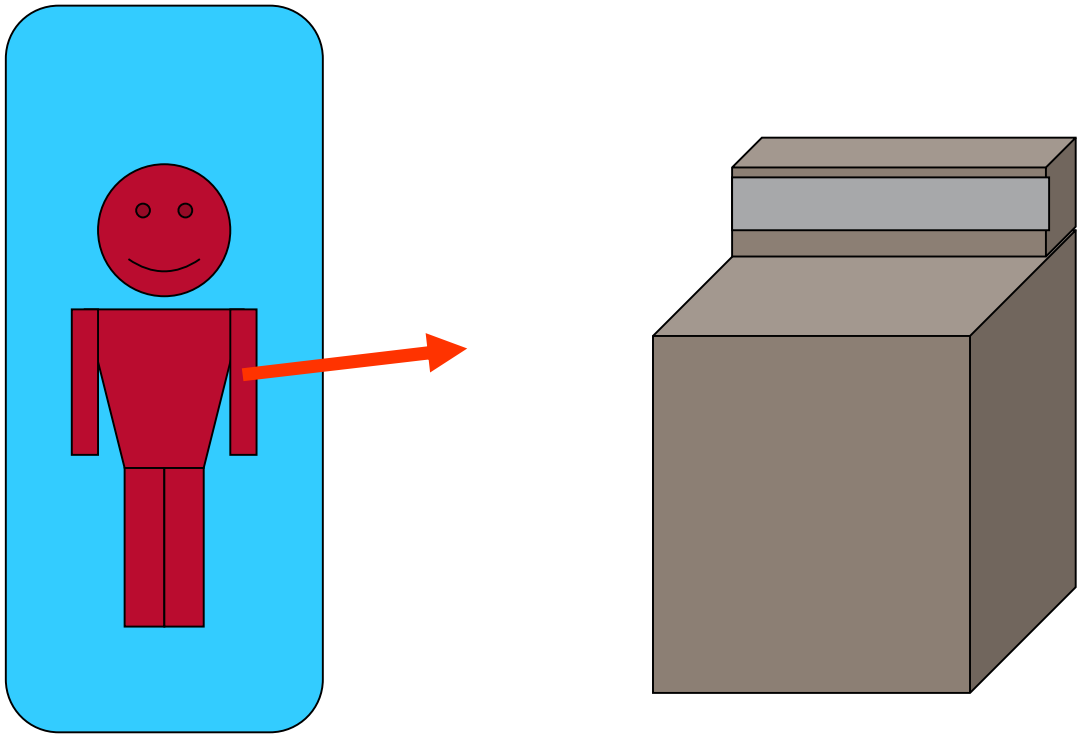


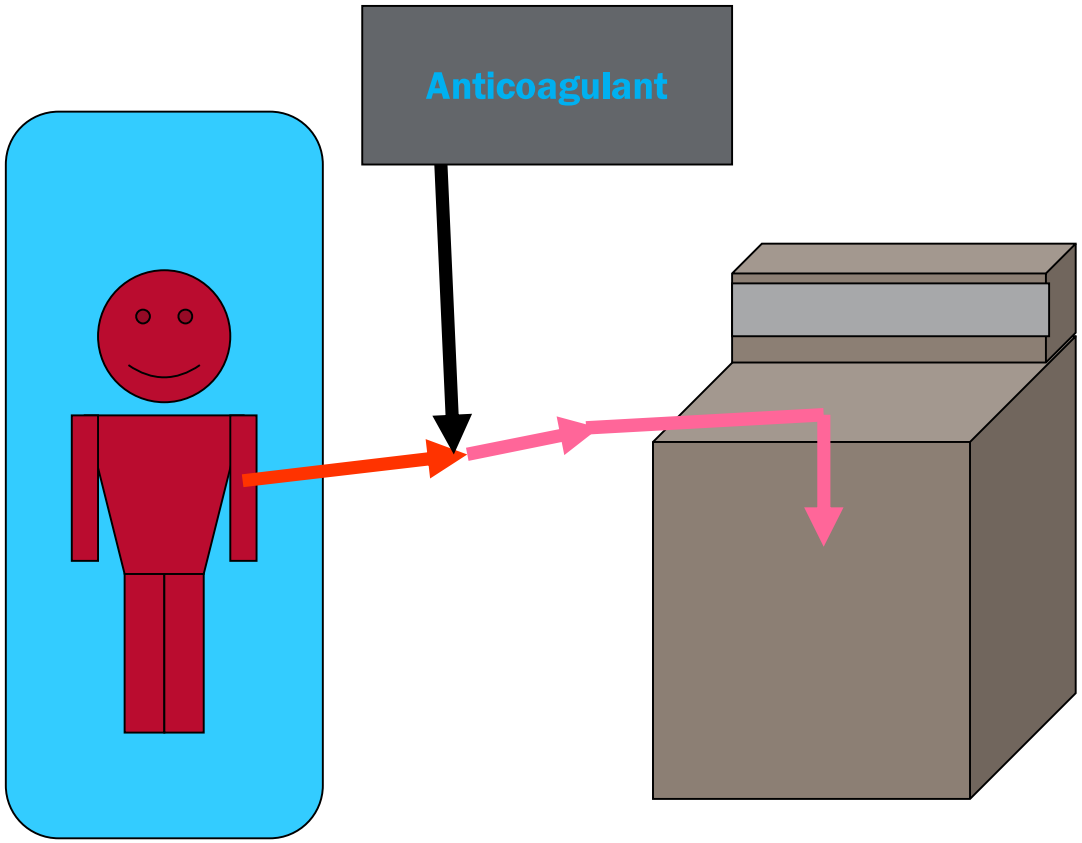
Patient

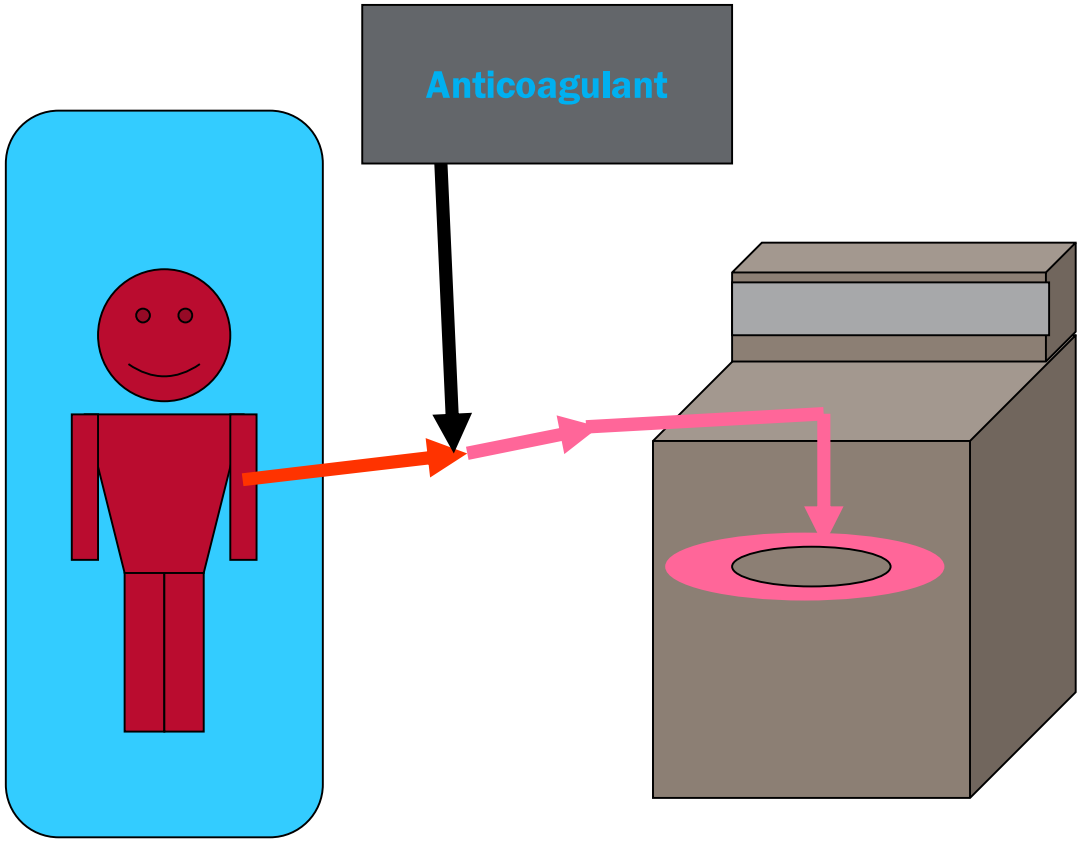




Apheresis Instrument




Anticoagulant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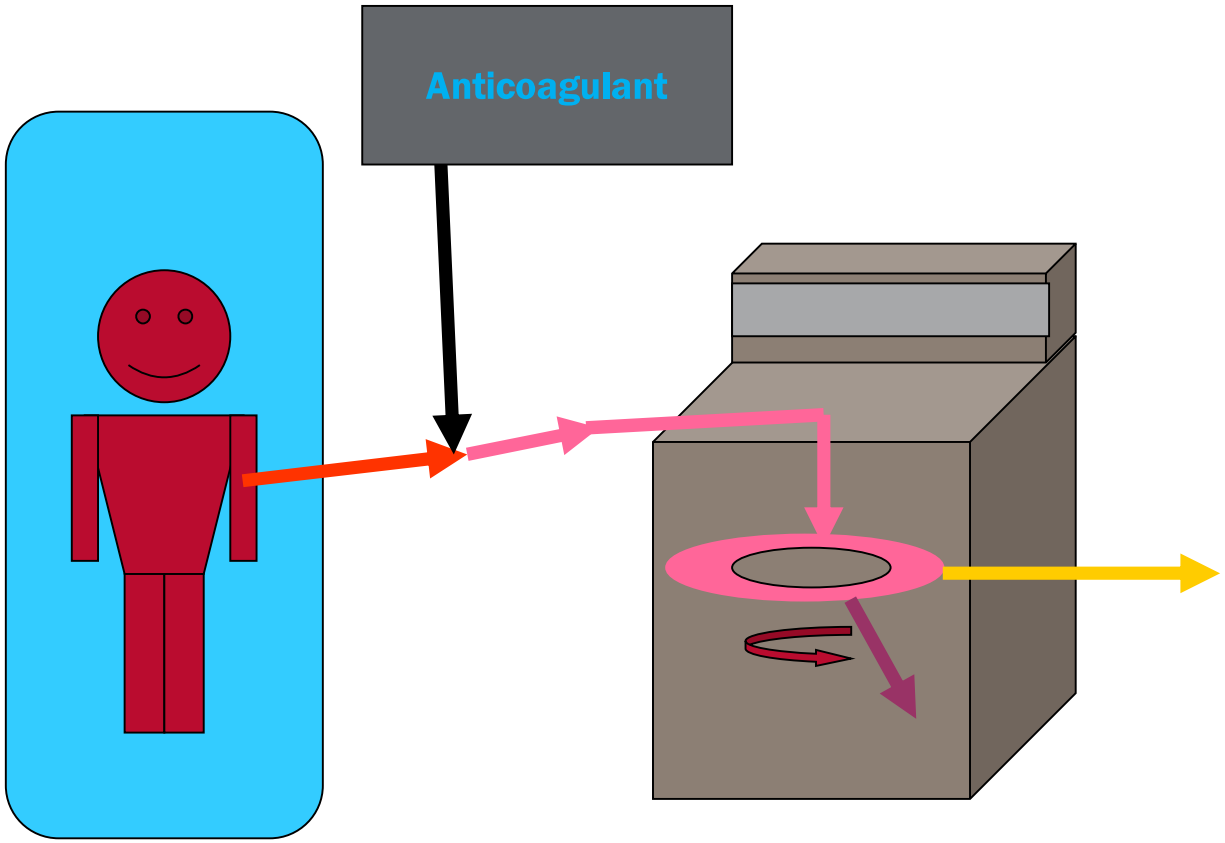
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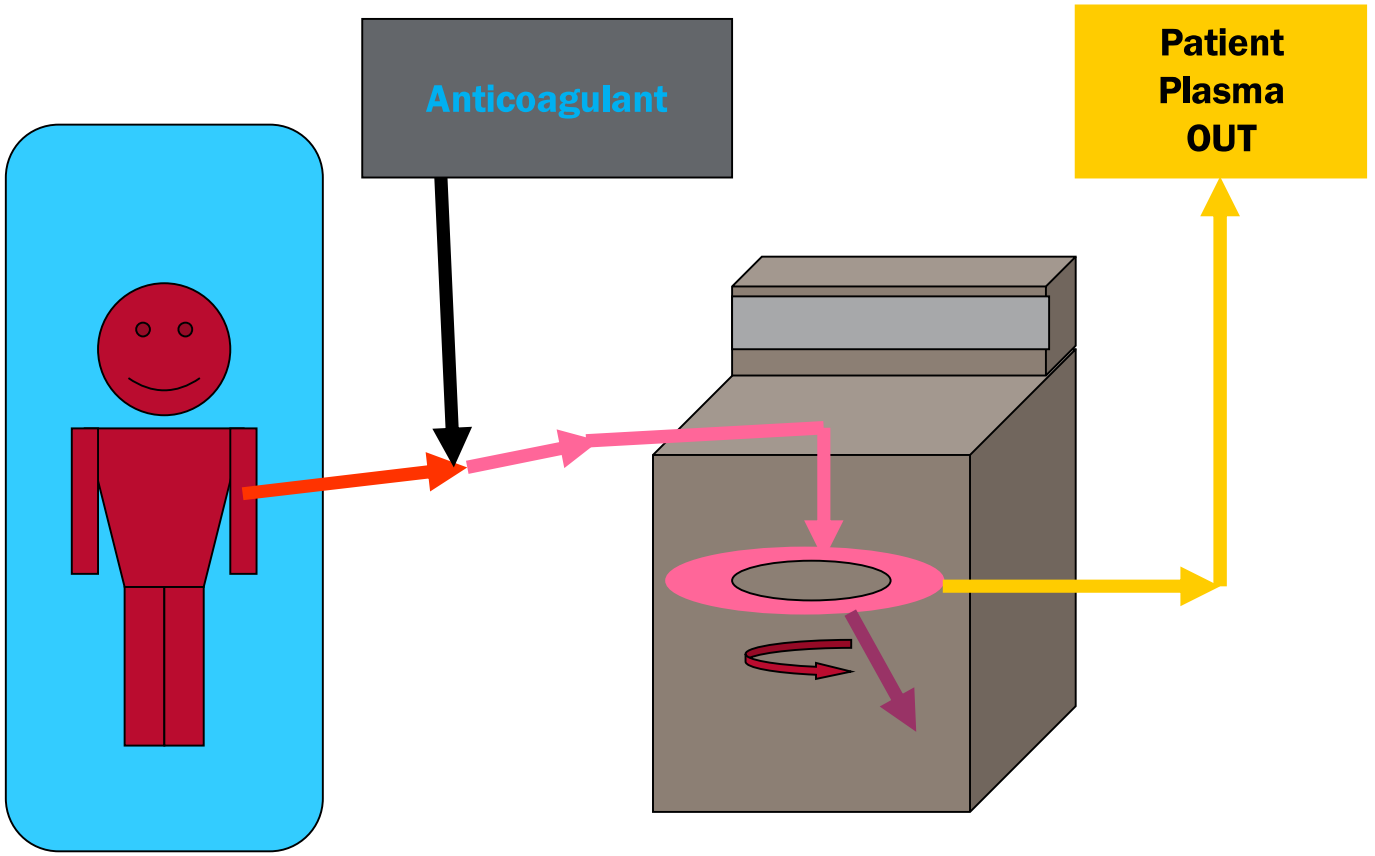
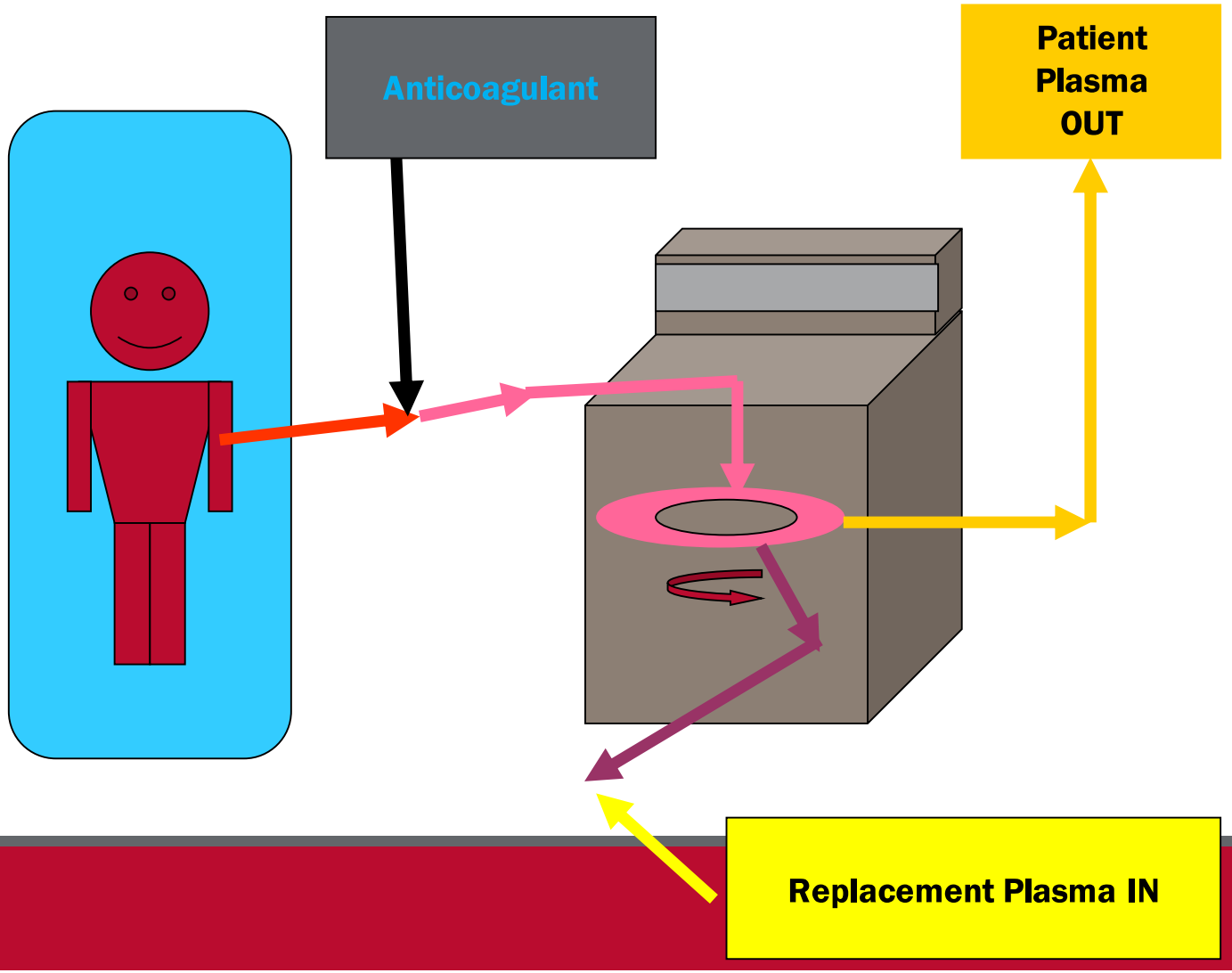
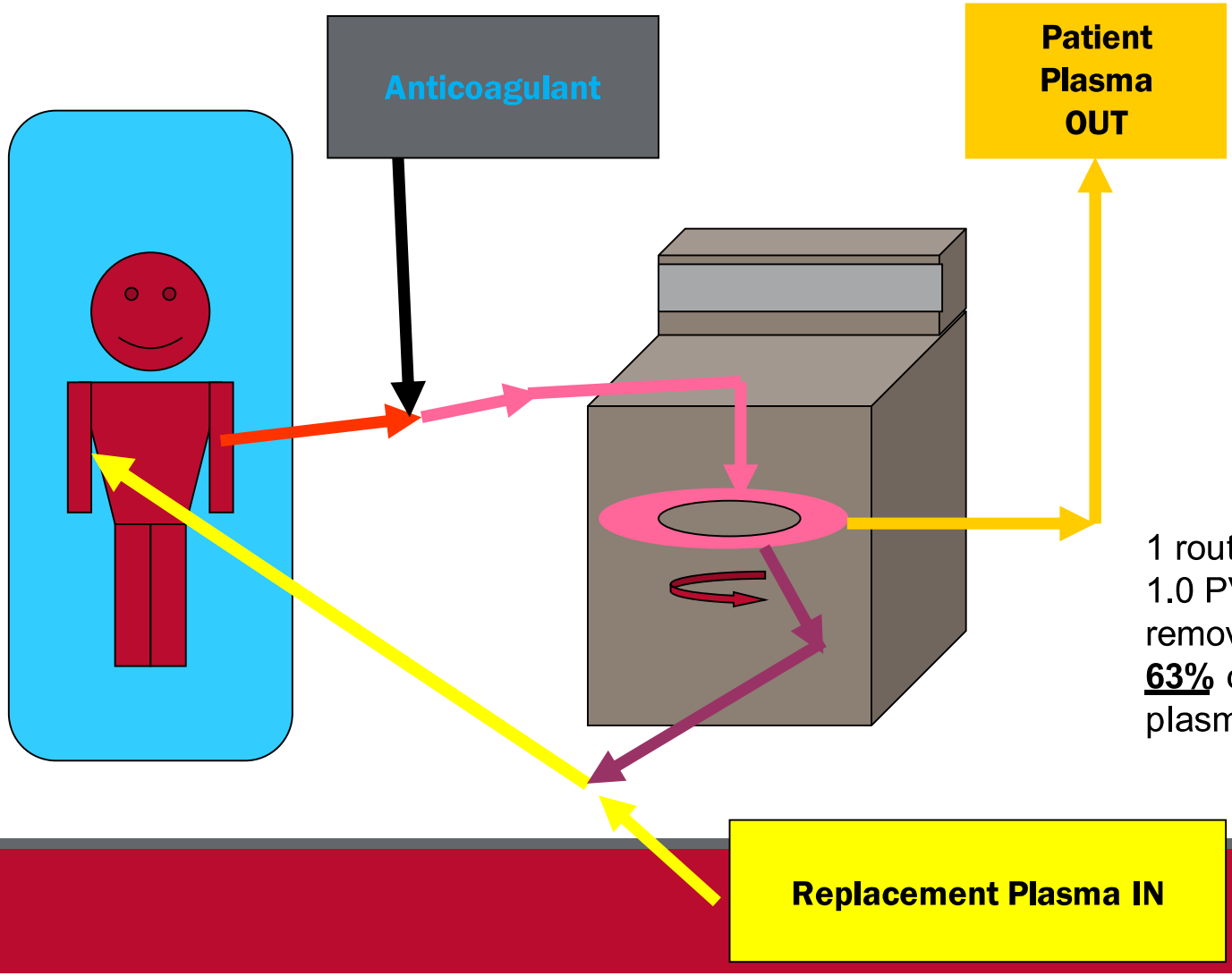
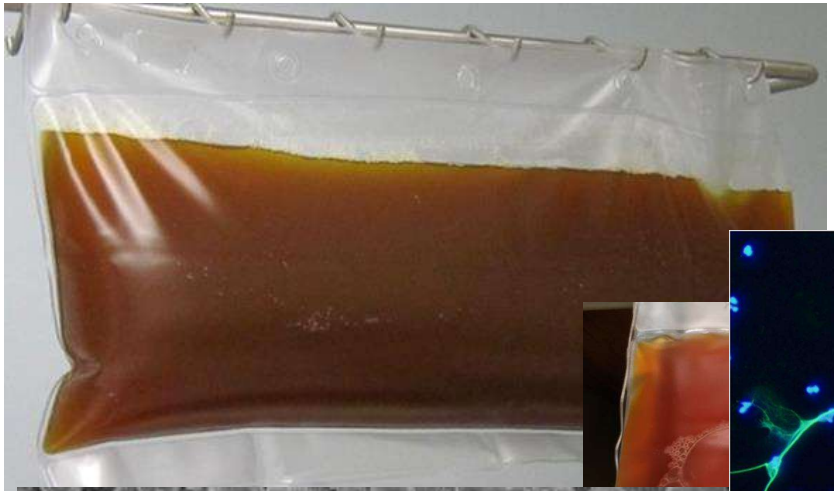
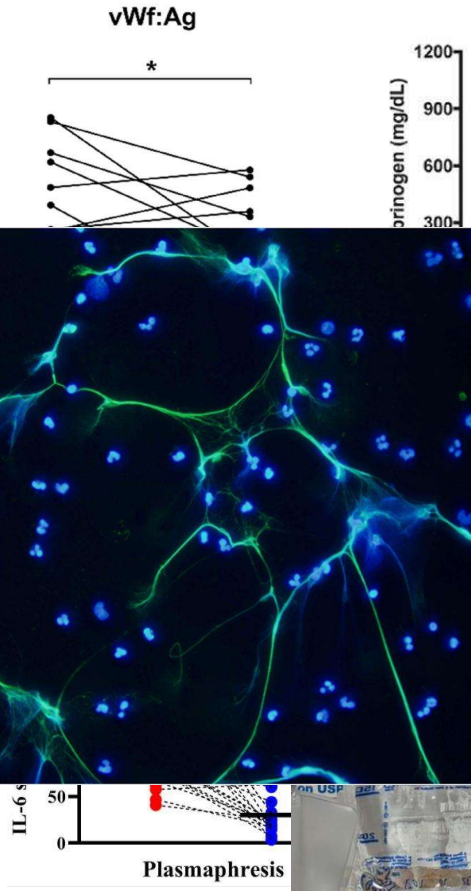

Anticoagulant
Patient
Plasma
OUT

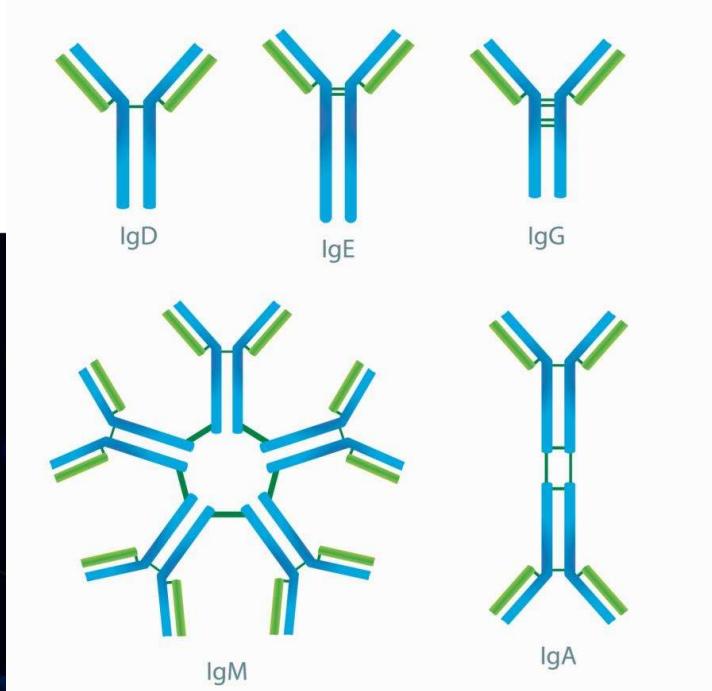

Anticoagulant
Patient
Plasma
OUT
Replacement Plasma IN

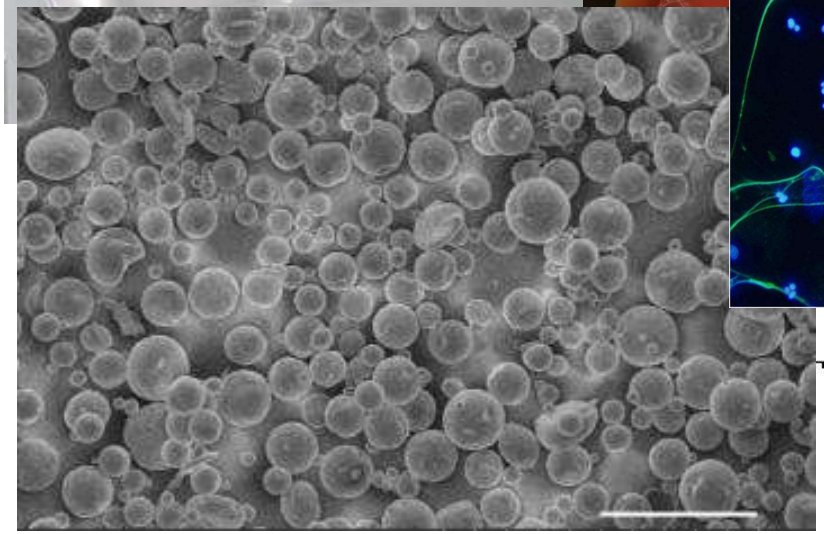


1 routine TPE = 1.0 PV that removes/replaces **63%** of pre-existing plasma in patient









Awai H et al, Crit Care Med 1998; Raval JS et al, J Clin Apher 2012; Truong AD et al, Transfusion 2021; Hashemian SM et al, Pulmonology 2021; Hassaniazad M et al, Resp Med 2021; Kaplan MJ et al, J Immunol 2012, Willerth S, Engineering Neural Tissues from Stem Cells 2017

Conditions in the ASFA Guidelines with Coagulopathy, Inflammation, Endotheliopathy, and/or MODS

Acute liver failure

Burn shock resuscitation

Catastrophic antiphospholipid syndrome

Coagulation factor inhibitors

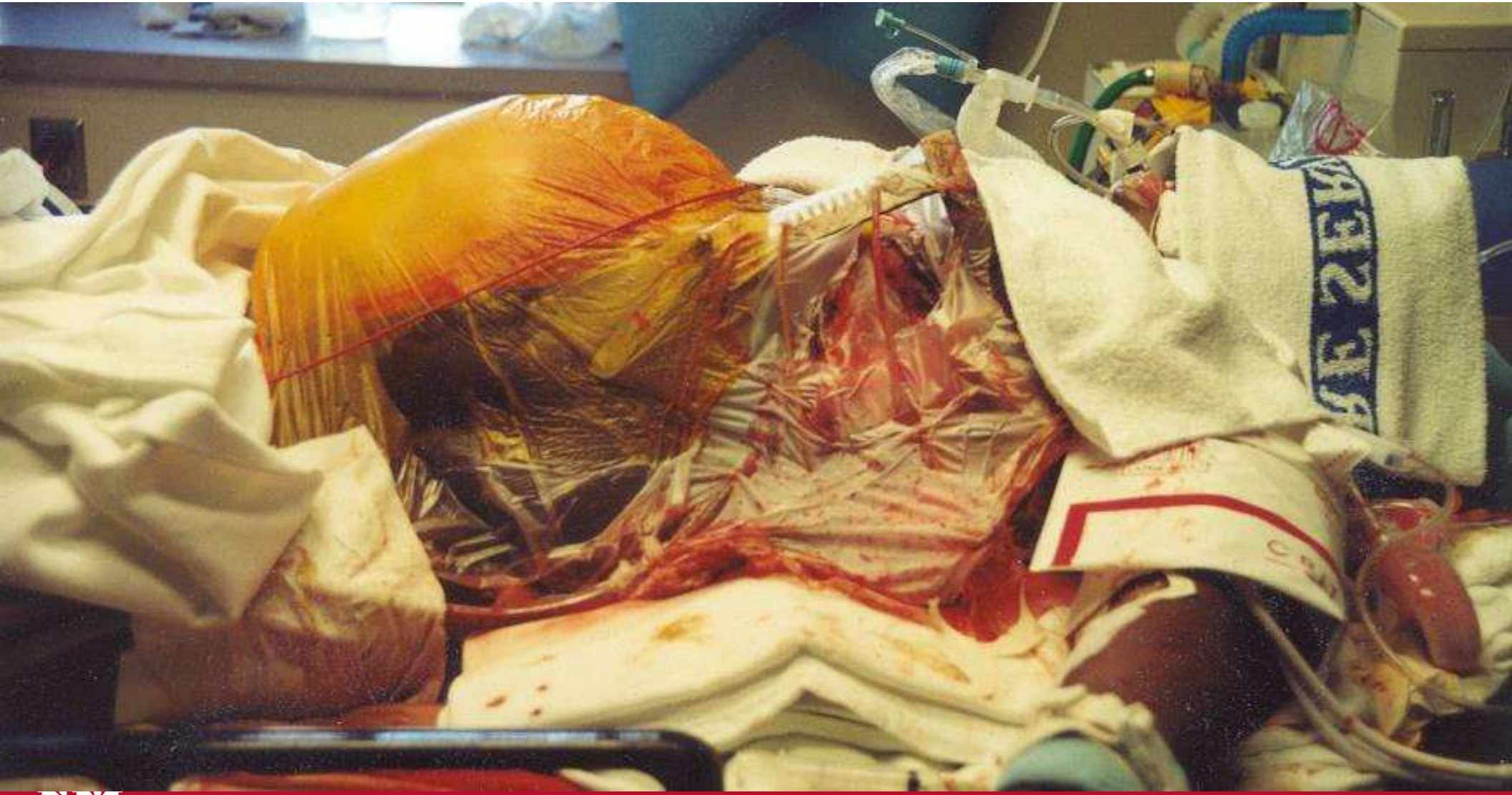
HELLP syndrome

HLH/Macrophage activation syndrome

HIT

Sepsis w/ multiorgan failure

TMA (mediated by complement, coagulation factors, drugs, infection, transplant, TTP)



Courtesy Dr. Macky Neal

Sentinel Event

INITIAL PRESENTATION

22 YO M trauma patient
- MVC, unrestrained driver, ejected from vehicle
- ISS 41

3 rounds of blood products via MTP in OR
- Hemorrhage successfully controlled

Transferred to TSICU

IN THE FOLLOWING 24 HOURS

Shock, profoundly hypocoagulable
- Hyperfibrinolysis, thrombocytopenia, INR ≥2.2
- Hypotensive on 3 vasopressors, AKI
- Numerous pharmaceutical adjuncts administered (including TXA, aFVII)

16 units plasma, 5 units platelets transfused
- Minimal surgical blood losses

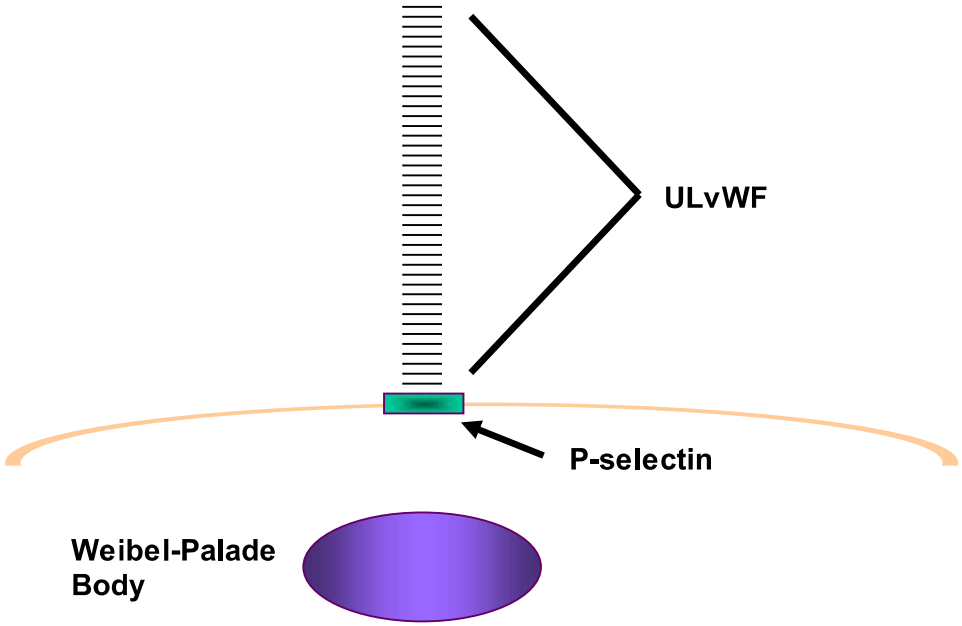
Developed transfusion associated circulatory overload (TACO, i.e., volume overload)
- Diuresis, then CRRT to manage fluid balance while transfusing plasma/platelets

Died of injuries on POD #3

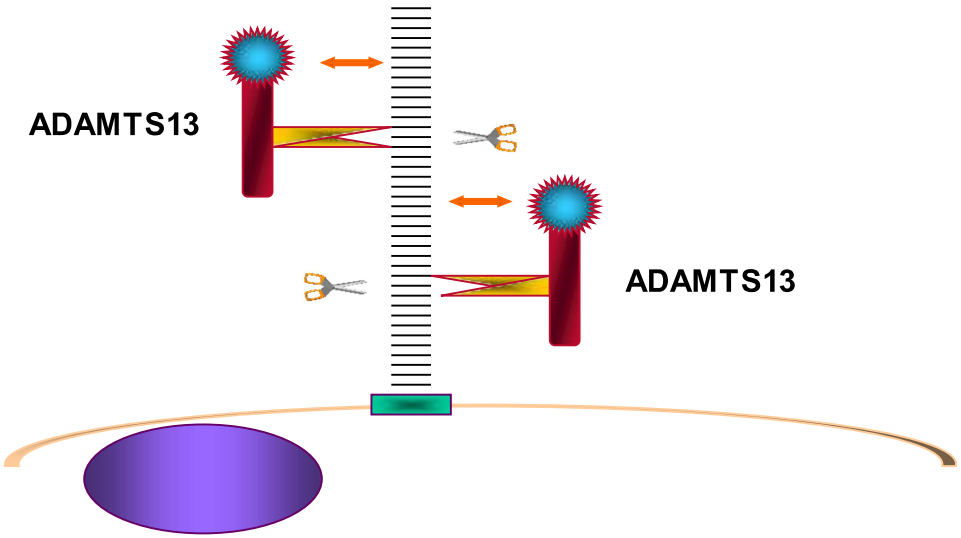
TABLE III. Modified McLeod's Criteria for Evaluation of Therapeutic Apheresis Efficacy [9]

Evidence	McLeod's criteria	Explanation
Mechanism	"Plausible Pathogenesis"	The current understanding of the disease process supports a clear rationale for the use of therapeutic apheresis modality.
Correction	"Better Blood"	The abnormality, which makes therapeutic apheresis plausible, can be meaningfully corrected by its use.
Clinical Effect	"Perkier Patients"	There is a strong evidence that therapeutic apheresis confers benefit that is clinically worthwhile, and not just statistically significant.

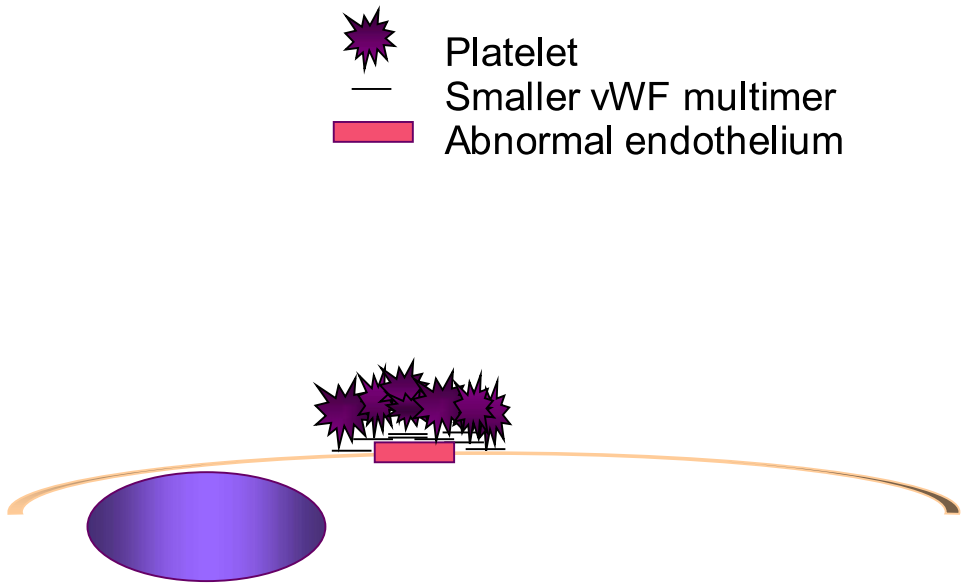
Normal vWF Processing Activity



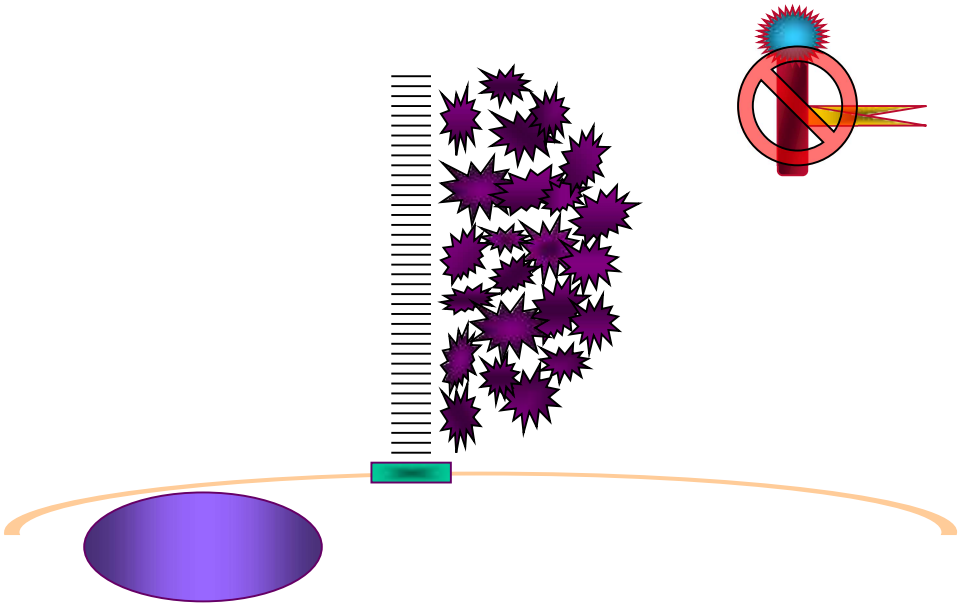
Normal vWF Processing Activity



Normal vWF Processing Activity



ADAMTS13 Deficiency Pathophysiology (TTP, TAMOF)



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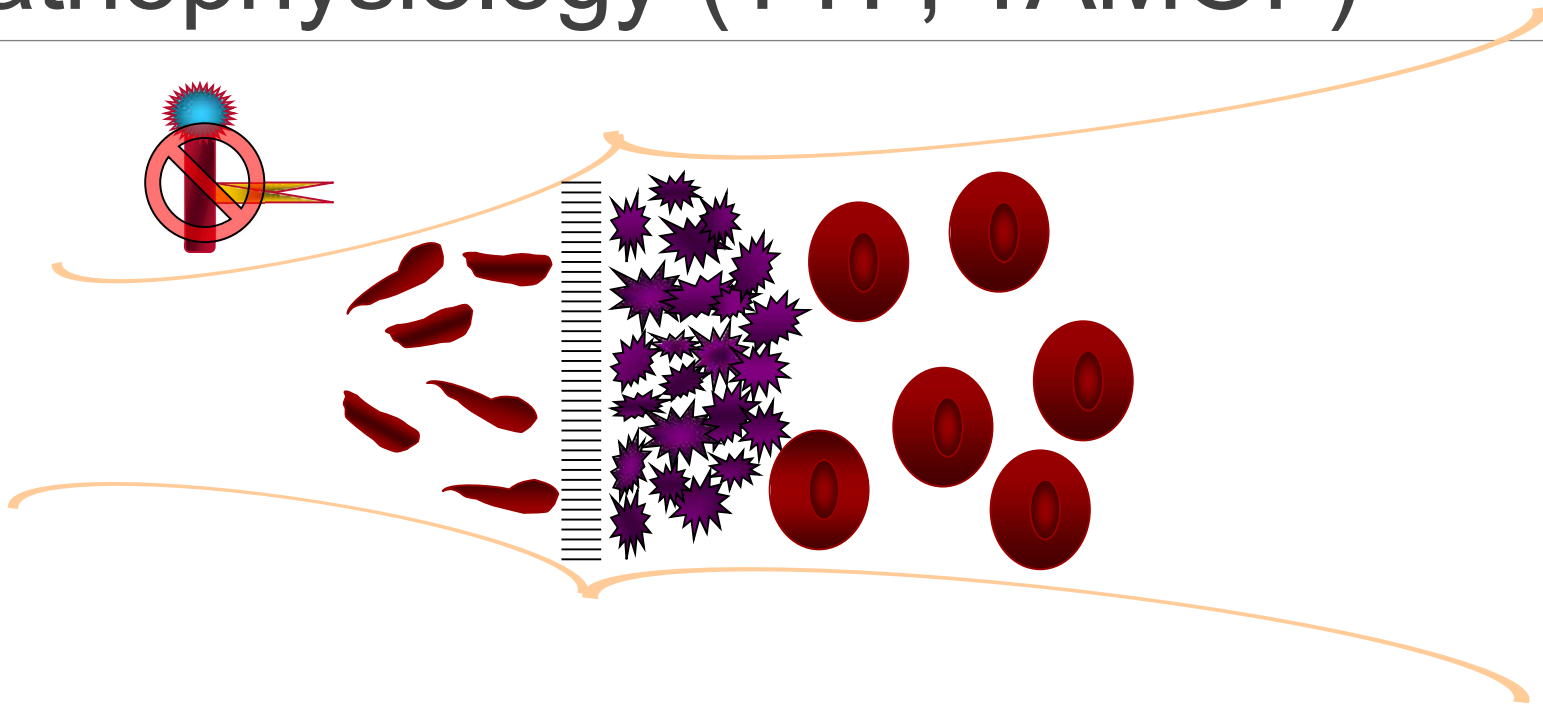
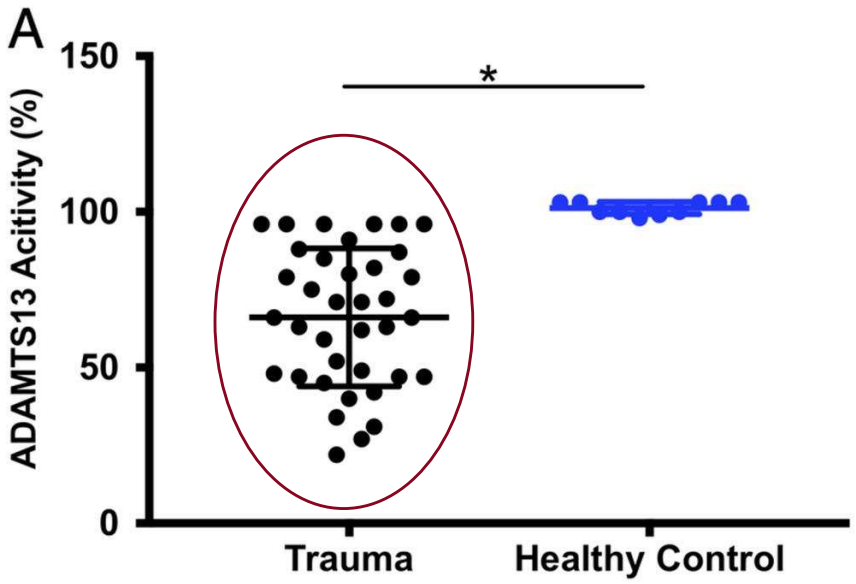
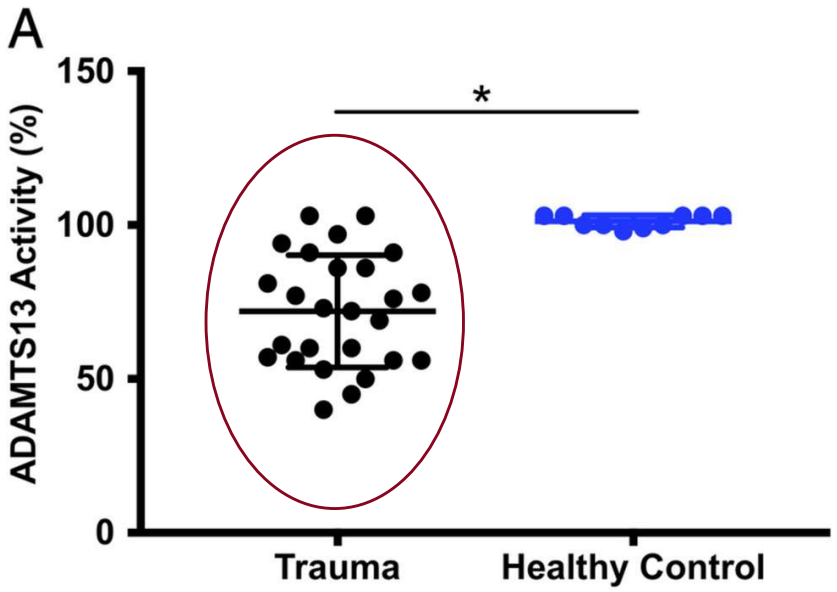


ADAMTS13-vWF-Platelet Axis Dysregulation

T+0 HRS AFTER TRAUMA



T+24 HRS AFTER TRAUMA



Dyer MR et al, Transfusion 2020

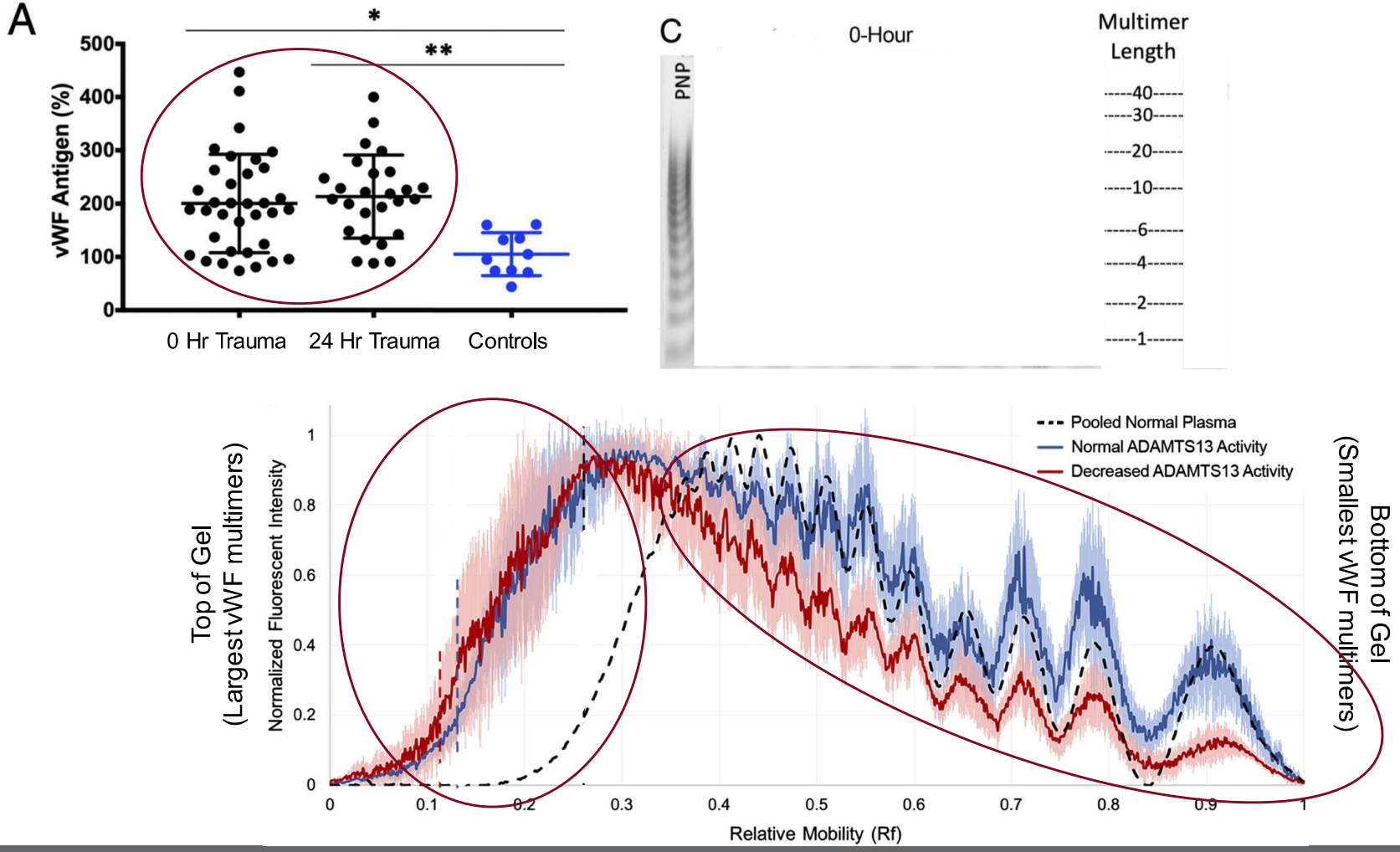
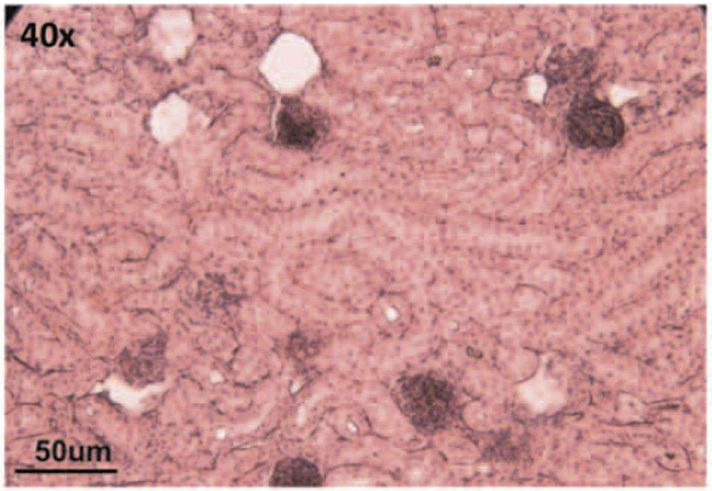
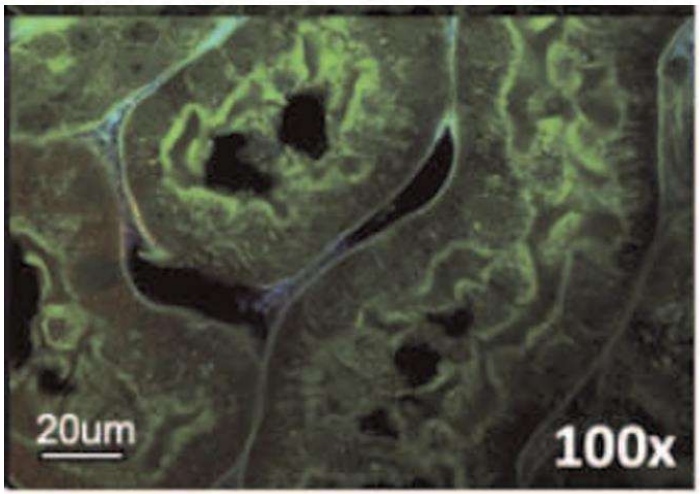

A
*
**
vWF Antigen (%)
500
400
300
200
100
0
0 Hr Trauma
24 Hr Trauma
Controls
C
0-Hour
PNP
Multimer Length
-----40-----
-----30-----
-----20-----
-----10-----
------6------
------4------
------2------
------1------
Pooled Normal Plasma
Normal ADAMTS13 Activity
Decreased ADAMTS13 Activity
Top of Gel
(Largest vWF multimers)
Normalized Fluorescent Intensity
Bottom of Gel
(Smallest vWF multimers)
Relative Mobility (Rf)

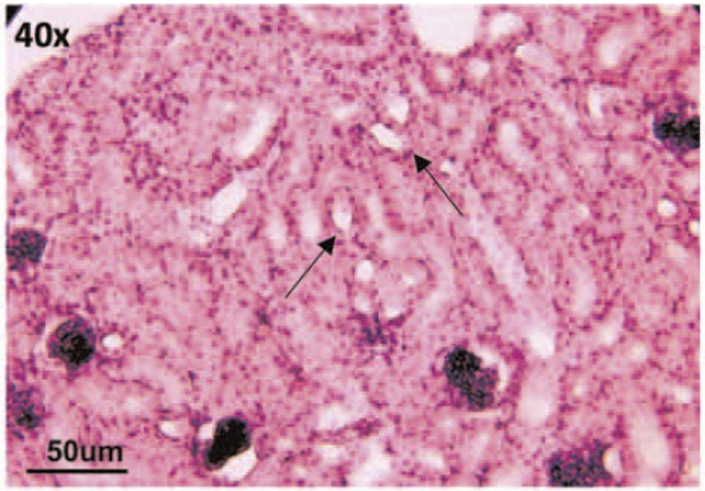
TABLE 2. ADAMTS13 correlates with laboratory and clinical markers of coagulopathy

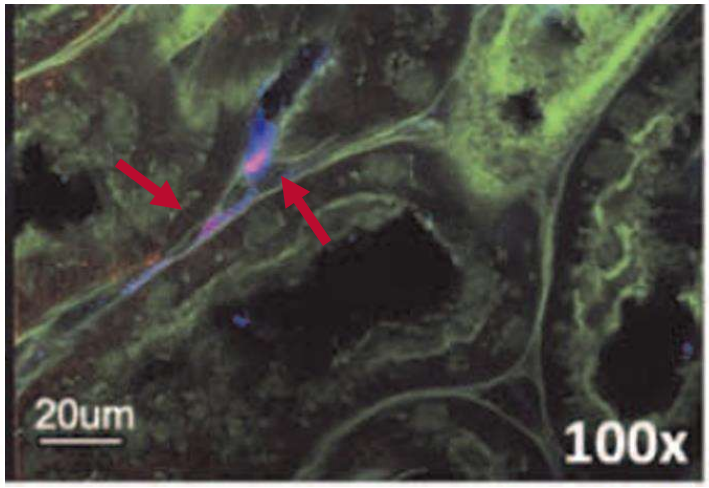
Variable	ρ	p value
INR	−0.63	<0.001
TEG-activated clotting time	−0.36	0.044
TEG maximum amplitude	0.36	0.047
24-hour blood product requirement	−0.45	0.008
24-hour RBC requirement	−0.43	0.011
24-hour PLT requirement	−0.34	0.049
24-hour plasma requirement	−0.45	0.007
ISS	−0.34	0.043

Healthy Kidney









Trauma Kidney

TPE Protocol for Trauma Patients

Strong multidisciplinary desire to implement TPE-based strategy

- TPE was viewed favorably since critically ill patients routinely treated with this technology
- Euvolemically replacing 63% of patient plasma w/ healthy donor plasma highly appealing
- Compelling findings from the Neal Research Lab

Potential patients must have

- Traumatic Injury + TIC ± SIRS
- Surgical/mechanical control of hemorrhage
- Mechanical ventilation + vasopressor requirement
- Plasma, platelet, and/or cryoprecipitate transfusion dependence
- Persistence of platelet count <150,000/μL AND/OR laboratory evidence of coagulopathy

TPE Protocol for Trauma Patients

Apheresis specifics

- TPE #1 initiated within 12 hrs of consult; ADAMTS13 activity and IL-6 collected
- **Vascular access**: Non-tunneled double lumen dialysis catheter or use other extracoporeal circuit
- **Perform TPE procedures once-daily x 3** (95% of native plasma removed after 3 TPE)
- **Plasma exclusive replacement fluid** (mean 3.5 L or 14 units plasma per procedure)
- Citrate anti-coagulation: Monitor Ca^{2+} and correct prn (in addition to maintenance IV calcium)
- Patients on vasopressors and/or inotropes may require infusions to be increased during TPE
- May perform up to additional 3 procedures if requested

Outcomes

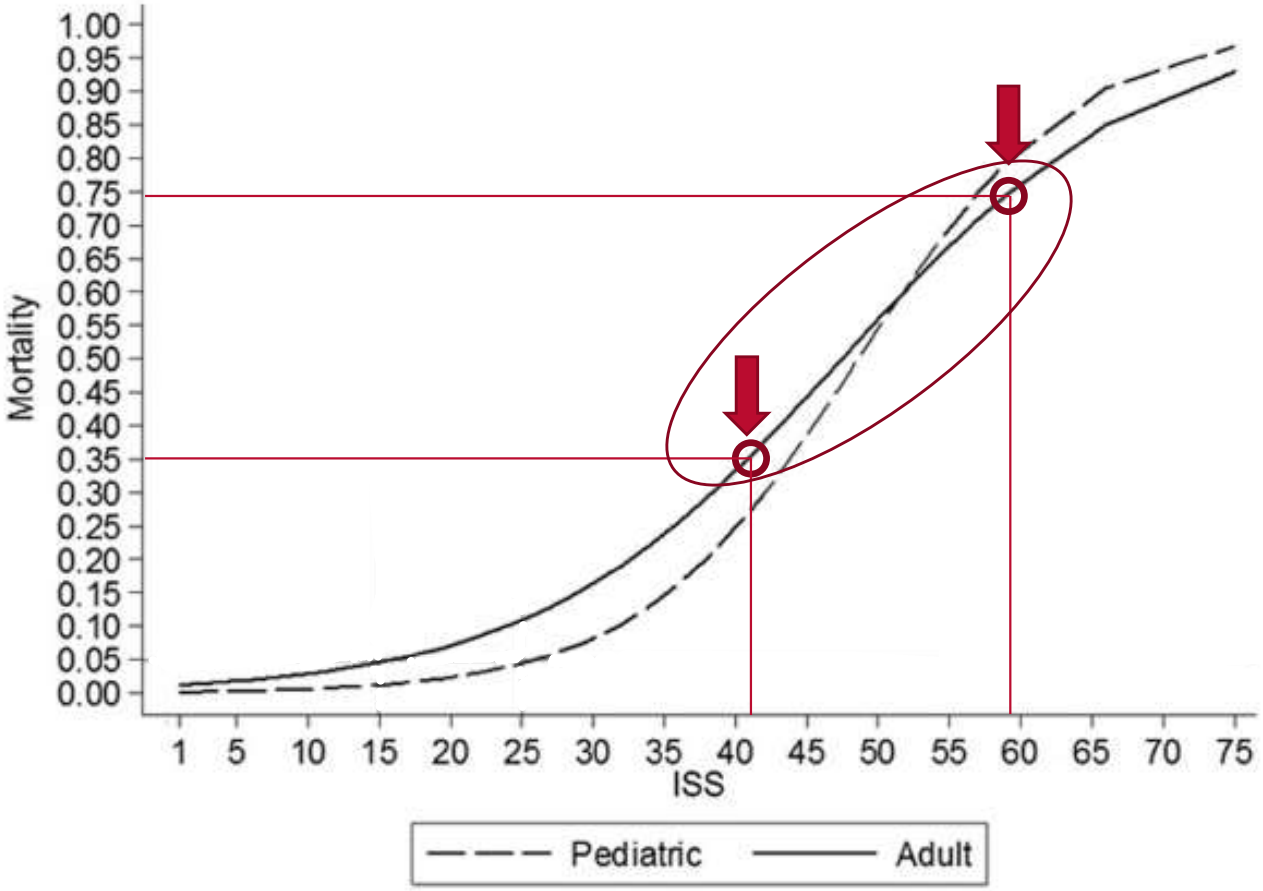
- Feasibility/tolerability assessed
- Post-TPE survival, platelet recovery, coagulation impacts, plasma/platelet/cryo use
- Surgeon/Critical Care impressions

UNM Experience of TPE for TIC

Patient*	Age	Sex	Injury	ISS	↓ Plt Cnt	Coagulopathy	SIRS	CRRT	Injury-Consult Time
1	25	M	Blunt (MVC)†	59	Y	Y, ML_{60min}=0%	Y	Y	3 days
2	47	M	Blunt (MVC)†	57	Y	Y, ML_{60min}=0%	Y	Y	3 days
3	67	M	Blunt (MVC)	43	Y	Y, ML_{60min}=0%	Y	Y	2 days
4	45	M	Blunt (Crush)	41	Y	N	Y	Y	1 day
5	32	M	Blunt (MVC)†	48	Y	Y, ML_{60min}=0%	Y	N	1 day
6	19	M	Blunt (MVC)†	43	Y	Y, ML_{60min}=0%	Y	N	1 day
7	18	M	Blunt (MVC)	50	Y	Y, ML_{60min}=0%	Y	Y	1 day
Median, %	32	7/7 M	7/7 Blunt	48	7/7 Y	6/7 Y	7/7 Y	5/7 Y	1 day

†TBI

*At time of consult, all patients had: MTP activated (≥3 rounds issued) and 3+ organ system dysfunction


Mortality
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
1 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
ISS
Pediatric
Adult

Patient	ADAMTS13 Activity (n >69%)	IL-6 (n ≤2 pg/mL)	# TPE	Δ Platelets (x10^9 /L)	Δ INR	Δ Fibrinogen (mg/dL)	Δ Creatinine (mg/dL)
1	36%	10,044	4	37 → 63	2.8 → 1.4	65 → 298	3.3 → 2.1
2	28%	66	3	74 → 115	3.4 → 1.2	74 → 115	5.3 → 2.7
3	40%	124	3	49 → 131	3.1 → 1.3	531 → 395	3.0 → 1.8
4	31%	432	3	57 → 108	1.6 → 1.2	---	3.3 → 1.7
5	20%	98	3	29 → 83	2.0 → 1.1	143 → 190	1.5 → 0.8
6	35%	140	3	43 → 92	1.7 → 1.4	106 → 177	2.6 → 1.4
7	41%	279	4	71 → 99	2.7 → 1.2	109 → 220	4.1 → 2.9
Median	35%	140	3	49 → 99	2.7 → 1.2	107 → 300	3.3 → 1.8

Patient	Platelets Units Tx'd During TPE Days	Plasma Units Tx'd During TPE Days	Cryo Doses Tx'd During TPE Days	Outcome Post-TPE
1	4	8	4	Died at 1 day (CMO)
2	3	5	5	Died at 1 day (CMO)
3	3	6	4	Died at 7 days (sepsis)
4	3	0	0	Alive at 30 days
5	2	2	2	Alive at 30 days
6	2	4	2	Alive at 30 days
7	2	3	2	Alive at 30 days
Median, %	3	4	2	4/7 Alive at 30 days

Additional Benefits

Decreases in

- CK (33-89%)
- Lactate (10-85%)
- ESR (47-64%)
- CRP (57-67%)
- Ferritin (50-84%)
- Fever (up to 1.2°C)

Increases in

- pH (0.07-0.24)
- ADAMTS13 (19-55%)

Cessation of CRRT faster than anticipated (mean 4 days in survivors)

TPE in Trauma: Feasible and Tolerable

All patients completed all TPE procedures (23/23, 100%)

Most common event was laboratory-diagnosed hypocalcemia (7/23, 30.4%)

Vasopressors had to be acutely increased in 2 patients (2/23, 8.7%)

Transfusion reactions were rare (1 mild ATR; 1/23, 4.3%)

No vascular access issues

No codes/arrests/deaths on circuit

Surgery/Critical Care Impressions

1. Do you feel that the performance of TPE is considered safe in your trauma patient?
   - Yes (14/14, 100%)
2. Do you have any concerns about providing vascular access for TPE?
   - No (14/14, 100%)
3. Do you view the 1-2 hours immediately after TPE as the time period with best possible coagulation status in your patient?
   - Yes (14/14, 100%)
4. Would you preferentially schedule interventional procedures or maneuvers with increased bleeding risks immediately after a TPE procedure was completed?
   - Yes (14/14, 100%)
5. Outside of major interventional procedures or unforeseen complications, has bleeding improved?
   - Yes (11/14, 78.6%)
   - No (3/14, 21.4%) - Unchanged
6. Do you have any concerns about the volumes of plasma used during the TPE treatment series?
   - No (13/14, 92.9%)
   - Yes (1/14, 7.1%) – Risk of TRALI in critically ill trauma patients

Questions

Are we treating these severely injured trauma patients too late with TPE?

Are we missing potential trauma patients that may benefit from TPE?

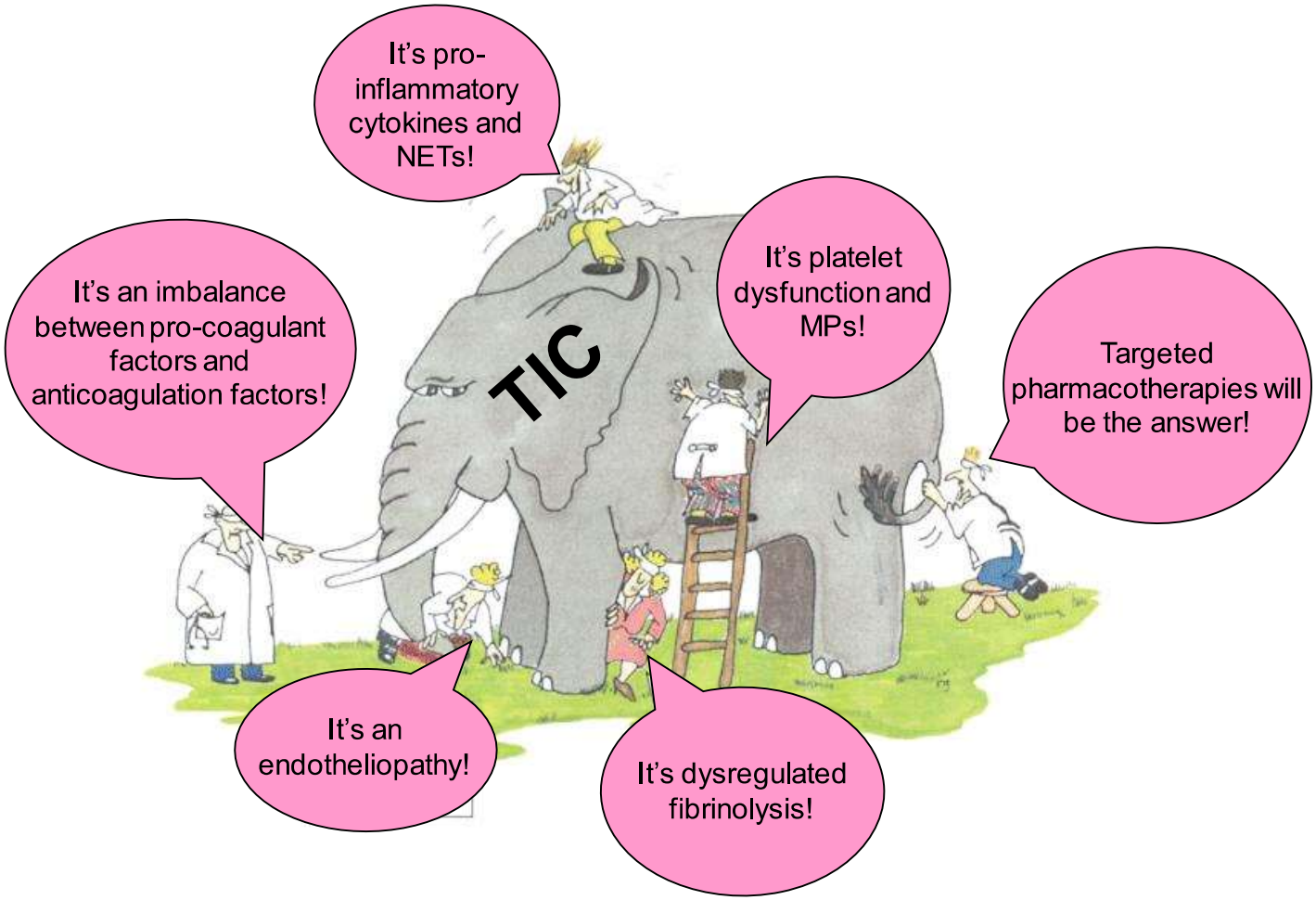
- Lower ISS
- Penetrating trauma, females, children
- Other ways of differentiating traumatically injured patients

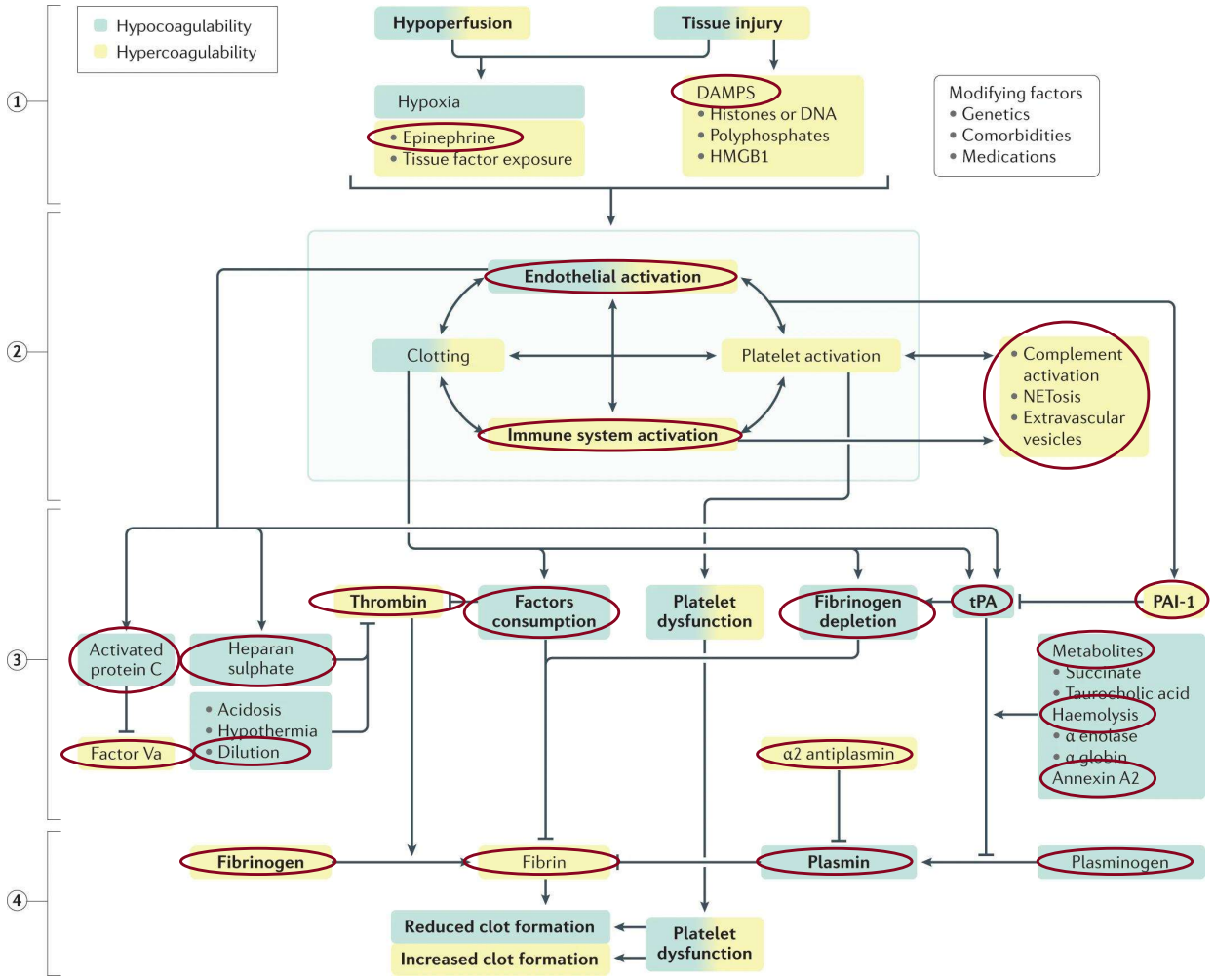
Are there meaningful biomarkers that we can serially follow to customize the TPE regimen intensity for each patient?

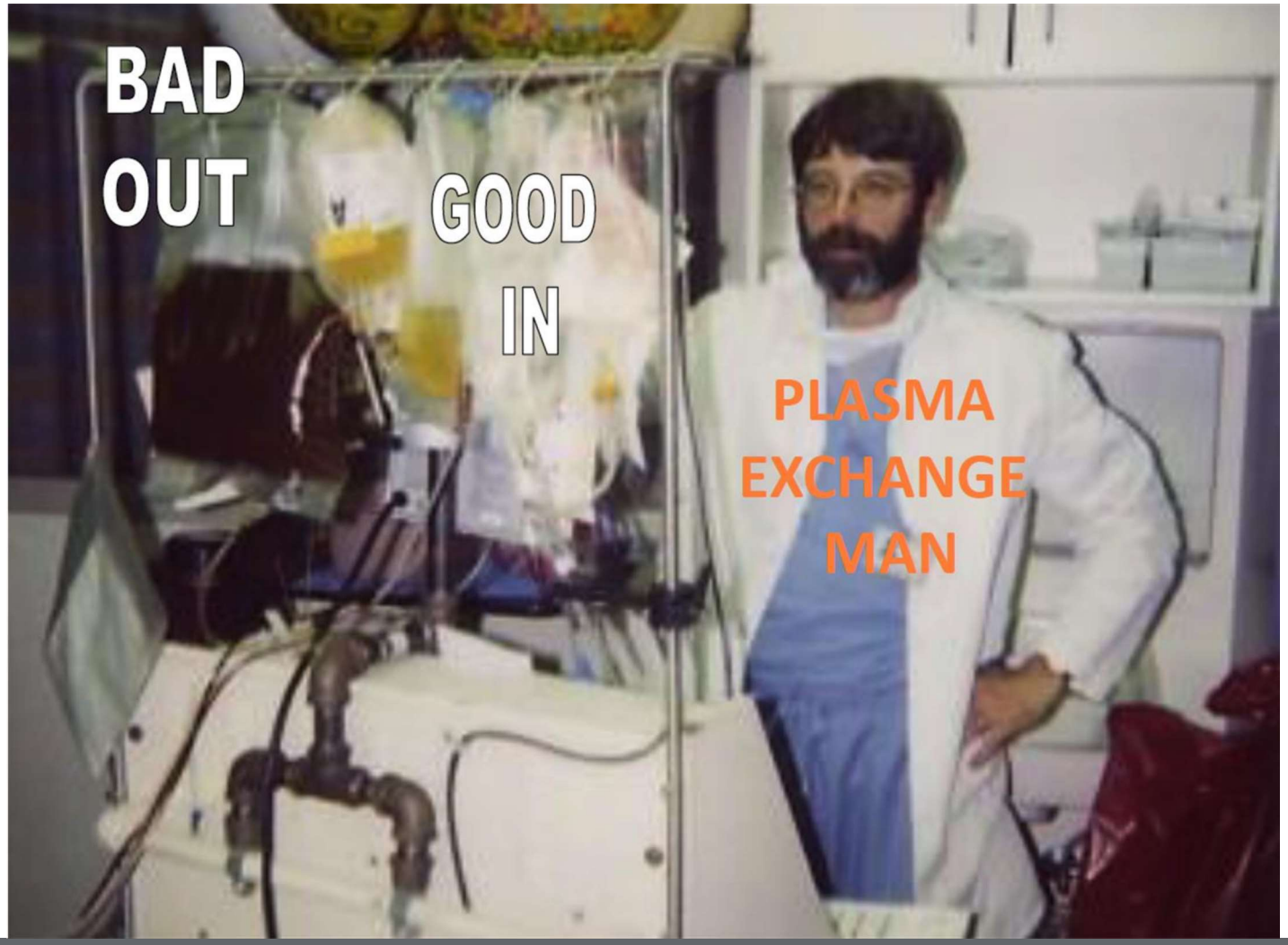
What are the mechanisms of TPE in improving kidney dysfunction?

What adjunctive therapies would improve observed positive impacts of TPE?

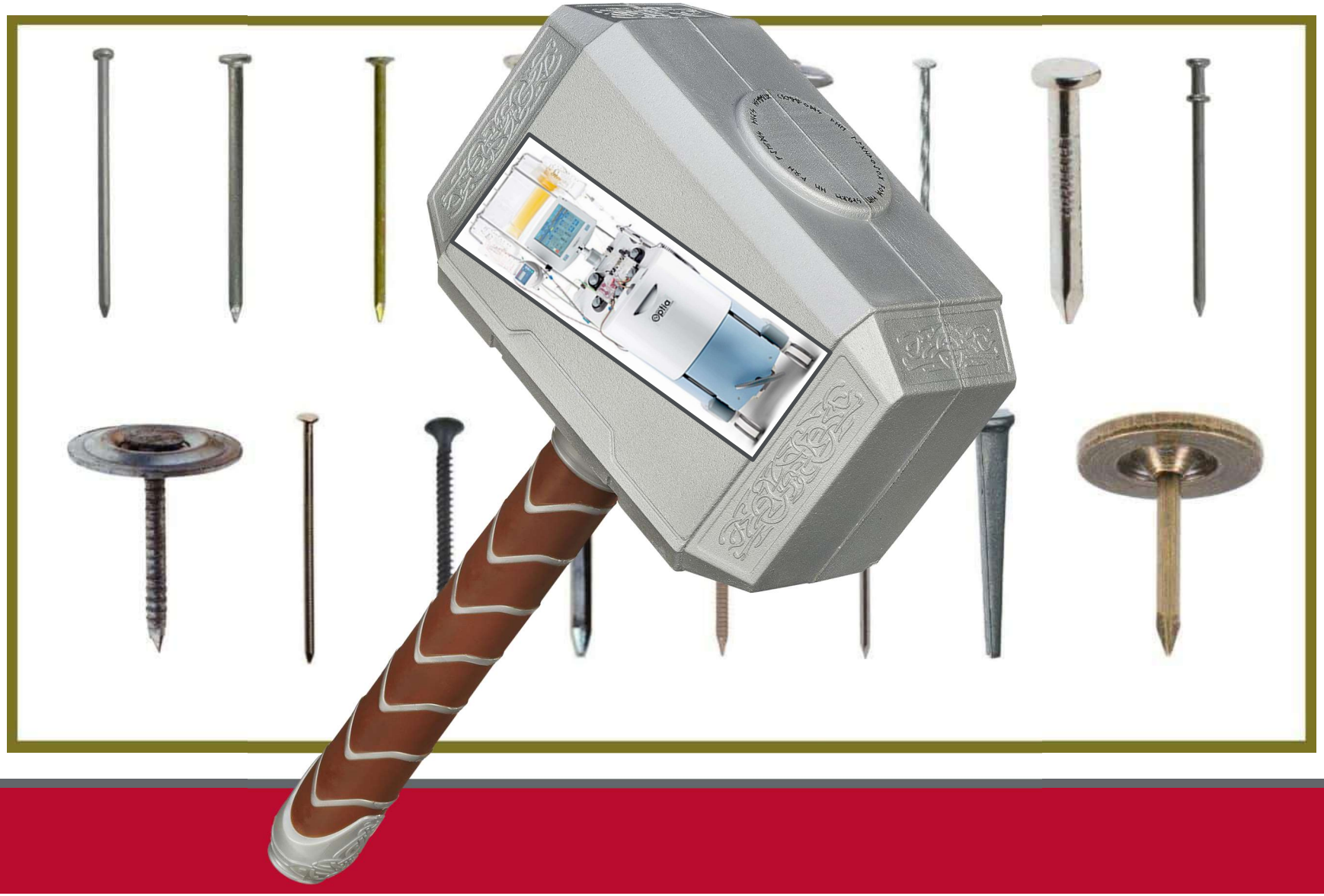
Can we modify the apheresis procedure to remove both plasma and fraction of buffy coat components to more thoroughly remove pathologic substances?


It's pro-inflammatory cytokines and NETs!
It's an imbalance between pro-coagulant factors and anticoagulation factors!
TIC
It's platelet dysfunction and MPs!
Targeted pharmacotherapies will be the answer!
It's an endotheliopathy!
It's dysregulated fibrinolysis!


Hypocoagulability
Hypercoagulability
1
2
3
4
Hypoperfusion
Tissue injury
Hypoxia
• Epinephrine
• Tissue factor exposure
DAMPS
• Histones or DNA
• Polyphosphates
• HMGB1
Modifying factors
• Genetics
• Comorbidities
• Medications
Endothelial activation
Clotting
Platelet activation
Immune system activation
• Complement activation
• NETosis
• Extravascular vesicles
Thrombin
Factors consumption
Platelet dysfunction
Fibrinogen depletion
tPA
PAI-1
Activated protein C
Heparan sulphate
• Acidosis
• Hypothermia
• Dilution
Factor Va
Metabolites
• Succinate
• Taurocholic acid
Haemolysis
• α enolase
• α globin
Annexin A2
α2 antiplasmin
Fibrinogen
Fibrin
Plasmin
Plasminogen
Reduced clot formation
Increased clot formation
Platelet dysfunction



Courtesy Dr. Joe Kiss


Optia

Conclusions

TIC is a complex system

TPE is a non-specific treatment option that can treat conditions with complex etiologies

Rapid, euvolemic, large-volume removal and replacement of plasma

TPE is feasible and tolerable in severely-injured trauma patients

Numerous clinical and laboratory parameters improve with TPE

Surgical and Critical Care colleagues pleased with this TPE protocol

While encouraging, still many unanswered questions

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