MASSIVE TRANSFUSION PROTOCOL

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Goals for this Lecture

- Review the clotting cascade
- History of blood transfusion
- Understanding the differences between Early and Secondary coagulopathy processes
- The current trends in MTP

10,000 ft. view of Hemostasis

Platelet/Coagulation Factor activation

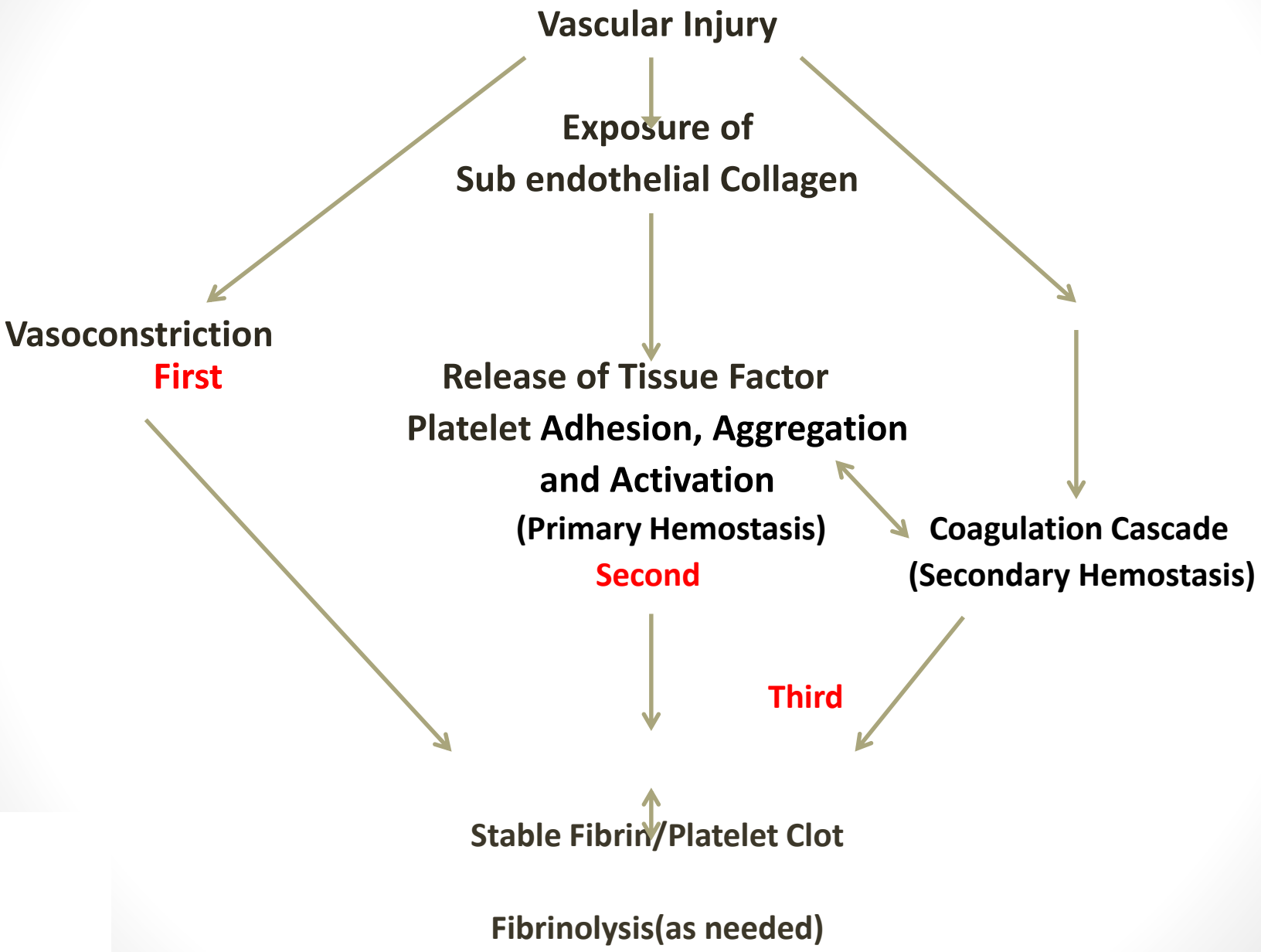
↓

Lots of EXCITING biochemistry

↓

CLOT

Clotting Cascade Review



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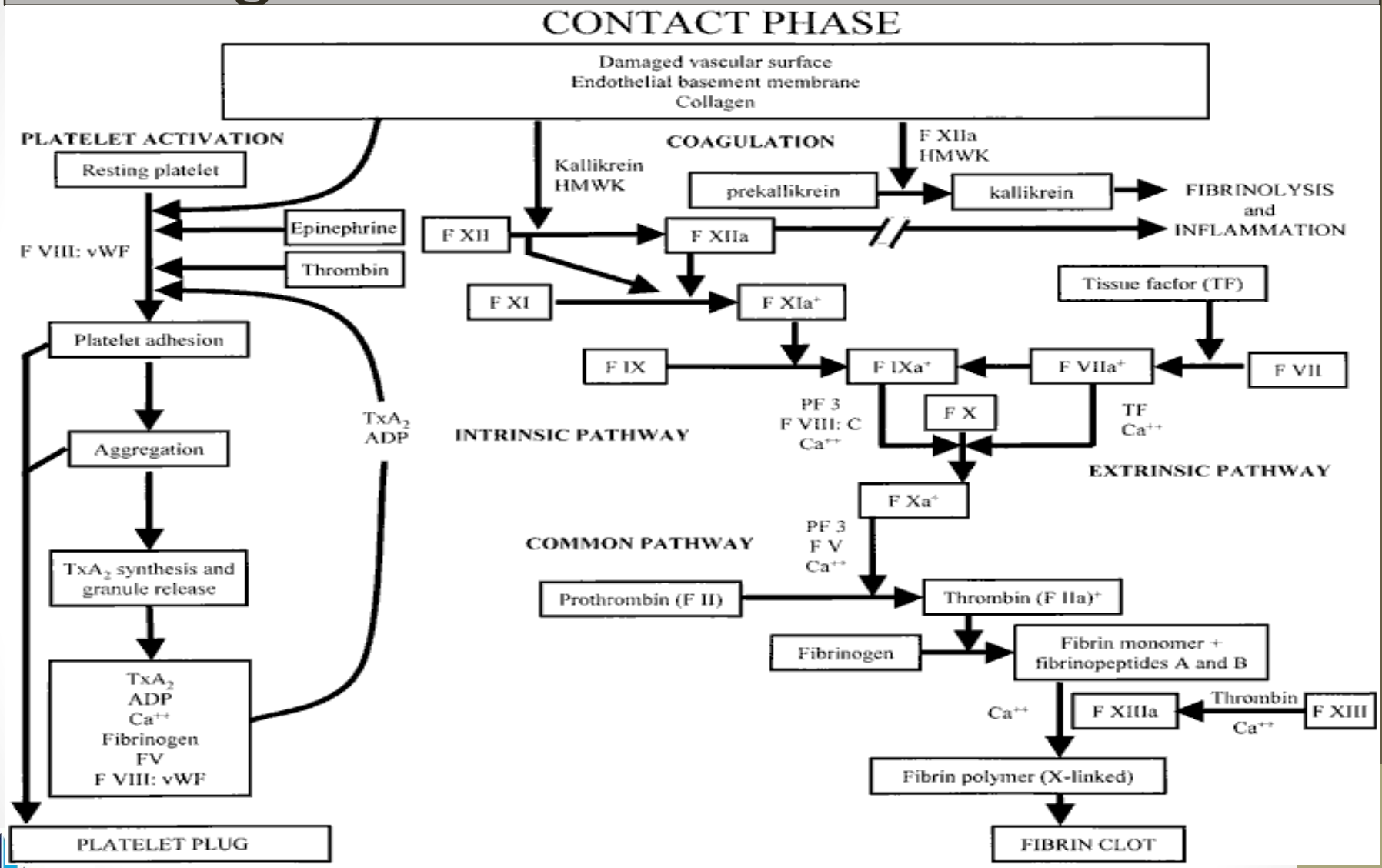

http://tele.med.rubookcardiac_anesthesia/text/he/he018.htm#he018p002

Coagulation Factor Facts

Videos

- https://youtu.be/Zk2sW0ifwSU
- https://youtu.be/cy3a__OOa2M
- https://youtu.be/MPGe-guZMqM
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	Factor	Production	T 1/2	Level for Surgery	Therapy
I	Fibrinogen	LIVER	72-100hr	>100 mg/dl	Cryoprecipitate
II	Prothombin	LIVER*	50-80 hr	15%-40%	Plasma
III	Tissue Factor or Tissue Thromboplastin	Platelets damaged endothelium	?	?	
IV	Calcium	GI Tract		9-12	Calcium
V	Labile Factor	LIVER, EC	15-36 hr	15%-25%	Plasma, Platelets
VII	Stable factor	LIVER*	5 hr	10%-15%	Plasma , rVIIa
VIII	Antihemophilic Factor A	EC	8-12 hr	100%	Factor concentrate , DDAVP
IX	Christmas Factor	LIVER*	24 hr	50%-70%	Factor concentrate
X	Stuart Power Factor	LIVER*	25-60 hr	10%-40%	Plasma
XI	Plasma Thromboplastin Antecedent	LIVER	40-80 hr	10%-25%	Plasma
XII	Hageman Factor	LIVER	60 hr	--	
XIII	Fibrin stabilizing factor	LIVER	4-7 days	<10%	Plasma
	von Willebrand factor	endothelium	?		Plasma, Factor concentrate
	Prekallikrein Flectcher Factor	LIVER	?	?	Plasma
	High-molecular-weight kininogen (HMWK)	LIVER	?	?	Plasma
	Protein C	LIVER	15 MIN	65–135 IU/dL	Plasma

Shock

- The lethal factor in shock is the irreversible anoxic cellular injury that kills a critical mass of cells.
- Inadequate cellular oxygen delivery via the microcirculation leads to this irreversible cellular damage.
- Successful resuscitation requires restoration of cellular oxygenation via increasing blood flow to microcirculation

The Key

- At rest, oxygen delivery is normally four times oxygen consumption
- If intravascular volume is maintained during bleeding and cardiovascular status is not impaired, oxygen delivery will theoretically be adequate until the hematocrit (packed cell volume) falls below 10 percent
- Increasing cardiac work to increase output requires more oxygen, so the “critical point” where oxygen consumption becomes delivery dependent is higher

Types of Coagulopathy

- Disseminated intravascular coagulation (DIC) with the fibrinolytic phenotype is characterized by:
    1. activation of the coagulation pathways
    2. insufficient anticoagulant mechanisms
    3. increased fibrinolysis
- Coagulopathy of trauma and acute coagulopathy of trauma-shock (COT/ACOTS) occurs as a result of:
    - ↑ activation of the thrombomodulin and protein C pathways → to the suppression of coagulation and activation of fibrinolysis

COT/ACOTS

- Occurs *secondary* to systemic anticoagulation via inhibition of cascade proteins- V (FVa) and VIII (FVIIIa), through soluble thrombomodulin-mediated protein C
- Decreased thrombin formation → tendency to bleed
- Platelet and fibrinogen levels should be in the normal
- There is little evidence of consumption of coagulation proteins as a relevant mechanism
- Coagulation parameters such as the PT and APTT are typically not prolonged

MASSIVE TRANSFUSION PROTOCOL

- History always runs in cycles….
- Blood transfusion practice largely based on the military
- WWI –(1917) first “banked blood” O Neg led to use in the final year of the war
- WWII –albumin and lyophilized (freeze-dried) plasma in combination of whole blood
- Vietnam War- component therapy(accepted with not random control trials)-vicious cycle-lethal triad

MASSIVE TRANSFUSION PROTOCOL

- In the 80's – early 90's lots of crystalloid up front
  - Abdominal Compartment Syndrome
  - ARDS
  - MOF
- Late 90's realized that WWII practice probably was the best…
- Today 1:1:1… WFWB(warm fresh whole blood) may come to a hospital near you

Trauma Induced Coagulopathy

- Important predictor for blood utilization and trauma related mortality
- Mainly iatrogenic or secondary coagulopathy (lethal triad)
  - Ongoing dilution and consumption of clotting factors
  - Acidosis
  - Hypothermia

Trauma Induced Coagulopathy

- New theory : may be preceded by Early Trauma-Induced Coagulopathy (ETIC)
  - Early- primary event-separate phenomenon
  - Prolong PT on admission
  - Unknown etiology –two theories 1) tissue factor-→thrombin-fibrin generation and use →DIC 2)Hypo-perfusion-→ischemia-→activated C protein-→ consumption of plasminogen activator-→ inhibit clotting cascade →DIC

ETIC

- Shaz BH, Dente CJ, Nicholas J, MacLeod JB, Young AN, Easley K, Ling Q,Harris RS, Hillyer CD: Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. Transfusion 2010, 50:493–500

The prevention and/or treatment of ETIC, based on the data, includes conservative intravenous fluid administration as well as adequate factor replacement through plasma transfusion or other factor containing concentrates.

- Patients with ETIC had been given more crystalloid in the pre-hospital admission phase; therefore they concluded ETIC may not be a unique pathophysiologic response but rather a secondary trauma induced coagulopathy that occurs before a patient reaches the hospital

Reducing Crystalloids

- Too much crystalloids initially can cause trauma induced coagulopathy

James MF, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS: Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth 2011, 107:693–702.

Ogilvie MP, Pereira BM, McKenney MG, McMahon PJ, Manning RJ, Namias N, Livingstone AS, Schulman CI, Proctor KG: First report on safety and efficacy of hetastarch solution for initial fluid resuscitation at a level 1 trauma center. J Am Coll Surg 2010, 210:870–880. 880–872

- The colloid enabled better tissue resuscitation by keeping a better intravascular volume

Damage Control Resuscitation

- Introduced in the mid 2000's as an alternative
  - 1)rapid control of surgical bleeding
  - 2)EARLY and increase use of blood products(1:1:1)
  - 3)Limitation of crystalloid
  - 4)Prevention of Hypothermia , hypocalcaemia, and acidosis
  - 5)Hypotension resuscitation methods
- Retrospective studies –High plasma ratio
  - Borgman and colleagues –Iraq
  - Holcomb- civilian
- Caveat---6 hour end point TRALI, ARDS, MOF

Platelets/Fibrinogen

- Currently shown to increase mortality with a high ratio
- Perkins and colleagues-(military) improved 24 hour and 30 day survival rates with (1:1:1), current protocol
- One unit of Fresh Whole Blood has 1000mg of Fibrinogen –replace with banked PRBC 500 mg of fibrinogen
- Replacement later to be done by cryoprecipitate(250 mg of fibrinogen)

  1 RBC/Cryo ?

WARM FRESH WHOLE BLOOD

- All info from US Army Institute of surgical research
- Iraq and Afghanistan
- 30% WFWB/ 70% component
- Survival rates exceeded in this group
- 500 ml of warm blood with no storage deficits
- Full amount of platelets, clotting factors and fibrinogen
- Implementation in the civilian population?

Recombinant Factor VII

- Factor VII- controversial, expensive and fallen out of use with (1:1:1)
- Morse and colleagues found no correlation with use and outcome benefit, Hauser et al found harm
- OB?

Tranexamic acid

- Tranexamic acid cheaper alternative
- Shakur et al. showed a significant reduction in risk of death (over 20,000 pt)
- “Should” be used in all MT case but note the outcomes from the control group were marginally superior d/t large population studied

Communication and MT Protocol

- This practice is NOT in every institution
- Talking with the blood bank
- Staying ahead
- Uncross match
- Thawing process
- Cost savings

Predicting and 8 ball readings

- Only 2% of the civilian population really needs MTP
- OVERUSE of MTP can cause harm and wastage
- Key indicators:
  - Trans-pelvic and multi-cavity gunshot wounds
  - Systolic pressures less than 90 mmHg and a base deficit greater than -10 units

POC

- Alternative to formula driven approaches
- Hg, PT, PLT, INR, Fibrinogen
- TEG(thromboelastography) or ROTEM(thromboelastometry)- measures speed and strength of clot which determines the activity of the plasma coagulation system, platelet function and fibrinolysis …it is the patterns the tells you how well or poorly blood can preform hemostasis (more accurate and faster)
- Not a standard and requires more studies to prove wide spread use

Banked Blood

- Blood transfusions may be the most common non-pain relieving therapy performed by anesthesia providers
- ABO-Rh typing has a 99.8% chance of a compatible transfusion
- Cross-matching with antibodies increases to 99.94%
- O- Neg /O pos (rhogam female O neg type)
- Shelf life of 35-42 days

Banked Blood

Decreases in stored blood

- pH
- 2-3 DPG
- Platelets
- RBC’ s (lyses)
- Factor V & VIII
- **Only K+ will increase minimally

Citrate Phosphate Dextrose (CPD)

- Maintains 70% RBC survival for 28 days (FDA approval for 21 days)
- Citrate ions bind with Calcium to prevent clotting (anticoagulant)
- Dextrose allows the RBC’s to continue glycolysis and maintain ATP
- Phosphate has a pH of 5.5 and acts as a buffer

Citrate Phosphate Dextrose (CPD)

Storage at 1-6 deg. C. slows the rate of glycolysis about 40 times

CPD with Adenine (CPDA-1) preservative with anticoagulant

- Prolongs storage to 35 days
- Adenine allows RBC’ s to resynthesize
- Contains 25% more glucose

Complications with Banked Blood

Metabolic acidosis is uncommon unless there is inadequate resuscitation

Blood pH is 6.9 after 21 days of storage, due to continued RBC metabolism of glucose to lactate and pyruvate and bags are impermeable to CO2

Preservative CDPA-1 pH 6.9 after 21 days and 6.71 after 35 days

Metabolic alkalosis (MA) is the most common pH abnormality after massive blood transfusions

Complications with Banked Blood

Progressive metabolic acidosis results as citrate & lactate in the transfusion convert to bicarbonate in the liver

Metabolic acidosis most likely to occur in patients with renal dysfunction since kidneys are responsible for HC03 elimination

If alkalosis occurs, there is a left shift for O2 affinity, and a possibility for cellular hypoxia. There is also a decrease in 2,3 DPG for a left shift of O2

Hyperkalemia

- Plasma K+ concentration of stored blood may be over 30mmol/l. Hyperkalemia is generally not a problem unless very large amounts of blood are given quickly

- Hypokalemia is more common as red cells begin active metabolism, and intracellular uptake of K+ restarts

Hypocalcaemia

- Each unit of blood contains approx. 3g. of citrate, this binds with ionized calcium

- Healthy adult liver will metabolize 3g. citrate every 5 min. Transfusion rates higher than this or impaired liver function, may lead to citrate toxicity and hypocalcaemia

Hypocalcaemia

- Hypocalcaemia clinically doesn't affect coagulation, but may transiently exhibit tetany and hypotension

- Calcium should only be given if there is a biochemical, clinical, or EKG evidence of hypocalcaemia

Hypothermia

- Leads to reduction in citrate and lactate metabolism (leading to hypocalcaemia and MA), increased affinity for HGB to O2
- Impairment of RBC deformability
- Platelet dysfunction
- Increased tendency for cardiac dysrhythmias

ARDS

- Exact etiology unknown
- Albumin < 30g/l also implicated
- Blood filters recommended for massive transfusions except with giving fresh whole blood

TRALI

- PREDOMINATELY PLASMA
- No current data in trauma studies
- Studies in non trauma patients…plasma transfusion was almost a three fold increase risk
- Proposed mechanism- antibodies from the donor blood components that are directed against the Human Leukocyte Antigen (HLA)
- Most numerous in women who have been pregnant ..use male plasma as a donor ..

What is the current suggestions?

- Evidence suggests that in severe trauma with hemorrhagic shock a MTP should be activated
- Patients should be resuscitated with warm fresh whole blood or best practice component therapy in a ratio of 1:1:1:1 (plasma:platelets:cryoprecipitate:RBCs)
- Tranexamic acid should also be considered

Take Home Message

- If the patient is hemorrhaging whole blood we should reconstruct whole blood as much as we can.
- The benefit of preventing an early hemorrhagic death far outweighs the risk of subsequent TRALI
- Transfusion of WFWB has been associated with improved survival during MT, and also substantially reduces recipient exposure to plasma and platelets, thereby reducing the risk of TRALI

Take Home Message

- Major logistical difficulties in supplying WFWB
- Once there is control of surgical bleeding in MT, and for all patients who did not need a MT point of care coagulation tests should be used wherever possible

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- The ultimate goal would be to individualize blood product ratios from patient to patient rather than having a set ratio for all cases

How to Implement

- Define the problem and population
- Multispecialty team needed
- Develop the implementation process
- Create a robust performance improvement or quality improvement process to monitor the implementation of such a protocol
- Education