

Bleeding and Clotting Emergencies in the ICU

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Conflicts of Interest

Scientific Ad Boards and Consulting:

Abbott

Anthos

Anylam

Bristol-Myers Squibb

Portola

Takeda

Research funding to the Institution

CSL Behring

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Agenda

Coagulopathy:

pathological condition that reduces the ability of the blood to coagulate, can lead to uncontrolled bleeding

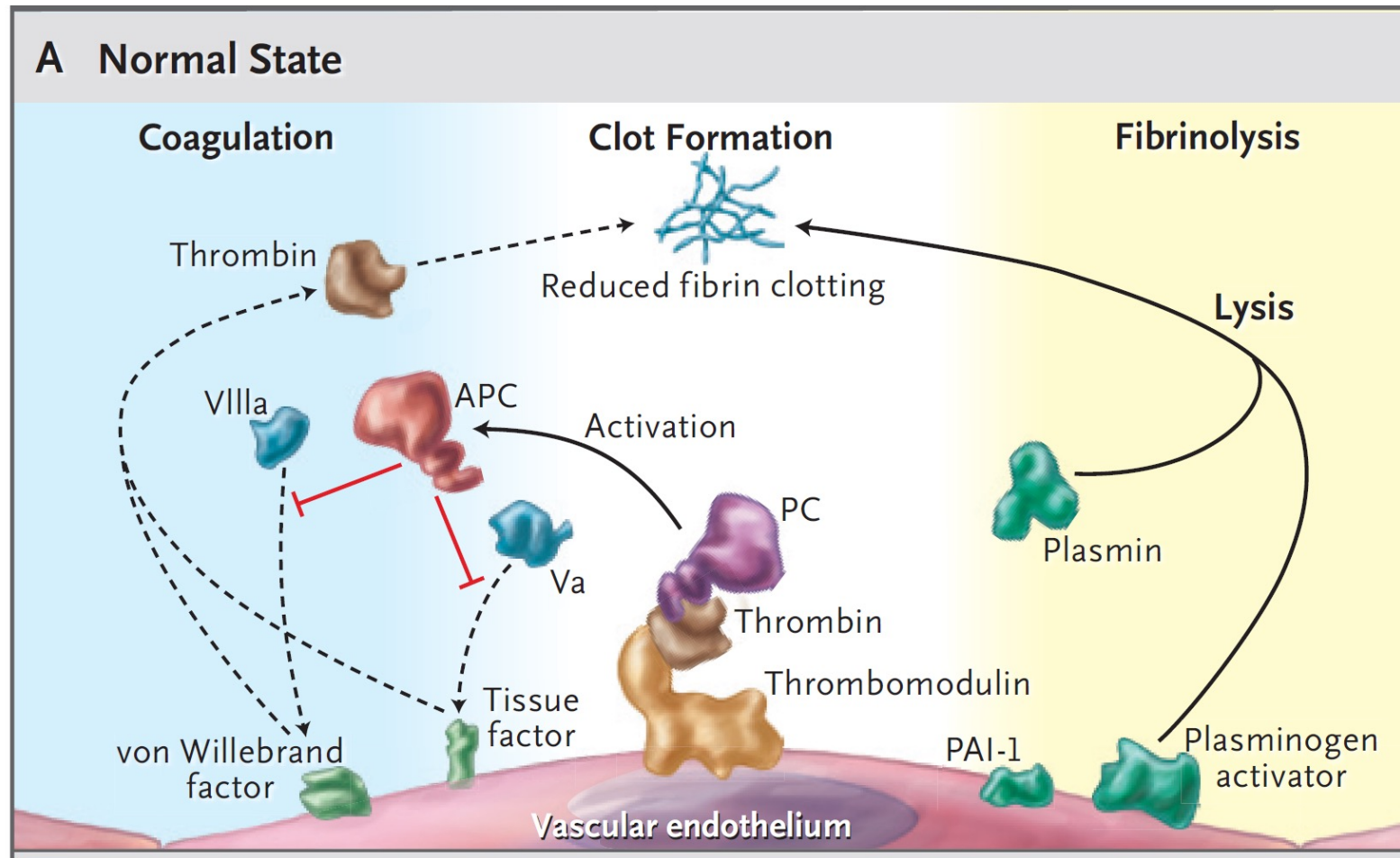
- review of coagulation tests
- bleeding management
 - DIC
- available hemostatic products

Treat the bleeding patient not numbers. An elevated PT or PTT does not mandate treatment if there is no bleeding.

Thrombosis

- Pathologic activation of coagulation leading to unwanted blood clots
 - Heparin induced thrombocytopenia

Normal Hemostatic Balance



Requirements for Hemostasis

- **Factors needed to stop bleeding:**
 - **Vasoconstriction**
 - Includes closing holes in vessels
 - **Platelets and vWF**—primary hemostasis
 - **Soluble coagulation factors**—secondary hemostasis, aka the clotting cascade

Ideally: normal body temperature, normal pH, normal Ca⁺⁺

Approach to evaluation of coagulopathy

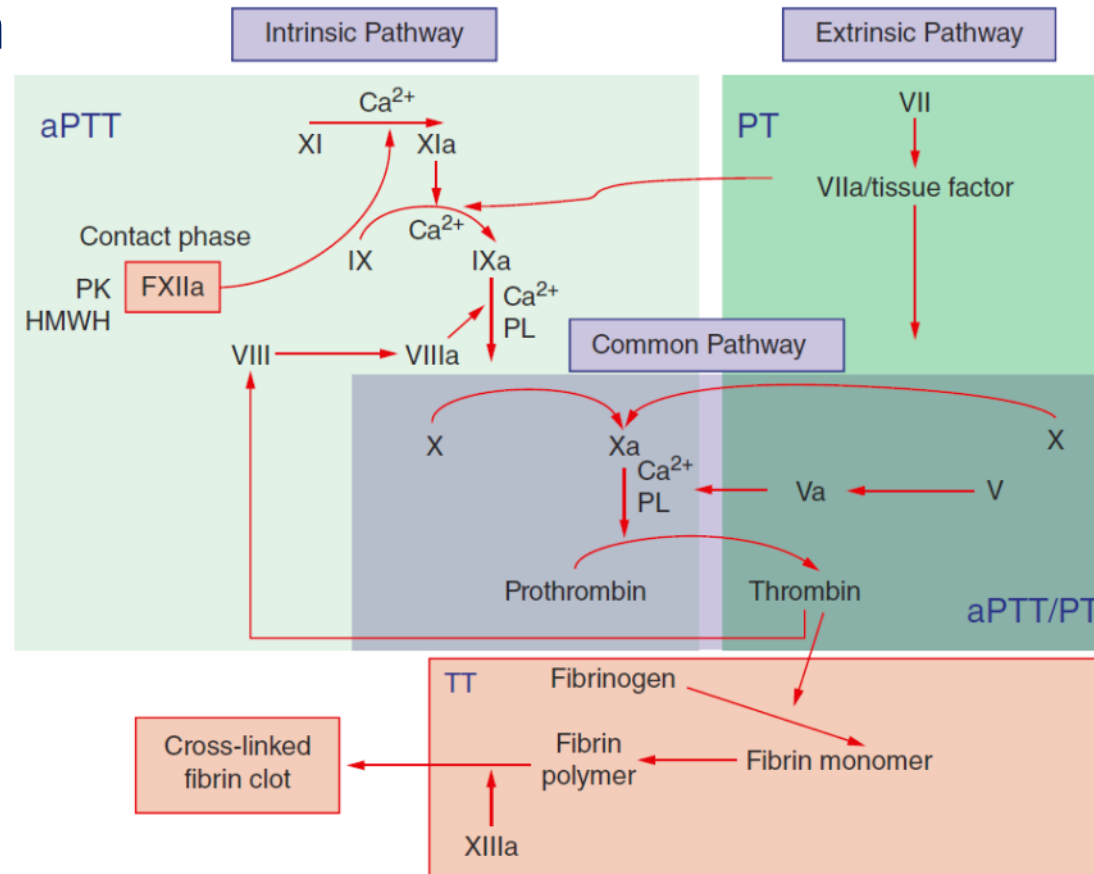
- **History**
 - Acquired versus inherited
- **Physical**
 - Type and location of bleeding
 - Diffuse oozing
 - Ecchymosis, petechiae
 - Surgical site
- **Laboratory tests**
 - CBC and review of peripheral smear
 - PT
 - PTT
 - Fibrinogen and D-dimer

Interpretation of lab tests

- **Elevated PT only**
 - **Factor VII** is low
 - Warfarin
 - Rivaroxaban, edoxaban

- **Elevated aPTT only**
 - **FXII, FXI, FIX, FVIII**
 - Lupus anticoagulant
 - Rare: specific factor inhibitor
 - heparin

- **Both PT and aPTT elevated**
 - Fibrinogen
 - Drug effect: heparin, DTI
 - Rare: **FX or FV** deficiency or inhibitor



Vitamin K

Management of Coagulopathy

- **Establish diagnosis**
 - **Production**
 - Cirrhosis
 - Shock liver
 - Vitamin K
 - **Dilution**
 - Trauma
 - Massive hemorrhage
 - **Consumption**
 - DIC
 - Snake bite, TPA
- **Supportive care**

Management of Coagulopathy

- Severity of bleeding, need for procedures drives treatment decisions
- **In general**
 - Fibrinogen > 100-200 mg/dL
 - Platelets >20-30 x 10⁹/L
 - Need for “normal” aPTT or PT?

Overt DIC scoring system

Platelet Count	
>100 x 10 ⁹ /L	0 Points
>50 - <100 x 10 ⁹ /L	1 Point
<50 x 10 ⁹ /L	2 Points

Increase in Fibrin-related Markers [D Dimers]	
No change	0 Points
Moderate rise	2 Points
Strong rise	3 Points

Prothrombin Time [PT] Prolongation	
3 s or less	0 Points
>3 s but <6 s	1 Point
>6 s	2 Points

Fibrinogen [Clauss] Level	
>1.0 g/L	0 Points
<1.0 g/L	1 Point

Score \geq 5 DIC

DIC: Management

- Identify and treat underlying condition
- Supportive care
 - If underlying condition rapidly reversible, watch and wait if patient not bleeding
 - use FFP, cryo, and platelets as needed
 - **Treat bleeding not numbers**
 - Fibrinogen >100-200, plts >20-30k, higher if bleeding
- Stop microvascular thrombosis?
 - consider heparin, tPA, or urokinase
 - Role more established in chronic DIC
 - Low dose 4-5 U/kg IV UFH
 - **No mortality benefit**

DIC--Management

- Control bleeding, use FFP, cryo, platelets as needed
 - RiaStap, Fibryga: fibrinogen concentrate
 - Kcentra: II, VII, IX, X, proteins S and C (4-PCC)
- Role for natural anticoagulant products?
 - **No mortality benefits have been shown for any**
 - Antithrombin
 - Activated protein C (drotrecogin/Xigris)
 - Recombinant thrombomodulin
 - TFPI
 - Other investigational agents: MAPK,IL-10,NAPc2

Plasma

- **FFP or TP**

- Contains all clotting and anti-clotting factors at **normal plasma concentration**
- 70 kg person has 2.8 liters plasma
- “Normal” PT and aPTT require factor levels >30%
- Each bag of plasma approx 250 ml (180-300)
- To obtain a 30% level when starting at <1% will require **4 to 6 bags of FFP** or approximately 20 ml/kg or **1000-1500 ml of plasma**

Cryoprecipitate

- Contains:
 - **Fibrinogen**
 - **vWF and FVIII**
 - **FXIII**
- Obtained from 1 unit whole blood
 - Cold insoluble fraction of high mw proteins as thawing FFP
 - resuspended in 15 ml plasma = 1 unit cryo
 - Minimum **80 IU FVIII** and **150 mg fibrinogen** per unit
- BWH: One order of cryo = 2 bags* = **10 units of cryo**
 - should increase **fibrinogen** level by 50-100 mg/dL

Adverse effects of FFP and cryo

- FFP: volume and infusion time
- Allergic
- TRALI—USA now uses only male donors for plasma
- TACO—Transfusion associated circulatory overload
- ABO type specific
- Pathogens--processed, pasteurized, solvent-detergent treated products
- Are lyophilized concentrates the future?

Factor Concentrates

- Benefits of factor concentrates:
 - low volume,
 - no cross matching
 - acellular
 - no alloimmunization
 - viral free
 - increasingly used in algorithms for bleeding
- For PCCs, most data are for warfarin reversal
- Limited single arm studies of prospective data for 4F-PCC in Xa inhibitor DOAC

Fibrinogen Concentrate

- RiaSTAP FDA approved for use in 2009, now others
- Fibrinogen concentrate made from pooled plasma
 - Heat treated, lyophilized
- Labeled indication for hypo- or afibrinogenemia, not dysfibrinogenemia
- Other off label use:
 - Acquired hypofibrinogenemia
 - Obstetric hemorrhage including post-partum hemorrhage
 - Post-operative hemorrhage
 - Trauma-associated hemorrhage
 - Increasingly used in Europe due to concerns for CJD from plasma

Kcentra (4F-PCC)

- non-activated 4 Factor Prothrombin Complex Concentrate
 - Contains vitamin K-dependent coagulation Factors II, VII, IX, and X and antithrombotic Proteins C and S* (and small amount of heparin)

Pre-treatment INR	2-< 4	4-6	> 6
Dose* of Kcentra (units [†] of Factor IX) / kg body weight	25	35	50
Maximum dose [‡] (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

- Dose: 25-50 units/kg
- Volume 25 units/ml
 - Volume for 70kg * 50 units/kg Kcentra = 140 mls
- Administer with vitamin K for sustained reversal of warfarin
- Off-label use for DOAC reversal, intra-op bleeding, liver disease

rVIIa: NovoSeven RT

- Recombinant Factor VIIa

- Black box warning: serious arterial and venous thrombotic and thromboembolic adverse events
- Older patients most at risk OR 2.4-3 (Levy NEJM 2010)

- Dose

- Uncontrolled bleeding associated with trauma or surgery in which no clear surgical source of bleeding can be identified
 - 40-90 mcg/kg bolus over 2-5 minutes

FEIBA: **F**actor **E**ight **I**nhibitor **B**ypassing **A**ctivity

Developed for hemophilia A patients with inhibitors to factor VIII

- *Activated* prothrombin complex concentrate (activated 4PCC)
 - Vitamin K-dependent clotting Factors 2, 9 and 10 mainly in non-activated form and Factor 7 in the **activated** form
 - Dose: 25-50units/kg
- Potentially lower thrombotic risk than rVIIa?
 - “Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity.” Aledort, JTH, 2004
 - 24 thrombotic AE per 100,000 infusions rVIIa (stroke)
 - 8.24 thrombotic AE per 100,000 infusions FEIBA (MI)



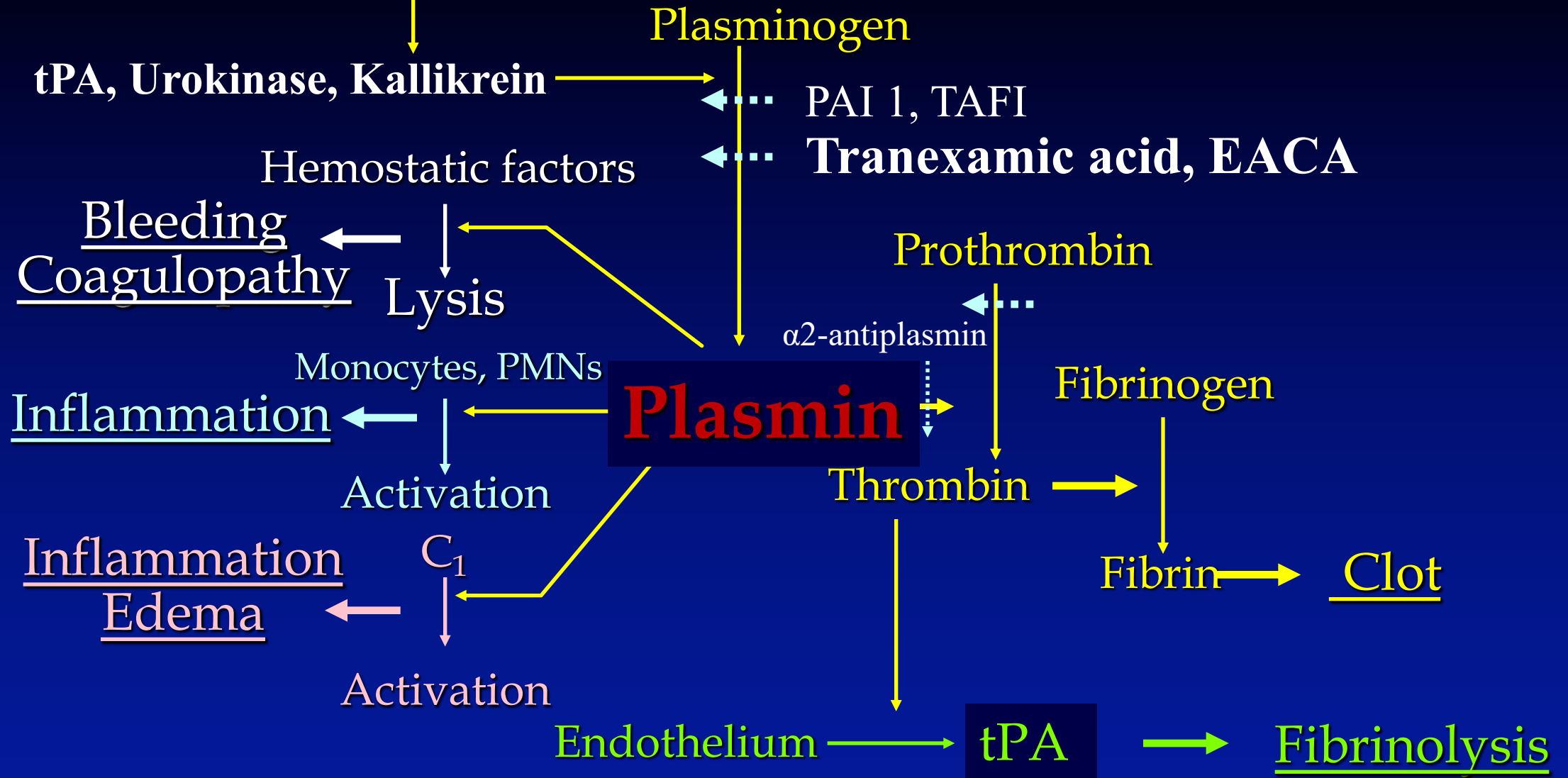
Prothrombin complex concentrates and activated factors

Vitamin K-dependent coagulation factors	4-Factor PCC*	Plasma	4F-PCC activated (FEIBA)	3-Factor PCC*	rFVIIa
II	✓	✓ †	✓	✓	
VII	✓	✓ †	✓ activated	Low levels	✓ activated
IX	✓	✓ †	✓	✓	
X	✓	✓ †	✓	✓	
Protein C	✓	✓			
Protein S	✓	✓			

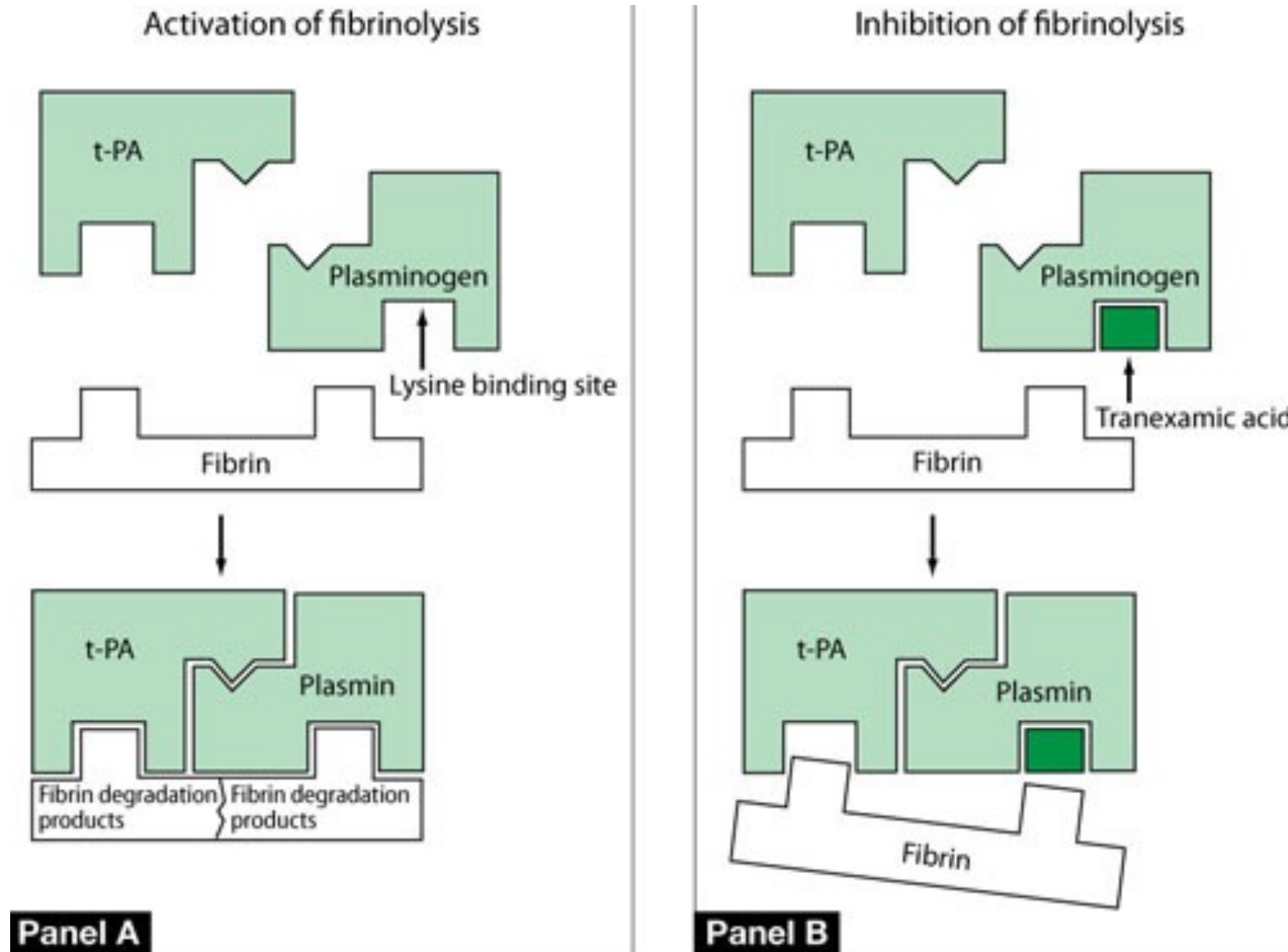
*Factors in PCCs are ~25x more concentrated than the factors in plasma.

†In plasma, total content of factors relative to volume is low; large volumes are required for reversal.

TISSUE INJURY



EACA and TXA are anti-fibrinolytics



Antifibrinolytics

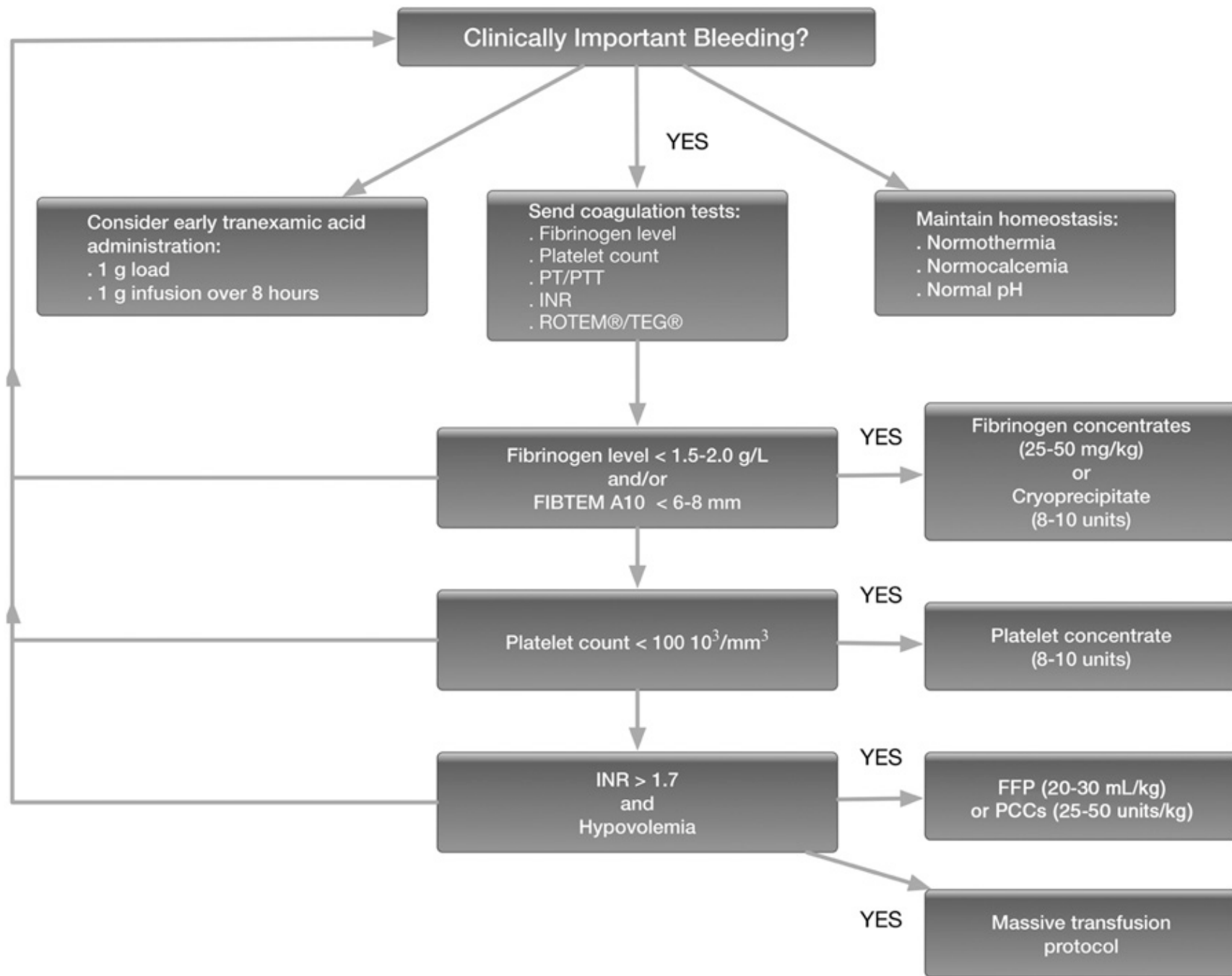
- **CRASH 2 trial** Lancet 2010
 - TXA for trauma: 20,000 randomized to 1gm bolus plus 1 gm over 8 hours vs placebo
 - Early treatment of trauma patients with TXA resulted in better survival, no difference in transfused products
 - Absolute Risk Reduction **1.5%**, 0.8% ARR reduction in death due to bleeding
- **WOMAN trial** Lancet 2017
 - TXA for PPH double blind RCT in **20,000** women
 - Randomized to 1 gm TXA over 10 mins
 - Absolute risk reduction **0.4%** in death due to bleeding; NNT 267
 - No difference in combined outcome of mortality and hysterectomy

Antifibrinolytics

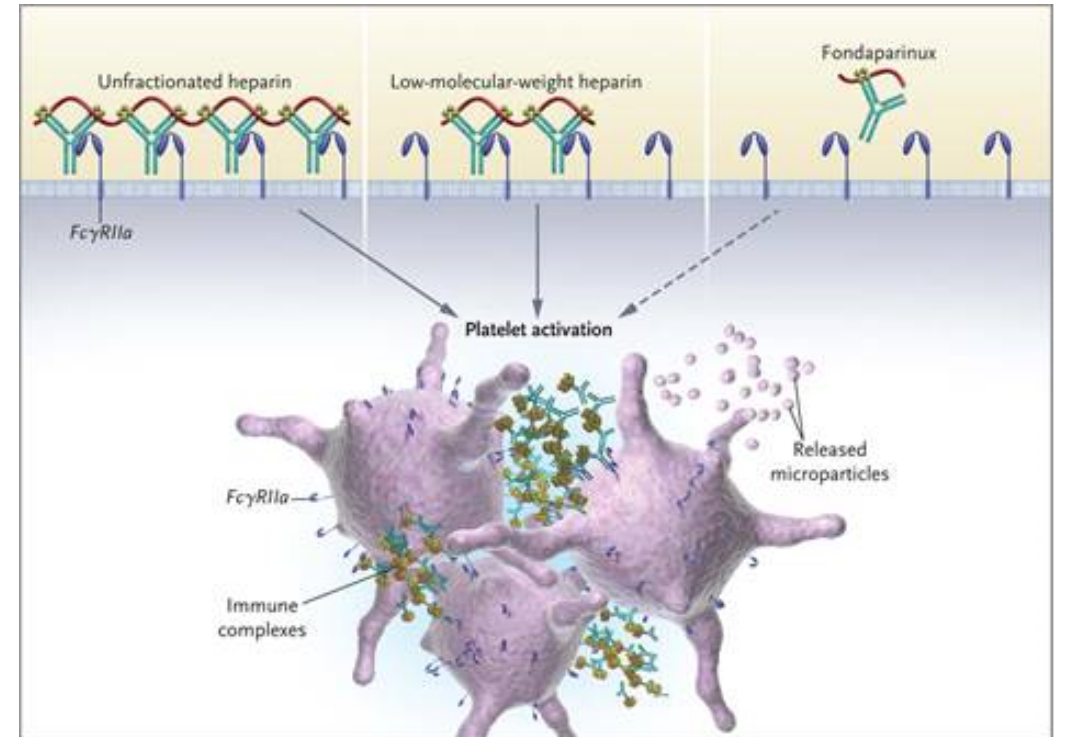
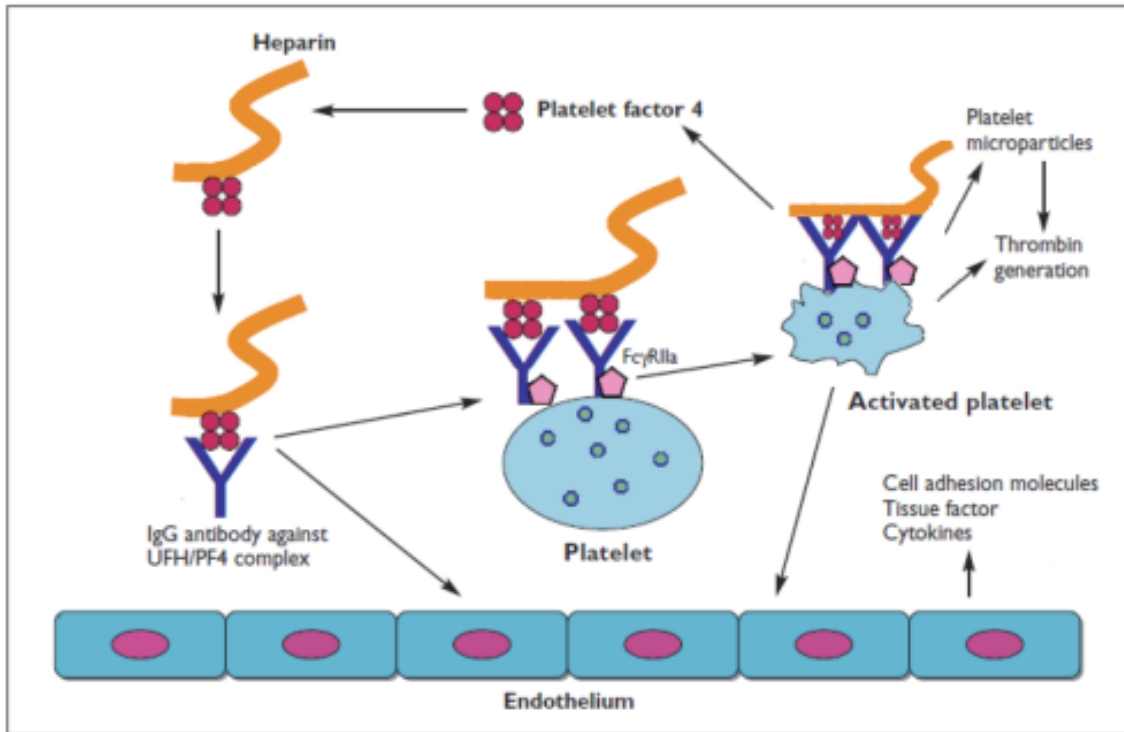
- **TICH-2** Lancet 2018
 - TXA for ICH: **no** difference in mortality or neuro outcomes
- **HALT-IT trial** Lancet 2020
 - GI bleeding
 - **RCT 12,000 patients**
 - loading dose of 1 g tranexamic acid then 3-g infusion over 24 hr
 - **No difference** in mortality
 - Increased VTE 0.8% vs 0.4%
- Why different effects in these trials?
 - Type of bleeding: mucosal ooze vs large holes in vessels?
 - Activation of fibrinolysis in trauma and childbirth
 - heterogeneous GI bleeds?

When to use what

- **Standard blood products should be used when practical**
 - FFP contains everything, less expensive, safe
 - Cryo contains more than just fibrinogen
- **Concentrates should be reserved for**
 - Patients with significant volume overload
 - Patients with single factor deficiencies or specific issues: warfarin, Xa inhibitor DOAC
 - Local storage use faster than obtaining blood products
- **Antifibrinolytics are in vogue but are the frosting, need the cake**



Heparin Induced Thrombocytopenia



BWH 4T Score Sheet

Brigham and Women's Hospital
HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) GUIDELINE

For patients with suspected heparin-induced thrombocytopenia, follow the step-wise approach below

Step 1: Calculate 4 T's Score:

- a. Thrombocytopenia* (platelet fall from baseline of): _____ pts
*Please consider effects of cardiopulmonary bypass on platelets in applicable patients
 Less than 30% (0 pts) 30-50% (1 pt) Greater than 50% (2 pts)
- b. Timing of platelet fall after heparin/LMWH exposure: _____ pts
 4 days or less with no prior exposure in the last 100 days (0 pts)
 Greater than 10 days OR ≤ 1 day and prior exposure in the past 30 to 100 days (1 pt)
 5-10 days OR ≤ 1 day and prior exposure within the past 30 days (2 pts)
- c. Thrombosis or other sequelae: _____ pts
 None (0 pts)
 Suspected thrombosis or non-necrotizing skin lesions (1 pt)
 Confirmed thrombosis, skin necrosis, or systemic reaction to UFH bolus (2 pts)
- d. Thrombocytopenia from oTher causes: _____ pts
 None (2 pts) Possible (1 pt) Definite (0 pts)
- e. Total Score (add a thru d) and determine clinical suspicion _____ pts
 Less than 3 Low Suspicion 3-5 Intermediate Suspicion Greater than 5 High Suspicion

NPV of low-risk score 0.998

HIT: Testing

Heparin /platelet factor 4 ELISA

- immunologic assay detects presence of Ab
- OD > 0.399 considered positive
- repeat in 48 hours if borderline or high clinical suspicion
- high sensitivity (95-99%) but high false +

50% surgical, 20% medical can develop antibodies

--NPV for negative result 95%

Serotonin release assay

- functional assay of ability of complexes to stimulate platelet aggregation/secretion
- gold standard but still not 100% specific or sensitive (88%-100% specificity)

Combined sensitivity PF4 and SRA is 99%

Clinical judgment still required

HIT: Treatment

STOP HEPARIN—all forms including line flush, dialysis; coated lines?

STOP WARFARIN

- If patient on warfarin **and** reverse with Vitamin K

Treat with direct thrombin inhibitors, fondaparinux, DOAC if clinically stable

- **When** clinically improved and platelet count $\geq 150,000$
 - start DOAC or
 - warfarin overlap with DTI for at least 5 days

Warfarin or DOAC rx for at least 3 months—debate about duration if no thrombosis

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Thank you

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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL



Question 1

A 68 yo man in the ICU for hypoxemia due to pneumonia develops altered mental status and is found to have ICH. He is on warfarin anticoagulation for a mechanical valve with an INR of 5.3. You reverse the warfarin with:

- a. FFP
- b. Vitamin K
- c. Cryoprecipitate
- d. 4F-PCC
- e. rVIIa