BRIGHAM HEALTH
BRIGHAM AND WOMEN'S
Department of Medicine

Dana-Farber
Cancer Institute

HARVARD
MEDICAL SCHOOL
Global and Continuing
Education

Bleeding and Clotting Emergencies in the ICU

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Conflicts of Interest

Scientific Ad Boards and Consulting:

- Abbott
- Anthos
- Alnylam
- Bristol-Myers Squibb
- Roche
- Sanofi
- Werfen

Research funding to the Institution

- CSL Behring

Jean M Connors MD

Agenda

Coagulopathy:

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

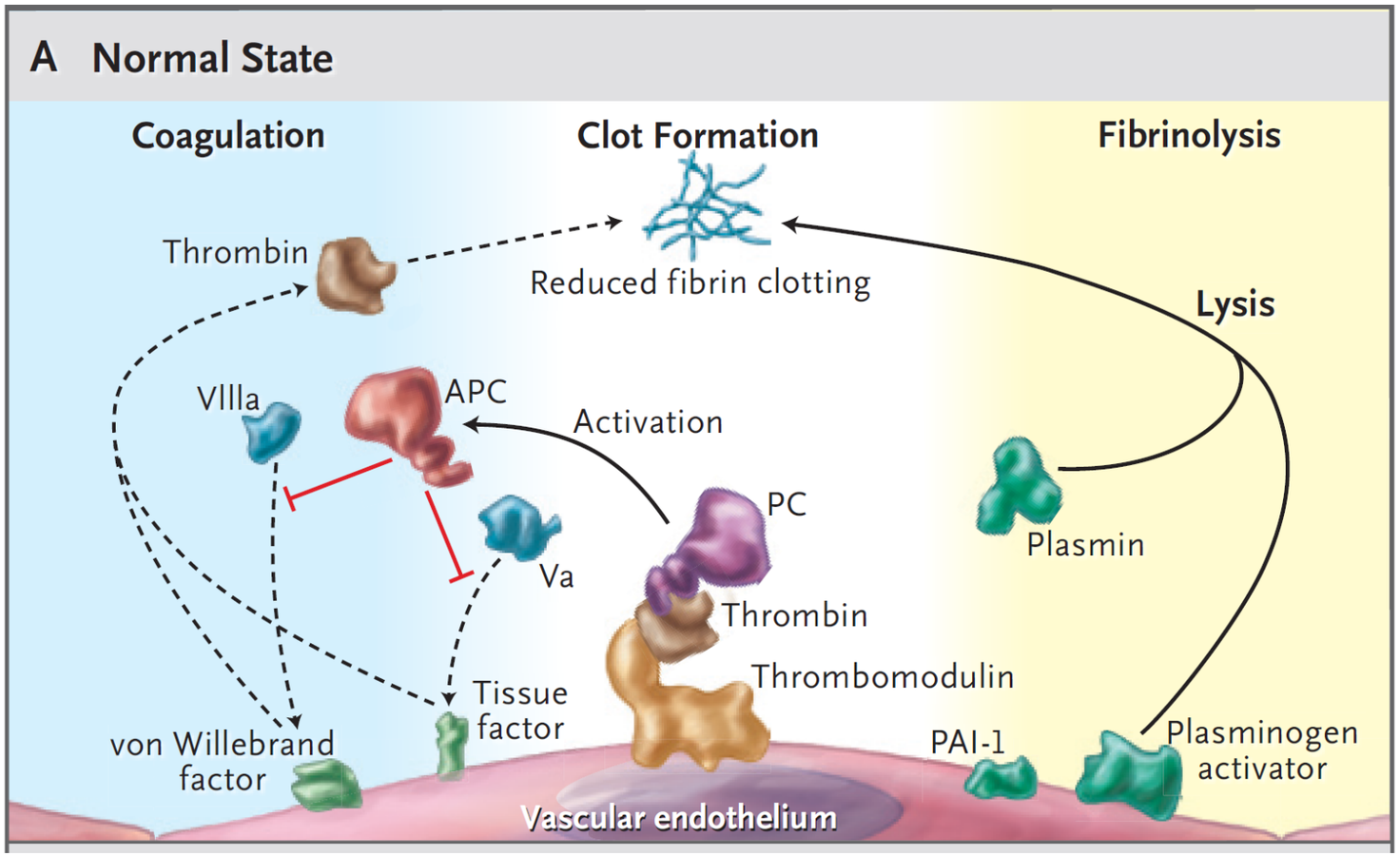
- review of coagulation tests
- available hemostatic products
- DIC
- Cirrhosis
- antifibrinolytics

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

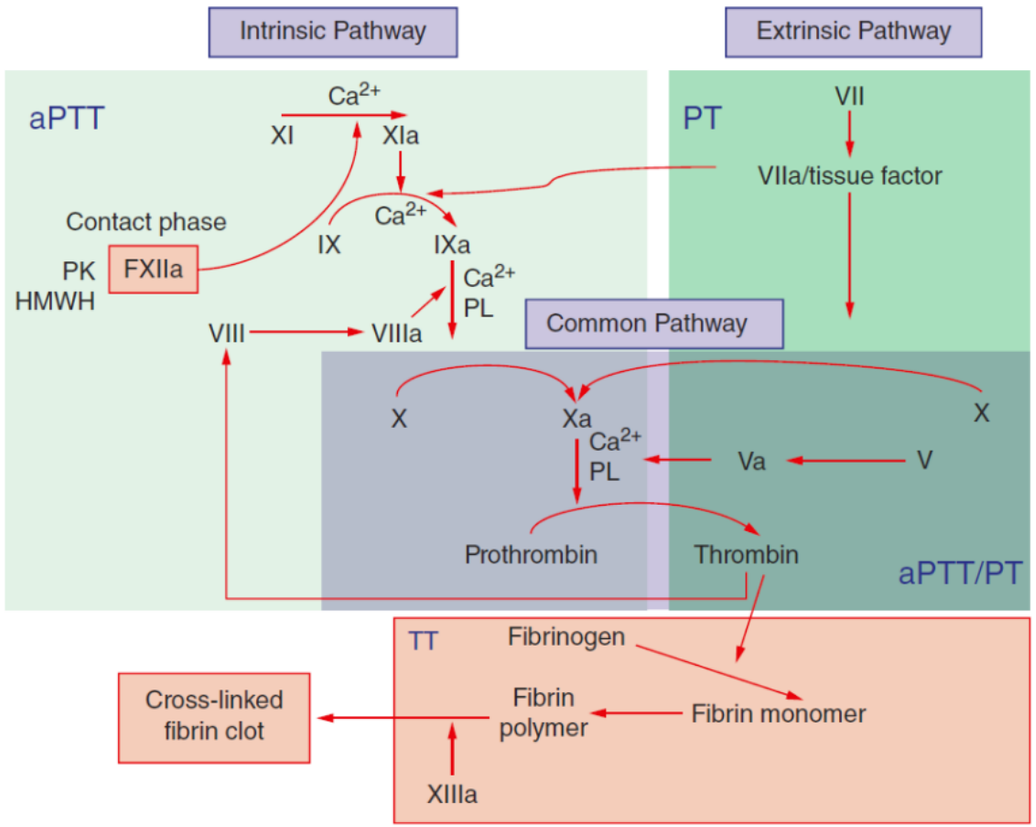
Ideally: normal body temperature, normal pH, normal Ca++

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



Harrison's Textbook of Medicine

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 10^9/L
  - Need for “normal” aPTT or PT?

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, lyophylized
- 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: Factor Eight Inhibitor Bypassing Activity

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.

Zareh M et al. *West J Emerg Med.* 2011;12:386-392. **2**. Bebulin (Factor IX Complex) Prescribing Information. Baxter Healthcare Corporation. July 2012. **3.** Profilnine (Factor IX Complex) Prescribing Information. Grifols Biologicals Inc. August 2011.

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 ≥ 5 DIC

J Thromb Haemost 2007; **5**: 604–6

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**

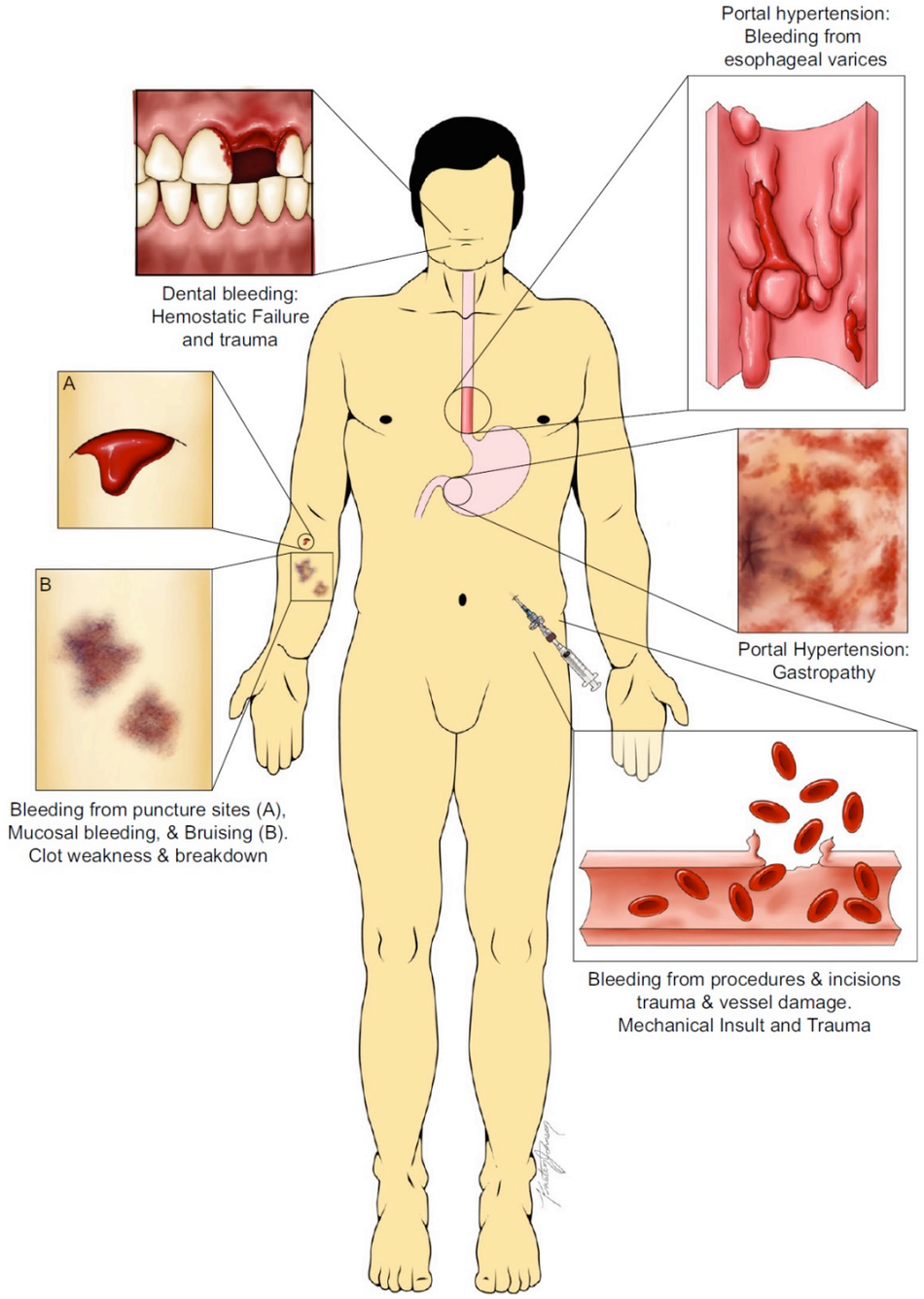
DIC--Management

- Control bleeding, use FFP, cryo, platelets as needed
  - RiaStap, Fibryga: fibrinogen concentrate
  - Kcentra: II, VII, IX, X, proteins S and C (4-PCC)

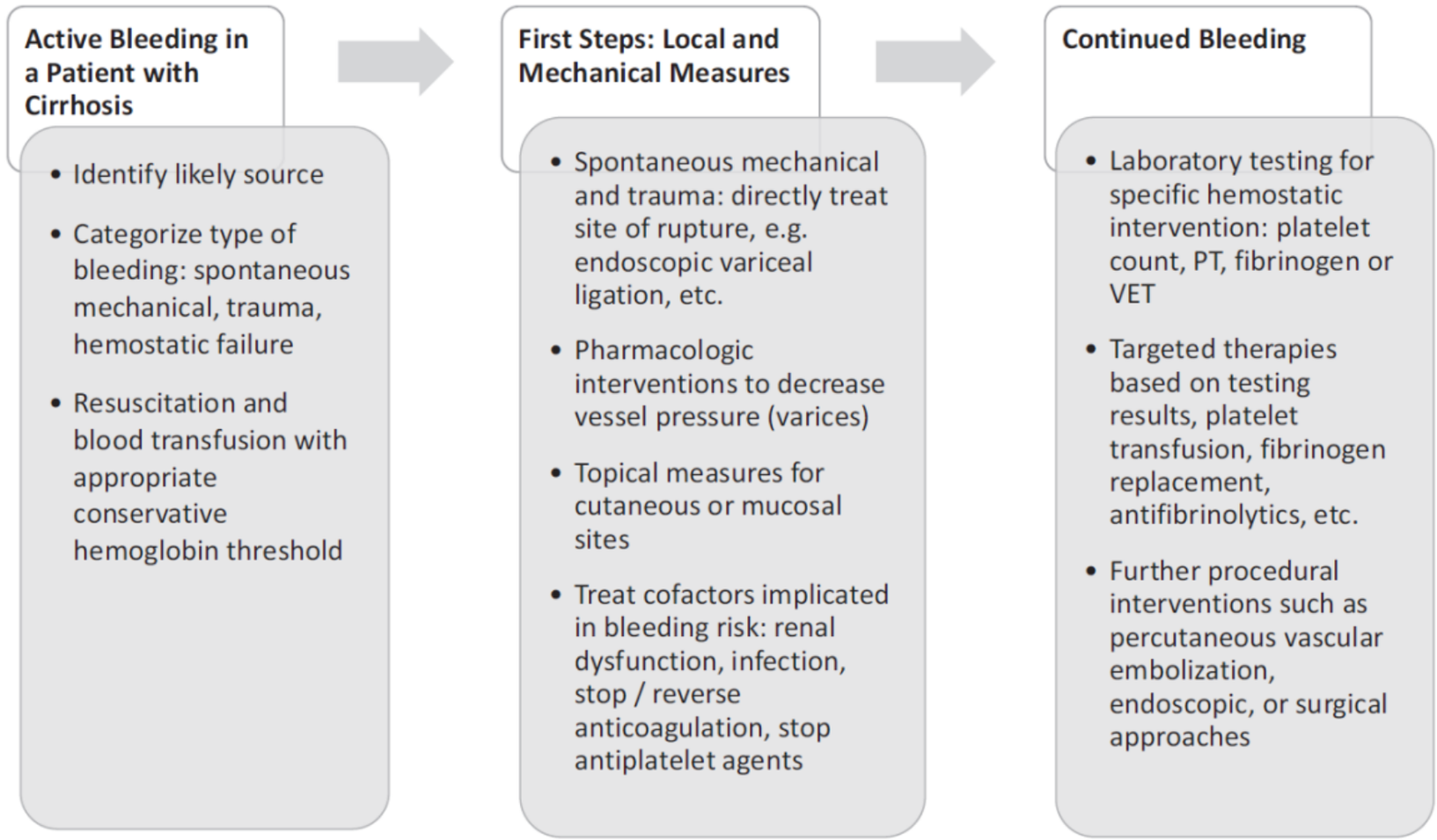
- Role for natural anticoagulant products?
  - **No mortality benefits have been shown for any**
    - Antithrombin
    - Activated protein C (drotrecogin/Xigris)
    - Recombinant thrombomodulin
    - TFPI
    - Other investigational agents: MAPK,IL-10,NAPc2

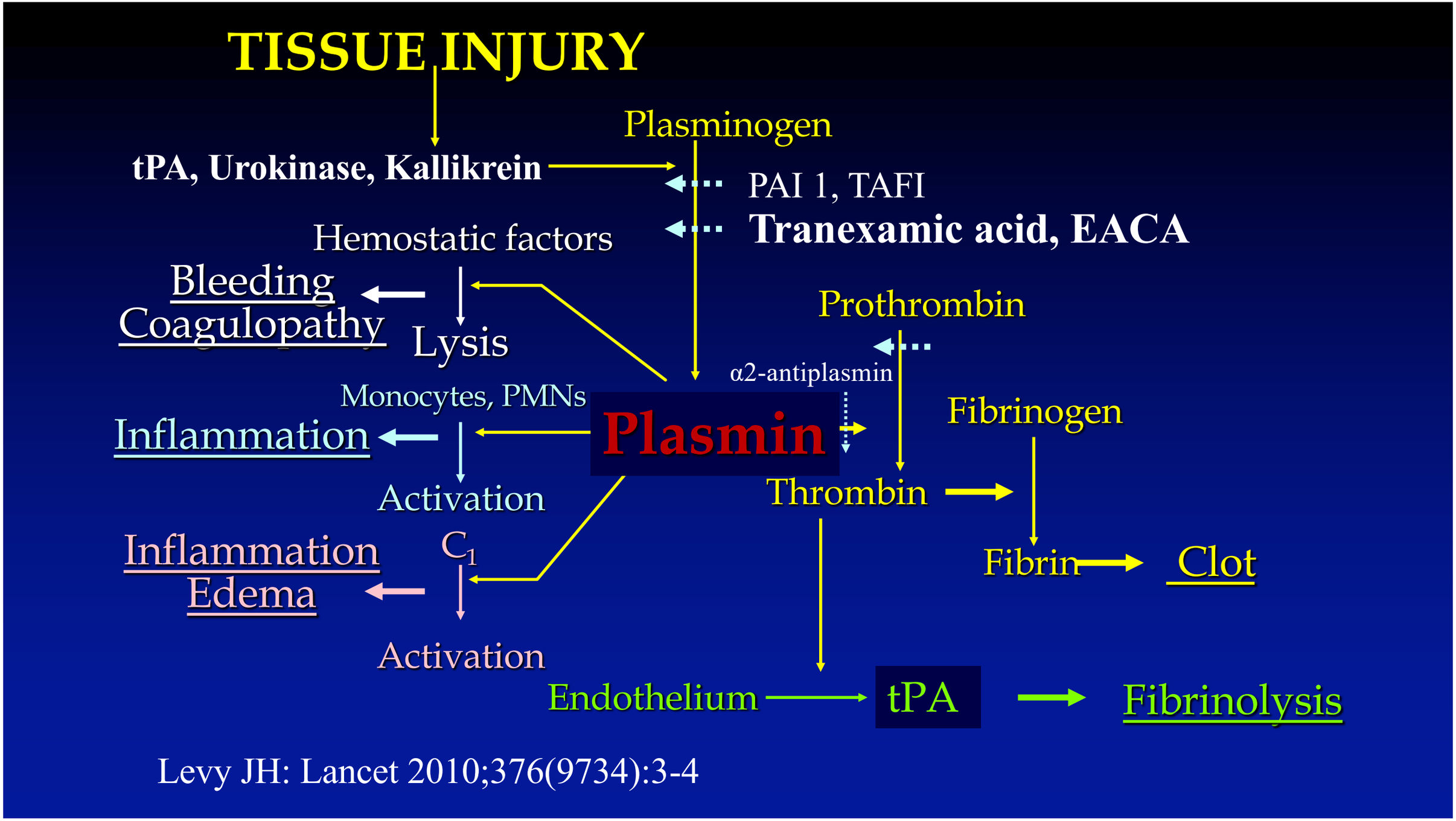
Cirrhosis

- Bleeding can be spontaneous due to mechanical sources such as rupture of varices
- Often acute medical illness on chronic cirrhosis with resultant bleeding due to medical procedures
- Rarely due to end-stage lack of factors



Cirrhosis


Active Bleeding in a Patient with Cirrhosis
• Identify likely source
• Categorize type of bleeding: spontaneous mechanical, trauma, hemostatic failure
• Resuscitation and blood transfusion with appropriate conservative hemoglobin threshold
First Steps: Local and Mechanical Measures
• Spontaneous mechanical and trauma: directly treat site of rupture, e.g. endoscopic variceal ligation, etc.
• Pharmacologic interventions to decrease vessel pressure (varices)
• Topical measures for cutaneous or mucosal sites
• Treat cofactors implicated in bleeding risk: renal dysfunction, infection, stop / reverse anticoagulation, stop antiplatelet agents
Continued Bleeding
• Laboratory testing for specific hemostatic intervention: platelet count, PT, fibrinogen or VET
• Targeted therapies based on testing results, platelet transfusion, fibrinogen replacement, antifibrinolytics, etc.
• Further procedural interventions such as percutaneous vascular embolization, endoscopic, or surgical approaches



Levy JH: Lancet 2010;376(9734):3-4

EACA and TXA are anti-fibrinolytics

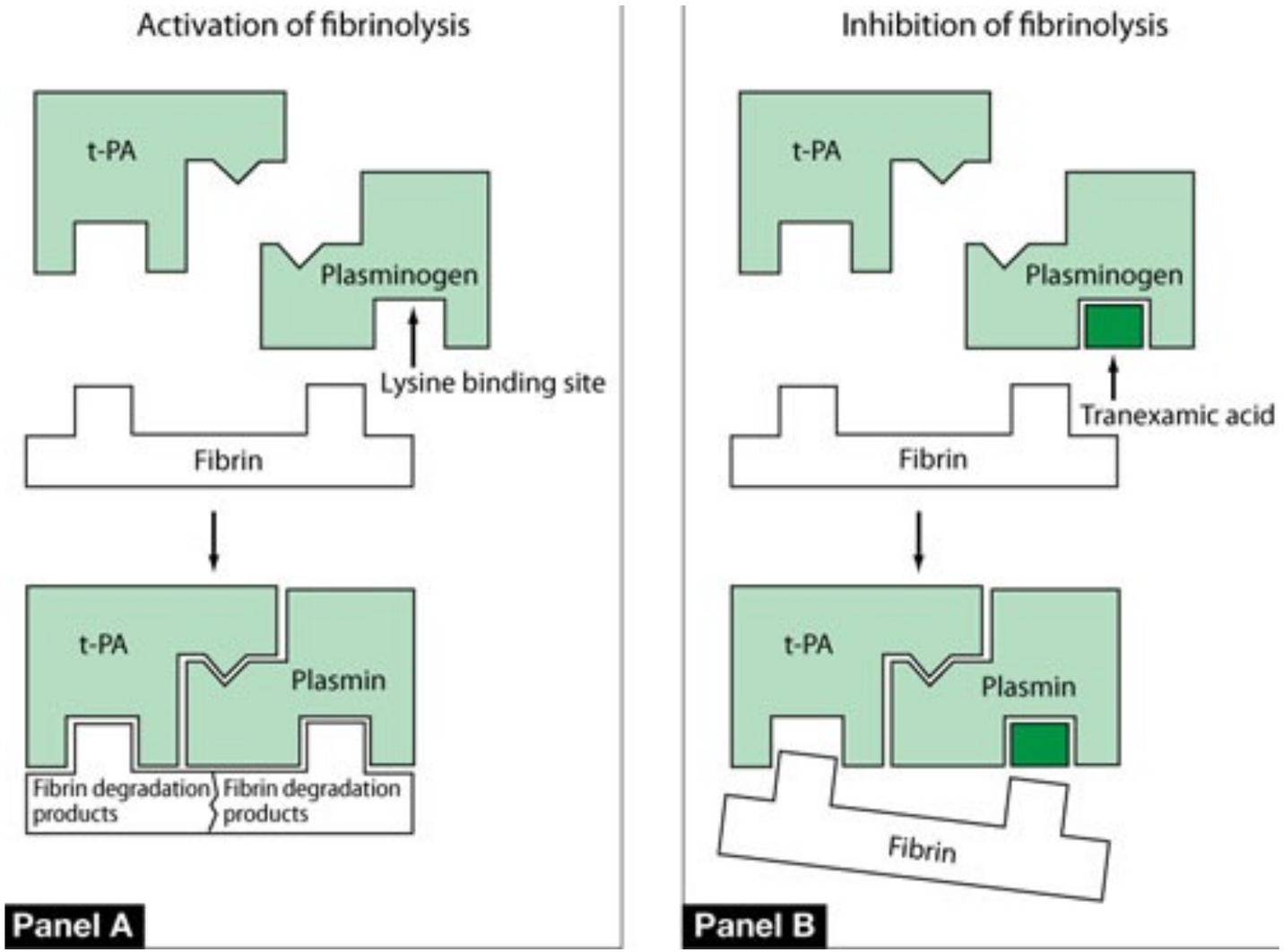


Image from www.obgmanagement.com, Oct. 2010 – Vol. 22, No. 10

Antifibrinolytics

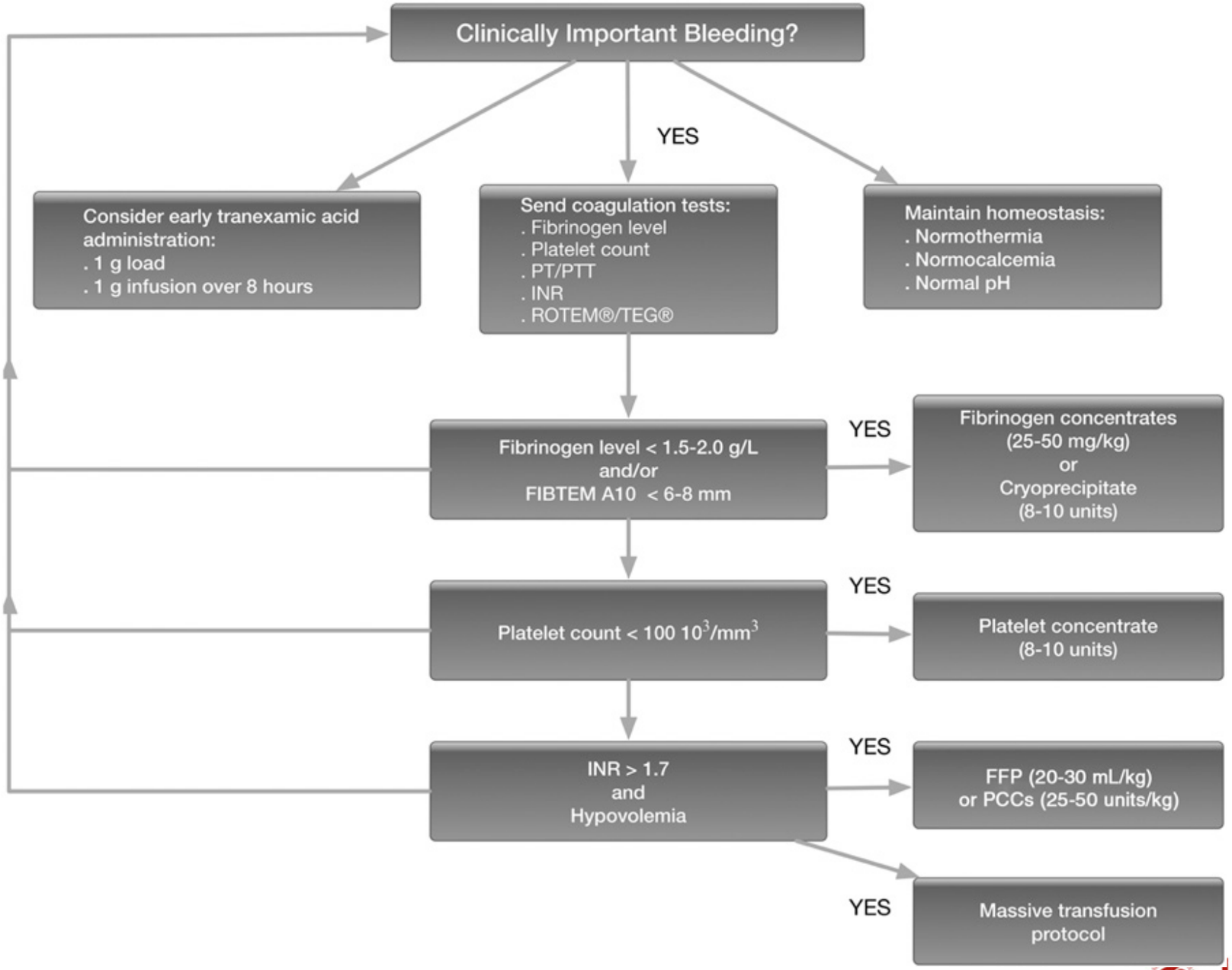
- **CRASH 2 trial** Lancet 2010
  - TXA for trauma: 20,000 randomized to 1gm bolus plus 1 gm over 8 hours vs placebo
  - Early treatment of trauma patients with TXA resulted in better survival, no difference in transfused products
  - Absolute Risk Reduction **1.5%**, 0.8% ARR reduction in death due 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

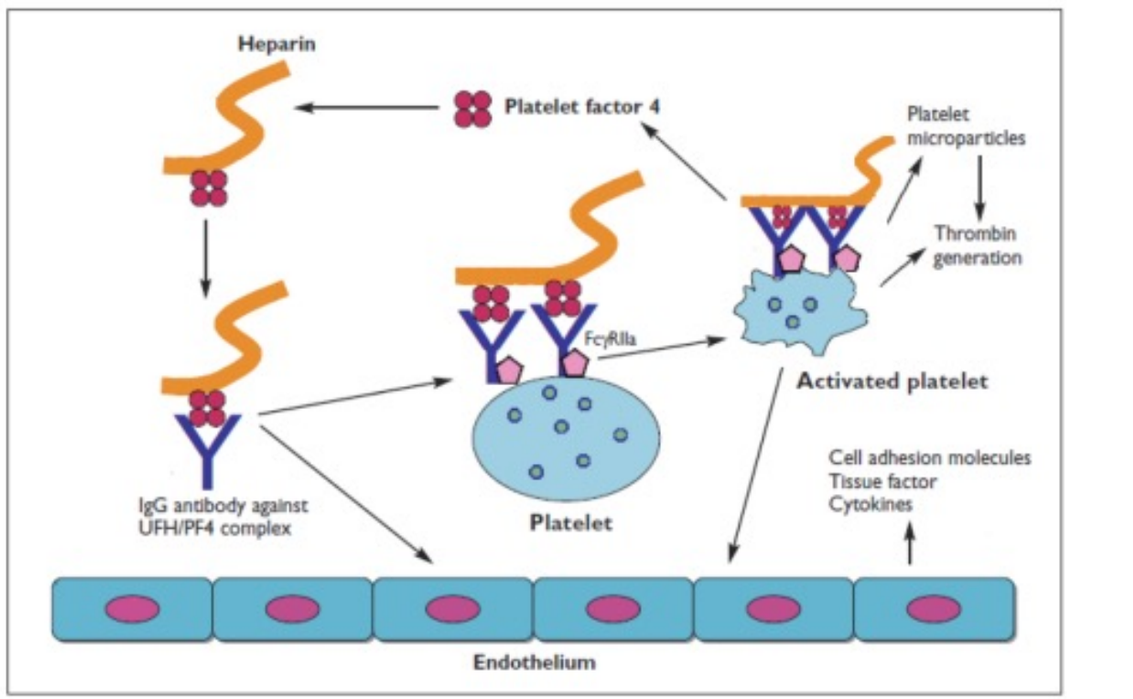
- **Standard blood products should be used when practical**
  - FFP contains everything, less expensive, safe
  - Cryo contains more than just fibrinogen
- **Concentrates should be reserved for**
  - Patients with significant volume overload
  - Patients with single factor deficiencies or specific issues: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

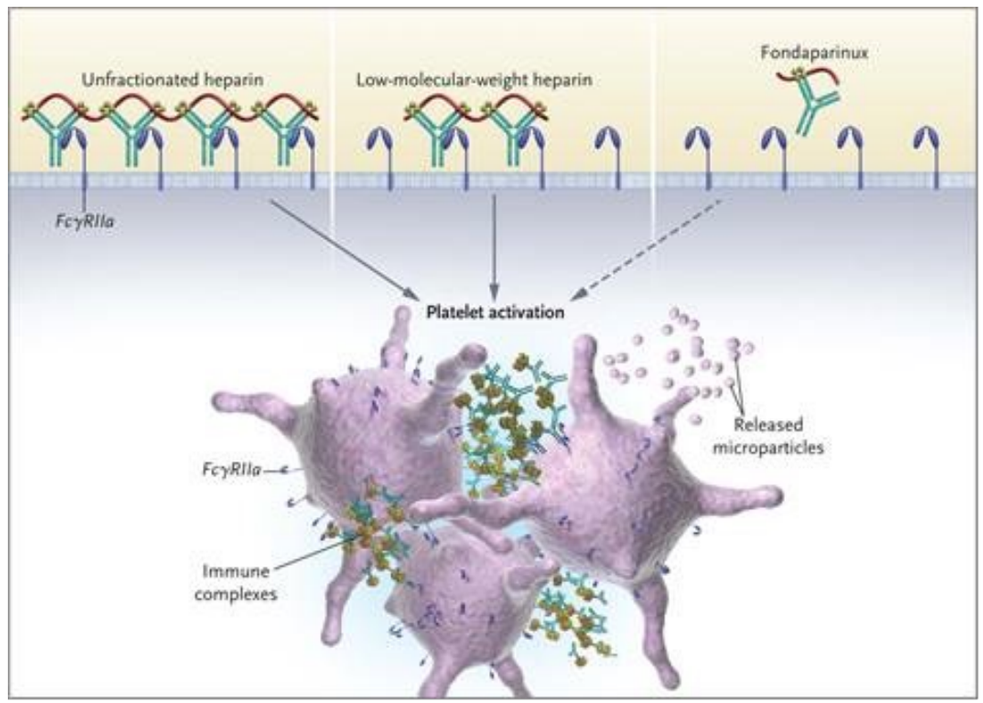


Jerrold H. Levy, and Lawrence T. Goodnough Blood 2015;125:1387-1393

blood

Heparin Induced Thrombocytopenia





Lefkowitz, An Algorithmic Approach to Hemostasis Testing, 2008; Greinacher, NEJM 2015.

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. **T**hrombocytopenia* (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. **T**iming 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. **T**hrombosis 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 o**T**her 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 than5 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 suspicio

--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 ≥ 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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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

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