Blood and Clots

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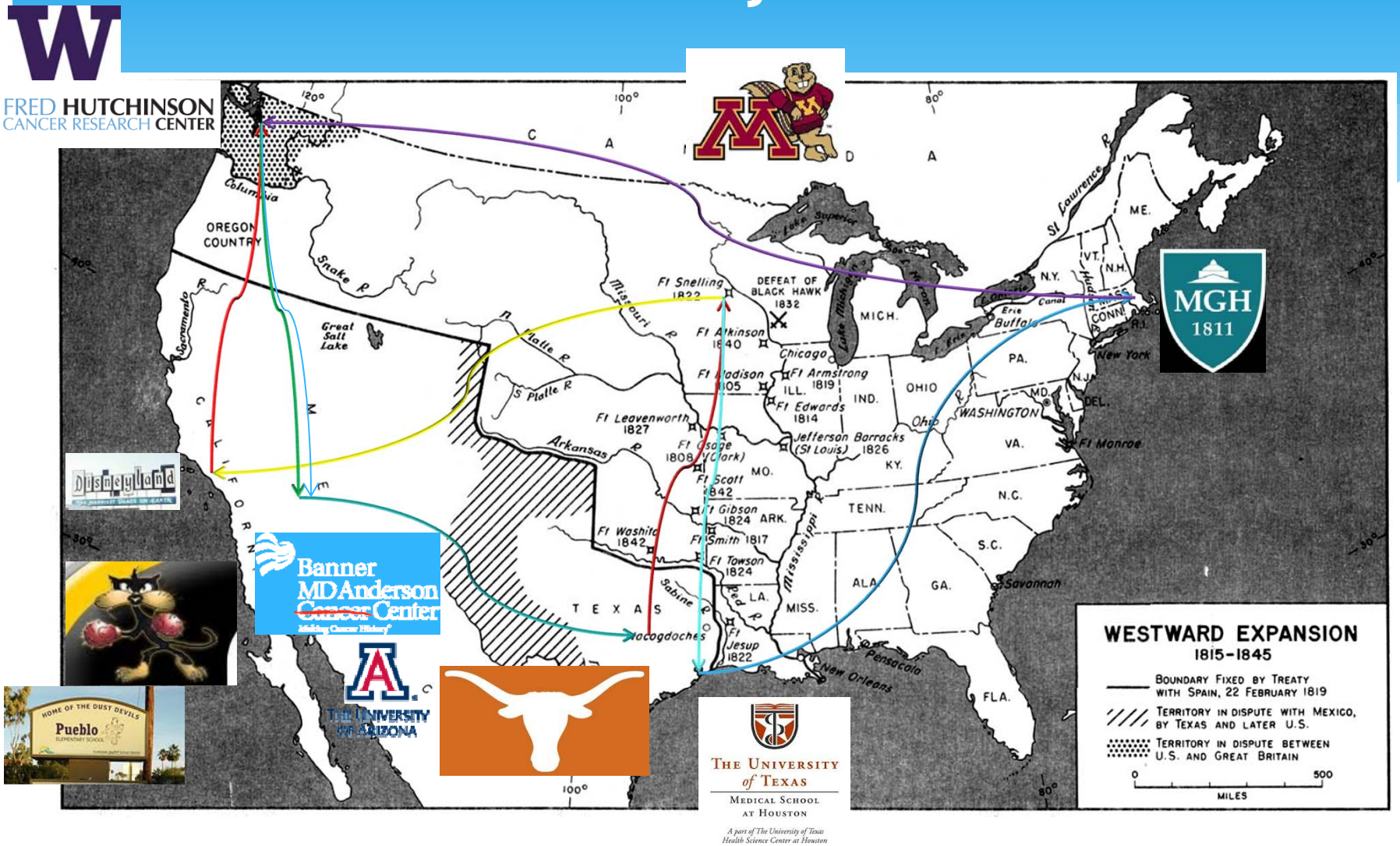
Where are you from?



Warning

* Sitting close to the back increases your risk of traumatic head injury when your speaker has bad aim

Warning

* Sitting close to the back increases your risk of traumatic head injury when your speaker has bad aim
* Helmets may be needed

Warning

* Sitting close to the back increases your risk of traumatic head injury when your speaker has bad aim
* Flying chocolate has been known to cause bleeding
* You can only take some of the things I say seriously

Objectives

* Discuss case-based approach to patients with coagulopathy – both acquired and inherited

The Bleeding History

* 1. Have you or a relative ever been told you had a bleeding problem? Bleeding after surgery? After dental work? With trauma? During childbirth or had heavy menses? Have you ever had bruises with lumps?
* 2. Have you ever required a blood transfusion or had abnormal blood counts? Do you have liver disease?
* 3. Are you currently taking or have you recently taken anticoagulation or antiplatelet medications (warfarin, heparin, aspirin, NSAIDs, clopidogrel)?

Concerning Bleeding symptoms

* Have you ever had any of the following symptoms?
  * Bleeding from trivial wounds lasting >15 minutes or **recurring spontaneously** during the 7 days after the injury?
  * Heavy, prolonged, or recurrent bleeding after surgical procedures?
  * Bruising with minimal or no apparent trauma, especially if you could **feel a lump under the bruise**?
  * Spontaneous nosebleed lasting >10 minutes or that required **medical attention**?
  * Heavy, prolonged, or recurrent bleeding after dental extractions that required **medical attention**?
  * Blood in your stool that required **medical attention** and was unexplained by an anatomic lesion (stomach ulcer, colon polyp)?
  * Anemia that required a **blood transfusion** or other type of treatment?
  * Heavy menses characterized by **clots >1 inch** in diameter, changing a pad or tampon **more than hourly**, or resulting in **anemia** or low iron?

Categorize Bleeding Symptoms

* Characterize bleeding
  * Superficial (mucocutaneous) vs. deep (muscle/joint)
    * Primary Hemostasis (plt, vWF) Coagulation factors
  * Spontaneous vs. Secondary (trauma, surgery, tooth extraction, menses, pregnancy/post partum)
  * Immediate vs. delayed
  * Acute (acquired) vs. lifelong (hereditary)
* Family history (X-linked/autosomal)
* Medications (e.g. aspirin, warfarin, EtOH)
* Comorbid disease (liver disease, uremia, malignancy)

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Case 1-Presentation

- 22-year old man presents to the ED
- Spontaneous knee and hip pain; similar to prior episodes. Also RLQ pain
- No prior surgeries
- Maternal grandfather died of bleeding complications
- Exam: Chronic knee & elbow joint deformities, RLQ pain worse with leg straight

Case 1 - Laboratory Results

		Normal Values
Platelet count	250,000/µl	150 – 400,000/µl
Fibrinogen	300 mg/dl	150 – 400 mg/dl
Prothrombin time	11 sec (INR=0.8)	11 – 13.6 sec
Partial thromboplastin time	130 sec	24 – 36 sec

What do you want to order next?

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Case 1 - Laboratory Results

	Normal Values
Platelet count 250,000/µl	150 – 400,000/µl
Fibrinogen 300 mg/dl	150 – 400 mg/dl
Prothrombin time 11 sec (INR=0.8)	11 – 13.6 sec
Partial thromboplastin time 130 sec	24 – 36 sec

1:1 mixing study leads to correction of PTT to 26 sec

Correction on mixing suggests factor deficiency

Case 1 Laboratory Results

Specific Factor Activity Assay:	*Normal Range*
Factor VIII:C = 90%	50 – 150%
Factor IX:C = < 1%	50 – 150%

What is the diagnosis?

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Case 1 Diagnosis of Hemophilia

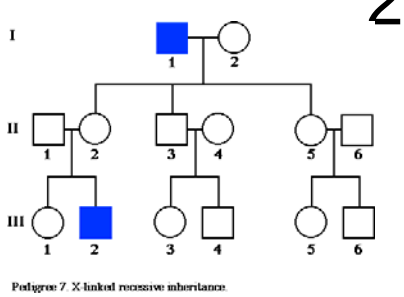
Inheritance: X-linked recessive (no male/male transmission)

Severity: Varies between families/mutations; ~ half severe

Screening test ↑ partial thromboplastin time (PTT)
(corrects with 1:1 mixing)

Confirm with genetic testing

Specific:	**A** 8	**B** 9
Clotting activity	↓ FVIII:C	↓ FIX:C
		(normal VWF:Ag)
Frequency	75-80%	20-25%



Pedigree 7 X-linked recessive inheritance

Treat by replacing missing factor with recombinant product

Cryo contains FVIII but must use FFP for FIX

Case 1 Family Testing

- 20-year old sister's factor IX:C = 60%
- DNA: Factor IX gene heterozygous for brother's hemophilic nonsense mutation

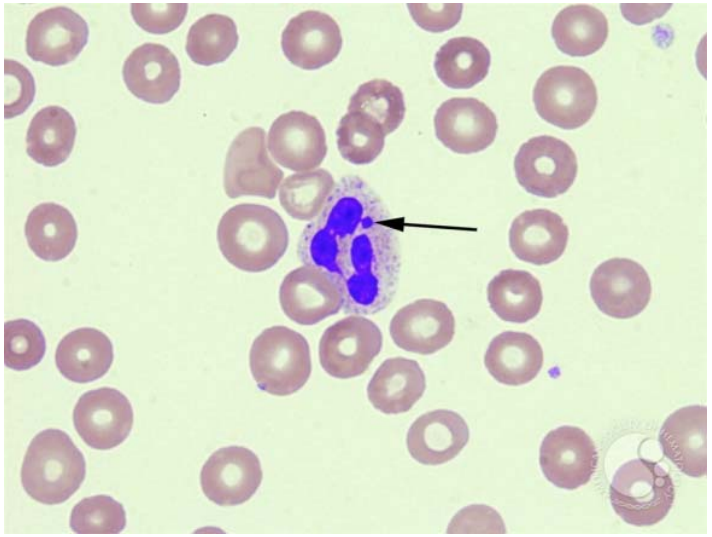


Image Courtesy of Jon Fukumoto

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Case 1 Family Testing

- 20-year old sister's factor IX:C = 60%
- DNA: Factor IX gene heterozygous for brother's hemophilic nonsense mutation

Females can have symptoms of mild hemophilia based on X-inactivation pattern

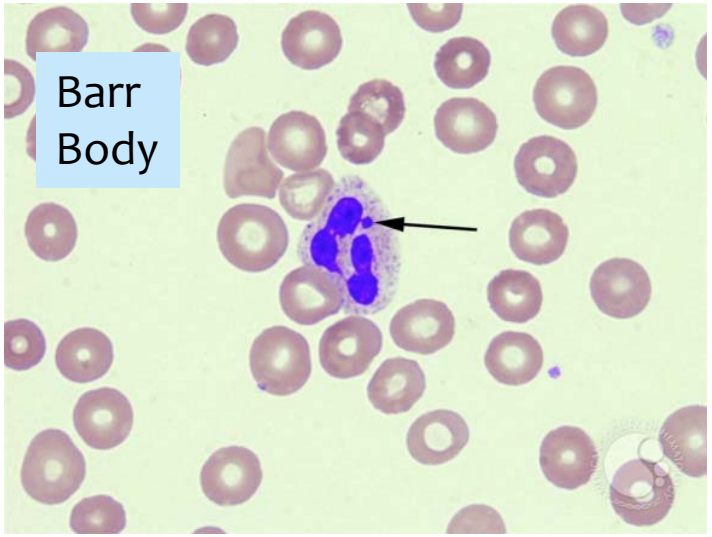

Image Courtesy of Jon Fukumoto

Usually must have factor <40% to have bleeding symptoms

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Case 2 - Presentation

- 30yo male physician, presents with melena, UGI bleed
- PMHx: transfused at 15yo for spontaneous GI bleed; oozed 5 days post prior tooth extraction
- Father with history of abnormal bleeding
- Upper endoscopy is negative for focal lesion

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Case 2 Laboratory Results

patient	*normal values*
Platelet count = 250,000/µl	150 – 400,000/µl
Prothrombin time = 12 sec (INR=1.0)	11 – 13.6 sec
Partial thromboplastin time = 58 sec	24 – 36 sec
Thrombin time = 20 sec	18 – 28 sec
Fibrinogen = 294 mg/dl	150 – 400 mg/dl

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Case 2 Laboratory Results

patient	*normal values*
Platelet count = 250,000/µl	150 – 400,000/µl
Prothrombin time = 12 sec (INR=1.0)	11 – 13.6 sec
Partial thromboplastin time = 58 sec	24 – 36 sec
Thrombin time = 20 sec	18 – 28 sec
Fibrinogen = 294 mg/dl	150 – 400 mg/dl

Mixing time corrects PTT to 27 sec

Next Tests?

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Case 2: vWF Roles in Hemostasis

1. Enhance platelet function:

   platelet adhesion to vascular endothelium
   - binds to platelet membrane glycoprotein Ib
   - depends upon high mol wt VWF multimers

2. Facilitate coagulation:

   binds & stabilizes circulating FVIII
   - depends upon amino-terminal VWF residues

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vWD is the most common bleeding disorder

Present in ~15% of women who undergo hysterectomy for menorrhagia (without structural cause)

Case 2 - Diagnosis of vWD

Clinical: varies from mild, type 1, to severe, type 3

Laboratory:	Screen	Specific assays
1. Platelet function	↑bleeding time plt function	↓ vWF:Antigen (except type 2) ↓ vWF activity (except 2N) (ristocetin cofactor assay)
2. FVIII activity	↑PTT	mild ↓ Factor VIII:C level

Specific subtype: VWF multimer analysis/genotype (types 2A/B)

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Von Willebrand Factor stabilizes Factor VIII, so decreased FVIII t ½ and activity with vWD

vWD Subtypes

Type	Inheritance	Deficiency
Type 1	Autosomal dominant	Quantitative
Type 2	Autosomal dominant	Qualitative
Type 3	Autosomal recessive	Severe/absent

Case 2 - Specific Assay Results

patient	*normal values*
vWF antigen level = 30%	50 – 150%
Ristocetin cofactor assay = 25% (vWF activity)	50 – 180%
FVIII:C activity = 20%	50 – 180%
Multimer analysis: normal pattern	

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Treatment of VWD

- DDAVP (des-amino-D-arginine vasopressin)
  - stimulates VWF/FVIII vascular endothelial release
  - useful to treat or prevent bleeding in mild VWD
  - not helpful in VWD type 2B
- vWF containing FVIII concentrates (e.g. Humate-P)
- vWF concentrates *(recombinant completed ph III trial)*
- Cryoprecipitate, can use if concentrate not available

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Case 3 - Presentation

* 60yo man presents with thigh hematoma
* No prior bleeding history
* No family history of bleeding
* Prior diagnosis of rheumatoid arthritis

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Case 3 Laboratory Results

	patient	*normal values*
Platelet count	= 250,000/µl	150 – 400,000/µl
Prothrombin time (INR=1.0)	= 12 sec	11 – 13.6 sec
Partial thromboplastin time	= 100 sec	24 – 36 sec
Thrombin time	= 20 sec	18 – 28 sec
Fibrinogen	= 294 mg/dl	150 – 400 mg/dl

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Case 3 Laboratory Results

patient	*normal values*
Platelet count = 250,000/µl	150 – 400,000/µl
Prothrombin time = 12 sec (INR=1.0)	11 – 13.6 sec
Partial thromboplastin time = 100 sec	24 – 36 sec
Thrombin time = 20 sec	18 – 28 sec
Fibrinogen = 294 mg/dl	150 – 400 mg/dl

1:1 Mixing initially corrects the PTT to normal, but at one hour the incubated PTT returns to 100 sec

Next Tests?

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American Board of Internal Medicine

Factor VIII Inhibitors

* Measured in 'Bethesda units'
* Consume Factor VIII – 'acquired hemophilia'
* Associated with autoimmune and malignant diagnoses, can also rarely occur post-partum
* Significant morbidity and mortality associated

* Treat bleeding with bypass agents (rFVIIa or prothrombin complex concentrate (PCC))
  * FFP will not correct coagulopathy from inhibitor
* Treat inhibitor with immune suppression (steroids, rituximab)

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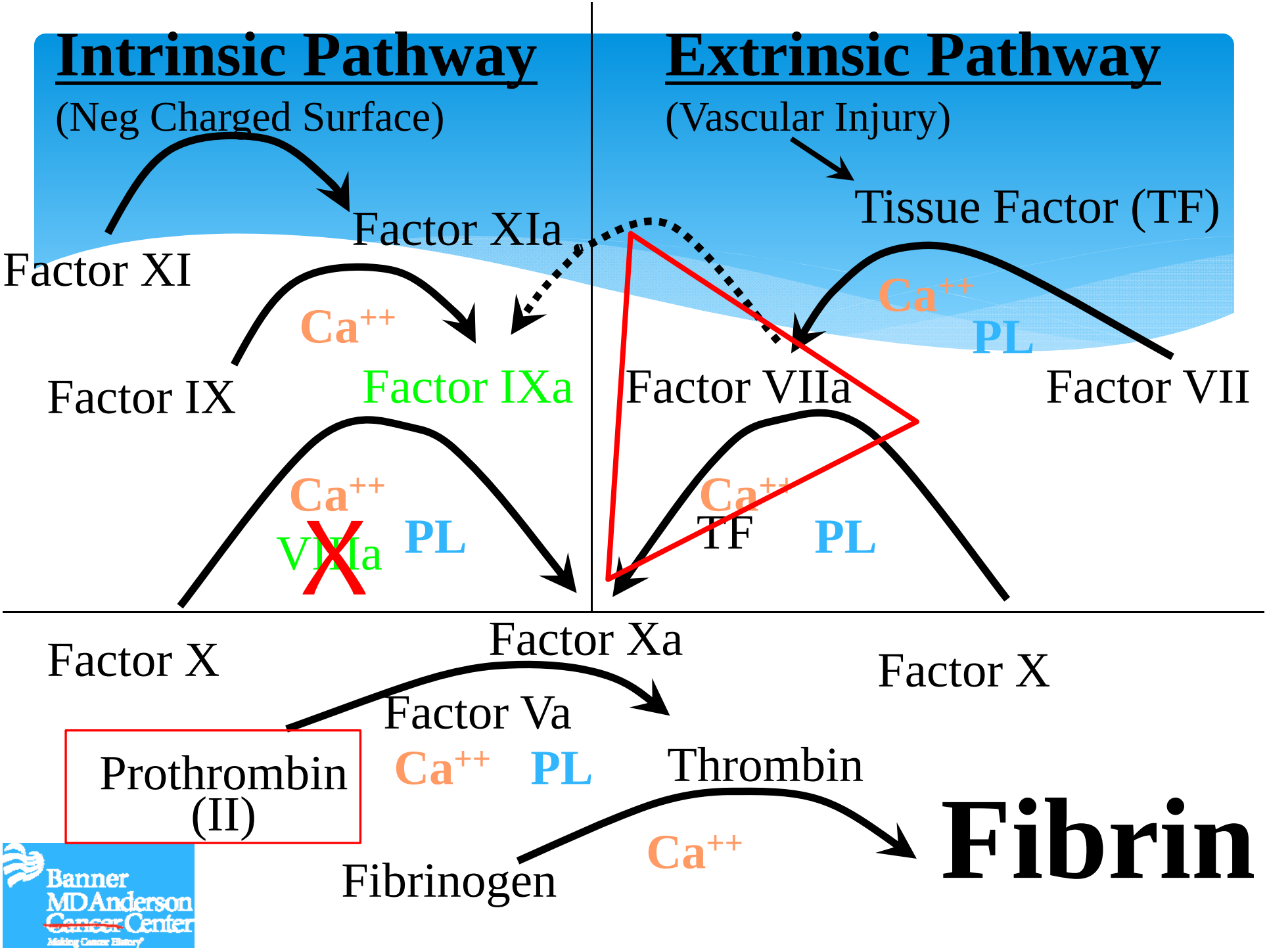
Intrinsic Pathway
(Neg Charged Surface)
Extrinsic Pathway
(Vascular Injury)
Tissue Factor (TF)
Factor XI
Factor XIa
Ca++
Factor IX
Factor IXa
Ca++
PL
Factor VIIa
Factor VII
Ca++
VIIIa
X
PL
Ca++
TF
PL
Factor X
Factor Xa
Factor X
Factor Va
Ca++
PL
Prothrombin
(II)
Thrombin
Ca++
Fibrinogen
Fibrin

Case 4

* A 66yo alcoholic man presents with hematemesis
* He has a prior history of IVDU and hepatitis C
* On exam he is icteric with palmar erythema, spider angiomata, gynecomastia, and caput. He has very limited peripheral veins noted on exam
* HR 115 BP 96/42
* CBC 2.4>7.1<42 ANC 1200
* Albumin 2.1 INR 2.8 PTT 65 sec

Case 4

* A 66yo alcoholic man presents with hematemesis
* He has a prior history of IVDU and hepatitis C
* On exam he is icteric with palmar erythema, spider angiomata, gynecomastia, and caput. He has very limited peripheral veins noted on exam
* HR 115 BP 96/42
* CBC 2.4>7.1<42 ANC 1200
* Albumin 2.1 INR 2.8 PTT 65 sec

What additional hematologic test would you order?

Case 4 - Cirrhosis

* Fibrinogen = 65 (thrombin time 37 sec (18-28sec))
  * Decreased production
  * Abnormal function (increased thrombin time)
  * Level <75 can spuriously increase the INR and PTT
  * Treatment: Replacement with cryoprecipitate for level <100

Liver Disease and Hemostatic Defects

Screening Test Result	Etiology
Platelets	
- Thrombocytopenia	↓thrombopoietin (made by liver) Folate deficiency (possible) Toxic EtOH effects ↑ splenic pooling (splenomegaly)
Coagulation	
- Prolonged PT & PTT	↓ vitamin K-dependent carboxylation ↓ factor synthesis (II,VII,IX & X)
- Prolonged thrombin time	Dysfibrinogenemia ↓ FDP clearance
- Low fibrinogen	↓ synthesis

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Case 4 - cont

* The nurse informs you that they are unable to get peripheral access.
* What do you recommend?

Can you place a line?

* Prospective study (N = 658) of patients with liver disease and coagulopathy
* All underwent CVC insertion
* 1 major bleeding complication (hemothorax) due to inadvertent subclavian artery puncture.
* Average INR of patients was 2.4; all thrombocytopenic
* Rates of superficial hematoma and ooze were increased compared to other populations, though these correlated more with number of passes required and ease of guidewire insertion than with INR or platelet count.
  * Intensive Care Med (1999) 25: 481-485

How about IR?

* Tunneled lines placed in interventional radiology
  * at least 25k platelets
  * INR less than 2.0
  * N=626 with either platelets <50k, INR >1.5, or both
  * No bleeding complications noted

* J Vasc Interv Radiol 2010;21:212–217

Transfusion Recs

* Platelets (usually last 3-5 days)
  * For major bleeding or on anticoagulation, >50k
  * For minor bleeding (epistaxis, gum bleeding) >30k
  * With no bleeding >10k (Stanworth, NEJM 2013. 368:1771)
* FFP
  * If active bleeding or need for procedure and INR >2
  * Effects wane after 4 hours, so must time procedure well
    * This often precludes a 'check then send' approach unless sent stat and procedure team immediately available
  * If no bleeding, no FFP regardless of INR
    * (*possibly for anticoagulation reversal)
* Cryo
  * 1 unit per 10kg body weight for fibrinogen <100 in setting of bleeding

Case 5

* 83yo man with atrial fibrillation presents after a fall. His wife reports that he is on dabigatran.
* He is confused and has an ecchymosis on the R forehead
* CT scan reveals an 8mm subdural hemorrhage

* CBC 5.7>12.5<140
* Cr 1.5 INR 1.1 PTT 38 sec

What additional testing do you recommend?

Target Specific Oral Anticoagulants

* Target-specific oral Anticoagulant bleeding

Anticoagulant	Mechanism	Laboratory testing
Dabigatran	Direct thrombin inhibitor	Thrombin time elevated
Rivaroxaban	Factor Xa inhibitor	Anti-Xa activity
Apixaban	Factor Xa inhibitor	Anti-Xa activity

Anticoagulant Reversal

GENERIC (BRAND) NAMES	ELIMINATION HALF-LIFE	REMOVED BY HD	STRATEGIES TO REVERSE OR MINIMIZE DRUG EFFECT
apixaban *(Eliquis)*	8-15 hours (longer in renal impairment)	NO	• Drug activity can be assessed with anti-factor Xa activity assay • If ingested within 2 hours, administer activated charcoal • **Adexanet** *its)* **NOT** d will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown
argatroban	40 – 50 minutes	~ 20%	• Turn off infusion • Degree of reversal can be assessed with PTT and/or plasma-diluted thrombin time
bivalirudin *(Angiomax)*	25 minutes (up to 1 hr in severe renal impairment)	~ 25%	• Turn off infusion • Degree of reversal can be assessed with plasma-diluted thrombin time
dabigatran *(Pradaxa)*	14-17 hours (up to 34 hrs in severe renal impairment)	~ 65%	• Drug activity can be assessed with aPTT and/or plasma-diluted thrombin time • **Idarucizumab** *its)* **NOTE:** PCC may partially correct aPTT and plasma-diluted thrombin time but will not increase drug clearance; correlation of lab results with reduction in bleeding risk is unknown
Rivaroxaban *(Xarelto)*	Healthy: 5-9 hrs Elderly: 11-13 hrs (longer in renal impairment)	NO	• Drug activity can be assessed with anti-factor Xa activity • **Adexanet** *units)* **N** y and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown

Siegal et al. N Engl J Med. 2015;373(25):2413-24

Crossing the Bridge

* Patients with Atrial Fibrillation (did not include DVT)
* LMWH vs placebo: start 3 days before procedure until 24 hours before procedure and continue for 5 -10 days after the procedure.
* Warfarin treatment stopped 5 days before procedure and resumed within 24 hours after procedure
* Incidence of arterial thromboembolism
  * 0.4% in the no-bridging group
  * 0.3% in the bridging group
* Incidence of major bleeding
  * 1.3% in no-bridging group
  * 3.2% in the bridging group

Douketis et al. *N Engl J Med* 2015; 373:823-833

Questions

American Society of
Hematology
www.hematology.org

The Coagulation Cascade

Slides courtesy of Alice Ma, M.D.

Coagulation Cascade

The PTT Pathway

The PT Pathway

Rather than thinking about the intrinsic and the extrinsic pathways, think about the PTT and the PT pathways.

Coagulation Made Easy

The PTT Pathway

The PT Pathway

The PT and the PTT pathway meet at Factor X, because “X” marks the spot.

Coagulation Made Easy

The PTT Pathway

The PT Pathway

Factor V is a cofactor for Factor X, and you can remember this because V fits into the notch of the X.

Coagulation Made Easy

The PTT Pathway

The PT Pathway

Prothrombin

Thrombin

Factor Xa converts prothrombin (Factor II) into thrombin, the most important enzyme on the planet.

Coagulation Made Easy

The PTT Pathway

The PT Pathway

Thrombin, among other things, converts the soluble molecule fibrinogen into a solid fibrin clot.

Prothrombin

Thrombin

Fibrinogen

Fibrin

The Common Pathway = Small Bills

V + X

II = prothrombin

I = fibrinogen

You can remember the factors in the common pathway by remembering the bills in your wallet smaller than a $20. *Don't forget the $2 bill!*

Coagulation Made Easy: The PT

The PT Pathway

7

PT has one less letter than PTT, and PT values are shorter than PTT values, because the pathway is shorter. It means that the PT pathway is also shorter. This means that there's fewer steps to remember, and this is lucky, so the lucky PT pathway uses lucky Factor 7 to activate Factor X.

Prothrombin

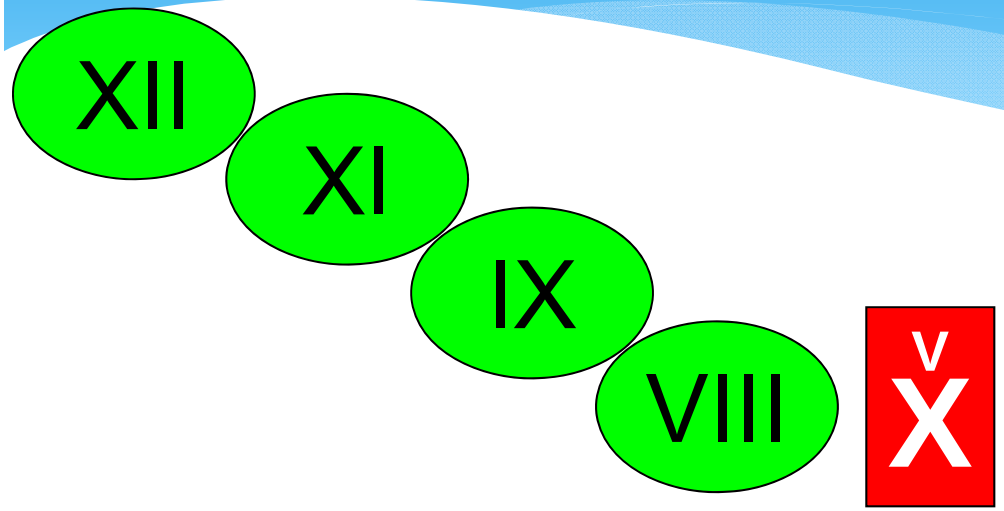
Thrombin

Fibrinogen

Fibrin

Coagulation Made Easy: The aPTT

The PTT Pathway



The PTT pathway has all those hideous roman numerals. . .

How are we going to remember them? Hmmmmm. . .

Prothrombin

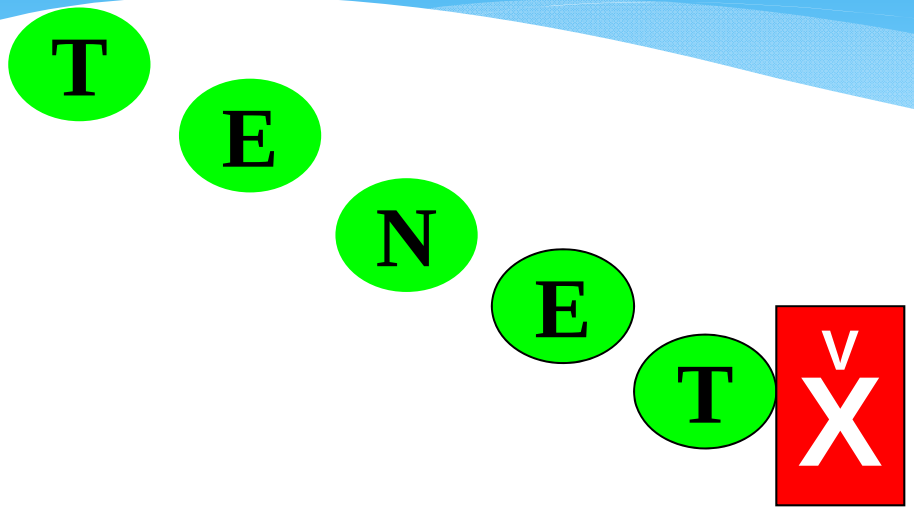
Thrombin

Fibrinogen

Fibrin

Coagulation Made Easy: The aPTT

The PTT Pathway



Well, just remember that the PTT is a basic TENET of hematology.

TENET stands for. . .

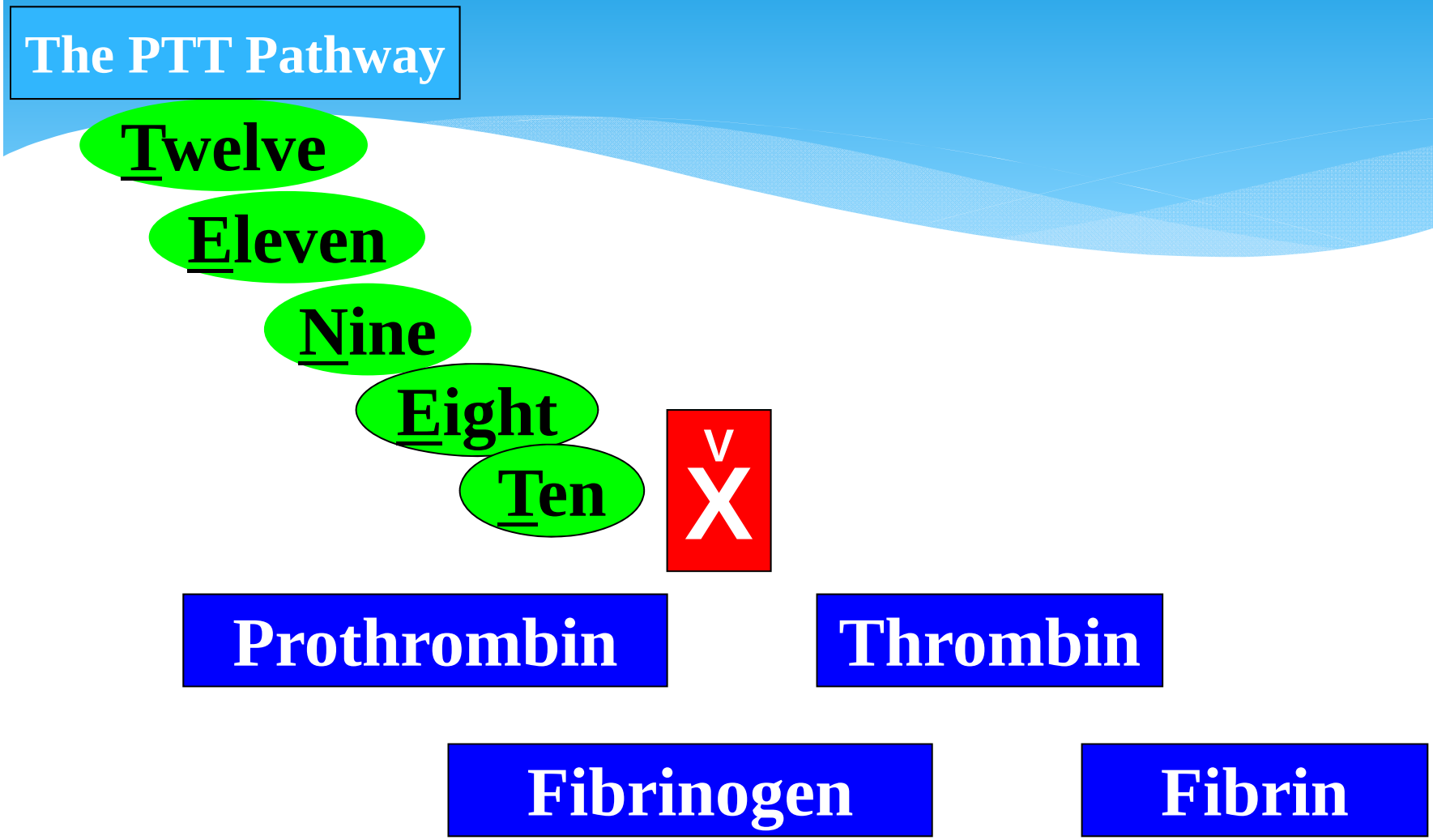
Prothrombin

Thrombin

Fibrinogen

Fibrin

Coagulation Made Easy: The aPTT



Coagulation Made Easy:
PT and PTT Both Prolonged

The PTT Pathway

The PT Pathway

These factors are in the common pathway.

Prothrombin (II)

Fibrinogen

Coagulation Made Easy: Only PT Prolonged

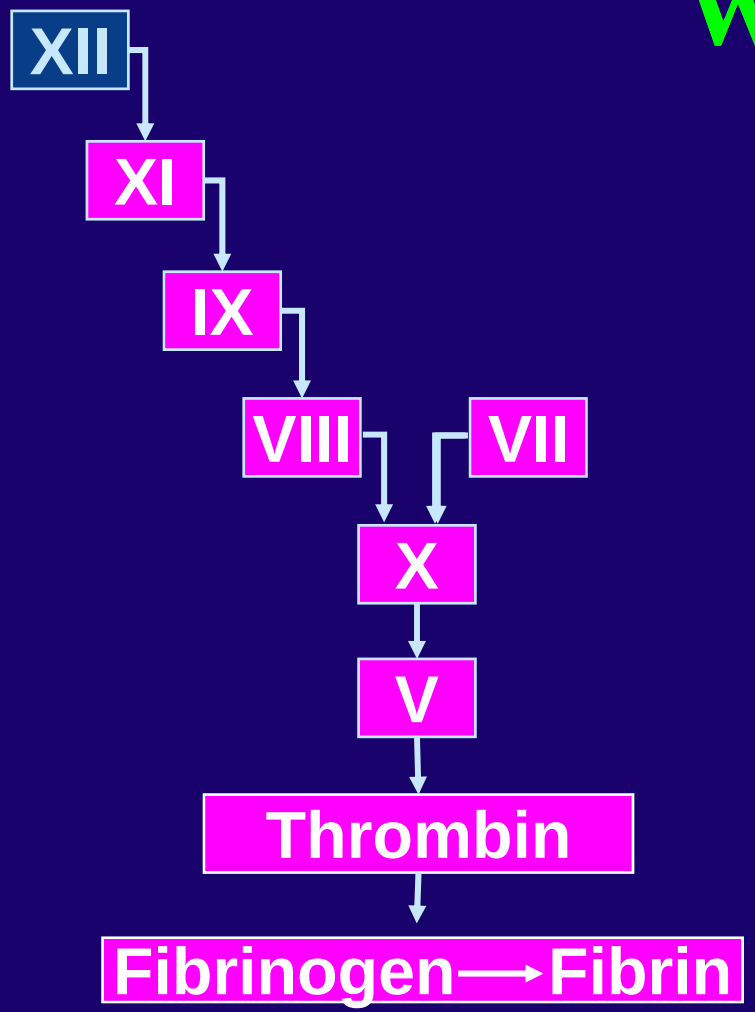
7

Deficiency of Factor VII will prolong the PT but not the PTT.

Coagulation Made Easy: Only PTT Prolonged

Deficiencies of Factors 12, 11, 9, and 8 will prolong the PTT and not the PT. Remember that Factor 10 is in the common pathway, and affects BOTH the PT and the PTT.

What Matters Clinically



- Deficiencies of Factor XI, IX, VIII, VII. X, V, prothrombin, and fibrinogen are clinically significant.
- Inhibitors of these factors are clinically significant for bleeding.
- Deficiency of Factor XII, and the presence of the lupus anticoagulant are not.

Coagulation Made Easy: The Mixing Study

* Useful to differentiate etiologies of prolonged clotting in a coagulation assay.
* Patient's plasma is mixed 50/50 with normal plasma. Coagulation assay is repeated.
* If "substantial" correction is noted after mix, suspect **clotting factor deficiency**, because you replaced deficient factors in the patient plasma with normal factors from the normal plasma.
* If no or not full correction is seen, suspect an **inhibitor**, because you added the inhibitor (think of this as an anticoagulant) in the patient plasma which inhibits clotting in the normal plasma.

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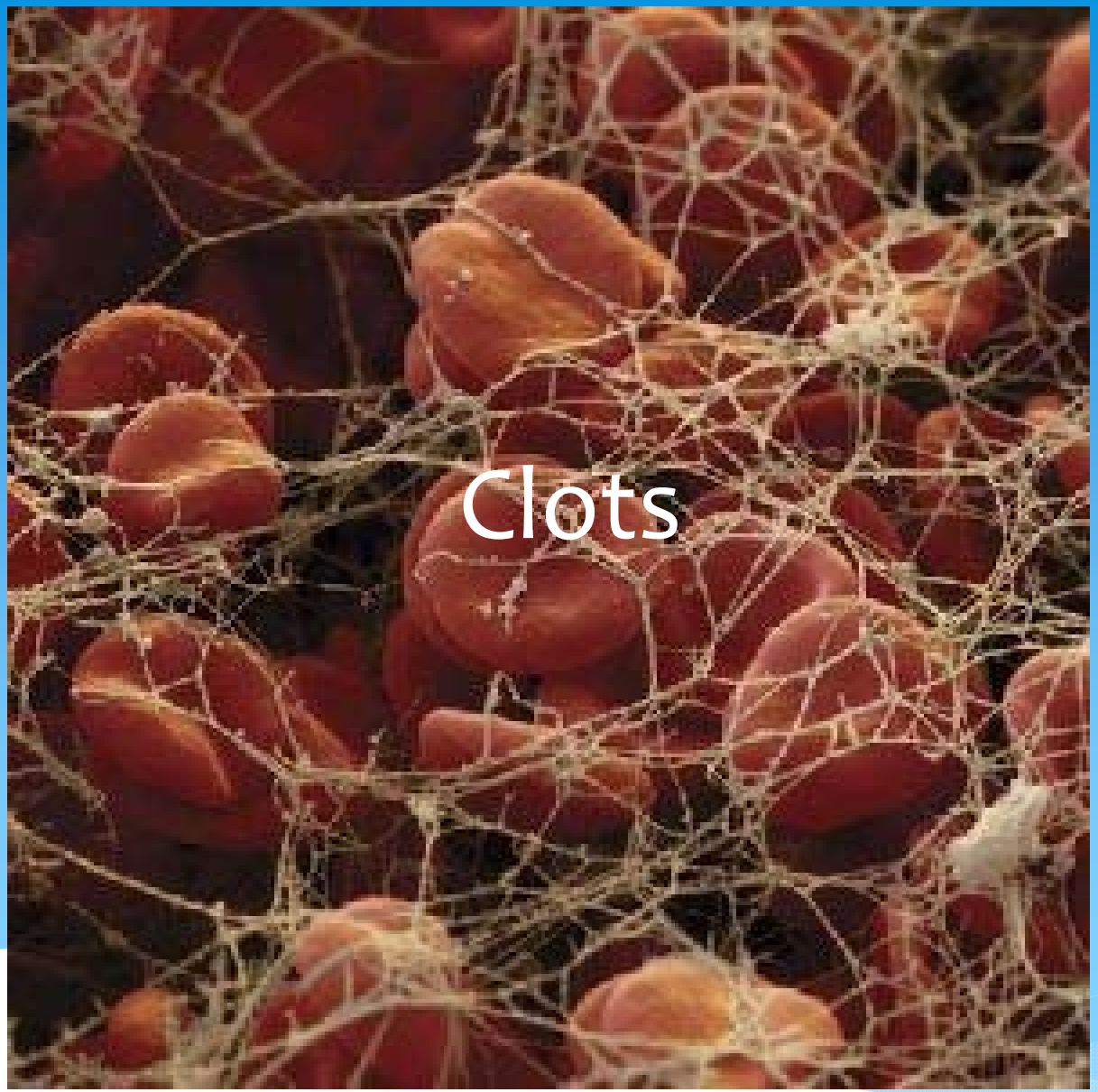

Discuss case-based approach to patients with thrombophilia

Temperament provokes clot

Fact-checking

www.hematology.org
www.nejm.org
https://www.ncbi.nlm.nih.gov/pubmed

‘Provoked’ DVT

* Immobility/Stasis

Dr. Rudolf Virchow
1821-1902

* Trauma (surgery)

* Hypercoagulable
  * Malignancy
    * Age-appropriate cancer screening
  * Hormones
    * Pregnancy, OCP/HRT

Dr. Armaund Trousseau
1801-1867

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SOME study (Screening for Occult Malignancy in VTE) *NEJM* 2015

New unprovoked VTE

Limited Screening	Limited + CT Abd/Pelvis
* PSA*	
* Mammogram*	
* CXR	
* Blood work	
* Pap smear*	

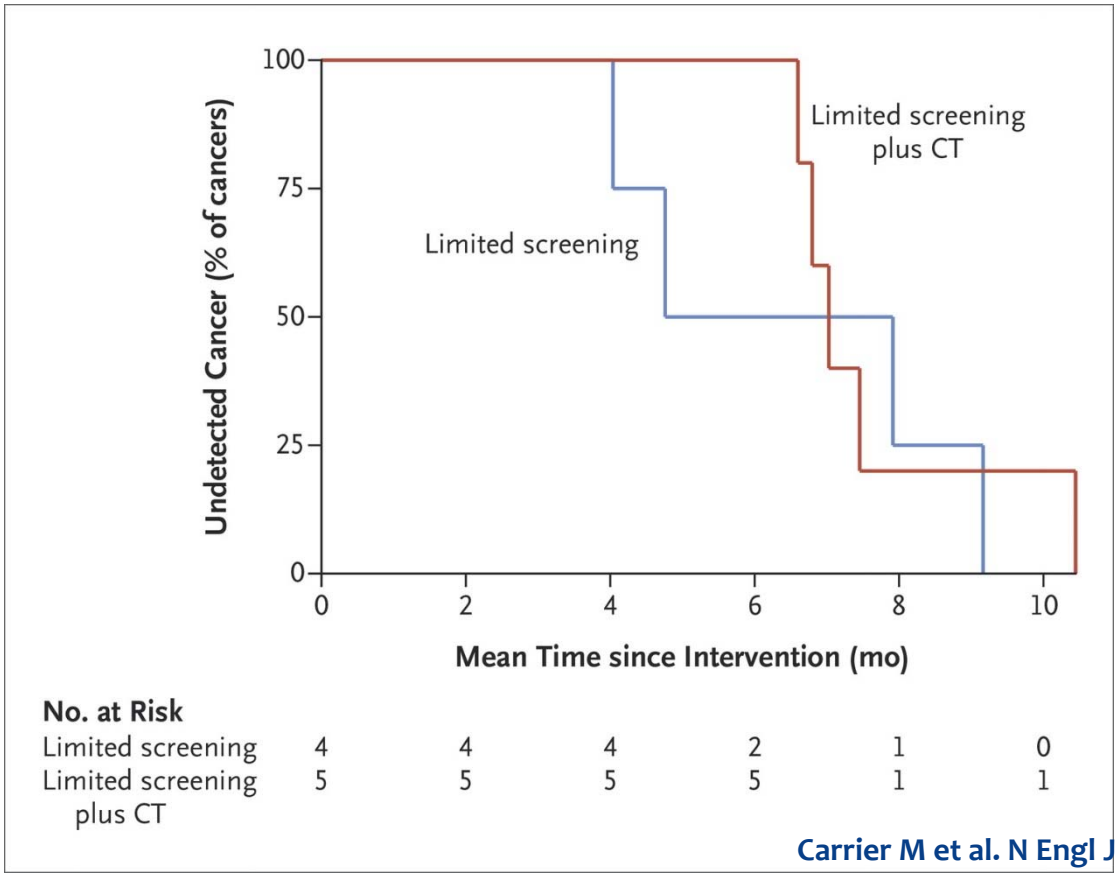
Carrier M et al. N Engl J Med 2015;373:697-704.

Primary endpoint: cancer missed by the screening but detected within 1 year of screening

SOME study (Screening for Occult Malignancy in VTE) *NEJM* 2015

New unprovoked VTE

Kaplan–Meier Curves for Time to Detection of Missed Occult Cancer.



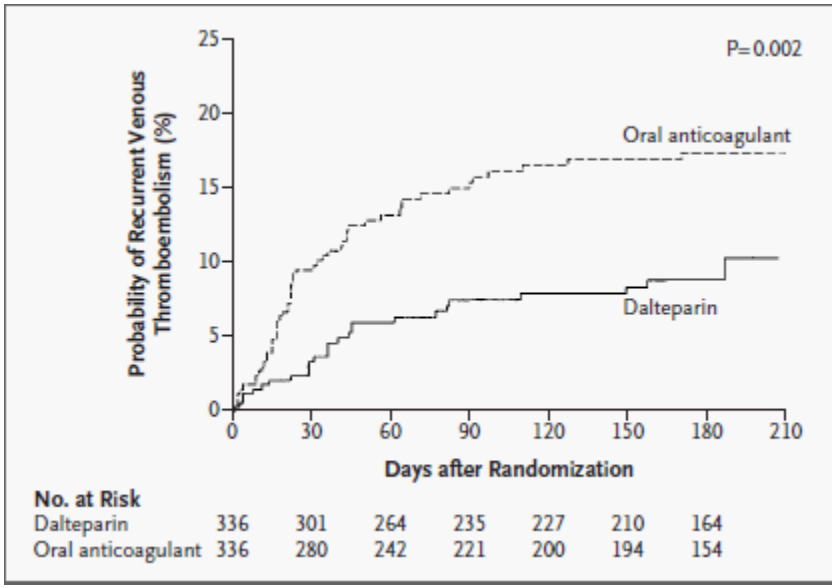
Carrier M et al. N Engl J Med 2015;373:697-704.

CLOT

- Dalteparin vs warfarin
  - Randomized, N=676
  - 6 months of treatment
    - Dalteparin (5 days) → Warfarin
    - Dalteparin
  - All with active malignancy within 6 months of enrollment
  - Recurrent VTE
    - Warfarin 17%, Dalteparin 9%
  - Major Bleeding
    - Warfarin 4%, Dalteparin 6%
  - Any Bleeding
    - Warfarin 19%, Dalteparin 4%

Lee, et al. NEJM 2003. 349:146

Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer



When to Consider Underlying Hypercoagulable State

- Recurrent unexplained episodes of VTE
- VTE at a young age (<40 years)
- Family history of unprovoked VTE
- Venous thrombosis at an unusual site
  (e.g. axillary vein, mesenteric vein, portal vein)

- American Society of Hematology (ASH) advises against sending hypercoagulable testing in patients with provoked VTE.

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Case 1 - Presentation

* 35yo s/p arthroscopy to her R knee 2 weeks ago
* Presents with RLE swelling and pain
* RLE DVT is diagnosed and she is started on anticoagulation

* She is referred to you because recent testing revealed low levels of protein C and protein S, and that she has a gene change in MTHFR
* What are your recommendations ?

When to send hypercoagulable testing (if at all)

Table 7-1 Conditions associated with acquired coagulation factor deficiencies.

Factor	Conditions associated with decreased factor levels
Protein C	• Acute thrombosis ⟸ • Warfarin therapy ⟸ • Liver disease • Protein-losing enteropathy
Protein S	• Acute thrombosis ⟸ • Warfarin therapy ⟸ • Liver disease • Inflammatory states • Estrogens (contraceptives, pregnancy, postpartum state, hormone replacement therapy) • Protein-losing enteropathy
Antithrombin	• Acute thrombosis ⟸ • Heparin therapy ⟸ • Liver disease • Nephrotic syndrome • Protein-losing enteropathy

Table 7-2 Influence of acute thrombosis, heparin, and vitamin K antagonists on thrombophilia test results.

Test	Acute thrombosis	Unfractionated heparin	Low molecular weight heparin	Vitamin K antagonists
Factor V Leiden genetic test	Reliable	Reliable	Reliable	Reliable
APC resistance assay	Reliable*	???*	???†	Reliable*
Prothrombin 20210 genetic test	Reliable	Reliable	Reliable	Reliable
Protein C activity or antigen	???‡	Reliable	Reliable	Low
Protein S activity or antigen	May be low	Reliable	Reliable	Low
Antithrombin activity	May be low	May be low	May be low	Reliable
Lupus anticoagulant	Reliable§	???‖	???‖	May be false positive
Anticardiolipin antibodies	Reliable§	Reliable	Reliable	Reliable
Anti–β_2-glycoprotein I antibodies	Reliable§	Reliable	Reliable	Reliable
Homocysteine	Reliable	Reliable	Reliable	Reliable

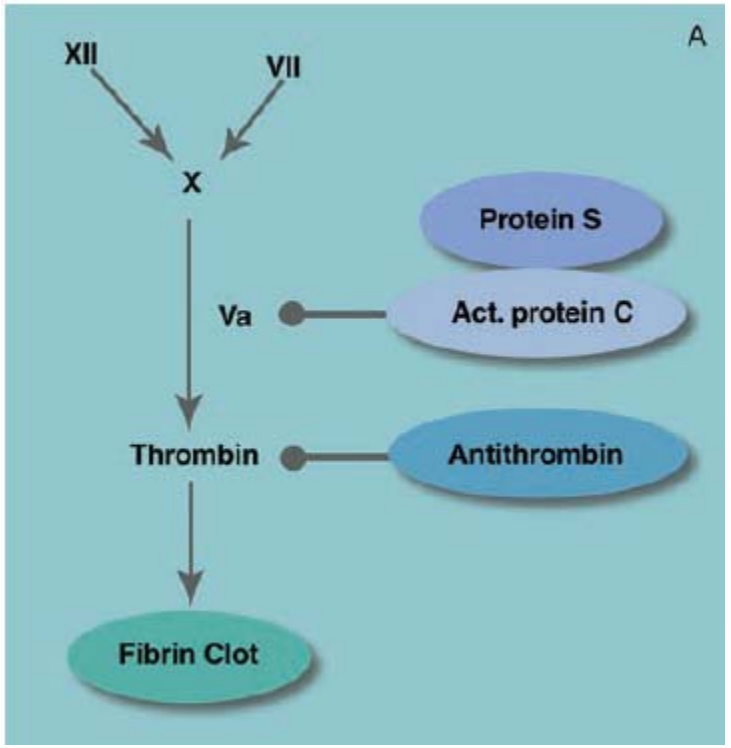
*Reliable if the assay is performed with factor V–depleted plasma; thus, clinician needs to inquire how the individual laboratory performs the assay.
†Depending on the way the assay is performed, results may be unreliable; the health care provider needs to contact the laboratory and ask how the specific test performs on heparin.
‡Probably reliable, but limited data are available in literature.
§Test is often positive or elevated at time of acute thrombosis, but subsequently negative.
‖Although many test kits used for lupus anticoagulant testing contain a heparin neutralizer, making these tests reliable on unfractionated heparin (UF) and possibly low molecular weight heparin (LMWH), clinicians need to ask their laboratory how their individual test kit performs in samples with UF and LMWH.
APC = activated protein C resistance.

Must be off VKAs for 2-3 weeks prior to testing PrC, PrS

* Tests to never send
  * MTHFR gene analysis/polymorphism (33% of population, no increase in VTE risk)
  * Homocysteine level (except for pt **<30yo** to eval for homocytsinuria)

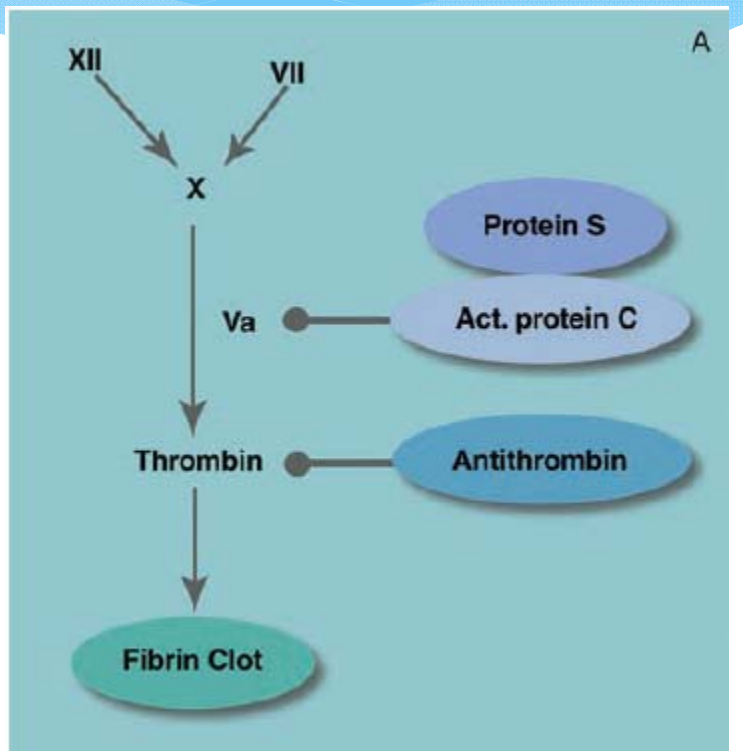
Thrombophilia

Incidence	Venous	Arterial
5%	Factor V leiden Heterozy -2.7x risk Homozy – 18x risk	No significant change
2%	Prothrombin G20210A Heterozy – 3x risk	Possible slight risk in young patients



Thrombophilia

Incidence	Venous	Arterial
5%	Factor V leiden Heterozy -2.7x risk Homozy – 18x risk	No significant change
2%	Prothrombin G20210A Heterozy – 3x risk	Possible in younger patients
0.2%	Protein C deficiency -24x risk	Risk in younger pts
0.1%	Protein S deficiency -31x risk	Risk in younger pts (<55yo)
0.1%	Antithrombin deficiency -30x risk	unclear



Absolute 10yr risk of VTE in FacV Leiden is 1-10% (population risk is 0.1% per year)
Protein C and Protein S deficiency has 1% per year risk

Anti-phospholipid antibody

* Risk for VTE AND arterial events (and pregnancy loss)
* Diagnose with:
  * Thrombotic event or late pregnancy loss AND
  * Lab evidence confirmed at least 12 weeks apart (not IgA)
    * High rate of false-positive, especially in ICU
* 5-15% rate of 'warfarin failure' (though may be partially due to misleading INR)

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Case 2 - Presentation

* 35yo female presents with abdominal pain and jaundice
* She has no history of liver disease, heavy EtOH intake, or thrombosis.
* Exam reveals ascites and RUQ pain, icteric sclerae

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Case 2 - Presentation

* 35yo female presents with abdominal pain and jaundice
* She has no history of liver disease, heavy EtOH intake, or thrombosis. No recent surgery, immobility, trauma, or plane flights.
* Exam reveals ascites and RUQ pain, icteric sclerae

* T Bili = 12
* RUQ ultrasound with doppler reveals portal vein thrombosis.

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Additional tests to consider

* Mesenteric/portal vein thrombosis without risk factor (cirrhosis):
  * JAK2 V617F mutation (~32% of all splanchnic vein thromboses associated with this mutation) (Dentali, Blood 2009, 113:5617)
    * ***about half of these patients will have abnormal blood counts at time of clot
  * Flow cytometry to evaluate for PNH (paroxysmal nocturnal hemoglobinuria) (*rare*)
    * Most of these patients will have intermittent 'hematuria'/hemolysis
    * May also present with cerebral thromboses
    * May also have cytopenias (aplastic anemia, MDS assoc)

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Case 3 - Presentation

* 65yo man admitted to the hospital for pneumonia
* Hospital day 7 – severe increase in respiratory distress
* Chest CT reveals saddle pulmonary embolism
  * Developed in spite of heparin SC prophylaxis since time of admission

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Case 3 - Labs

* CBC: 13>42%<52k ANC 6.8 Cr 1.0 T Bili 0.2
* Next test?

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Case 3 - Labs

* CBC: 13>42%<52k (platelets 140k on admission)

* Next test?

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Making Cancer History®

Case 3 - Labs

* CBC: 13>42%<52k (platelets 140k on admission)
* Anti-PF4 antibody: 2.40
* Interpretation:
  * Weak-positive OD 0.40–<1.00 - low probability (≤5%) of a strong-positive SRA
  * Strong positive OD ≥ 2.00 units - >90% with positive SRA (J of Thromb Hemost 2008. 6(8):1304)
  * High rate of mild false-positives, especially in setting of acute illness

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HIT

* 4T rule
  * Timing (within 5-14 days of heparin (~24hrs if recent exposure within 100 days)
  * Depth of thrombocytopenia <50% baseline (rare to get below 20K)
  * Thrombosis
  * No other causes of thrombocytopenia
* Treatment
  * Stop heparin
    * If heparin is stopped without other anticoagulant (in true HIT), ~50% of patients develop VTE within 30 days of diagnosis
  * Start bivalirudin or argatroban (direct thrombin inhibitor)

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HIT

* After stopping heparin, platelets should increase
* When plt >150k, can transition to warfarin
  * Must use chromogenic Factor X for transition or stop/start if on argatroban (since it elevates INR)

* For future prophylaxis – fondapariunx is an option (1 case report of HIT)
* Maturing data on the oral direct anticoagulants (Kunk, PR et al. J Thromb Thrombolysis. 2016 Sep 8.)
* If antibody-negative, heparin may be used in the future with close monitoring

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Chromogenic Factor X Assay

↑ CFX = ↓ INR

Chromogenic Factor X	INR
40-25%	2-3
35-20%	3-4

* Chromogenic Factor X levels
  * >40% indicate a likely sub-therapeutic anticoagulant effect (INR < 2)
  * <20% indicate a likely supra-therapeutic effect (INR > 3).

Am. J. Hematol. 85:185–187, 2010

Case 4

* 70yo presents with LLE edema and pain after total knee replacement
* Ultrasound confirms L popliteal DVT
* Started on enoxaparin → warfarin

* Do you recommend ambulation?
* How long do you recommend anticoagulation?
* Additional testing?

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Provoked DVT

* Following provoked DVT – 3 months anticoagulation is adequate (as long as provoking factor no longer present)
* No hypercoaguable testing recommended
* Ambulation after DVT has not been shown to increase risk of embolization, and decreases risk of post-thrombotic syndrome

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Case 5

* 40yo man presents with LLE edema and pain
* Ultrasound confirms L popliteal DVT
* No recent surgeries, no personal or family history of thrombosis.
* He drove from Gilbert to Phoenix the day before the event.
* No chest pain, dyspnea, or palpitations

* He is started on enoxaparin
* Additional testing at this time?
* How long do you anticoagulate?

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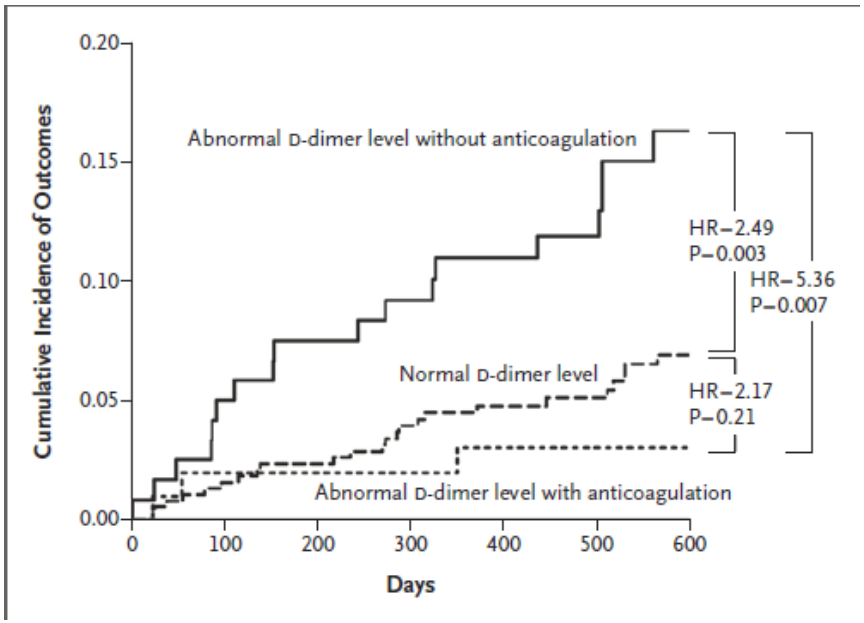
Unprovoked DVT

* No clear consensus!!
  * But with second event – always indefinite
* Two options for first event
  * Indefinite
  * Attempt to come off at three months for first event
    * 1 month after stopping anticoagulation – perform D-dimer
      * Elevated: 15% risk of recurrence
        * Decreased to 2.9% if warfarin is restarted
      * Normal: 6% risk of recurrence



Palareti NEJM 2006

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Line-associated DVT

* Incidence of line-associated DVT 6-13%
  * Usually within first 6 weeks after placement
  * Usually suggested by difficulty drawing and/or infusing through the catheter.
    * Inability to draw blood alone (i.e. “ball valve effect”) is a nonspecific finding and does not predict thrombosis of the catheter lumen or the vessel.

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Line-associated DVT

* Incidence of line-associated DVT 6-13%
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  * Usually suggested by difficulty drawing and/or infusing through the catheter.
    * Inability to draw blood alone (i.e. "ball valve effect") is a nonspecific finding and does not predict thrombosis of the catheter lumen or the vessel.
* Additional risk factors for CVC-associated DVT include:
  * Prior catheter placement and/or upper extremity DVT
  * Catheter malposition (e.g. tip is high in the SVC rather than at the caval-atrial junction
  * Stiffer catheter (e.g. polyethylene vs silastic)
  * Larger diameter catheter (e.g. indwelling tunneled pheresis catheter)
  * Line-associated infection
  * Infusion of sclerosing chemotherapy
  * Use of a thrombogenic agent (e.g. thalidomide)
  * Heparin-induced thrombocytopenia
  * Regional bulky lymphadenopathy
  * Procoagulant states (Fac V Leiden, PT G20210A)
* Ultrasound may not detect thrombus in SVC/proximal vessels

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Management of CVC-associated DVT

* May remove line
  * preferred especially if patient expected to have thrombocytopenia or central vessels affected
  * If no thrombocytopenia, anticoagulate x 3 months after line removal
* May treat with anticoagulation without removal if non-occlusive thrombus
  * Usually 3 month duration

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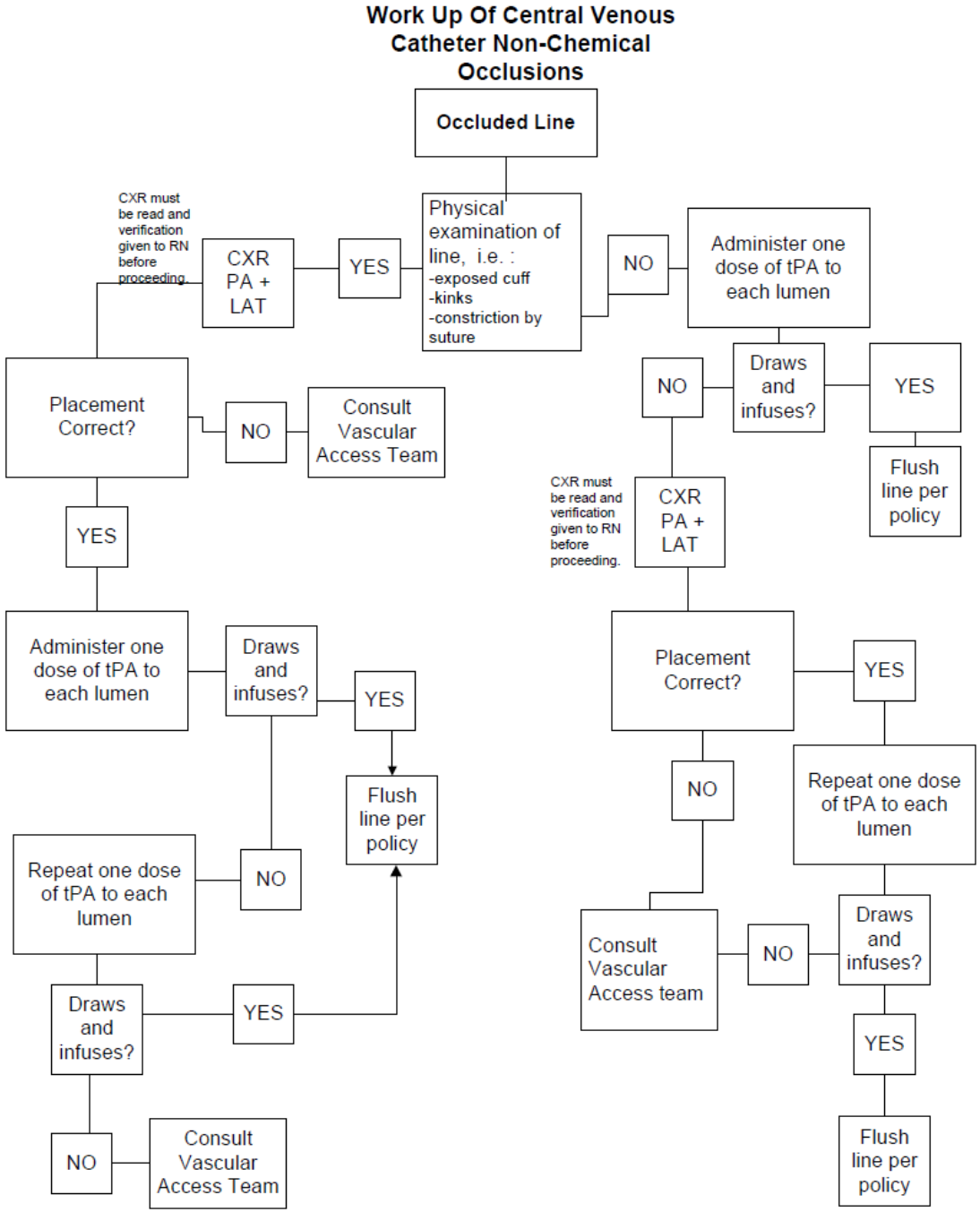
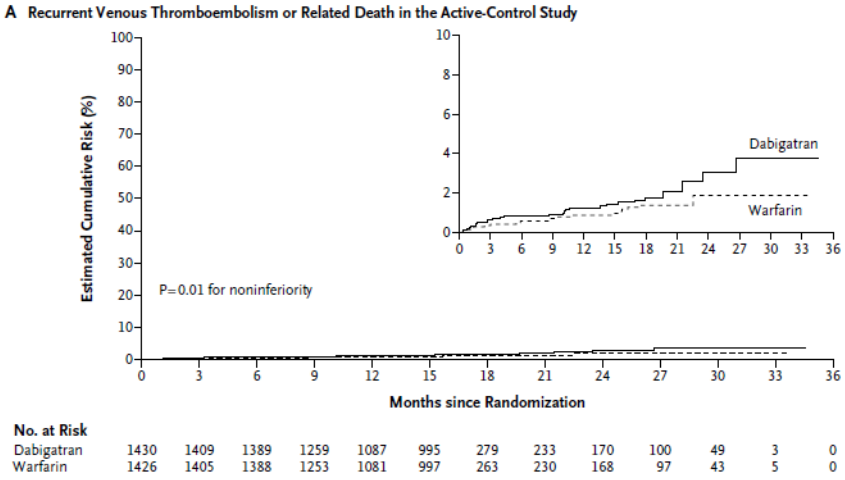
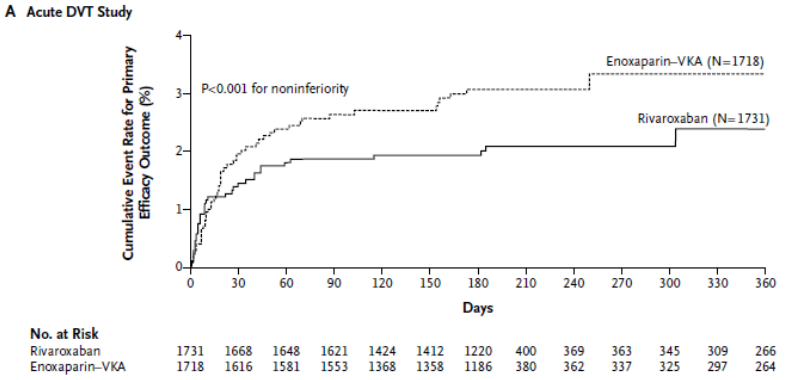
* COOL-2 Trial supports use of tPA in occluded lines
  * *JCO* 2002. 20:317
  * Restores flow in 87% of lines at 120min following up to 2 doses of tPA



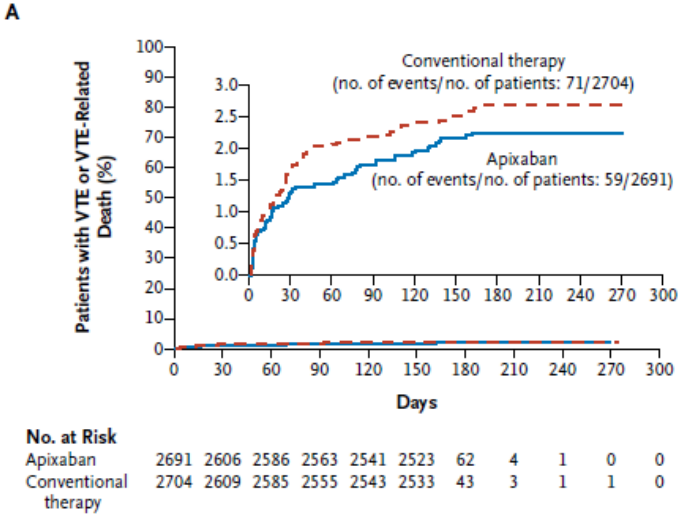
EINSTEIN, RE-MEDY/RE-SONATE, AMPLIFY



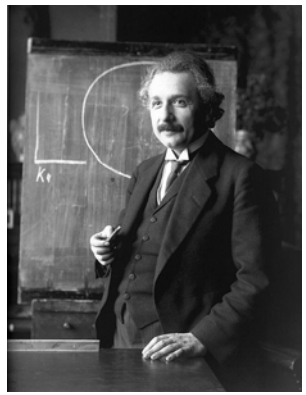
Schulman NEJM 2013



EINSTEIN, NEJM 2010



Agnelli, NEJM 2013



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Questions

Warfarin and Cancer Patients

* More drug interactions
* Less consistent oral intake
* More variable INR
  * More bleeding events
  * More VTE recurrence

Meliotus alba "Sweet Clover"

* 1920 – Bleeding cattle N USA, sweet clover implicated
* 1940 – Karl Link and H Campbell discovered coumarin
* 1948 – Warfarin synthesized by Link
* 1952 – Approved as rodenticide
* 1954 – Approved for human use

Wisconsin Alumni Research Foundation - arin

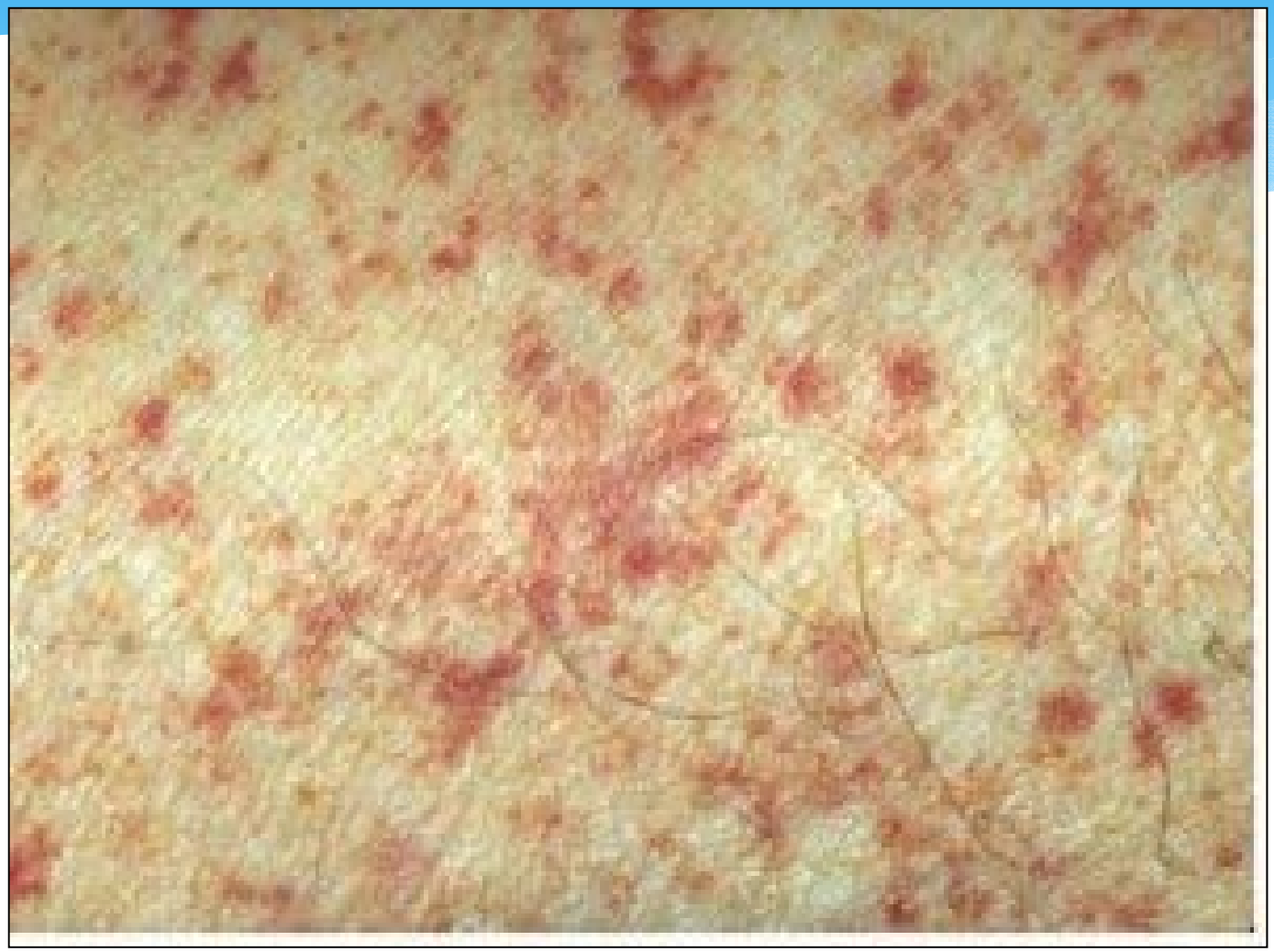
VTE: Other Anticoagulants

- Dabigatran, anti-thrombin
- Rivaroxaban, anti-FXa – only one approved by FDA for DVT/PE treatment
- Apixaban, anti-Fxa
- vs warfarin
  - More rapid onset
  - Uniform dosing (no INR checks) – caution with renal dysfunction or morbid obesity
  - No reversal agent
  - Higher cost

Case 4: Presentation

- 23 yo woman, aeronautical engineer
- cc = rash on ankles & shins, easy bruising ~ 10 days
  rash is not pruritic or painful
- Denies recent contact with new soaps or detergents
- Bruises on her arms & sides, unrelated to trauma
- Also has nosebleeds, gum bleeding with flossing and
  unusually heavy menses last week
- URI 3 weeks ago, now resolved.
- Exam: no lymphadenopathy, no hepatosplenomegaly
  stool is guaiac positive

Case 4: Skin Rash



Type of bleeding disorder?

Her signs and symptoms suggest what type of bleeding disorder?

Type of bleeding disorder?

Her signs and symptoms suggest what type of bleeding disorder?

- Abnormality of primary hemostasis

Additional History

- Bleeding problems in the past? Procedures or trauma? (include wisdom tooth extracted) None
- What medications are you taking? None
- Do you drink alcohol? If so, how often? No
- Do you use intravenous drugs? No
- Do you have unprotected sex? No
- Anyone in your family have a bleeding problem? No
- Any recent unexpected loss of weight? No

Laboratory Evaluation

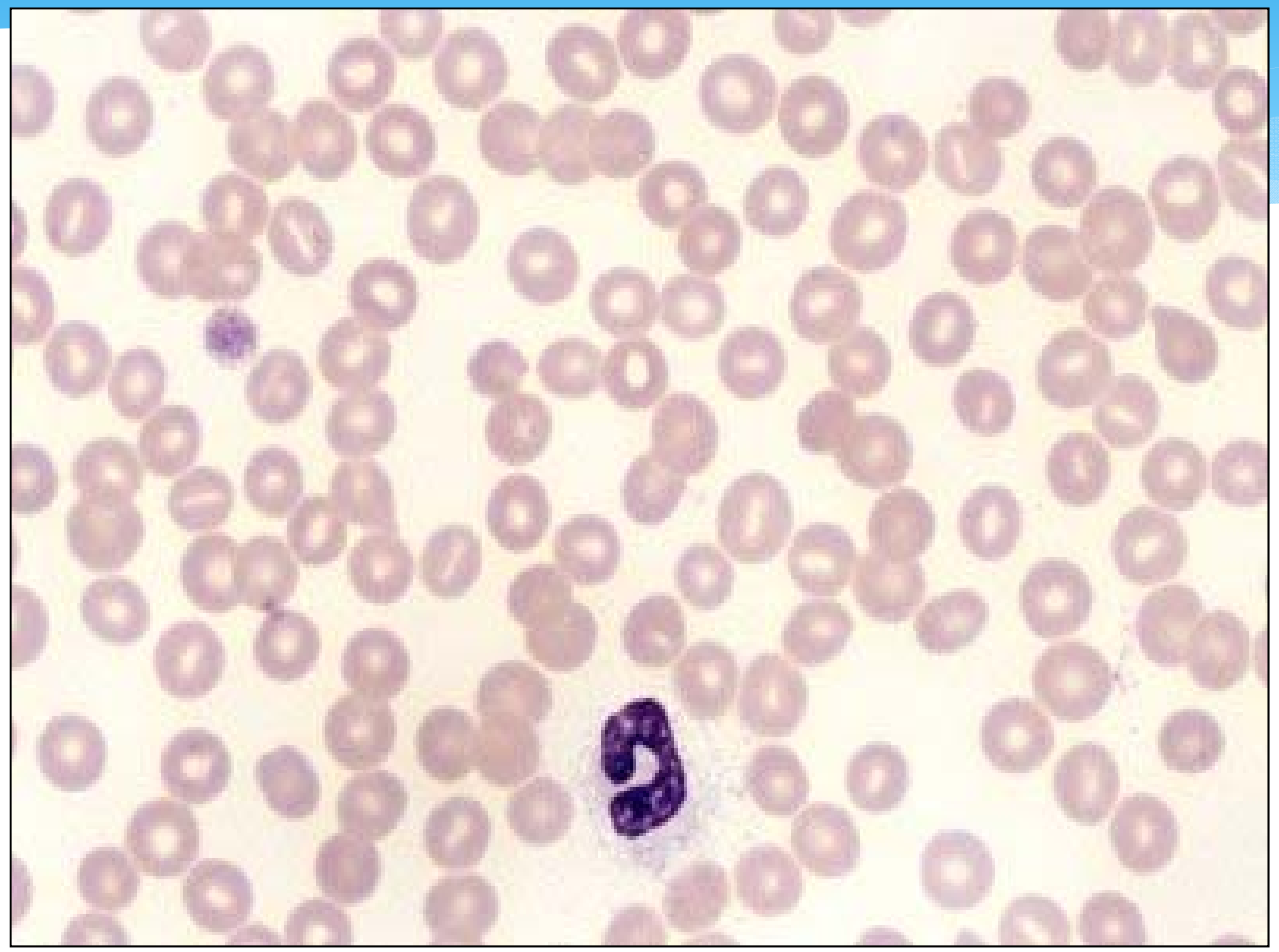
What laboratory tests would you order?

- CBC
- PT & PTT
- TT (Thrombin time)
- Peripheral smear

Laboratory Results

• WBC ($\times 10^3/mm^3$)	6.0	(4.3-10)
• Hgb (gm%)	13.1	(12-16)
• Hct (%)	39	(38-50)
• MCV (fL)	86	(78-96)
• Plt Ct ($\times 10^3/mm^3$)	3	(150-450)
• PT (sec)	11.6	(10.4 - 12.8)
• PTT (sec)	32	(24 – 36)
• TT (sec)	22	(18 - 28)

Peripheral smear



Thrombocytopenic Mechanisms

- Decreased production
  - decreased thrombopoietin (liver disease)
  - toxins (e.g. alcohol, radiation, drugs)
  - vitamin B12 or folate deficiency
  - marrow infiltration (malignancy, fibrosis/granuloma)
  - primary marrow disorders (aplastic anemia, myelodysplasia)
  - viral infections (e.g. HIV, HCV)
- Accelerated destruction
  - immune mediated
  - non-immune mediated (DIC, TTP, etc)
- Sequestration
  - hypersplenism

Differential Diagnosis

- Acute leukemia
- Aplastic anemia
- Hepatitis
- HIV
- Auto-immune thrombocytopenic purpura (ITP)
- Systemic Lupus Erythematosus (SLE)

Differential Diagnosis

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Treatment Options

- Platelet transfusion (life-threatining bleed)
  - Since platelets will be consumed as soon as transfused, only do so in setting of active bleeding
- Prednisone
- IV IgG & prednisone
- Anti-RhD immuneglobulin (WinRho)
- Cyclophosphamide
- Splenectomy

One Month Follow Up

- On prednisone 10mg/day
- Difficulty sleeping, marked irritability
- Exam: gained 10 kg, Cushingoid, facial acne
- Bruises anterior tibial legs, few palatal petechiae
- Platelet count = 12,000
- Liver function normal; HIV antibody, negative

What are your next step(s)?

- Increase steroid dose
- Immunization against encapsulated organisms

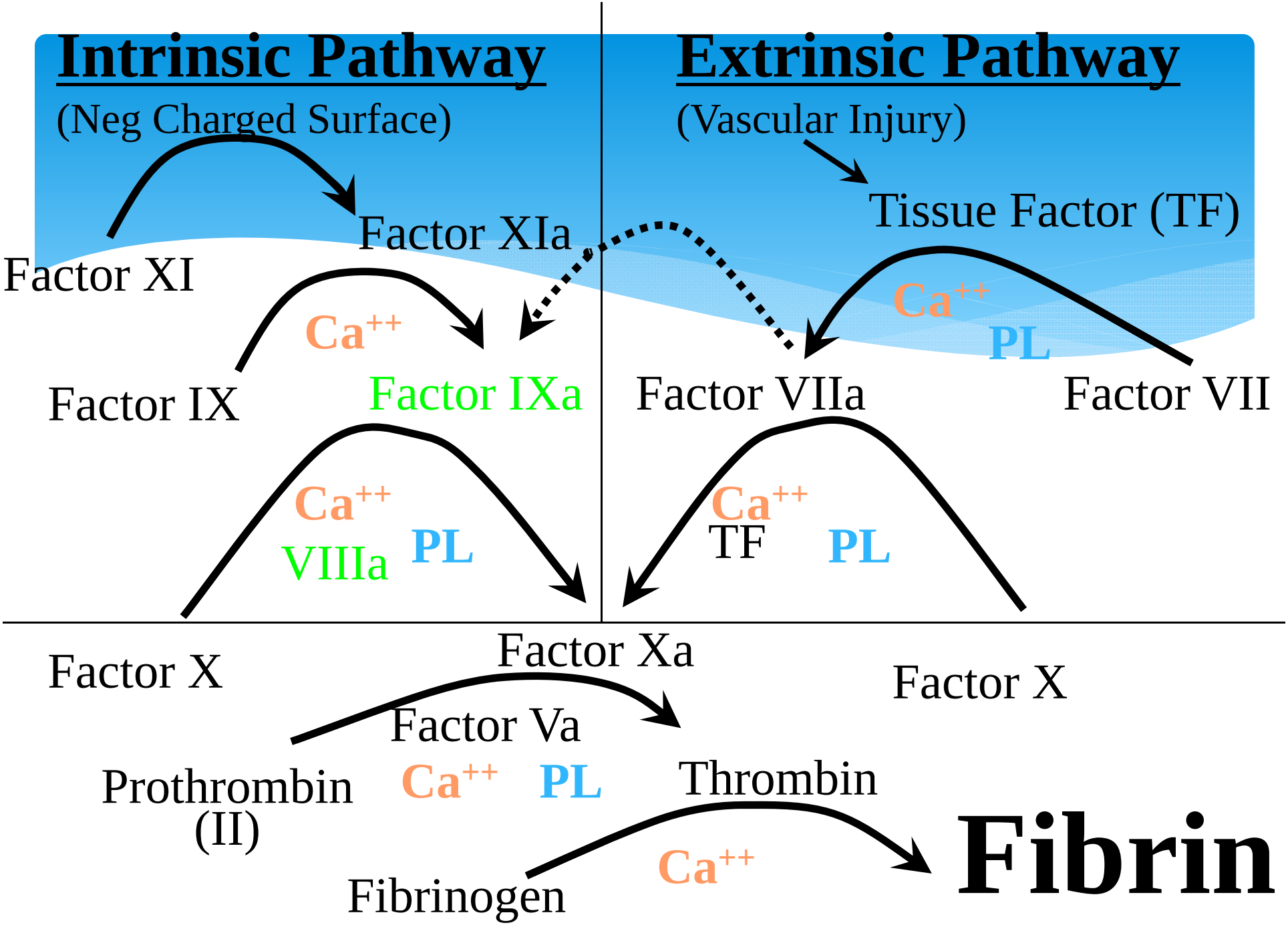
Second-Line Therapies

- Splenectomy
  - Pulse dexamethasone
  - Cyclophosphamide
  - Anti-CD20 antibody (Rituximab)
  - Thrombopoietin mimetic agents
- Other Rx options if above fail:
  - MMF
  - Azathioprine
  - Danazol

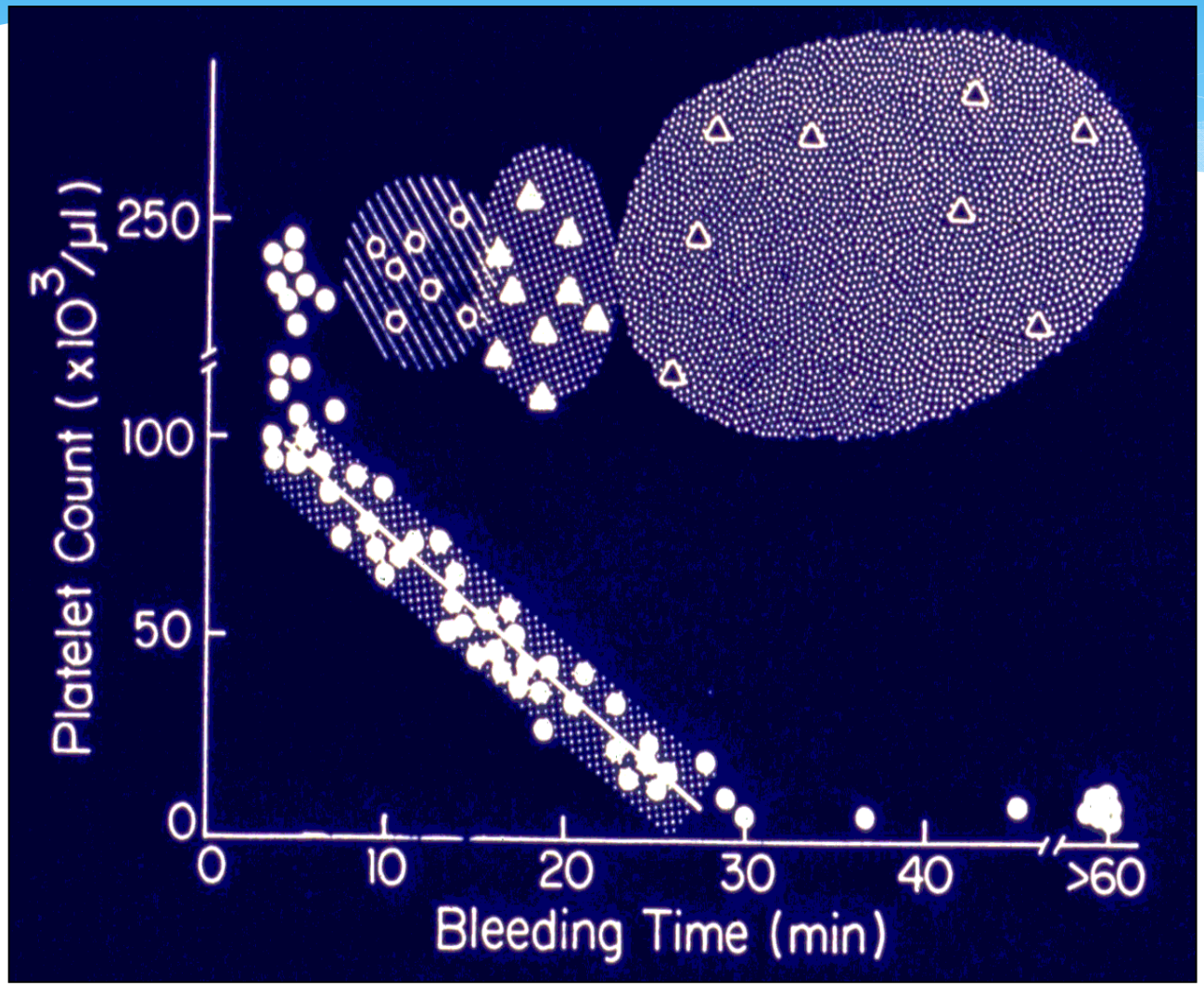
Questions?

Case 1 Treatment of Hemophilias

	A	B
Therapeutic concentrates	plasma derived or rHu FVIII	plasma derived or rHu FIX
- recovery (%)	90	35
- $t_{1/2}$ (hrs)	8-10	16-24
• DDAVP (response)	+ if mild	none
• ε-aminocaproic acid (EACA, Amicar®)	minor procedures (eg, dental extractions)	
• None of the above available	cryoprecipitate	FFP


Intrinsic Pathway
(Neg Charged Surface)
Extrinsic Pathway
(Vascular Injury)
Tissue Factor (TF)
Factor XI
Factor XIa
Ca++
PL
Factor IX
Factor IXa
Factor VIIa
Factor VII
Ca++
VIIIa
PL
Ca++
TF
PL
Factor X
Factor Xa
Factor X
Factor Va
Prothrombin
(II)
Ca++
PL
Thrombin
Ca++
Fibrinogen
Fibrin

H4-4. Relationship Between Platelet Count & Bleeding Time



o ASA

▲ mild VWD

sev VWD

H6-7. Laboratory Results

- PT, PTT, TT, fibrinogen = normal
- Antithrombin III, Protein C & Protein S all = normal
- Prothrombin gene = GG20210, homozygous normal
- PTT not prolonged with activated PC → APC resistance
- Factor V gene homozygous 506QQ (Leiden alleles)

H6-8. Recurrent VTE: Congenital Risks

congenital disorder	*frequency (%)*
Activated Protein C (APC) resistance	20-50
Prothrombin mutation (PT20210A)	10-20
Protein C deficiency	<5
Protein S deficiency	<5
Antithrombin III (ATIII) deficiency	<3
Other (Plasminogen, Dysfibrinogenemia)	<1

H4-9. VWD Subtypes

		inheritance	*deficiency*
1.	Type 1	Autosomal dominant	Quantitative
2.	Type 2	Autosomal dominant	Qualitative
3.	Type 3	Autosomal recessive	Severe/absent

Dabigatran reversal agent

BRIDGE trial (NEJM 2015)

CT for occult cancer after VTE (NEJM 2015)