Bleeding, Clotting, and Making Sense of the PT and PTT

Danielle Nance, MD

Hemostasis and Thrombosis

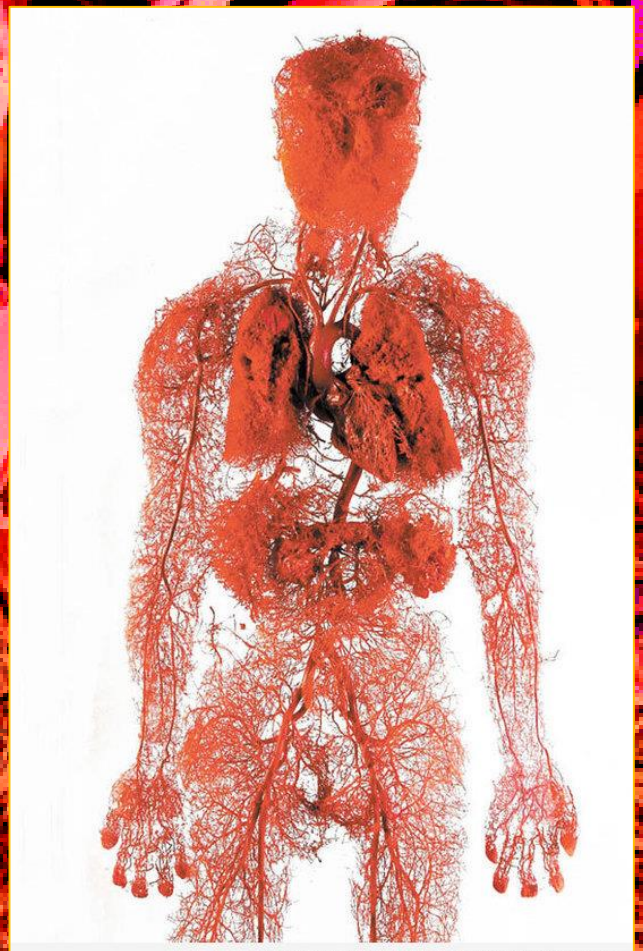
September 11, 2018

Contents

- Hemostasis – its about the endothelial cell
- Common Bleeding Disorders
- Thrombosis – its still about the endothelial cell
- Common Thrombotic Disorders

- Disclosures: Ad boards for Alnylam; Bioverativ; Genentech; Octapharma; Shire. Speaker fees from Octapharma. Grant funding from Bayer.

Hemostasis – 100K Miles of Vessels



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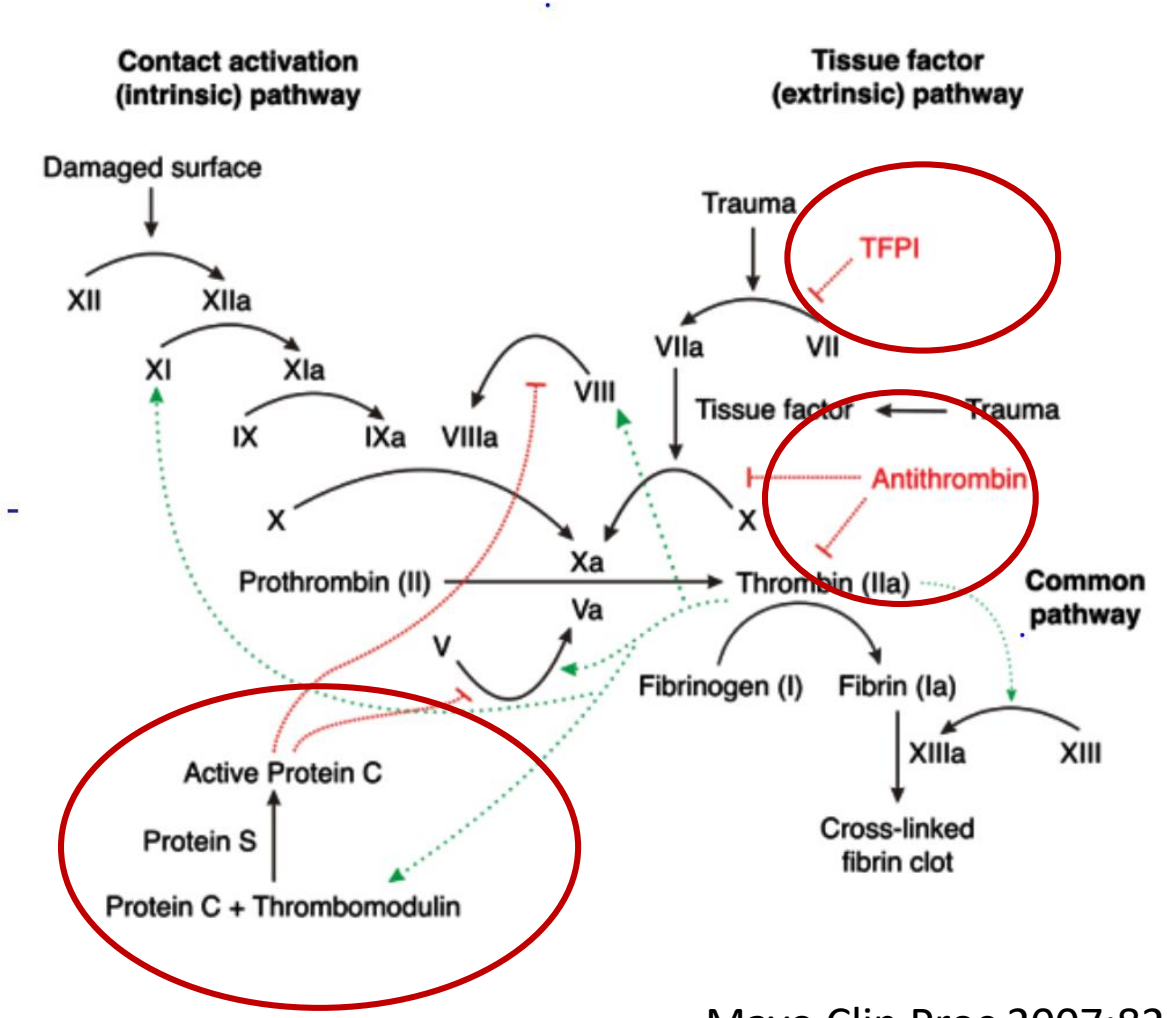
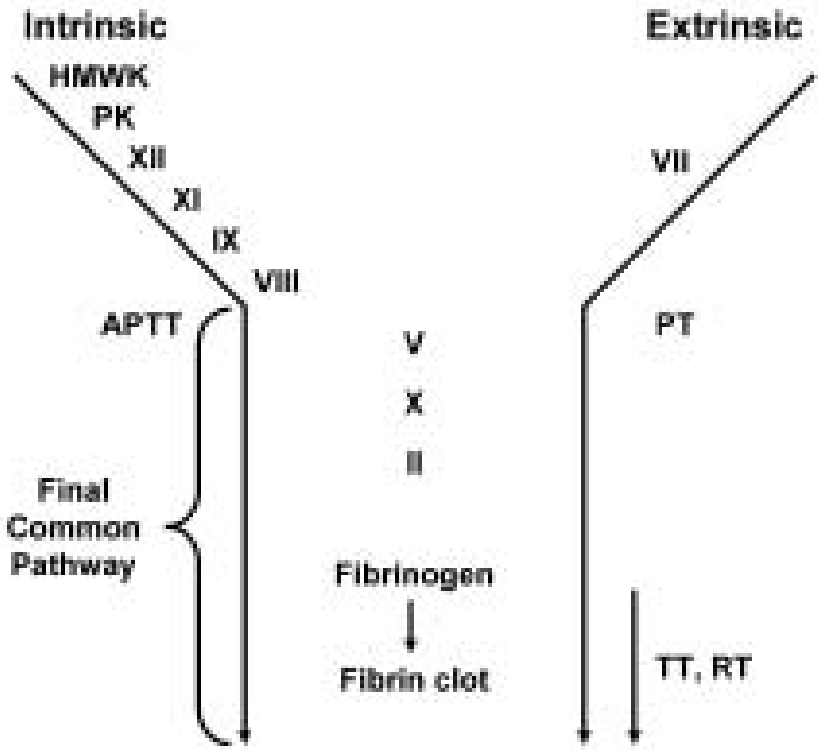
Hemostasis - an evolving model of :

- A sticky surface
  - Permissive endothelium, activated platelets
- Coagulation factors in the right amounts
  - Tissue factor/FVII trigger, then propagation
- Containment of the growing clot (thrombus)
  - Natural anticoagulants
- Remodeling as wound healing progresses
  - Fibrinolysis, inflammation

Coagulation Cascade





Mayo Clin Proc 2007;82(7):864-873

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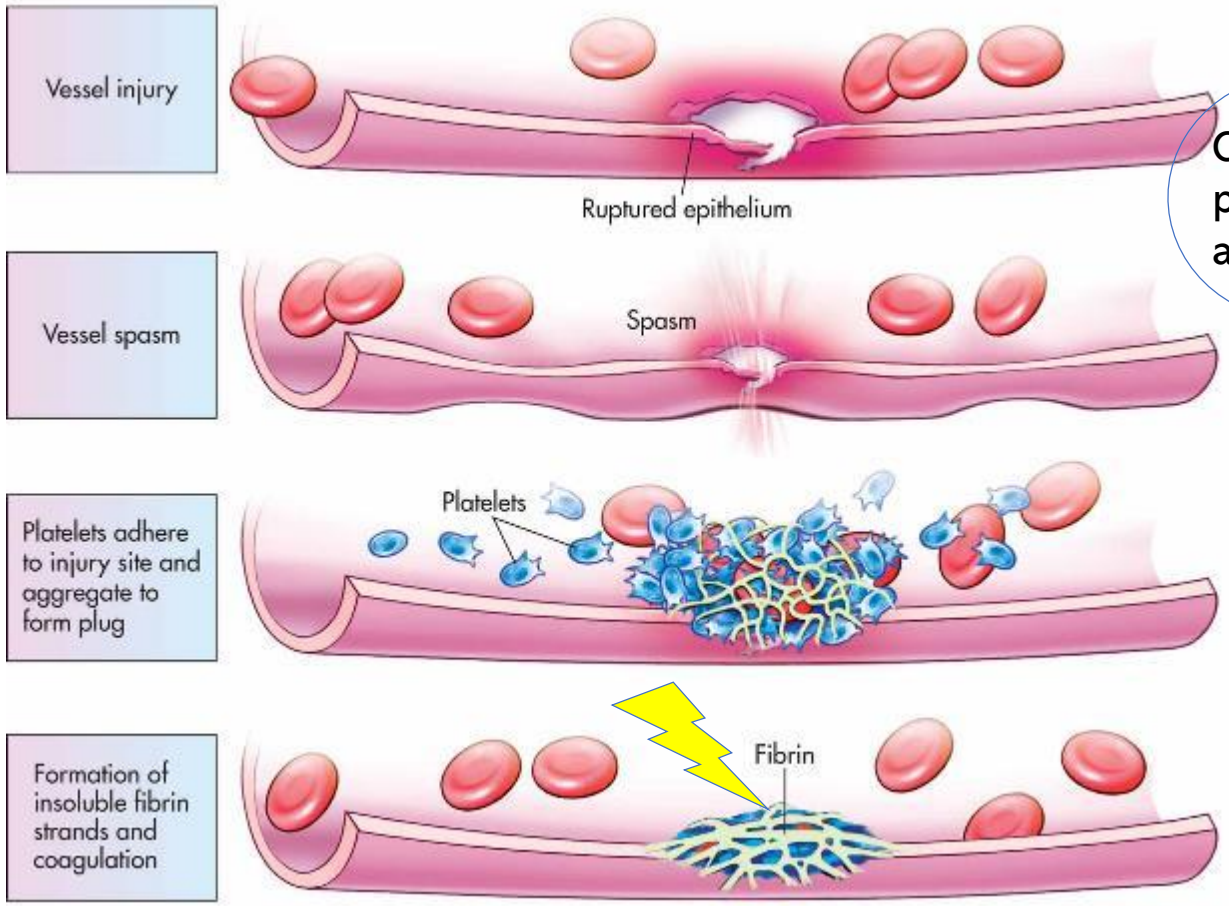
Hemostasis



Collagen provides the anchor

VWF is the tether

Platelets are the surface

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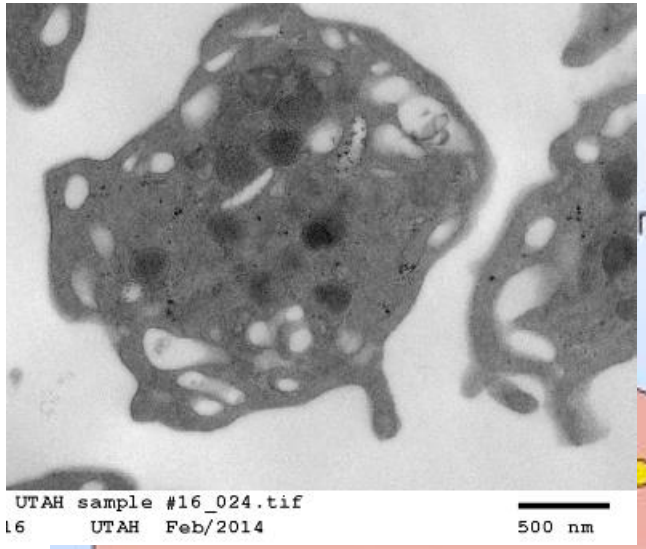
Platelet Plug (Primary Hemostasis)



Am J Physiol Cell Physiol 285: C797–C805, 2003.

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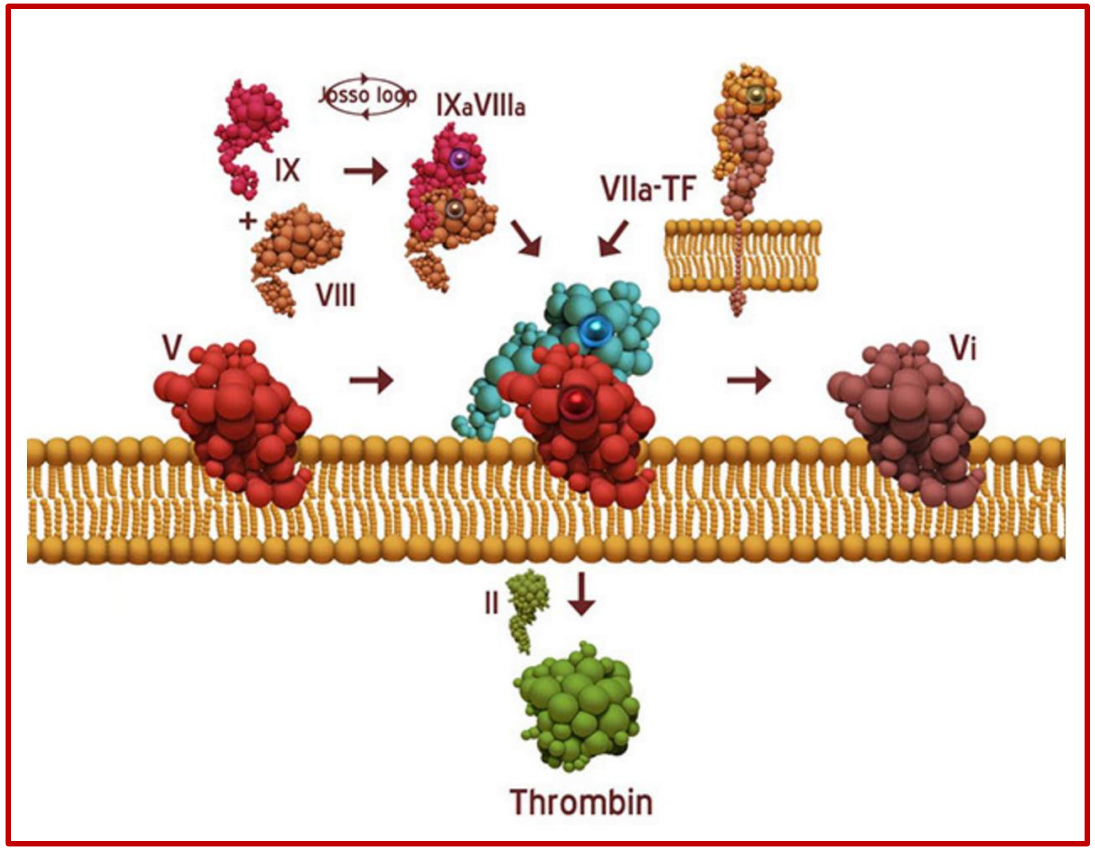
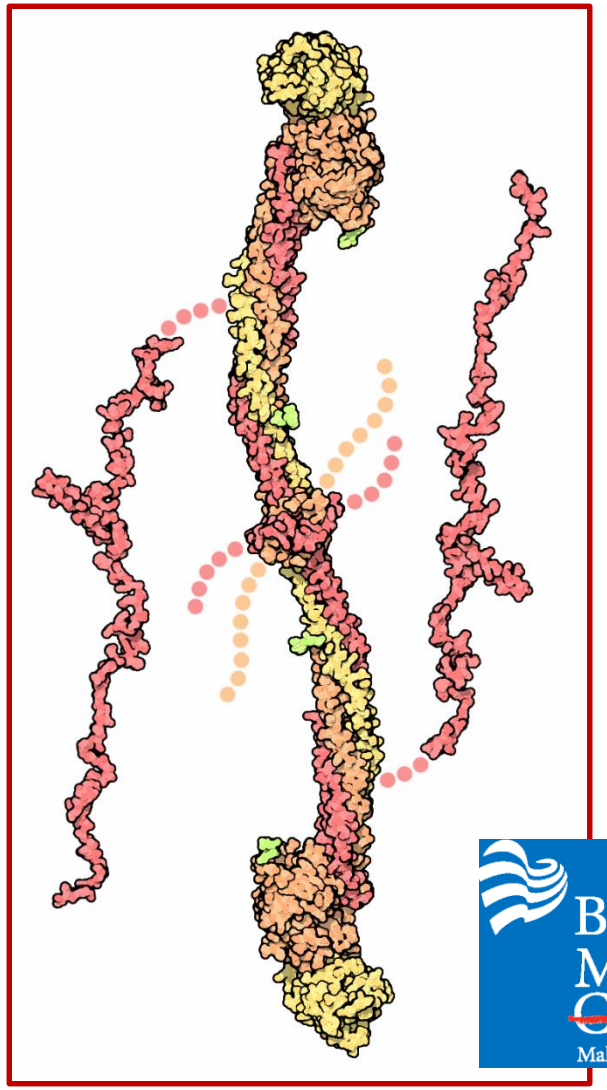
Fibrin Strands (Secondary Hemostasis)





Multiple sites of feedback loops on the surface of the growing thrombus

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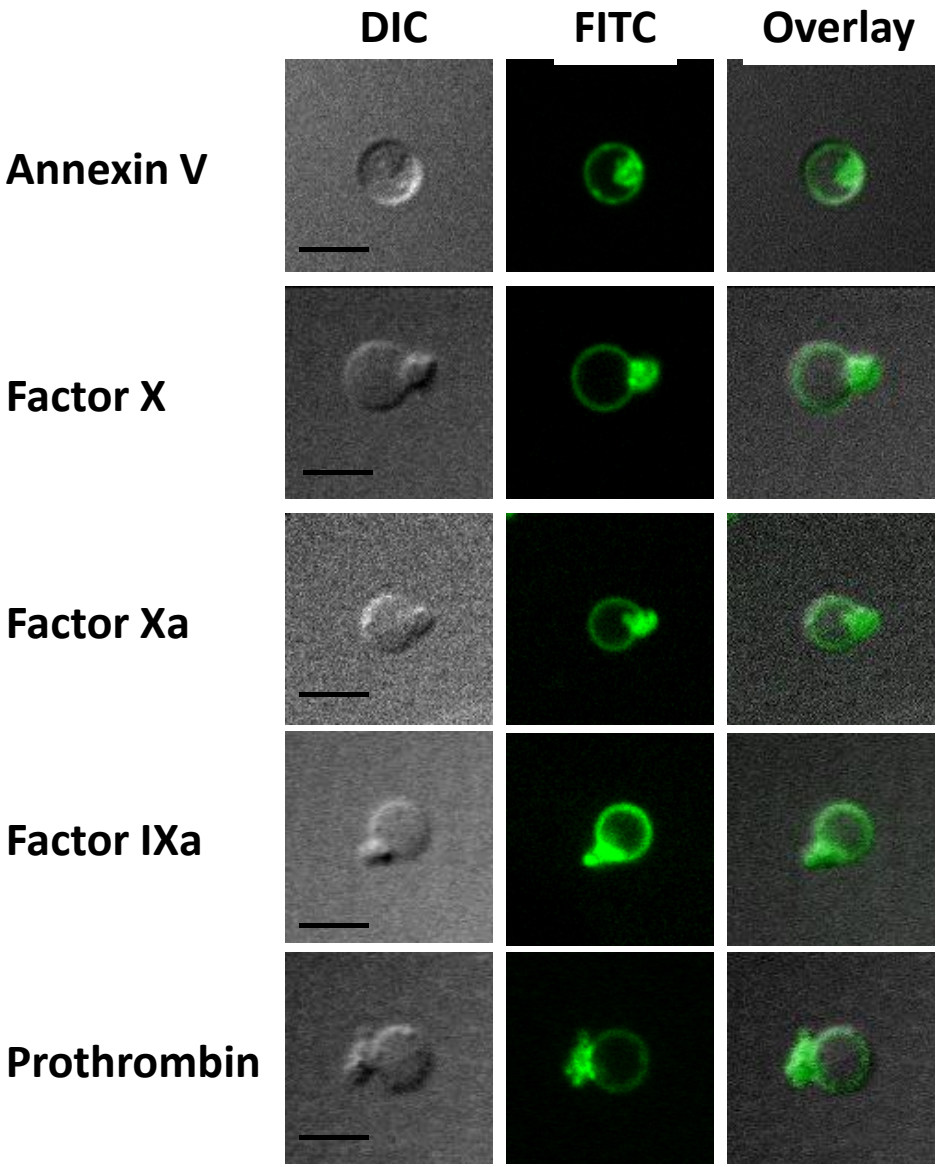
Concentrate Factors (Procoagulant Caps)



- Attract the factors to the wound
- Gather the factors together
- Accelerate healing

Podoplelova et al. Blood 29 Sept 2016 128(13):1745-1755

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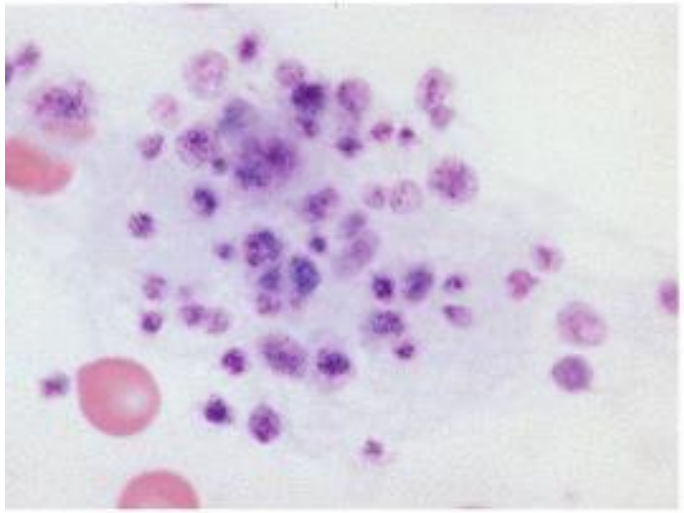
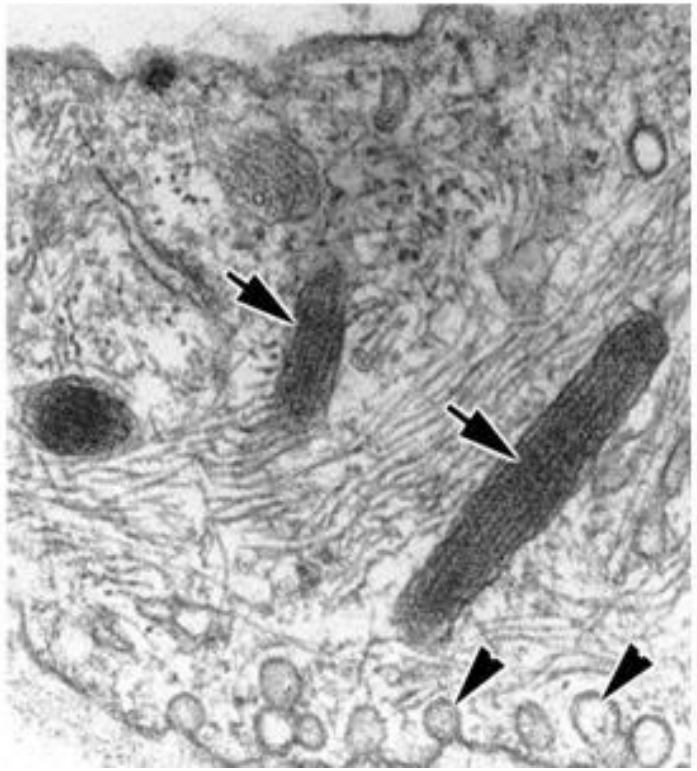
Platelets are pretty cool!

Granulated platelets



Endothelial Weibel-Palade bodies



Images courtesy of Kristi Smock, MD

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Bleeding disorders can affect the PT or PTT

TABLE 1. **Causes of Congenital Coagulation Factor Deficiencies***

Congenital coagulation factor deficiency	Deficient factor	PT	APTT	Prevalence	Mode of inheritance
Hemophilia A	Factor VIII	Normal	Prolonged	1:5000†	X-linked recessive
Hemophilia B	Factor IX	Normal	Prolonged	1:30,000†	X-linked recessive
Hemophilia C	Factor XI	Normal	Prolonged	Up to 4%‡	Autosomal
von Willebrand disease	von Willebrand factor	Normal	Normal/prolonged	Up to 1%	Autosomal
Factor VII		Prolonged	Normal	1:500,000	Autosomal
Rare coagulation factor deficiencies					
Factor V		Prolonged	Prolonged	1:1 million	Autosomal
Factor II		Prolonged	Normal/prolonged	Rare§	Autosomal
Factor X		Prolonged	Normal/prolonged	1:500,000	Autosomal
Factor XIII		Normal	Normal	Rare§	Autosomal
Combined factors VIII and V		Prolonged	Prolonged	Rare§	Autosomal

*APTT = activated partial thromboplastin time; PT = prothrombin time.
†Live male births.
‡Among Ashkenazi Jews.
§Case reports.

Mayo Clin Proc 2007;82(7):864-873

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Case 1: 20 year old woman with menorrhagia

- Diagnosed during treatment for B Cell ALL age 5 with excessive bleeding and bruising with line placement in spite of a normal platelet count
- The patient has had swollen ankles after injury, epistaxis, and heavy menstrual bleeding causing iron deficiency anemia
- The patient's mother, and younger fraternal twins also experience bleeding symptoms
- VWF:Ag 33, VWF:Rco 31, VWF:Collagen Binding:35, Multimers normal but decreased
- PT, PTT are normal. Platelet count is normal.

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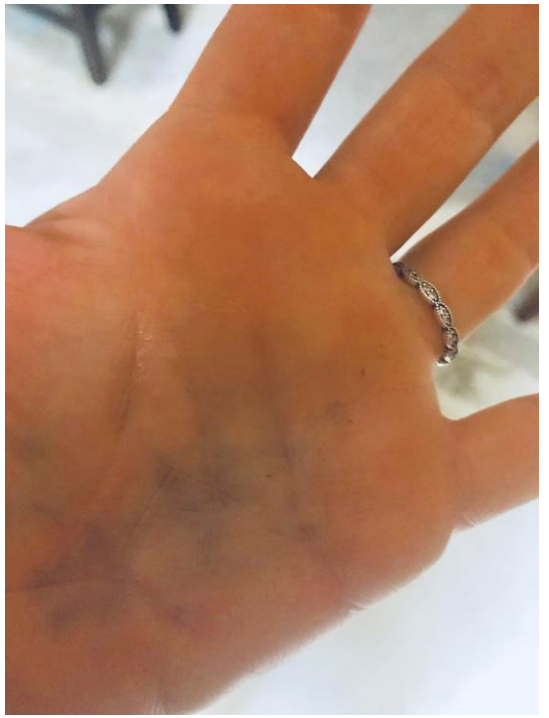
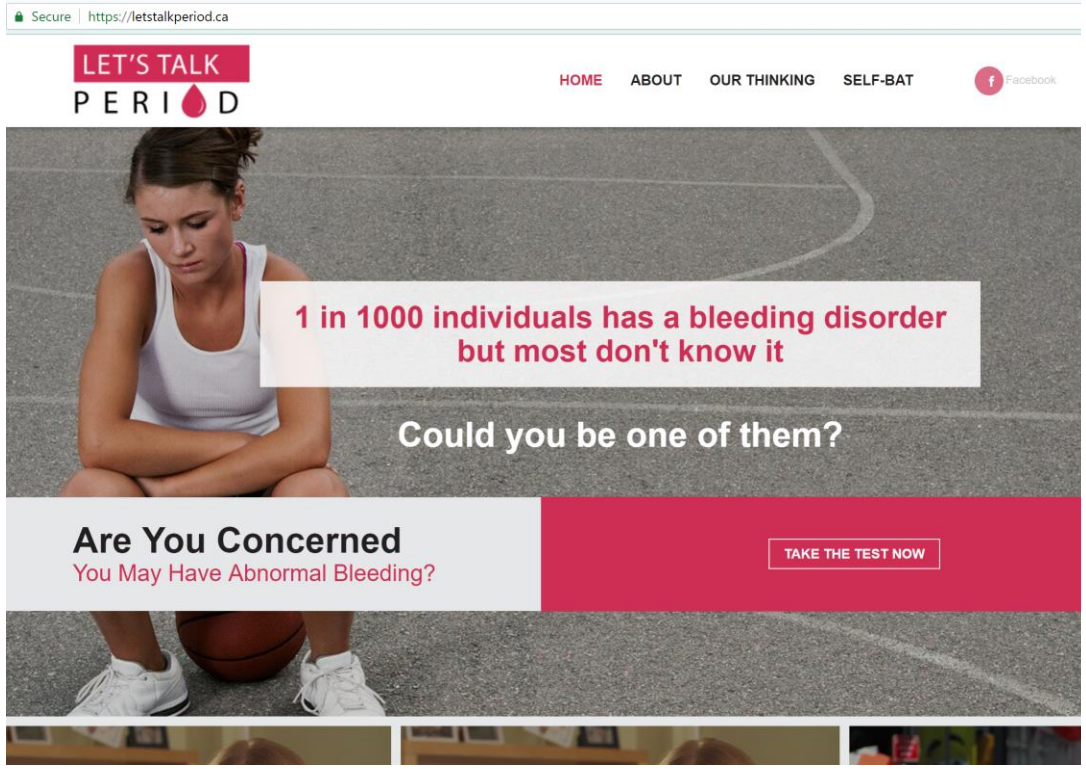
Bleeding History: ISTH BAT

- Symptoms since childhood?
  - Bruising, epistaxis, hematomas
- Heavy menstrual bleeding?
  - Change protection > q2 hrs
  - need to change at night
  - more than 8 days
- Surgical bleeding?
- Oral bleeding?
- Bleeding after trauma?



- Was a medical provider concerned?
- > 2 for kids, 4 for men, 5 for women Yes = hemostastic evaluation!

Letstalkperiod.ca



Self-BAT (Self Administered Bleeding Assessment Tool)

Self Administered Bleeding Assessment Tool

- 1. This Self-Administered Bleeding Assessment Tool ("Self-BAT") is for informational and research purposes only and does not constitute medical advice, nor is the result of the Self-BAT a substitute for professional medical advice, diagnosis or treatment. You should seek the advice of your physician or other qualified, licensed healthcare practitioner if you have any medical questions or concerns based the result of the Self-BAT and you should never disregard professional medical advice or delay in seeking treatment or advice based on the result of this Self-BAT.
- 2. This Self BAT is provided free of charge. As a condition of your using the Self-BAT, you understand and agree that none of Queen's University nor any of its Trustees, employees, faculty, representatives, staff, volunteers or agents (all together referred to as "Queen's University") will be responsible, or liable to you, for any loss, injury or damage beyond its or their control that you may incur based on the Self-BAT or your result of the Self-BAT and in using this Self-BAT you release Queen's University from all such responsibility and liability to you and you waive all such claims.

Bleeding Assessment
Abnormal

Sex
Female

Your Age
45

Your Bleeding Score
29

Normal Range
(0-5)

Have you ever had a nosebleed?
Spoke to doctor about nosebleeds but did not need medical treatment

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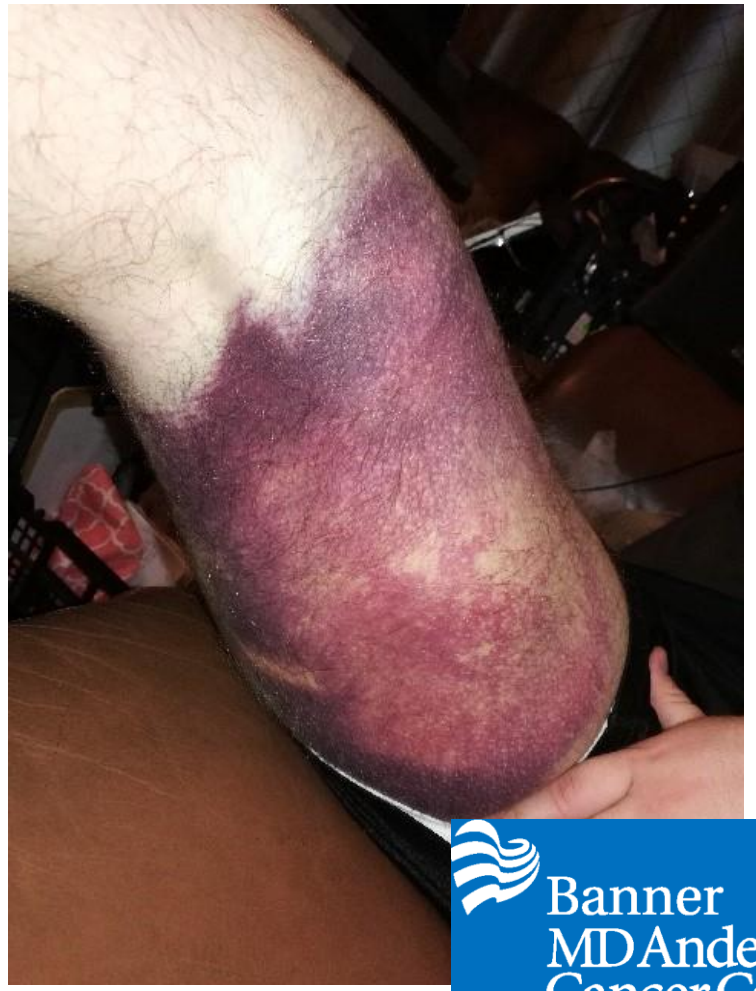
Case 2: 20 y/o male, factor IX level 6%

- Family history: Maternal Grandfather with similar factor level
- Lifelong bleeding history: bruising, ankle bleeds, nose bleeds since childhood
- Started on prophylaxis (regular clotting factor replacement) age 14 due to bleeding symptoms several times a month
- Calls in to report persistent pain after motorcycle accident



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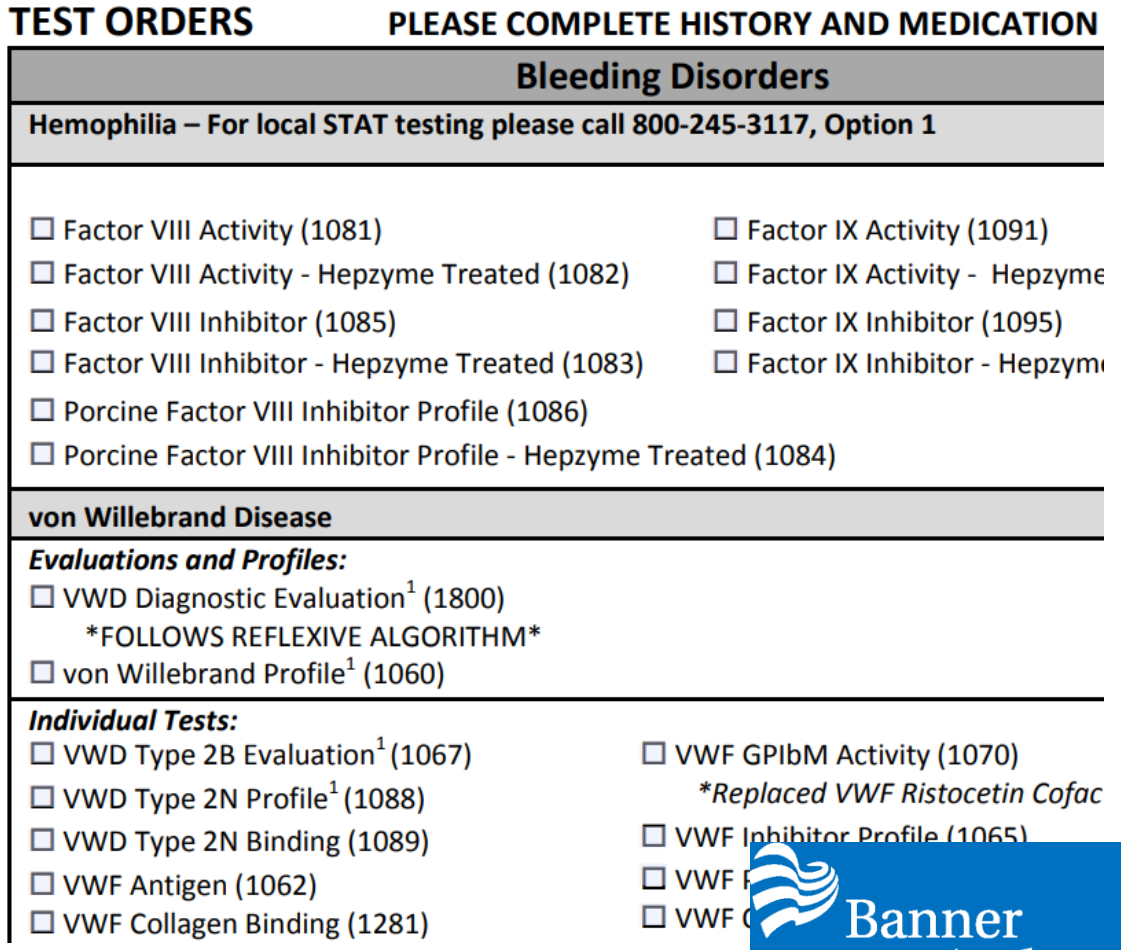
My Patient Bleeds Too Much

- CBC with differential
- TSH, CMP
- PT, PTT
- Von Willebrand Panel
- “Mixing Study”
- Platelet Aggregation Studies

- Individual Factor Testing



TEST ORDERS **PLEASE COMPLETE HISTORY AND MEDICATION**

Bleeding Disorders

Hemophilia – For local STAT testing please call 800-245-3117, Option 1

- ☐ Factor VIII Activity (1081)
- ☐ Factor VIII Activity - Hepzyme Treated (1082)
- ☐ Factor VIII Inhibitor (1085)
- ☐ Factor VIII Inhibitor - Hepzyme Treated (1083)
- ☐ Porcine Factor VIII Inhibitor Profile (1086)
- ☐ Porcine Factor VIII Inhibitor Profile - Hepzyme Treated (1084)
- ☐ Factor IX Activity (1091)
- ☐ Factor IX Activity - Hepzyme
- ☐ Factor IX Inhibitor (1095)
- ☐ Factor IX Inhibitor - Hepzym

von Willebrand Disease

Evaluations and Profiles:

- ☐ VWD Diagnostic Evaluation[1] (1800)
  FOLLOWS REFLEXIVE ALGORITHM
- ☐ von Willebrand Profile[1] (1060)

Individual Tests:

- ☐ VWD Type 2B Evaluation[1] (1067)
- ☐ VWD Type 2N Profile[1] (1088)
- ☐ VWD Type 2N Binding (1089)
- ☐ VWF Antigen (1062)
- ☐ VWF Collagen Binding (1281)
- ☐ VWF GPIbM Activity (1070)
  *Replaced VWF Ristocetin Cofac
- ☐ VWF Inhibitor Profile (1065)
- ☐ VWF
- ☐ VWF

It’s always ok to enlist the help of the friendly hematologist!

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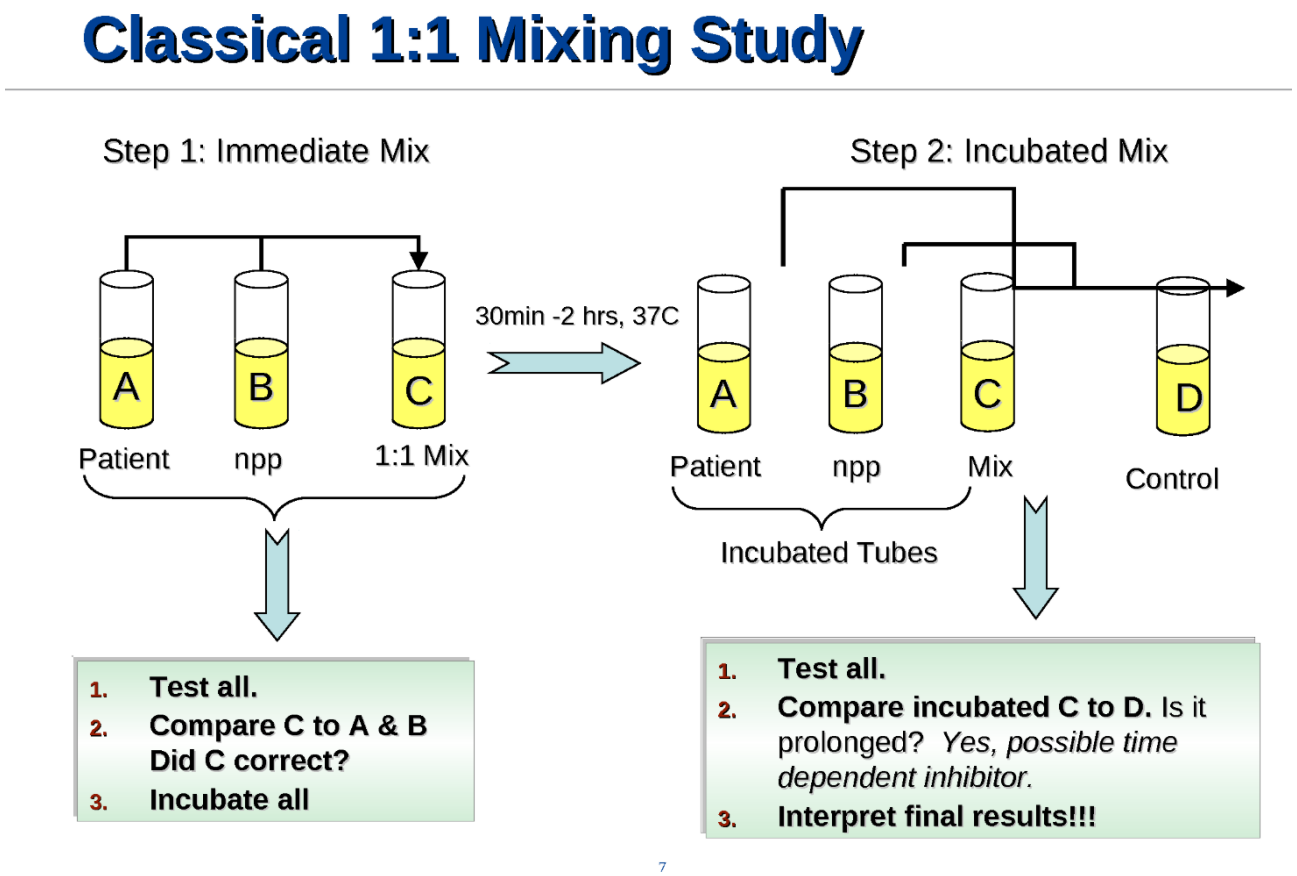
Lab testing and mixing studies

Patient plasma is mixed 1:1 with normal plasma

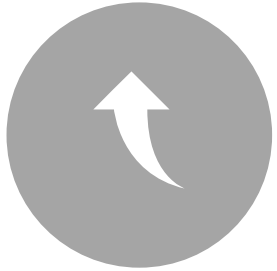
- Corrects = factor deficiency
- Doesn't correct = inhibitor

Inhibitors can be artifacts (lupus anticoagulant) or pathologic (alloimmune or autoimmune)



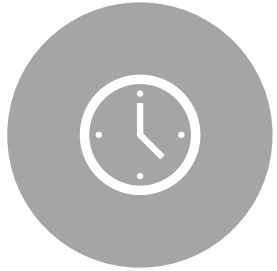
Mild, Moderate or Severe?

PATIENTS BLEED AT THE SAME RATE AS EVERYONE ELSE, BUT HEMOSTASIS IS DELAYED, INTERRUPTED, AND REBLEEDING OCCURS.



ONCE AN INJURY HAS BEEN SUSTAINED OR A BLEED HAS STARTED, THE TREATMENT PLAN IS TYPICALLY GOING TO BE THE SAME REGARDLESS OF THE SEVERITY OF THE UNDERLYING DIAGNOSIS.

FACTOR LEVELS NEED TO BE MAINTAINED AS CLOSE TO NORMAL AS POSSIBLE.



TREATMENT SHOULD CONTINUE DURING THE ENTIRE DURATION OF HEALING (10 DAYS TO 3 WEEKS).

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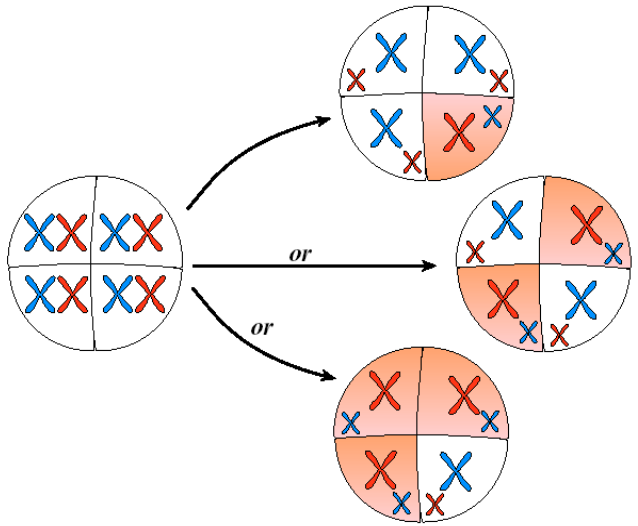
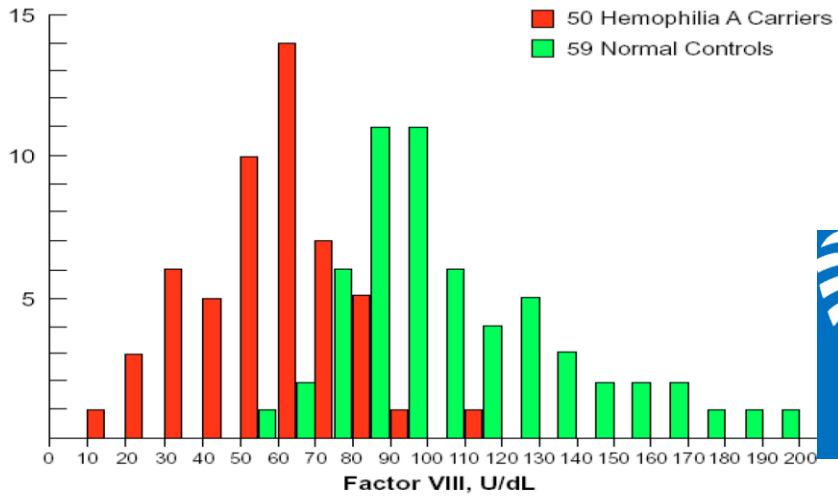
Women and Bleeding Disorders

- Carriers of hemophilia
- Von Willebrand Disease
- Platelet function disorders
- Rare factor deficiencies





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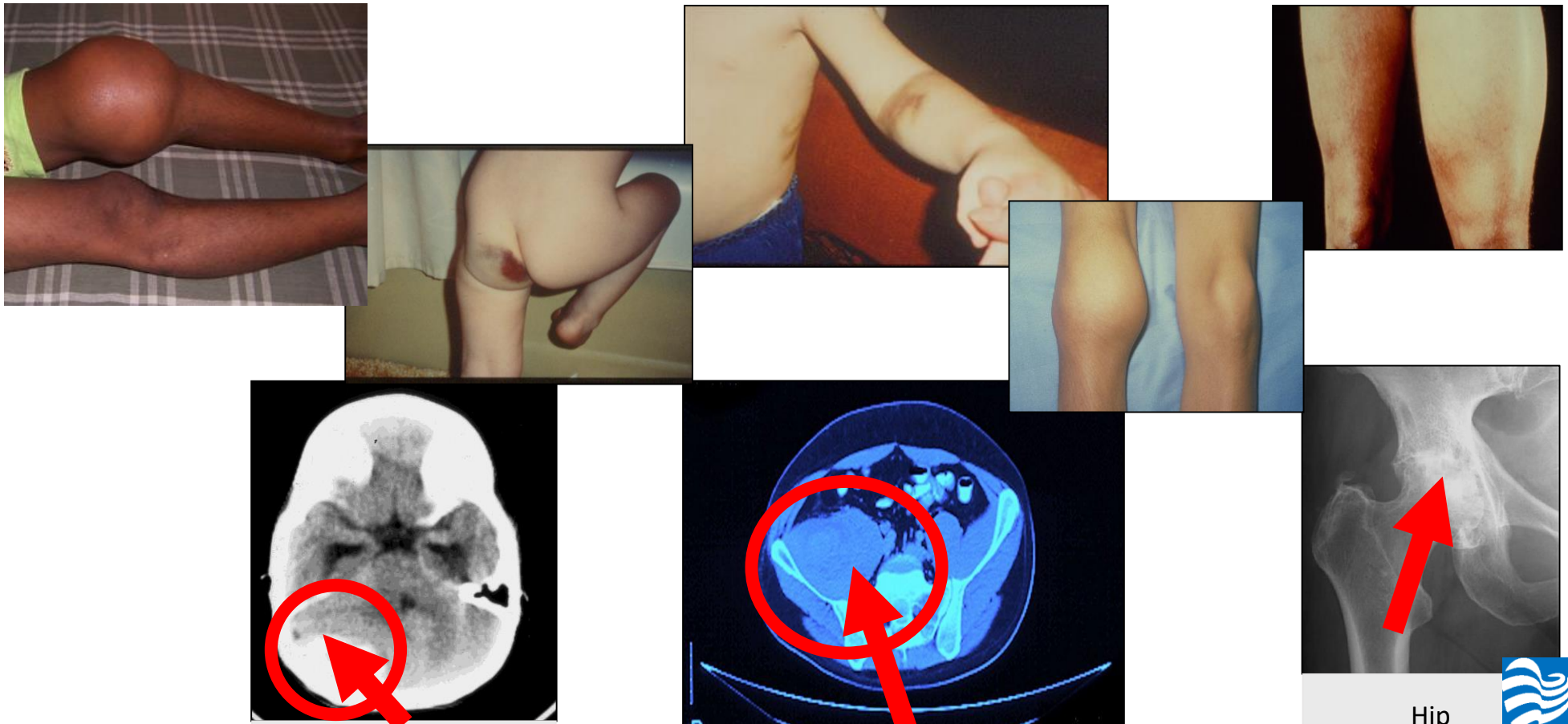
Bleeds



Intracranial

Iliopsoas Muscle

Hip

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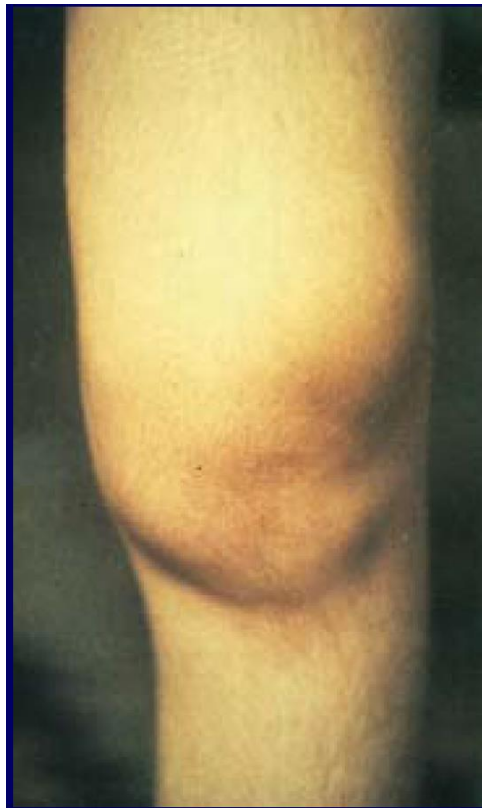
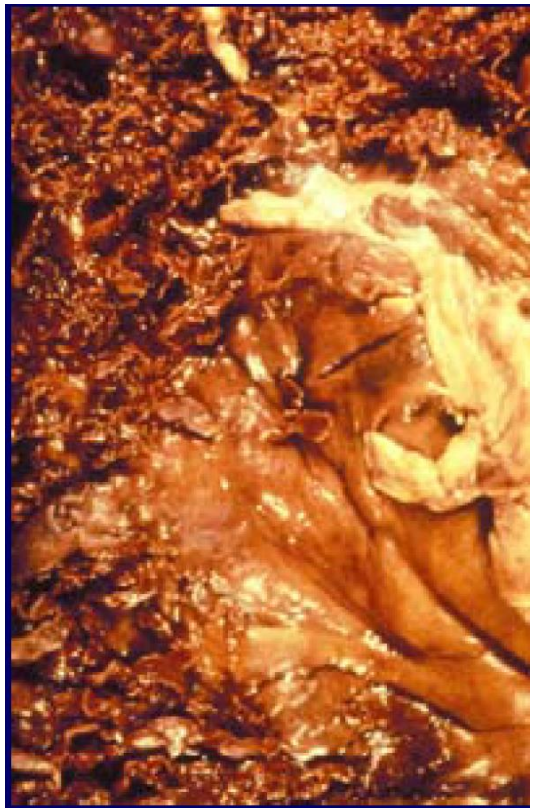
Most Common Bleeds

- Post trauma
- Post surgical
- Immediate bleeding – mucocutaneous, joint muscle
- Delayed bleeding or re-bleeding
- Prolonged healing – weeks to months
- Gender specific -reproductive years
- Age specific -aging





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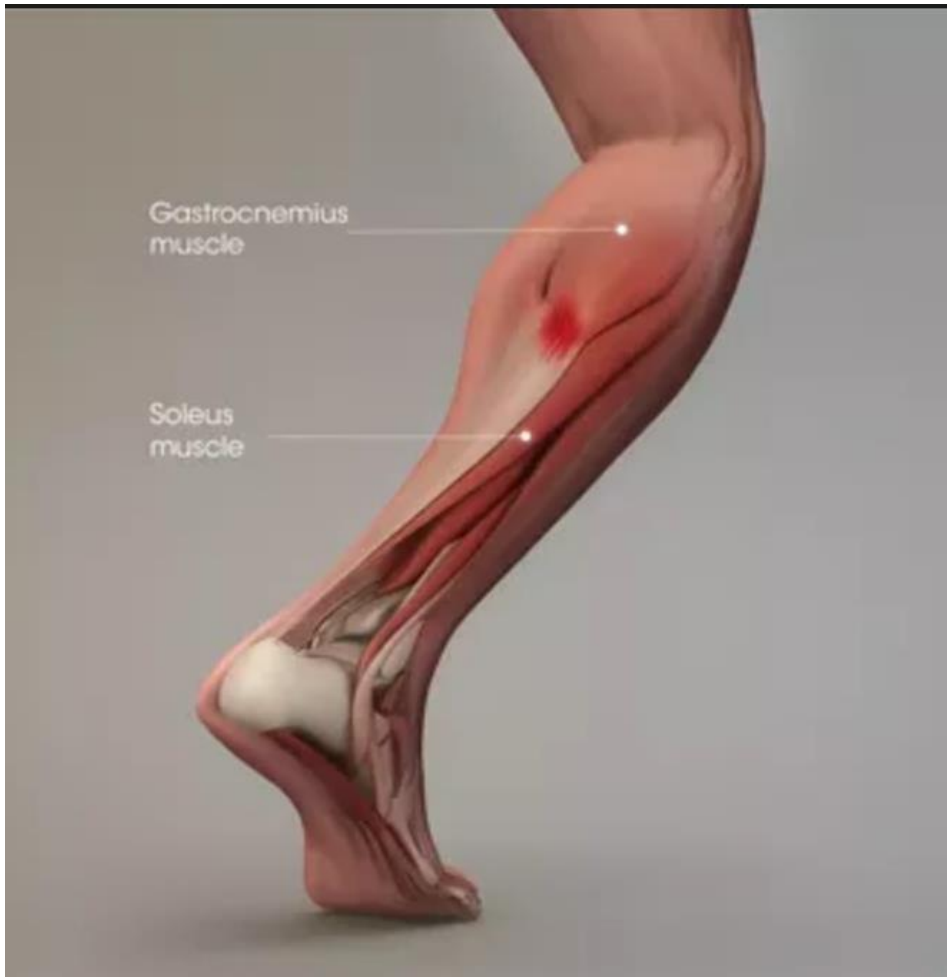
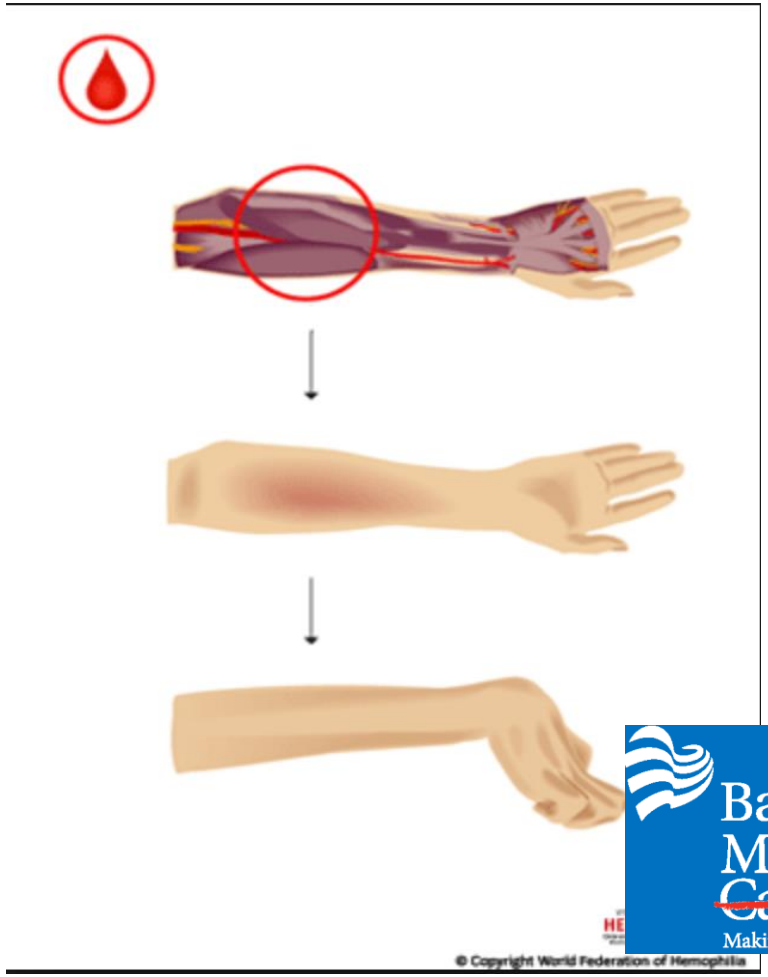
Muscle and tendon Injuries in bleeders





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What could emerging therapies achieve?

Mimics the function of FVIII[1]

Blocks anti-thrombin production[2]

Inhibits TFPI activity, resulting in increased FXa and thrombin generation[3]

Replaces defective FVIII gene[4]

- The methods by which emerging therapies work differ from those of established therapies
- These differences result in different treatment profiles

1. Uchida et al. *Blood* 2016 **2.** Franchini and Mannucci. *Blood Transfus* 2018 **3.** Chowdary et al. *J. Thromb Hemost* 2015 **4.** Mannucci. *J Thromb Hemost* 2003

Not all pain symptoms are bleeding disorder related

- 34 year old man sustained a twisting injury to the wrist/forearm. After 10 days of twice a day therapy, pain persisted and MD was notified.
  - MRI showed no evidence of hemosiderin or bleeding, but did show edema of the tendons
- 38 year old with chronic hip pain which was exacerbated after pushing a car. Pain did not resolve after 6 days and I got a call
  - MRI showed no hemosiderin, but did show chronic arthritis

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Pain control…
Is there anything better than opiates?

Hayden Wariner Morgan
1993 - 2015

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Thrombosis Risk Factors

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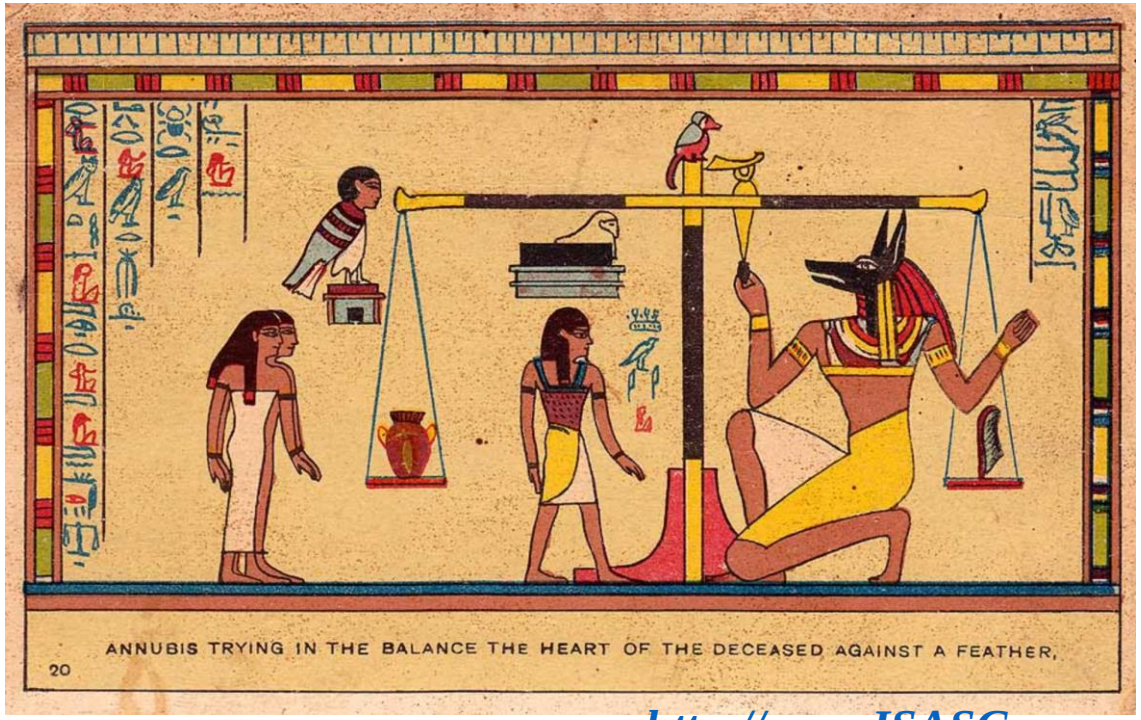
Bleeding

Congenital deficiency
EDS
Cold
Anemia
Surgery
Trauma
Age
Medications
DIC
Hypertension
Liver Disease



http://www.ISASC.org

Clotting

Surgery
Trauma
Pregnancy
Inpatient status

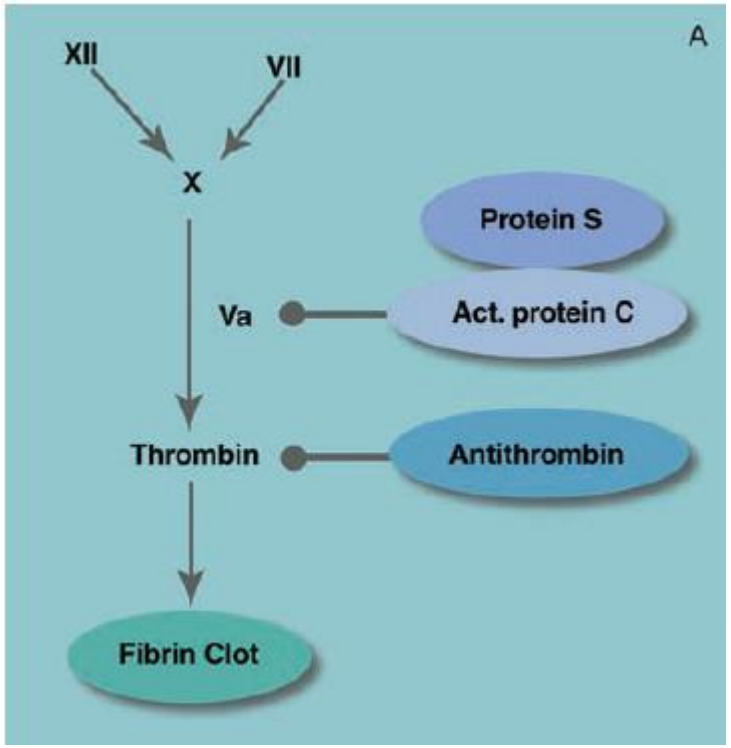
Common risk factors

Malignancy + Chemo
Malignancy
Age
Medications
Neurologic disease
Obesity
Cardiovascular disease
Tobacco use
OCP Use
Venous architecture

Virchows Triad:
Stasis, Endothelial Injury, Hypercoaguable state

Congenital hypercoaguable states

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

Hypercoagulable workup

- Prothrombin Gene mutation
- Factor V Leiden
- Antithrombin
- Protein C
- Protein S
- Lupus anticoagulant
- Antiphospholipid antibody syndrome
- Family History
- Recent pregnancy (or loss)
- Travel history
- Infectious history
- Autoimmune disease

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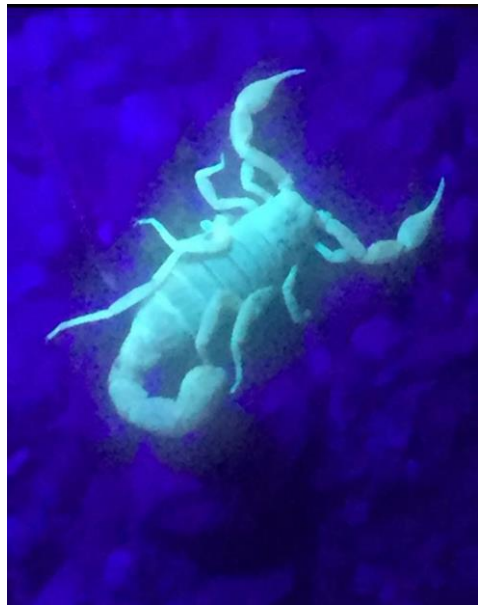
When to consider a hypercoagulable workup?

- 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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Acquired hypercoaguable states

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.

* Tests to never send

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

  * MTHFR gene analysis/polymorphism (33% of population, no increase in VTE risk)
  * Homocysteine level (except for pt **<30yo** to eval for homocytsinuria)

Your Turn: Provoked or Unprovoked?

- 26 year old woman presents with pain of the L calf, 1 week post SAB
- 35 year old man with a BMI of 30 presents with SOB 3 days after returning from a trip to China
- 22 year old woman presents with abdominal pain and found to have splancnic vein thrombosis
- 27 year old obese woman with recent diagnosis of fibromyalgia presenting with headache and found to have venous sinus thrombosis
- 48 year old man with a remote injury to the calf (3 months ago) presenting with calf pain and cough
- 50 year old man now on his 2nd episode of DVT, no obvious cause. He has 3 daughters. His father also had DVTs.

- Friendly Hematologists:
- Danielle Nance, MD mobile 480-269-7933
- Esteban Gomez, MD

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