Acquired Bleeding Disorders

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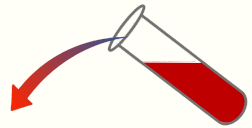
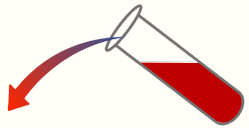
Disclosures

- Research Support:
  - Amgen
  - Janssen Scientific Affairs
  - Dova Pharmaceuticals
- Advisory Boards (In past 5 years)
  - Amgen
  - Janssen Scientific Affairs
  - Dova Pharmaceuticals
  - Bristol-Myers Squibb, Pfizer
  - Novartis
  - Anthos Therapeutics



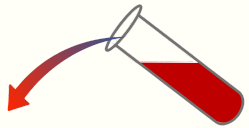
Topics To Cover

1. Hematology Consult for “Bleeding”
2. Vascular Bleeding Disorders
3. Thrombocytopenia
4. Acquired Bleeding Disorders:
5. Managing Anticoagulant-Related Bleeding
6. Management of Vitamin K Antagonist-Related Bleeding
7. Protamine: Reversal of IV Unfractionated Heparin
8. Management of Direct Oral Anticoagulant-Related Bleeding
9. Coagulopathy of Liver Disease
10. Vitamin K Deficiency
11. Disseminated Intravascular Coagulation
12. Uremic Coagulopathy
13. Acquired Hemophilia
14. Acquired von Willebrand Disease
15. Acute Promyelocytic Leukemia
16. Workup of Coagulopathy



Hematology Consult for "Bleeding"

Module: 1



Hematology Consult for “Bleeding”

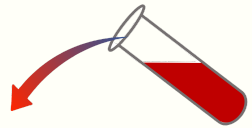
Are we working up the patient, the laboratory tests, or the surgeon?

- Is the patient symptomatic, or is the surgeon symptomatic?
- Are we consulting for a bleeding patient or a scary lab value?
- aPTT of 55” can be from von Willebrand Disease (bleeding), moderate hemophilia (bleeding), Factor XI deficiency (possible risk for post-op bleeding), or Anti-phospholipid antibody syndrome (prothrombotic).

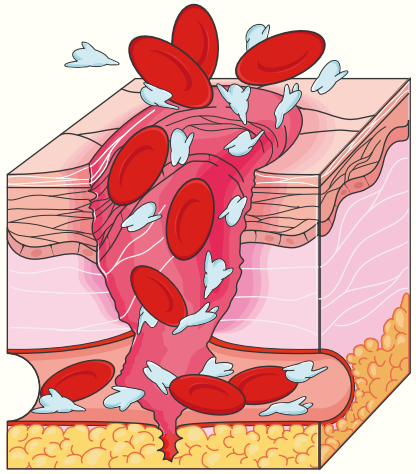
https://depositphotos.com/stock-photos/surgeons.html

Pattern of Bleeding/History:

- Clinical Presentations Help Define Differential Diagnosis
- Mucocutaneous versus deep bleeding?
- Immediate versus late bleeding?
- Local versus systemic?
- Acquired versus congenital?
- Family history?



Major Components of Hemostasis



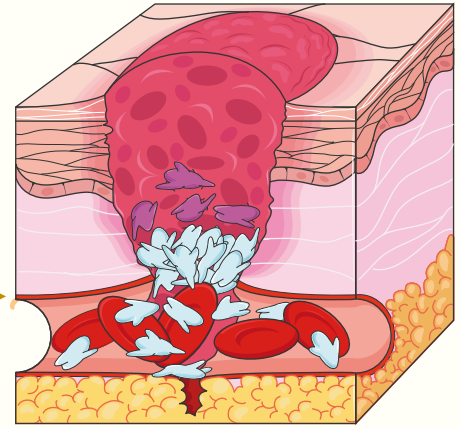
Vascular Injury

Hemostasis

Vasoconstriction

Platelet Plug Formation

Coagulation Cascade



Primary Hemostasis

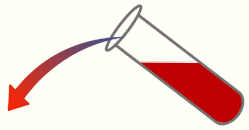
Secondary Hemostasis

Patterns of Acquired Bleeding Disorders in a Tertiary Care Hospital

- A total of 1342 reported cases of bleeding disorders were analyzed during 1-year period (2006).
  - 1040 (77.4%) had an underlying acquired cause
  - 302 (22.6%) had an inherited cause.
  - Asthana et al. Clinical and Applied Thrombosis/Hemostasis Volume 15 Number 4 August 2009 448-453, 2009

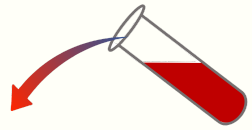
Distribution of Various Types of Acquired Bleeding Disorders

Cause	Total	Percentage
DIC	297	28.5
Deranged liver function	218	20.9
Neurosurgical causes	154	14.8
Malignancy related	89	8.5
Miscellaneous	282	27.1



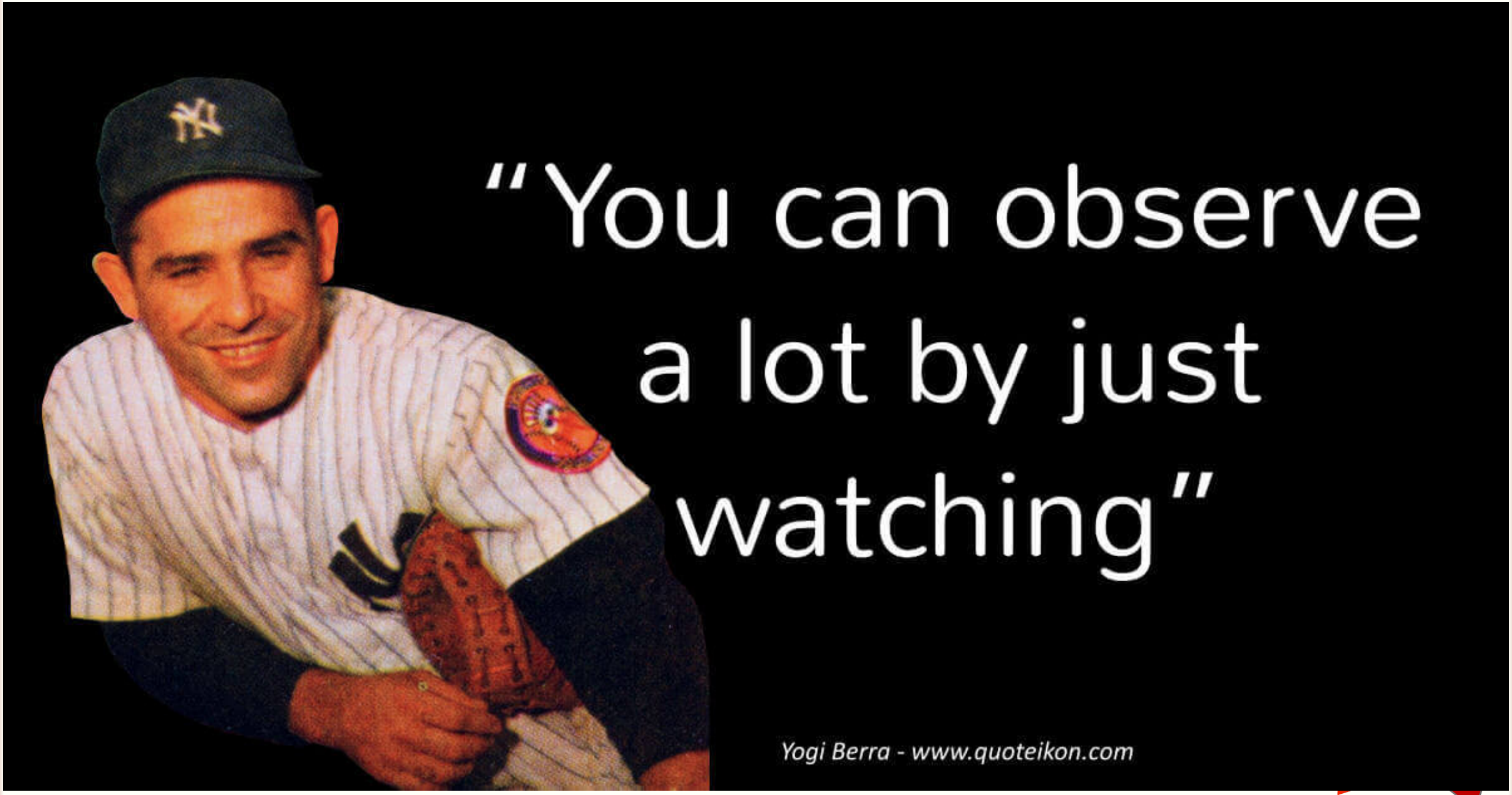
Clinical Features of Bleeding Disorders

	Primary Hemostasis	Secondary Hemostasis
Defect	Thrombocytopenia Platelet Function Disorders Vascular Defects	Coagulation Factor Disorders
Site of Bleeding	Skin Petechiae/Purpura/Ecchymoses, Mucous membranes Epistaxis, gum, vaginal, GI	Deep: Soft tissues, joints, muscles
Bleeding after surgery or trauma	Immediate, usually mild	Delayed (1-2 days), often severe



History and physical often provide strong evidence of the cause of bleeding!

https://thenounproject.com/photo/doctor-checking-a-patients-throat-4mdXB5/


"You can observe a lot by just watching"
Yogi Berra - www.quoteikon.com

Ecchymosis/Purpura

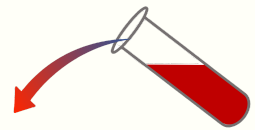
- Flat, not warm, not tender
- Defect in primary hemostasis. (Platelets and small vessel)

Hematoma:

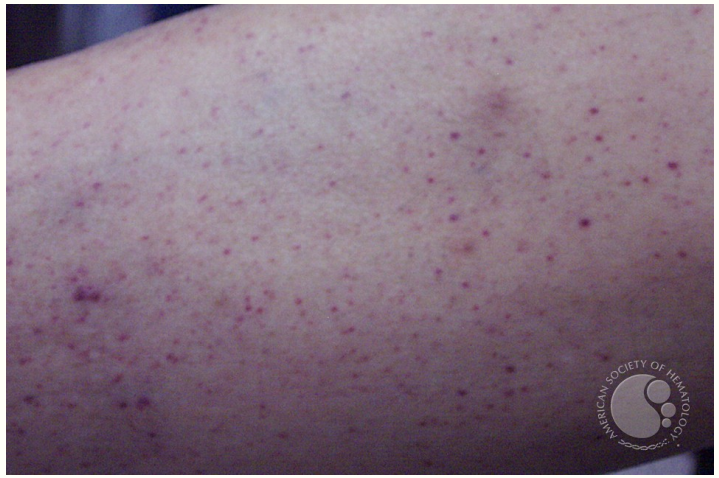
(Subcutaneous, Intramuscular)

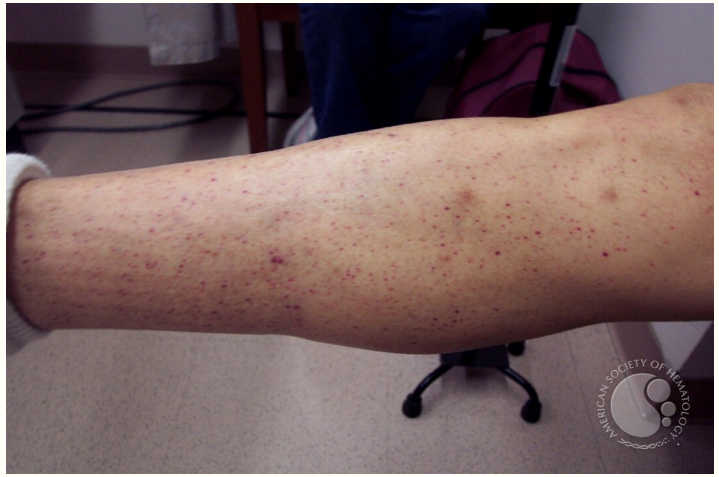
Hemarthrosis

- Raised, tender, painful, warm
- Defect in Coagulation Factors



Petechiae: <3 mm





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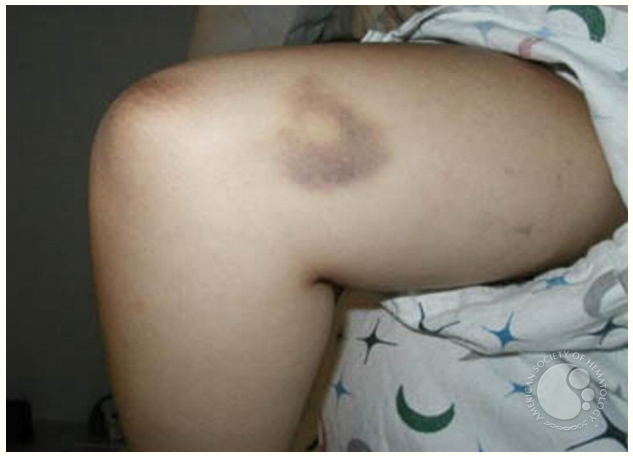
Purpura: 3–10 mm/Ecchymosis: >10 mm



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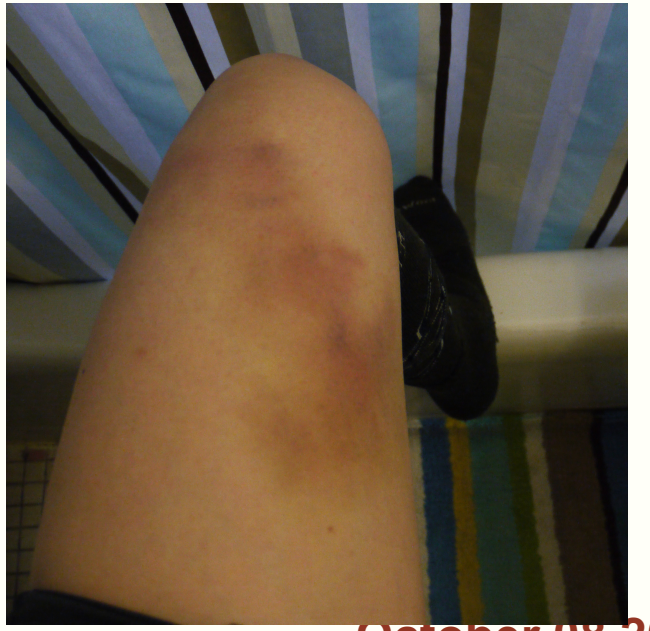
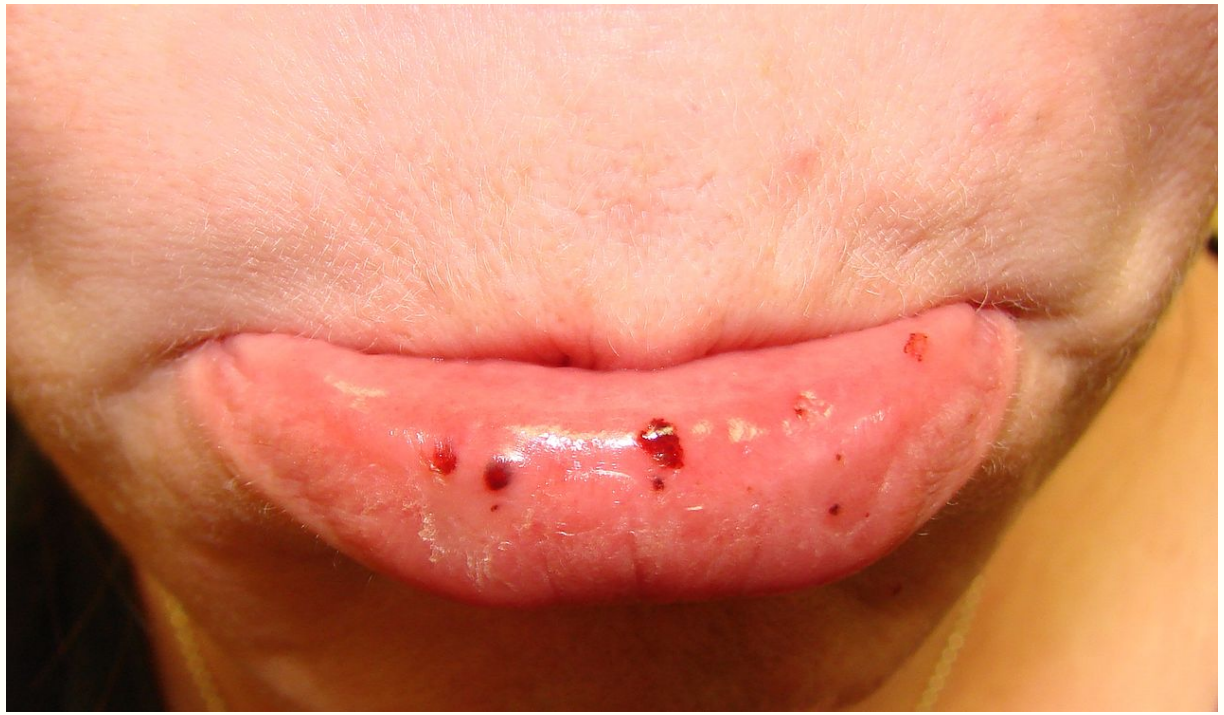


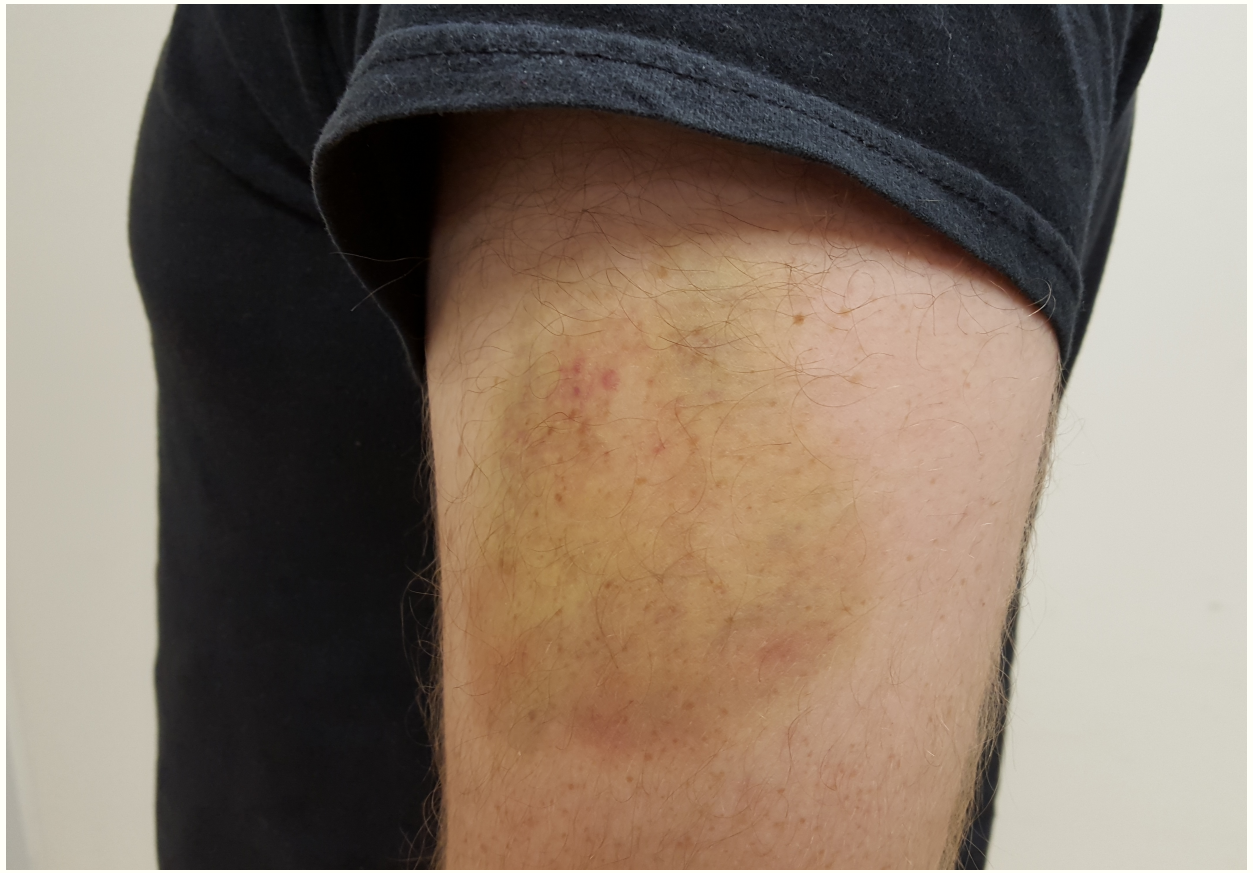
https://www.flickr.com/photos/thirteenofclubs/5220240420. Creative Commons ©

Oral Petechiae/Purpura



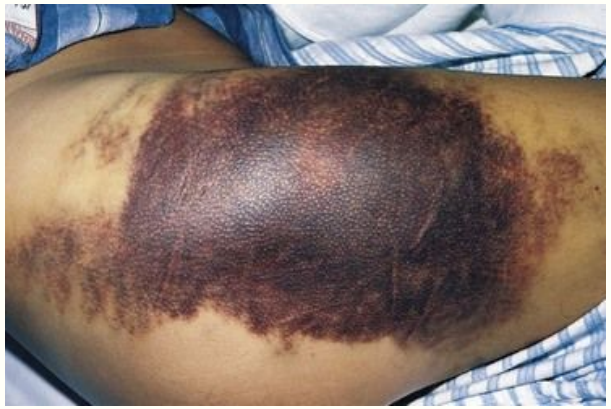
- https://commons.wikimedia.org/wiki/File:Oral_petechiae.JPG

Bruising in “Atypical Sites: Upper Arm Bruise

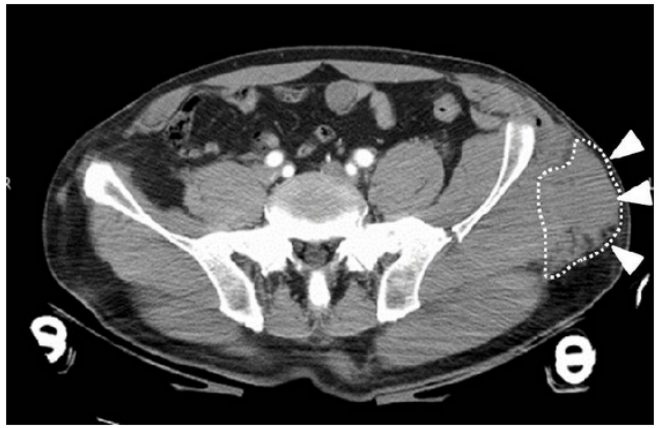


https://commons.wikimedia.org/wiki/File:Upper_Arm_Bruise.jpg

Muscle Hematoma



Hoffbrand AV, Pettit JE: Color atlas of clinical hematology, ed 4, London, 2010, Mosby



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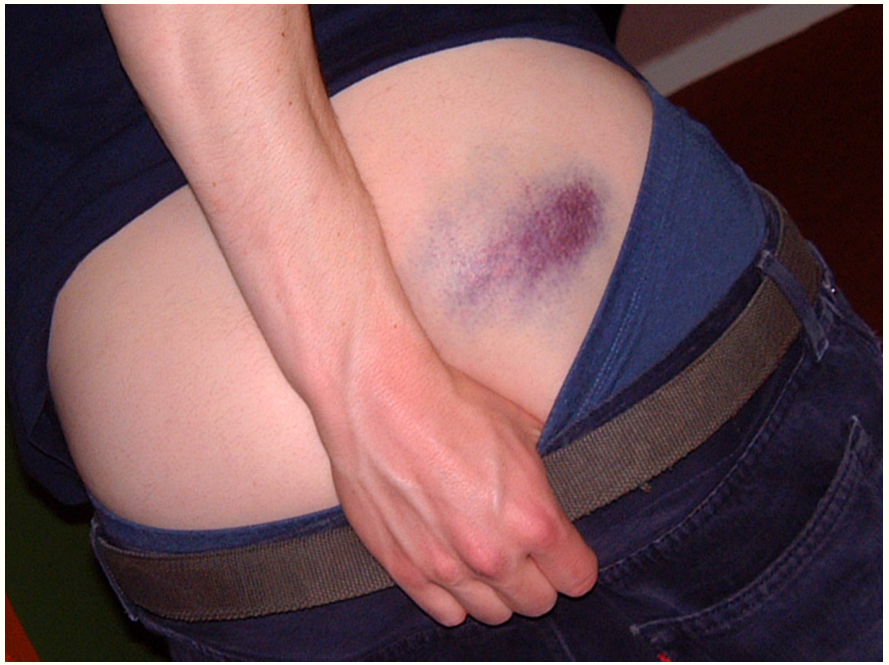
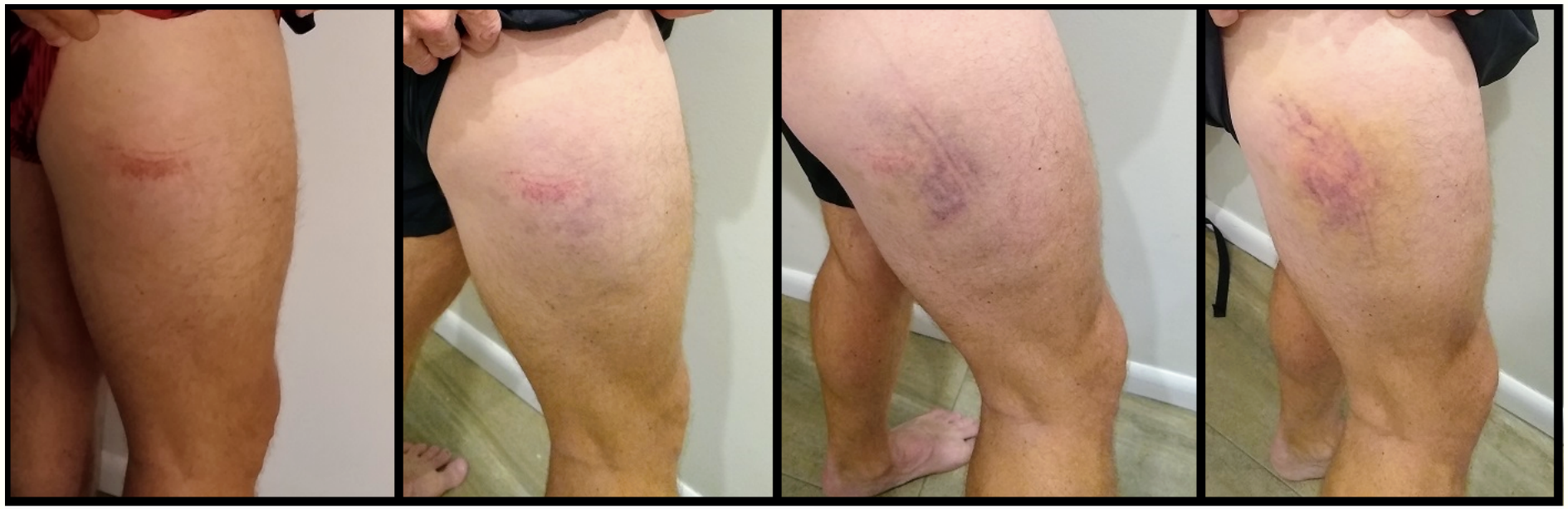
Subcutaneous Hematoma



https://commons.wikimedia.org/wiki/File:Hematoma_at_backside.jpg#filelinks

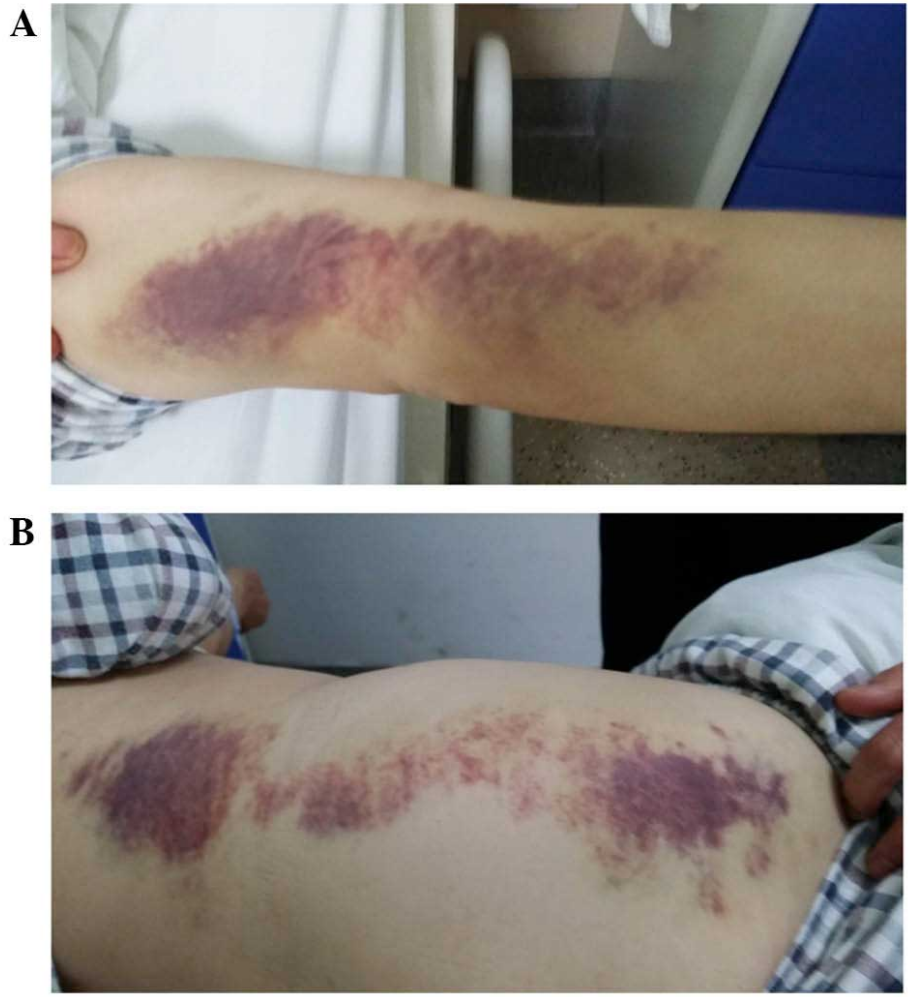
Muscle Hematoma



- Muscle hematoma can follow trauma. But spontaneous Muscle hematoma is indicative of factor deficiency.

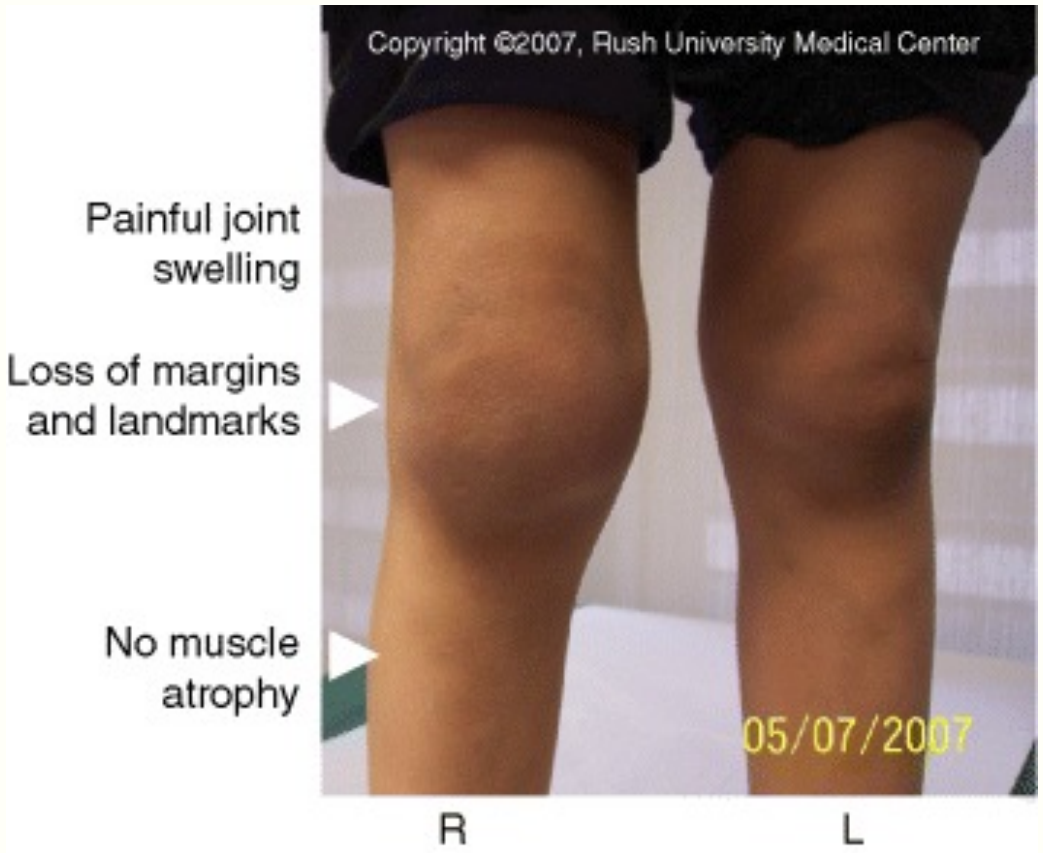
  - https://commons.wikimedia.org/wiki/File:Hematoma_development.png
  - Whoisjohngalt / CC BY-SA (https://creativecommons.org/licenses/by-sa/4.0)

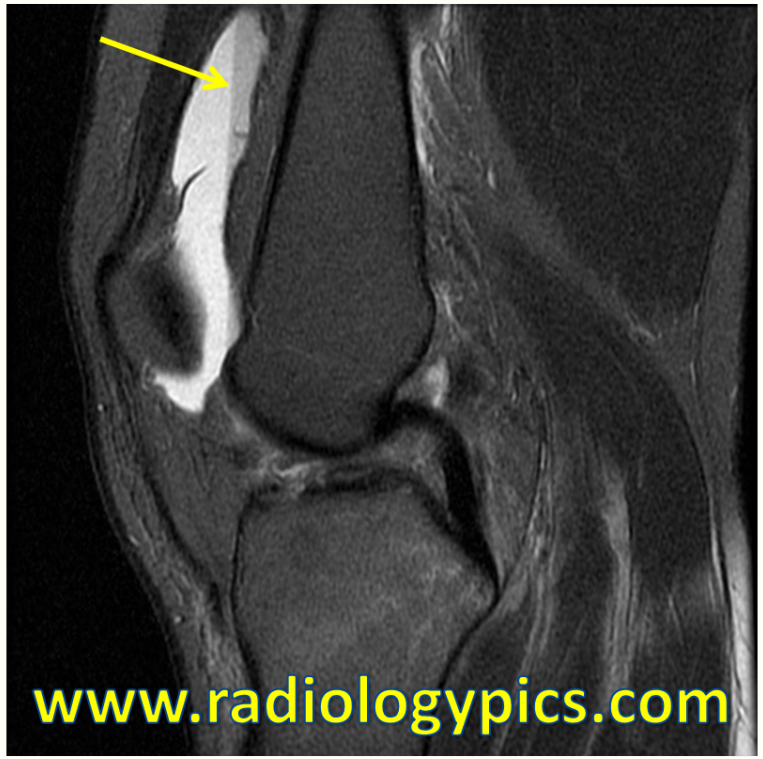
Subcutaneous Hematomas in Patient With Acquired Hemophilia



Large diffuse subdermal hematoma on the patient's (A) arm and (B) right waist and hip.

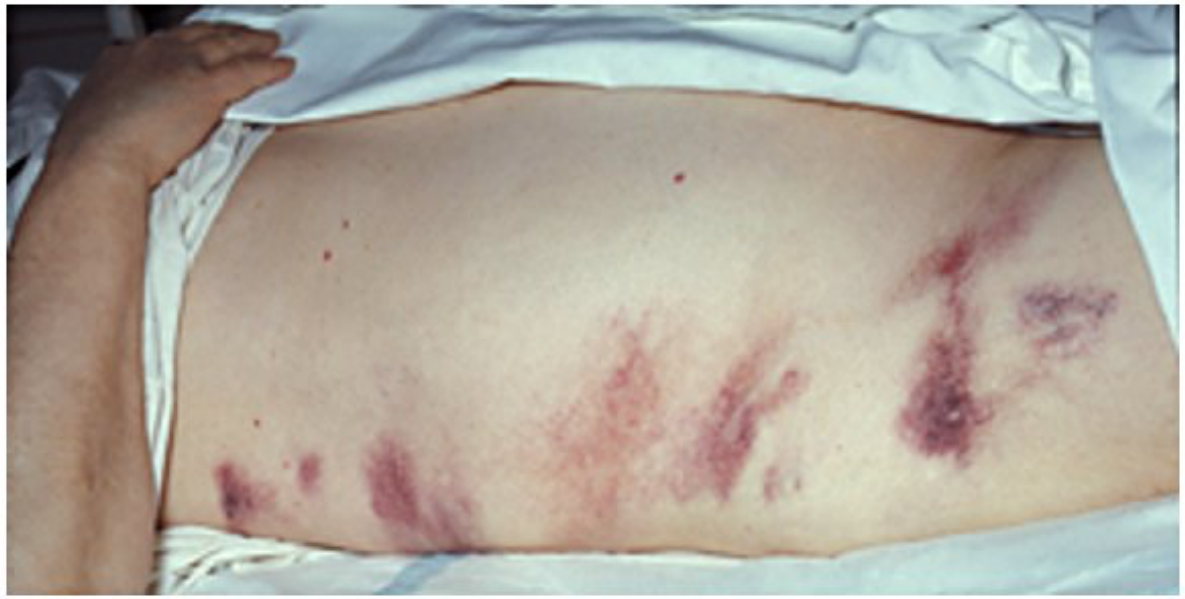
Hemarthrosis





https://www.researchgate.net/profile/Steven_Pipe/publication/6016957/figure/fig5/AS:267796365967398@1440859038152/Figure-1-Acute-hemarthrosis-The-right-R-knee-is-swollen-warm-and-painful-to-touch.png

A deep bleed may appear to “spread” with time, as the deep blood products migrate to the skin

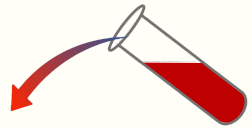


- Grey-Turner’s Sign:
- Appears to be “bruising.”
- A sign of retroperitoneal hematoma.
- Grey Turner's sign usually take 24–48 hours to develop.

https://en.wikipedia.org/wiki/Grey_Turner%27s_sign#/media/File:Hemorrhagic_pancreatitis_-_Grey_Turner's_sign.jpg

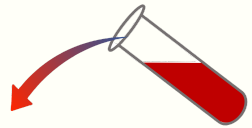
Vascular Bleeding Disorders

Module: 2

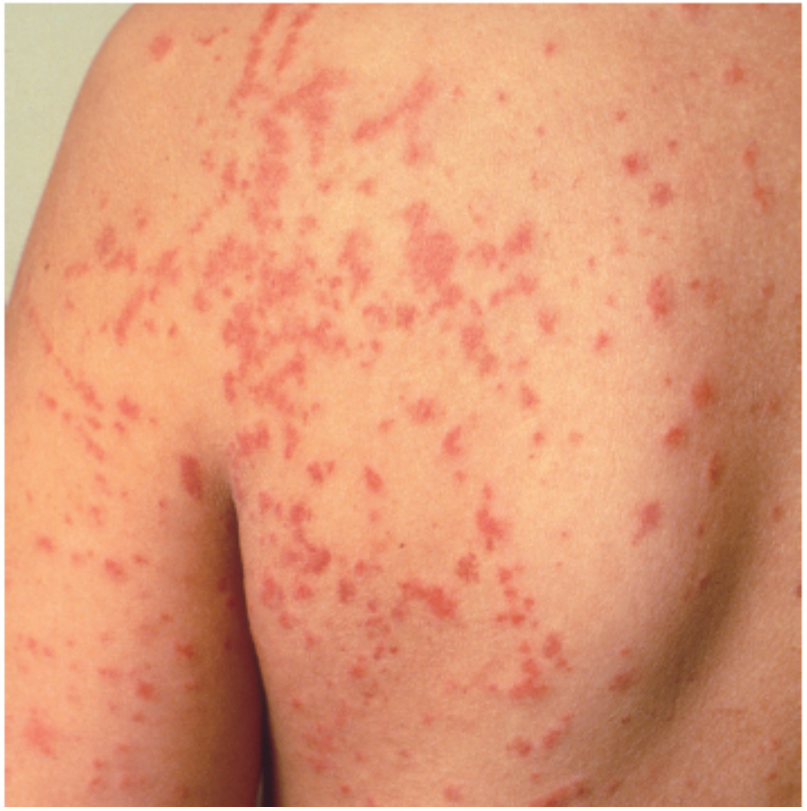


Vascular Bleeding Disorders

- Defects in blood vessels
- Clinical Manifestations:
  - Often petechiae, purpura, and bruising
- Causes:
  - Vasculitis: Inflammatory, Scurvy, immunoglobulin A–associated vasculitis
  - Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)
  - Ehlers-Danlos syndrome: Deficiencies of vascular and perivascular collagen
- Diagnosis:
  - Coagulation tests normal
  - Specific tests are available for some.



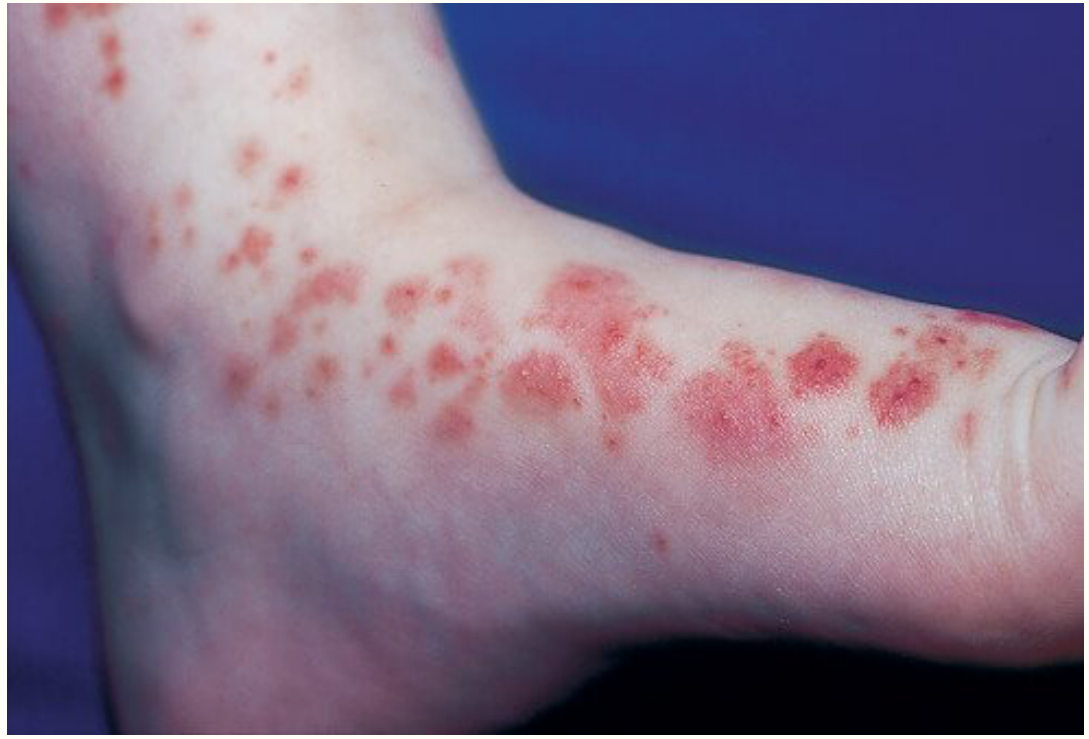
Mimics of Bleeding: Hypersensitivity Vasculitis



https://arapc.com/vasculitis-nutshell/

- Hypersensitivity vasculitis, or cutaneous small vessel vasculitis:
  - Allergic reaction
  - Reaction to an infection
  - Idiopathic
- Lesions of vasculitis tends to be diffuse, while thrombocytopenia/ITP tends to be more in dependent areas.

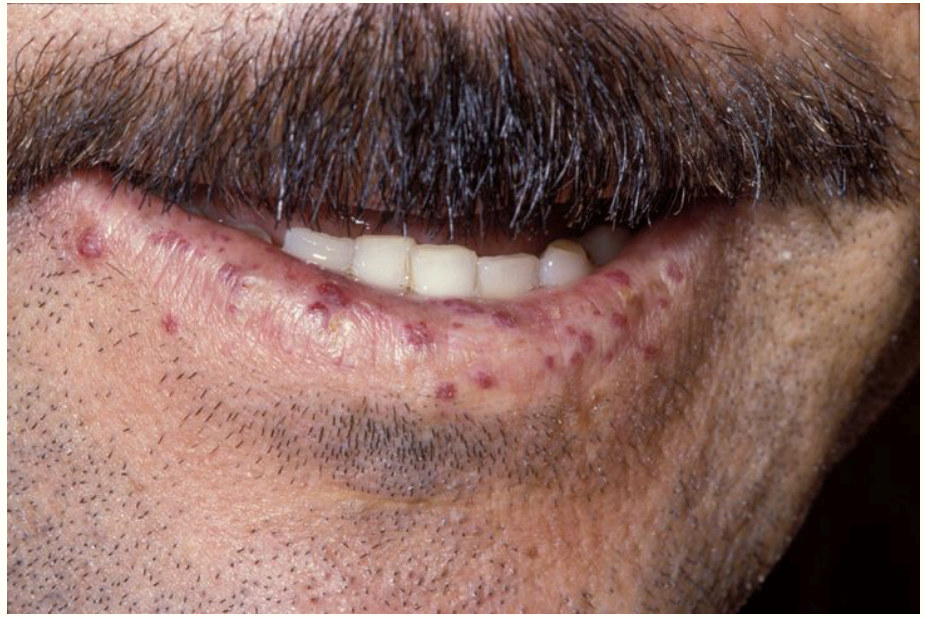
Mimics of Bleeding: Henoch-Schonlein Purpura



- Henoch-Schonlein purpura is a disease involving inflammation of small blood vessels.
- It most commonly occurs in children.
- The inflammation causes blood vessels in the skin, intestines, kidneys, and joints to start leaking.
- “Palpable purpura”

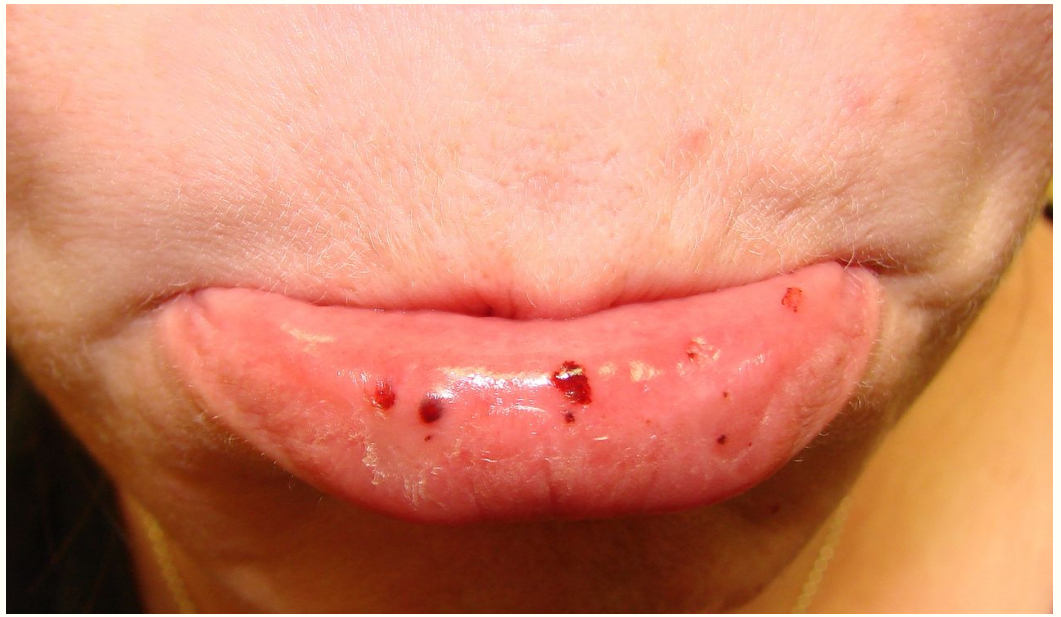
https://www.medicinenet.com/image-collection/henoch-schonlein_purpura_picture/picture.htm

Hereditary Hemorrhagic Telangiectasia



- https://commons.wikimedia.org/wiki/File:Case_115.jpg
- Herbert L. Fred, MD and Hendrik A. van Dijk / Attribution

Oral Petechiae/Purpura

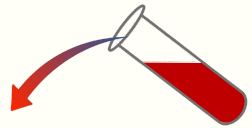


- https://commons.wikimedia.org/wiki/File:Oral_petechiae.JPG

Thrombocytopenia

Thrombocytopenia, including ITP, are to be discussed in separate talks in the next few weeks.

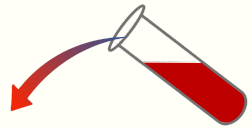
Module: 3



Acquired Bleeding Disorders:

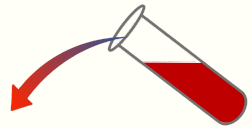
- Anticoagulant Therapy/Antiplatelet drugs.
- Liver disease
- Vitamin K deficiency
- Disseminated intravascular coagulation
- Uremic coagulopathy
- Acquired hemophilia
- Acquired von Willebrand disease
- Acute Promyelocytic Leukemia

Module: 4



Synergy Of Risks

- Some patients with mild-moderate hereditary bleeding tendency do not have clinical manifestations, until an added hemostatic challenge is added, such as:
  - Surgery,
  - Trauma,
  - Dental extraction
  - Menstruation/pregnancy
- Examples:
  - Von Willebrand Disease
  - Factor XI Deficiency



ISTH Definitions of Bleeding

Major Bleeding in Non-Surgical Patients

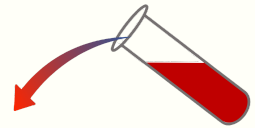
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome.

and/or

- Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.
- J Thromb Haemost 3 (4): 692-4. 2005 doi:10.1111/j.1538-7836.2005.01204.x.

Clinically Relevant Non-Major Bleed

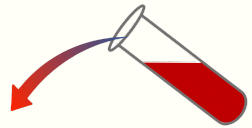
- A clinically relevant Non-Major bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:
  - A hospital admission for bleeding, or
  - A physician guided medical or surgical treatment for bleeding, or
  - A change in antithrombotic therapy (including interruption or discontinuation of study drug).
- J Thromb Haemost 8 (1): 202-4. 2010 doi:10.1111/j.1538-7836.2009.03678.x.

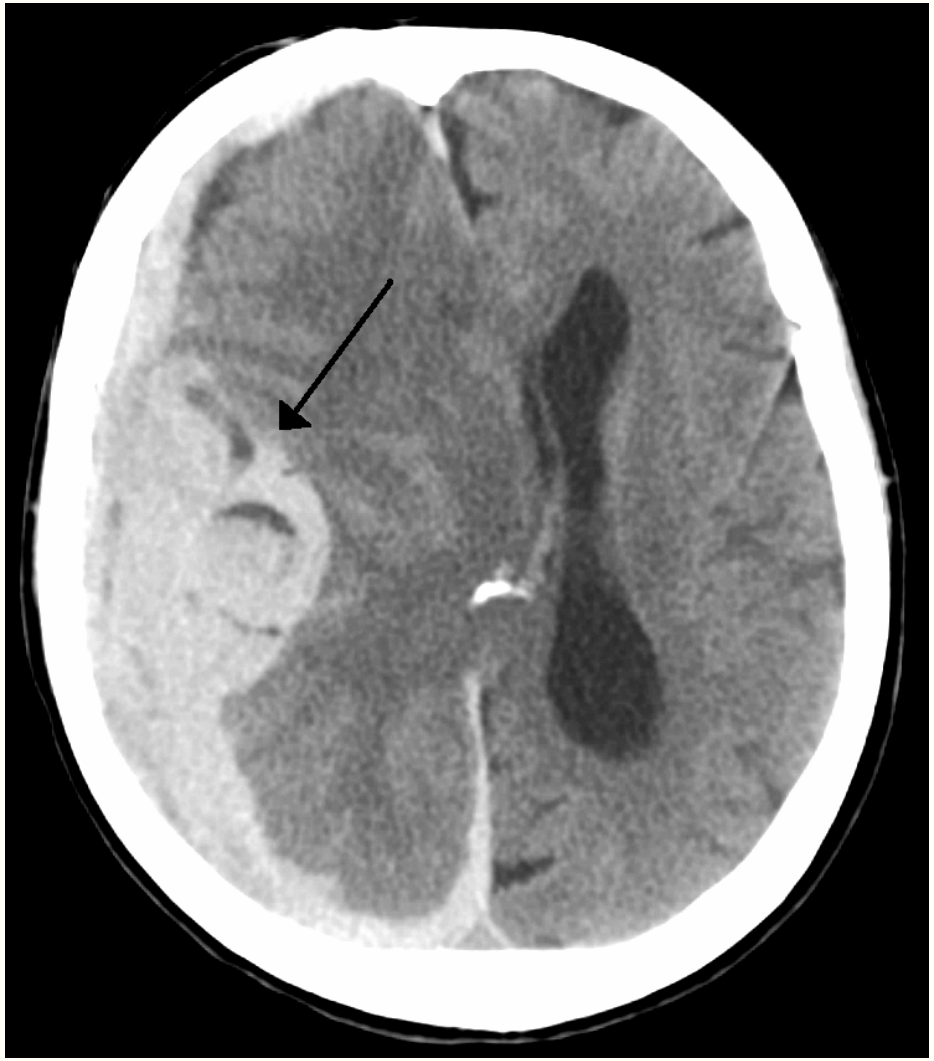


Managing Anticoagulant-Related Bleeding

- Bleeding is a common side effect of anticoagulant use.
- However, the majority of bleeding events are not life threatening and can be managed conservatively.
  - 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. Tomaselli et al. J Am Coll Cardiol 2017;70:3042–67.
  - Hanigan et al. American College of Cardiology 2019. Managing Anticoagulant-related Bleeding in Patients with Venous Thromboembolism

Module: 5



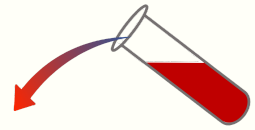


- https://commons.wikimedia.org/wiki/File:Intracranial_bleed_with_significant_midline_shift.png
- James Heilman, MD / CC BY-SA (https://creativecommons.org/licenses/by-sa/3.0)

Management of Vitamin K Antagonist-Related Bleeding (Warfarin)

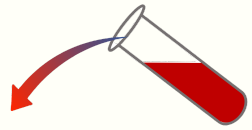
- "In the setting of a life-threatening bleed related to vitamin K antagonist (VKA) use, rapid reversal of the VKA drug effects and replenishing clotting factors is a priority."
- "To achieve that goal, administer vitamin K 10 mg intravenously along with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) to achieve a sustained reduction of the international normalized ratio (INR)."
- "Generally, a goal INR of ≤1.3-1.5, depending on the site of the bleed, is targeted."
  - Hanigan et al. American College of Cardiology 2019. Managing Anticoagulant-related Bleeding in Patients with Venous Thromboembolism

Module: 6

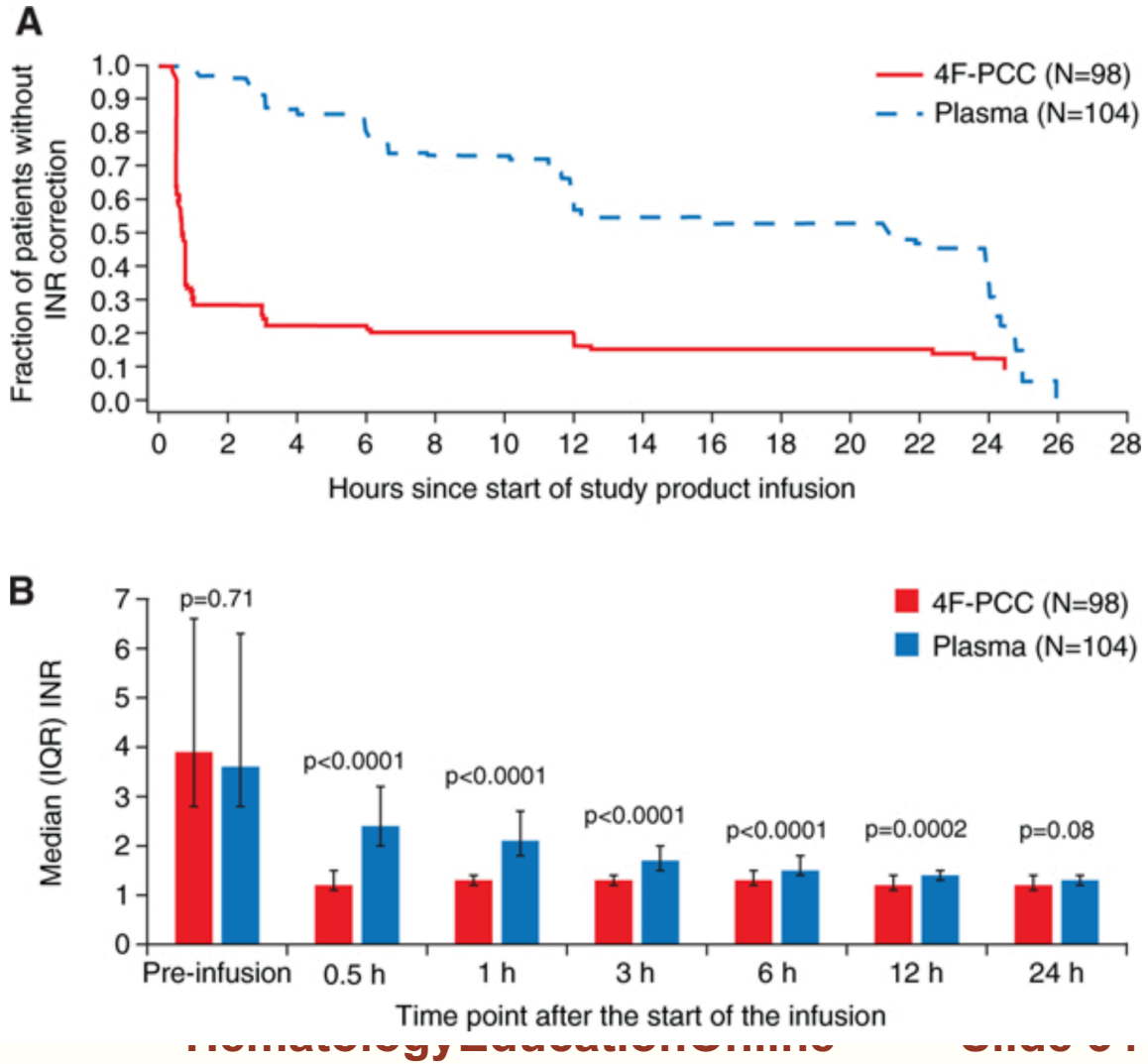


Limitations of FFP Use to Reverse VKA-Associated Bleeding

- Need for blood typing and thawing that results in administration delays
- Large volume requirement that leads to prolonged infusion times
- Potential for transfusion-associated circulatory overload (TACO)
- Risk of transfusion-related acute lung injury (TRALI).
- Hanigan et al. American College of Cardiology 2019. Managing Anticoagulant-related Bleeding in Patients with Venous Thromboembolism



Prothrombin Complex Concentrate Versus Plasma for Management of Vitamin K Antagonist-Related Bleeding (2)



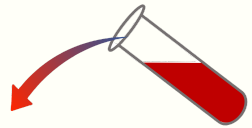
- Prothrombin complex concentrate (Kcentra ®) provides more factors/volume, and has less risk of infusion-related infection than plasma.
  - Sarode et al. Circulation. 2013 September 10; 128(11): 1234–1243. doi:10.1161/CIRCULATIONAHA.113.002283.
- Weight/INR based dose versus fixed dose?

Protamine: Reversal of IV Unfractionated Heparin

- Binds heparin chains
- Administer 1 mg of protamine per 100 U of circulating heparin
- Need to estimate the amount of residual heparin.

Time Elapsed	Dose of Protamine (mg) to Neutralize 100 units of Heparin
Immediate	1-1.5
30-60 min	0.5-0.75
>2 h	0.25-0.375

Module: 7



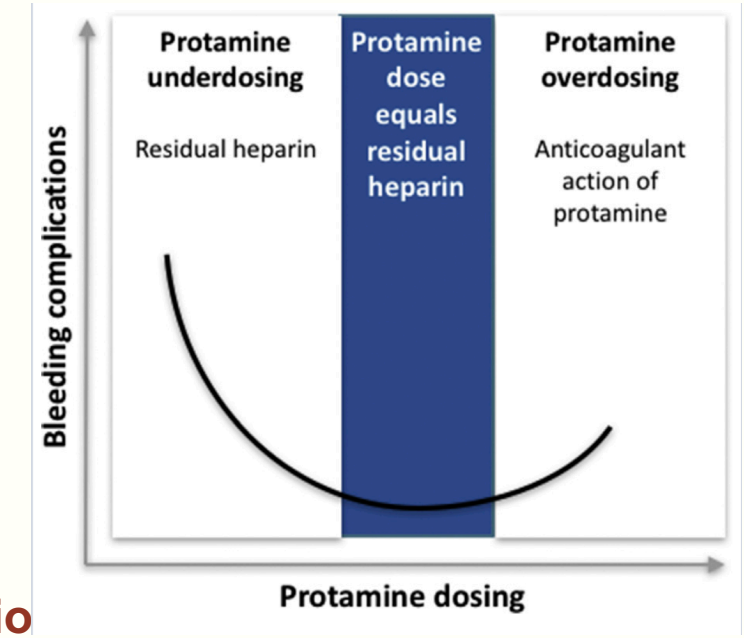
Protamine

Anticoagulant Properties When In Excess Of Heparin

- Interferes with platelet function
- Interferes with activation of coagulation factors,
- Potentiates clot lysis.

Infusion Reactions

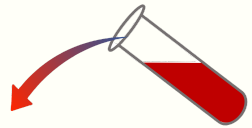
- Hypotension/circulatory collapse
- Pulmonary edema
- Pulmonary hypertension



Boer et al. British Journal of Anaesthesia, 120 (5): 914e927 (2018)

Reversal of LMWH

- Protamine
  - Neutralizes about 60-75% of activity
  - Consider half-life of enoxaparin
    - Enoxaparin administered ≤8 hours prior: give 1 mg of protamine per mg of enoxaparin.
    - Enoxaparin administered > 8 hours prior: give 0.5 mg of protamine per mg of enoxaparin.

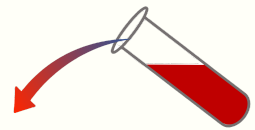


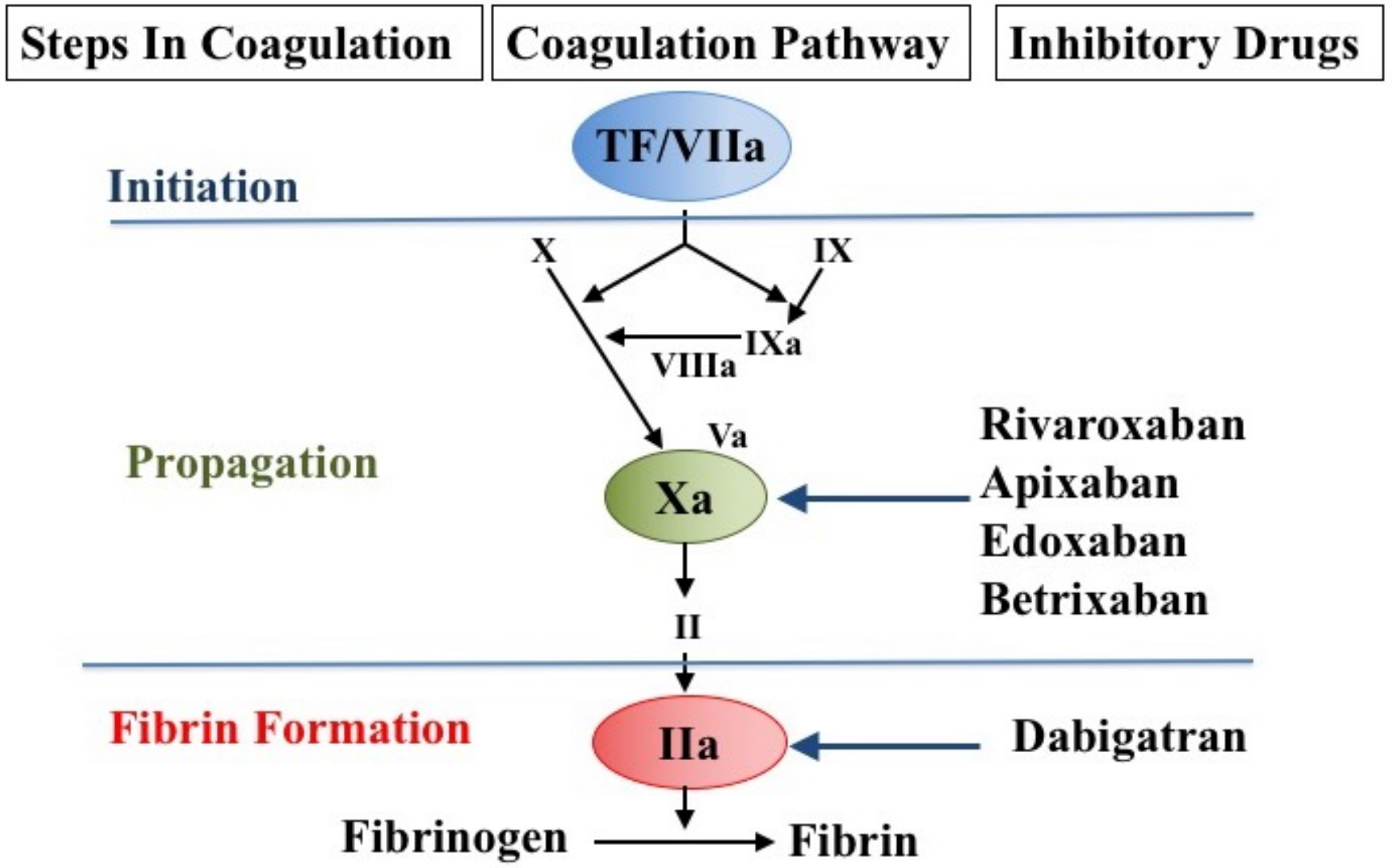
Management of Direct Oral Anticoagulant-Related Bleeding

Module: 8

Early Strategies for Reversal of Xa-DOAC's

- 4-factor PCC
  - 12 healthy volunteers (*in vivo*); PT and thrombin generation ETP normalized
    - Eerenberg ES et al, Circulation 2011.
- Antifibrinolytics
  - No hard evidence for their use.



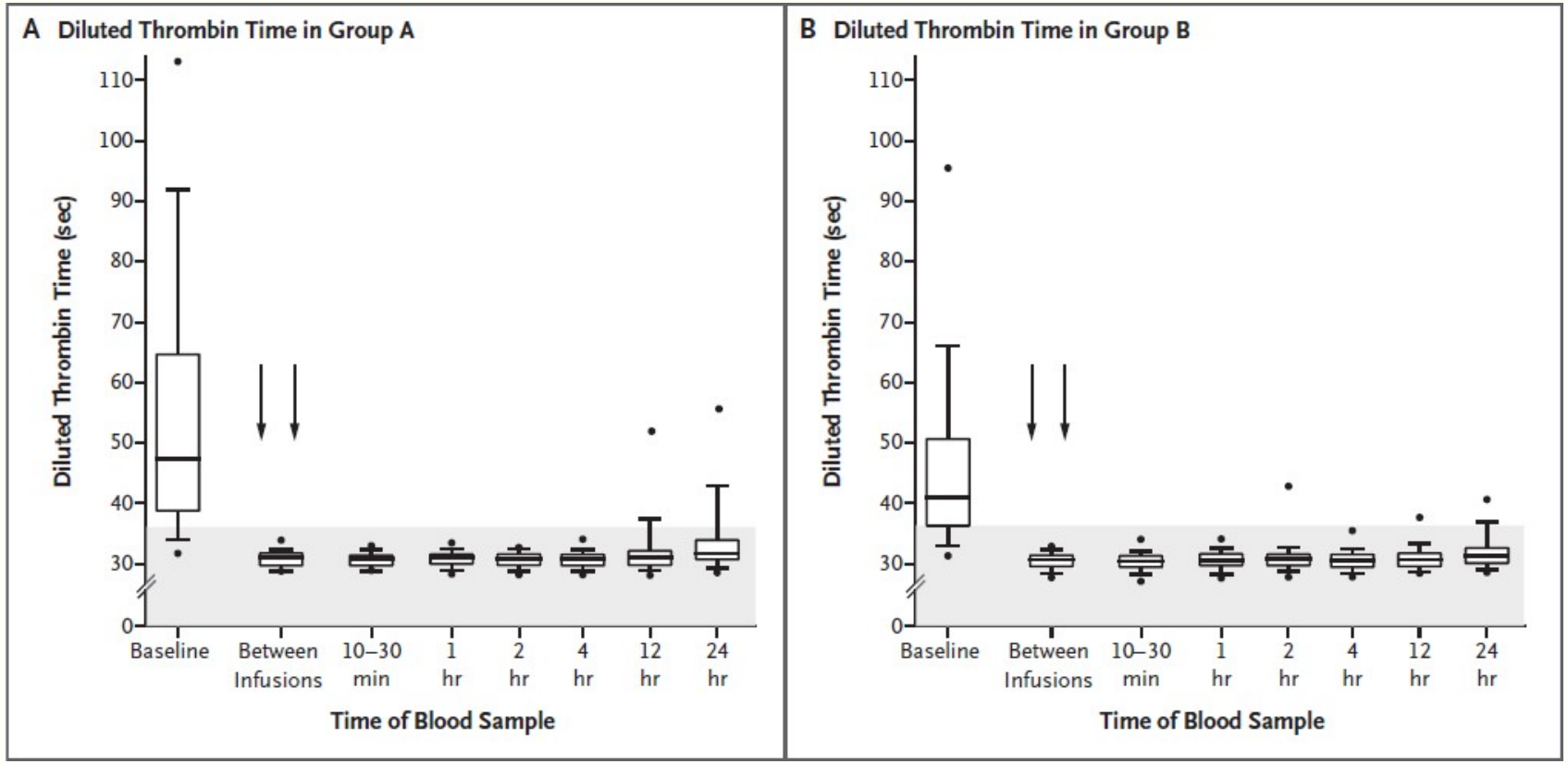


- Adapted from Soff, Arteriosclerosis, Thrombosis, and Vascular Biology 2012, 32:569-574.

Idarucizumab for Dabigatran Reversal

- Humanized anti-dabigatran Ab
- Final analysis of 503 patients in need of reversal
  - Serious bleeding (group A): n=301
  - Emergent procedure (group B): n=202
- Fixed dose of 5 g IV
  - Two separate boluses of 2.5 g given no more than 15 min apart.
  - Pollack CV *et al*, N Engl J Med 2017.

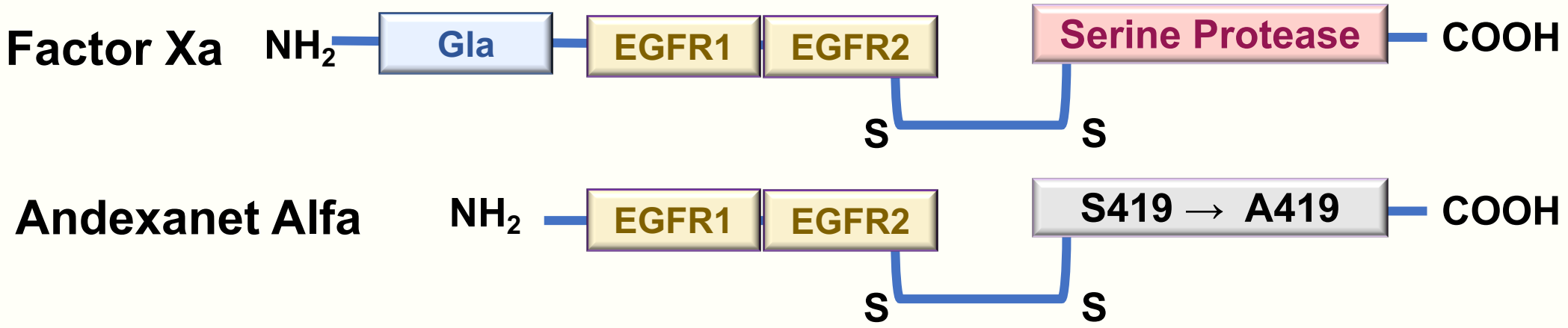
Dilute Thrombin Time



The median maximum reversal <4 hours was 100%.

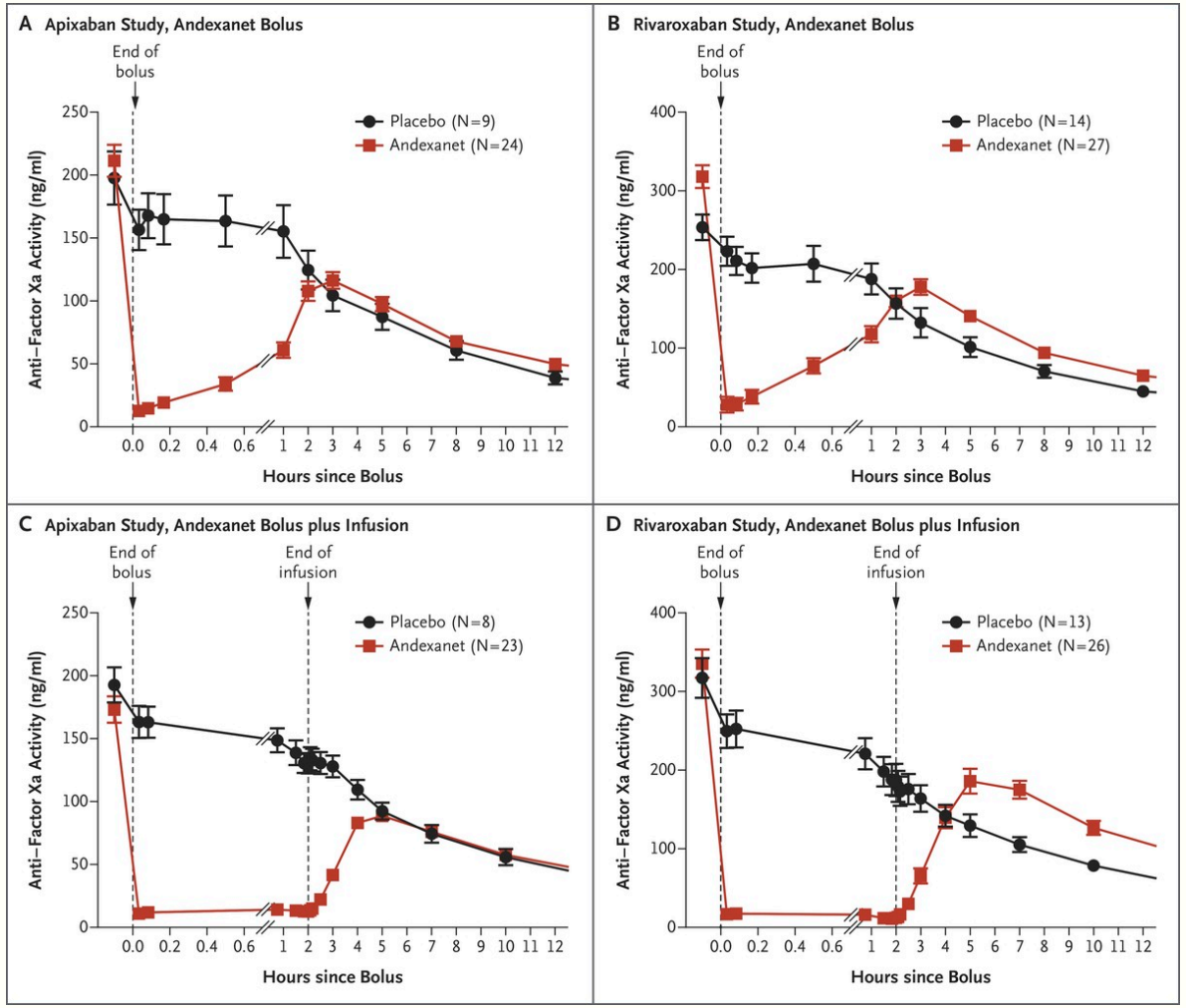
Pollack CV *et al*, N Engl J Med 2017.

Reversal of Xa-DOAC's



- Xa Decoy (Andexanet Alfa)
- "Decoy" Xa drug neutralizes the effect of anti-Xa agents
  - Inactive mimetic binds the anticoagulant
  - Serine, the active site of FXa, was substituted with alanine
  - The Gla domain of FXa was removed to prevent its assembly into the prothrombinase complex.

Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet.



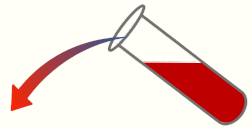
Siegal DM et al. NEJM 2015;373:2413-2424.

Dosing Recommendations for Andexanet Alfa

Xa Inhibitor	Last FXa Inhibitor Dose	Last FXa Inhibitor Dose < 8 Hours Prior/Unknown	Last FXa Inhibitor Dose ≥ 8 Hours Prior
Rivaroxaban	≤ 10 mg	Low dose	Low dose
Rivaroxaban	> 10 mg or unknown	High dose	
Apixaban	≤ 5 mg	Low dose	
Apixaban	> 5 mg or unknown	High dose	

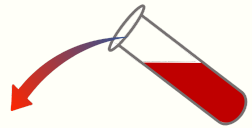
	Bolus	2-hour IV infusion
Low dose	400-mg IV	4 mg/min
High dose	800-mg IV	8 mg/min

https://www.fda.gov/media/113279/download



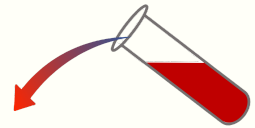
Coagulopathy of Liver Disease

Module: 9



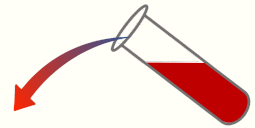
Coagulopathy of Liver Disease

- Patients with CLD have multiple abnormalities that contribute to hemostatic imbalance.
- Decrease in coagulation factor synthesis:
  - All coagulation factors, except Factor VIII and vWF are made in hepatocytes.
  - Factor VIII is produced in liver sinusoidal cells and vascular endothelial cells.
  - von Willebrand factor: Vascular endothelium and megakaryocytes (α-granules of platelets)
- Decrease in physiologic anticoagulants:
  - Protein C, Protein S, Antithrombin.
- Concomitant Vitamin K deficiency
  - Poor nutrition,
  - Malabsorption of fat-soluble vitamins
- Thrombocytopenia
  - Splenic sequestration
  - Decreased thrombopoietin (TPO)

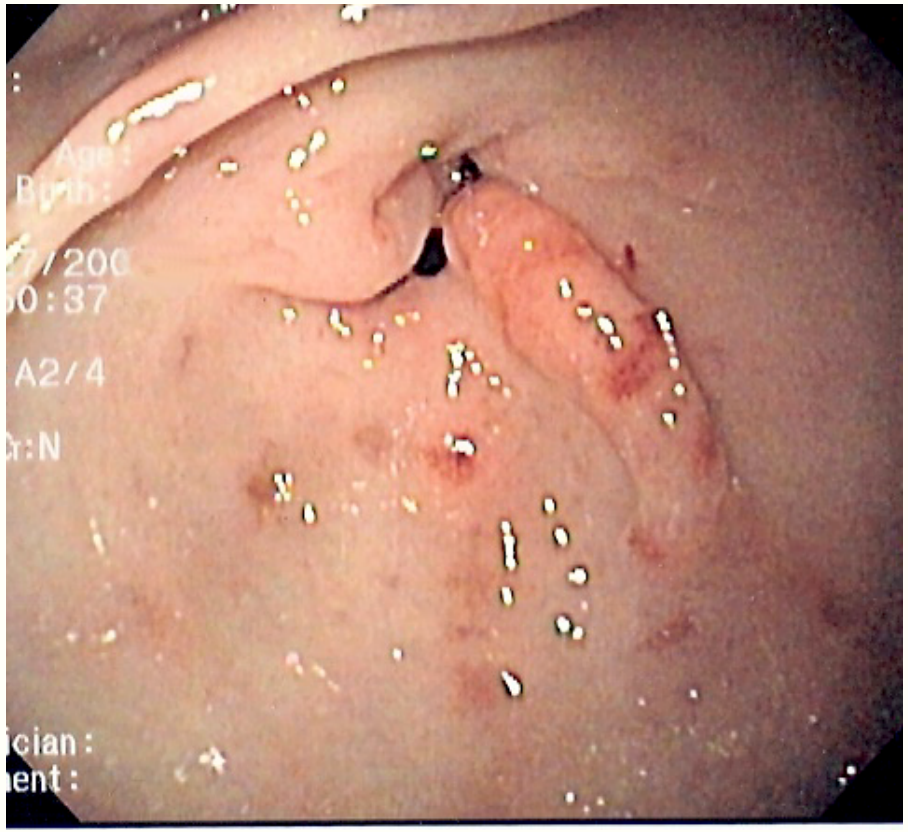


Dysfibrinogenemia in CLD

- The most common cause of acquired dysfibrinogenemia
- Prevalence as high as 80% depending on the assay technology.
- The abnormal fibrinogen is characterized by an increased content of sialic acid residues that results in delayed fibrin aggregation
  - Martinez J et al Blood. 1983;61(6):1196.



Liver disease Associated with Varices, An Anatomical Risk for Bleeding.



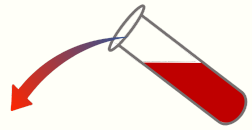
Variceal Bleeding in CLD

- https://commons.wikimedia.org/wiki/File:Gastric_antral_vascular_ectasia_(before_and_after).png

Laboratory Findings In Coagulopathy of Liver Disease:
The PT/INR is more sensitive to prolongation in CLD, compared with aPTT.

- Prothrombin Time:
  - Factor VII has the shortest half-life of procoagulant factors
  - Acquired Vitamin K deficiency concomitant with CLD.

- Increase in Factor VIII shortens the aPTT
  - In CLD, this blunts the aPTT prolongation.
  - “Acute phase reactant”

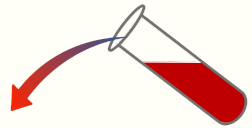


Management of Coagulopathy of CLD

- Treatment not always necessary.
- Supportive care.
- Try empiric Vitamin K.

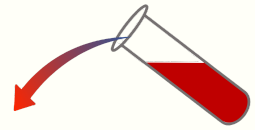
- In general treatment is reserved for acute bleeding or before procedures
- FFP 10-15 ml/kg if bleeding or procedure
- 4-Factor PCC “off label”
  - Factors II, VII, IX and X, Protein C, Protein S.
- Cryoprecipitate
  - Keep fibrinogen above 100 mg/dl in the acute setting
- Platelet transfusions not usually needed unless severe thrombocytopenia and bleeding.
  - De Simone & Sarode. Semin Thromb Hemost 2013;39:172–181

- PCC and Cryoprecipitate together have all of the essential factors, except for Factor V. Factor V is present in platelet alpha granules.



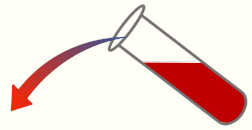
Thrombopoietin Receptor Agonists in CLD scheduled to undergo a procedure.

- Avatrombopag (Doptelet ®)
- Lusutrombopag (Mulpleta ®)
  - Thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.
  - Avatrombopag : Begin 10 to 13 days prior to the scheduled procedure.
  - Lusutrombopag: Begin 8 to 14 days prior to the scheduled procedure.



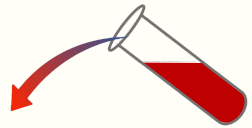
Liver Disease Does Not Constitute "Auto-Anticoagulation"!

- Decrease in physiologic anticoagulants!
  - Protein C, Protein S, Antithrombin III
  - May have thrombotic tendency at same time as hemorrhagic tendency.
- 50% decrease in anticoagulant proteins is associated with thrombotic tendency.
- 50% decrease in procoagulant proteins is not associated with hemorrhagic tendency.

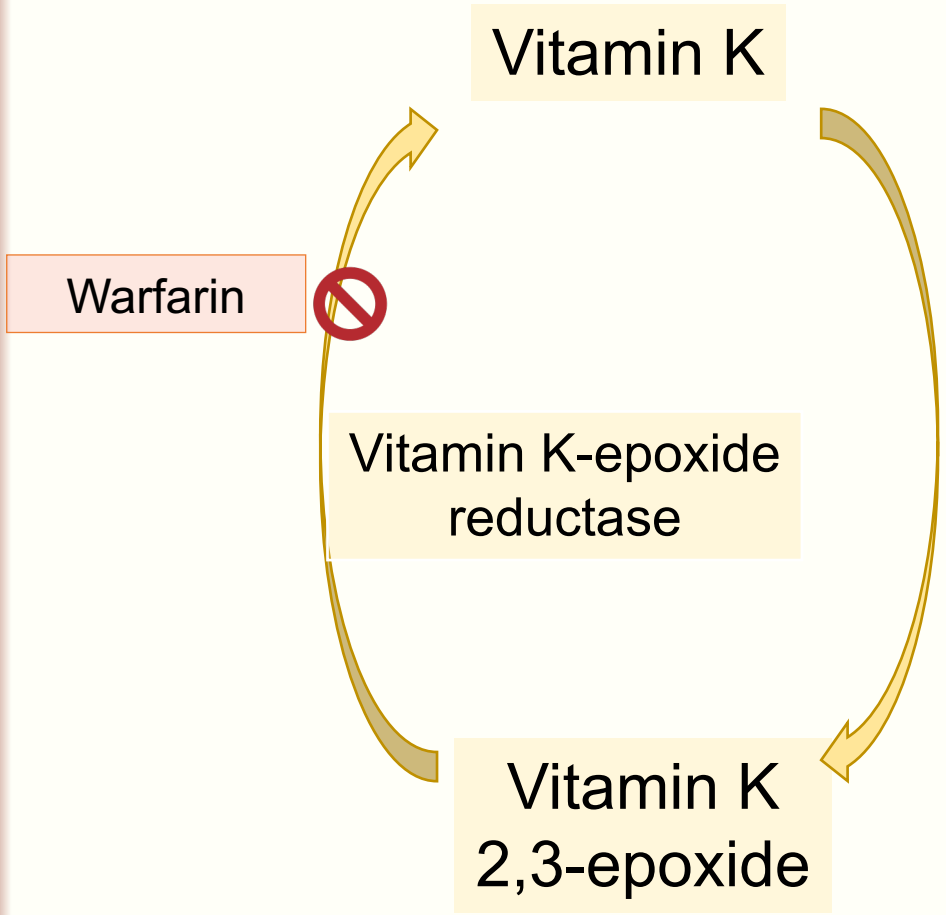


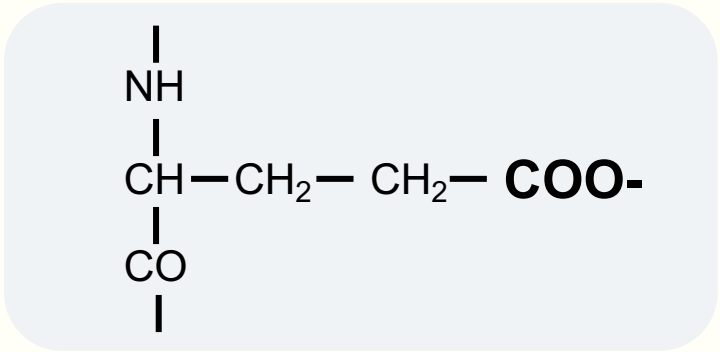
Vitamin K Deficiency

Module: 10

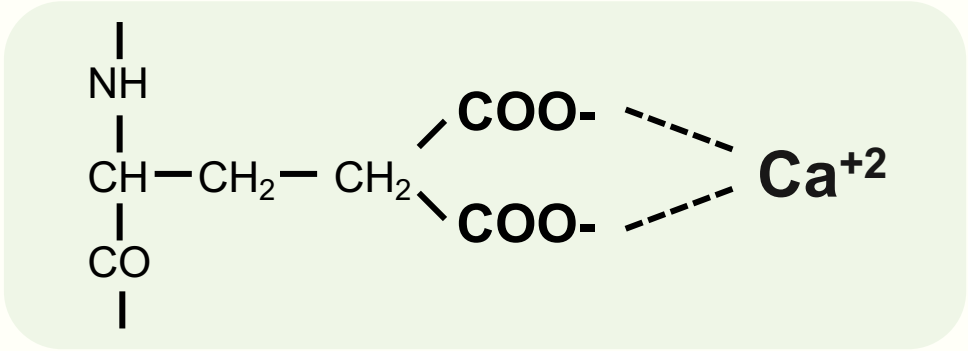


Vitamin K Mediated γ-Carboxylation of Glutamic Acid





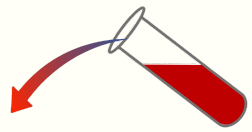
Glutamic Acid:
Single negative charge



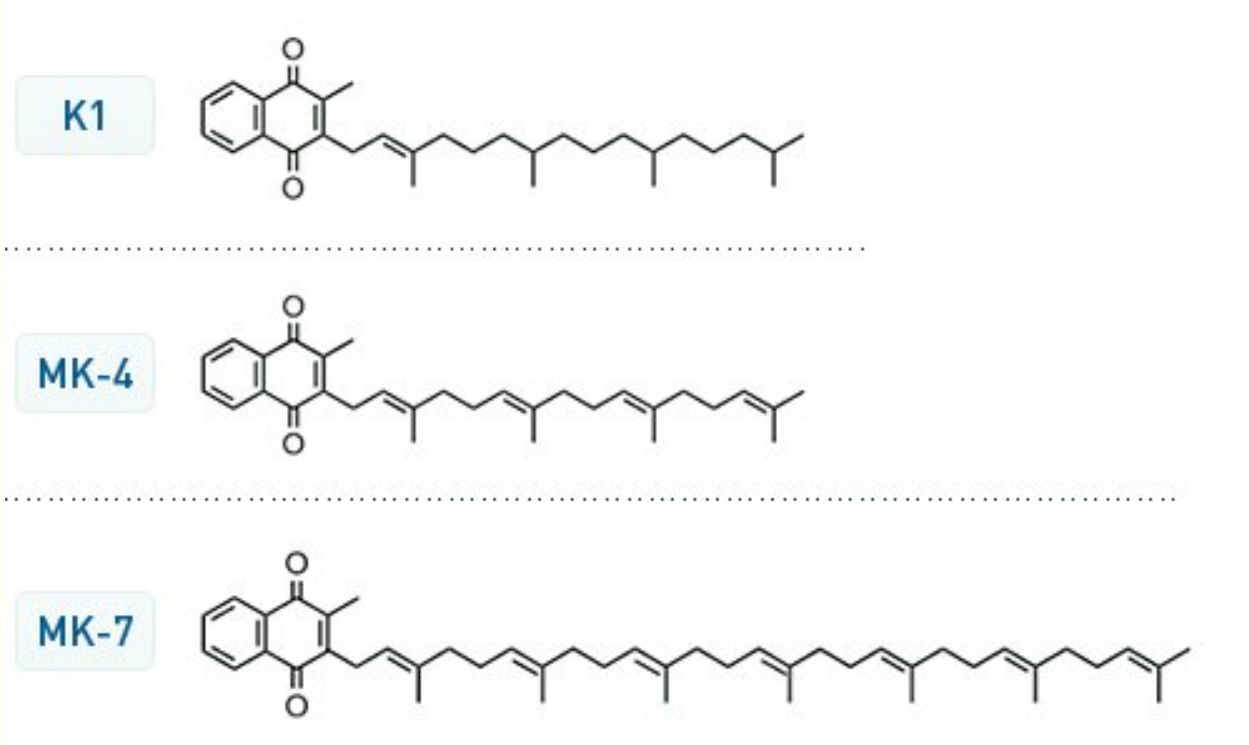
Gamma-Carboxyglutamic Acid (Gla):
Divalent negative charge. Can bind calcium

Vitamin K-Dependent Factors

- Factors II (Prothrombin), VII, IX, X
- Protein C, Protein S
- All are enzymes, except protein S
- While both procoagulants and anticoagulants are affected, the net effect of vitamin K deficiency or antagonism is anticoagulation.
- Deficiency of vitamin K-dependent factors prolongs both the PT and aPTT, but effect of greater on PT.



Vitamin K

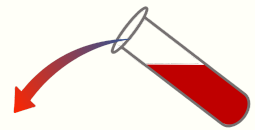


https://en.wikipedia.org/wiki/Vitamin_K

- Vitamin K1 (phylloquinone), is made by plants, and is found in highest amounts in green leafy vegetables.
- Bacteria in the gut flora can convert K1 to K2 and then into a range of vitamin K forms.
- It is not clear if the K2-related forms have greater effect on coagulation than K1.

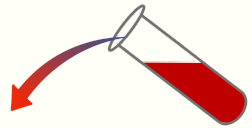
Vitamin K Deficiency

- Most common causes:
  - Insufficient dietary intake,
  - Inadequate absorption,
  - Decreased storage of the vitamin due to liver disease,
  - Decreased production in the intestines.
- Malabsorption,
  - especially impaired absorption of fats due to diseases such as cystic fibrosis, celiac disease, chronic pancreatitis or Cohn's disease.
- Antibiotics can decrease the quantity of K2 produced in the intestines.



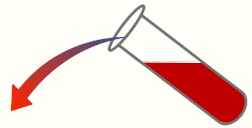
Vitamin K Deficiency Replacement

- Vit. K: Typically 10 mg PO or IV
  - Excess replacement does not make patient hypercoagulable.
- SC route has unreliable absorption and is no faster than PO administration



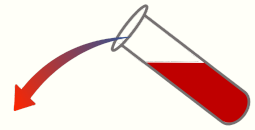
Disseminated Intravascular Coagulation

Module: 11



Disseminated Intravascular Coagulation Is Not A Disease, But a Process

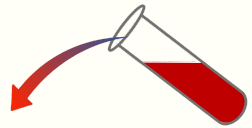
- Systemic, unregulated activation of the coagulation system.
- Tissue Factor
  - Shift of Tissue Factor to the circulation
  - Expression of TF by monocytes secondary to bacterial endotoxin
- Endothelial injury
- Consumptive coagulopathy.
- Severe/acute is associated with hemorrhage.
- Low-Grade DIC
  - Cancer: Associated with thrombotic tendency.



Add slides on mechanisms of bleeding

Acute DIC With Hemorrhage

- Sepsis
- Obstetrical catastrophe
- Amniotic fluid embolism, abruptio placentae, HELLP, eclampsia/severe preeclampsia, retained dead fetus, septic abortion
- Trauma with crush injury and/or brain damage
- Intravascular hemolysis
- Snake venom
- Fulminant liver failure
- Pancreatitis
- Acute leukemia
- Acute promyelocytic leukemia



Disseminated Intravascular Coagulation:

Modified from Levi & Scully, Blood (2018) 131 (8): 845–854.

Condition	Examples	Impact of precipitating condition
Severe Infectious Diseases	Gram-positive or -negative organisms, malaria, hemorrhagic fevers	Thrombosis may contribute to organ failure (eg acute kidney failure)
Malignancy	Solid tumors (eg, adenocarcinomas)	Primarily thrombotic consequences/VTE
	Acute promyelocytic leukemia or monocytic leukemia	Severe thrombocytopenia and factor deficiency may lead to bleeding
Trauma	Trauma	Primary feature is acute bleeding, followed by thrombosis
	Brain injury	
	Burns	
Obstetrical Complications	Abruptio placentae	Profuse bleeding in combination with thrombotic complications[27,28]
	Amniotic fluid embolism	
	Retain Placental Parts	
Vascular Malformations	Kasabach-Merritt syndrome	Bleeding primarily with severe thrombocytopenia and hypofibrinogenemia
	Giant hemangiomas	
	Other vascular malformations	
	Large aortic aneurysms	
Severe Immunologic Reactions	Transfusion reaction	
Heat stroke		Thrombotic features more common than bleeding
Post–Cardiopulmonary Resuscitation		Thrombosis is a greater risk than bleeding

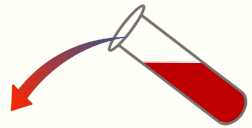
Disseminated Intravascular Coagulation

Laboratory findings:

- Prolonged PTT, PT
- Thrombocytopenia
- Fibrinogen decreased
- High D-dimers
  - Non-specific
- Schistocytes
  - Non-specific

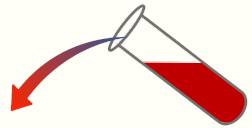
Treatment:

- UNDERLYING CAUSE
- Supportive Care:
- Keep the fibrinogen > 100 mg/dl
- 10 U cryoprecipitate
- FFP for bleeding or procedures
- Avoid inhibitors of fibrinolysis (EACA, tranexamic acid, aprotinin)
- No specific therapy has been validated.



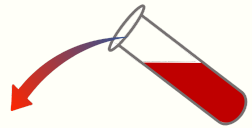
Uremic Coagulopathy

Module: 12



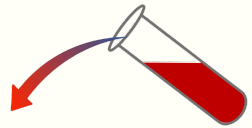
Uremic Coagulopathy

- Mucocutaneous bleeding
- Multifactorial Pathophysiology:
- Nitric Oxide (NO): ↑[cGMP]
  - Relaxes smooth muscle cells, vasodilation
  - Inhibits platelet function
- NO levels increase in renal failure
  - Reduced binding to Hemoglobin
  - Other mechanisms?
  - Anemia contributes to the dysfunction.
- Functional defect is not within the platelets, but uremic plasma inhibits the platelet function.
  - Transfusion of normal platelets will not help.
- PT/PTT not elevated by uremia.



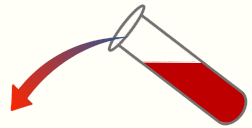
Uremic Coagulopathy: Treatment

- Acute treatment:
  - Desmopressin (ddAVP)
  - Cryoprecipitate
  - Mechanism of effect not clear. Possibly increase in fibrinogen & vWF allow for improved platelet function without correcting the underlying defect.
- Chronic Management:
  - Supplemental erythropoietin or red cell transfusion to bring Hgb to >10 gm/dL.
  - Dialysis
  - Estrogens



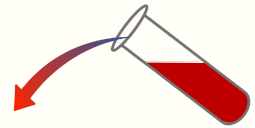
Acquired Hemophilia

Module: 13

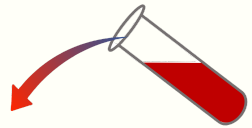


Acquired Hemophilia

- Antibody directed against FVIII: Acts as an inhibitor
- Isolated prolongation of the PTT
- Mixing study often corrects initially, followed by prolongation after incubation
- Factor VIII levels often very low (<1%)
  - "Corrects" with serial dilutions
- Can be seen in anyone but more common in:
  - "Older" individuals (ie >50 YO)
  - Rheumatoid arthritis
  - Cancer
  - SLE
  - Drug Reaction
  - Peripartum
- Bleeding is similar to severe hemophilia, except patients do not typically experience hemarthrosis.



Add slide with representative case



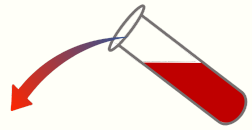
Acquired Hemophilia: Treatment

Acute Control of Bleeding

- Low titer inhibitor:
  - FVIII concentrate
- High titer inhibitor:
  - Activated PCC (FEIBA®)
  - rFVIIa
  - rPorcine FVIII

Elimination of the inhibitor:

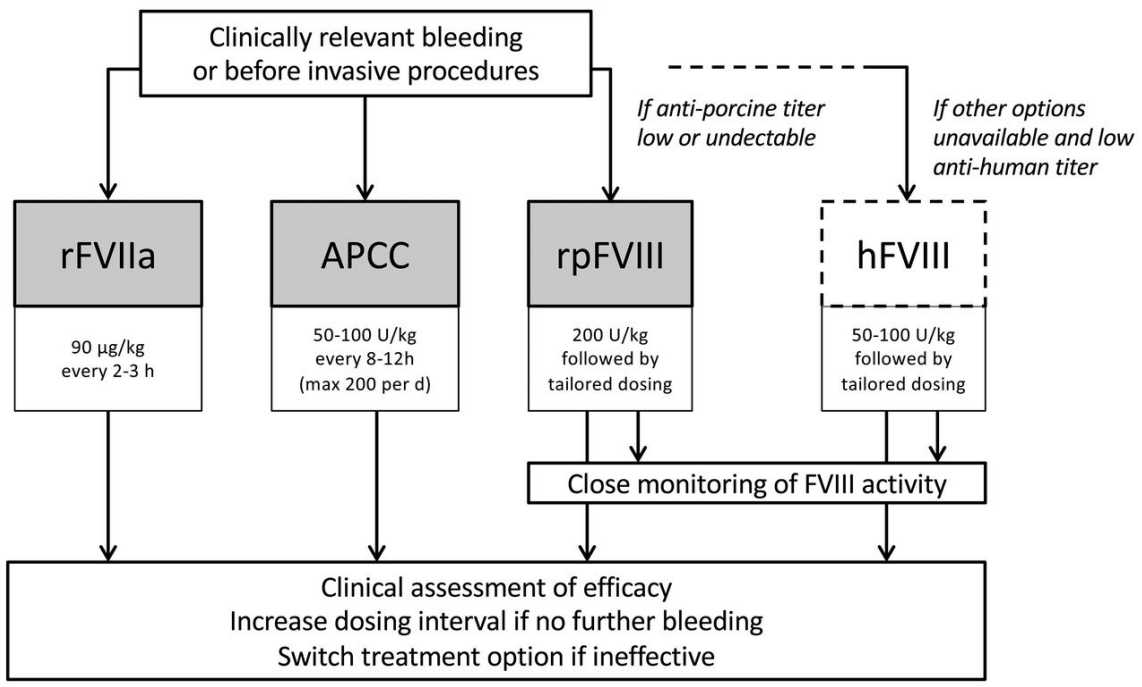
- Prednisone +/- cyclophosphamide
- Rituximab



International Recommendations on Treatment of Acquired Hemophilia A

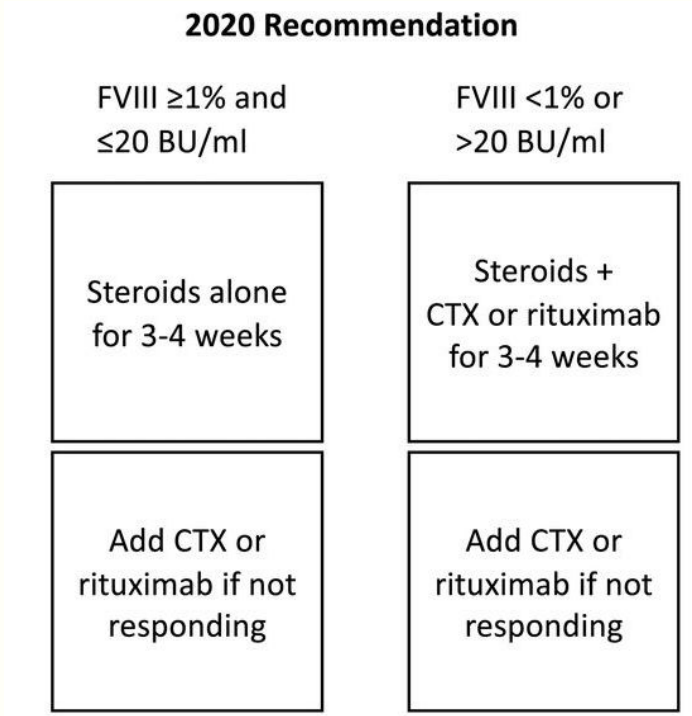
Tiede et al. Haematologica. 105 , 2020 https://doi.org/10.3324/haematol.2019.230771

Acute/Emergent Treatment



- rFVIIa, recombinant activated factor VII
- APCC, activated prothrombin complex concentrate;
- rpFVIII: recombinant porcine factor VIII
- hFVIII, human (plasma-derived or recombinant)

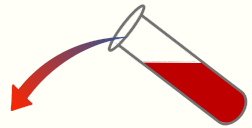
Antibody Suppression



- BU: Bethseda unit;
- CTX, cyclophosphamide.

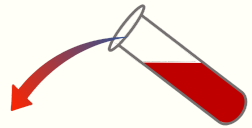
Acquired von Willebrand Disease

Module: 14

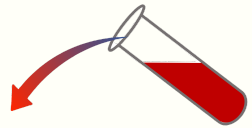


Acquired vWD: Mechanisms & Associations

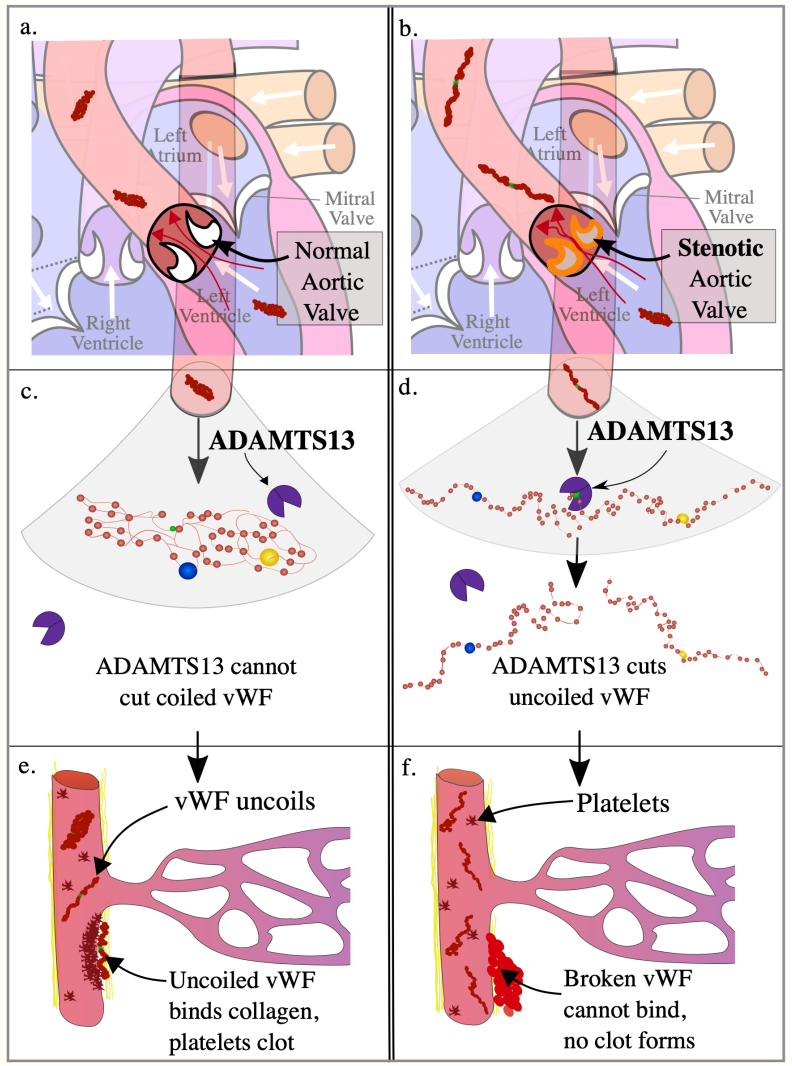
- Myeloproliferative neoplasms
  - Adsorption of vWF on platelets
- Wilms tumor:
  - High levels of hyaluronic acid increases viscosity and binds von Willebrand factor (vWF)
- Auto-antibodies:
  - Connective Tissue disorders, idiopathic
- Heyde's syndrome:
  - Acquired vWD-2A deficiency secondary to aortic stenosis.
  - GI Bleeding, from angiodysplasic lesions



Add slide for mechanism??



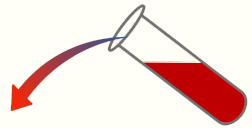
Heyde's Syndrome Triad



- Aortic stenosis
  - Shear stress on vWD results in "uncoiling", and cleavage by ADAMTS13.
- Acquired coagulopathy (vWD type 2A)
- Anemia due to bleeding from intestinal angiodysplasia or from an idiopathic site.

Acute Promyelocytic Leukemia

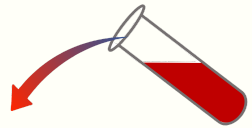
Module: 15



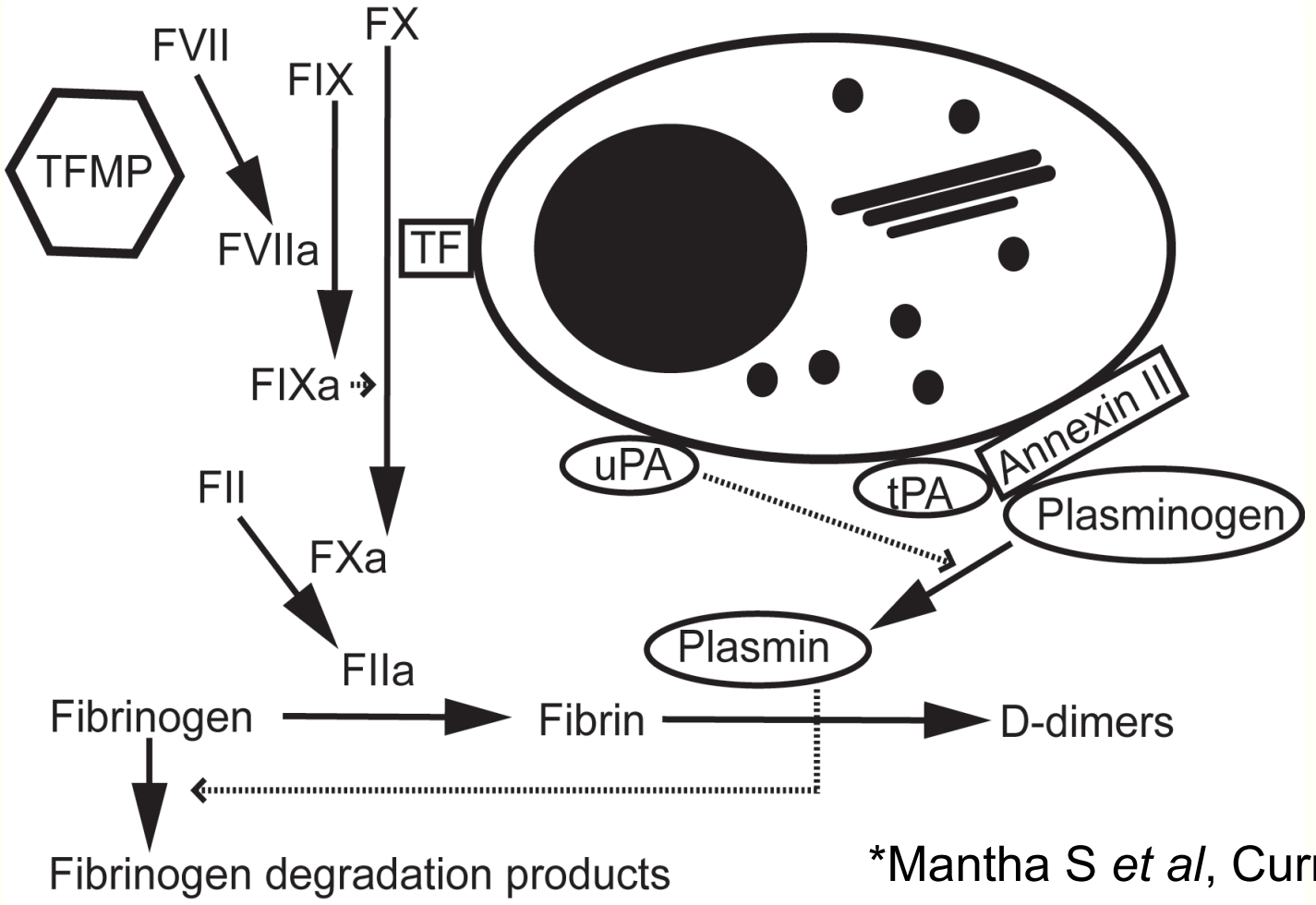
Acute Promyelocytic Leukemia

- t(15;17)
  - PML-RARA gene rearrangement
- Persistently high rate of early death from hemorrhage
  - 5-10% in different series
- Pathogenesis of coagulopathy multifactorial.
  - No single mechanism is clearly established.
  - Leukemic blasts express tissue factor, leading to DIC
  - Increased plasminogen activators promote primary fibrinolysis.
  - High blast counts correlates with bleeding.

  - Mantha et al Blood. 2017 Mar 30; 129(13): 1763–1767.



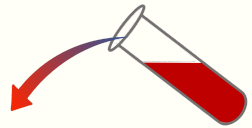
Acute Promyelocytic Leukemia



*Mantha S *et al*, Curr Opin Hematol 2016

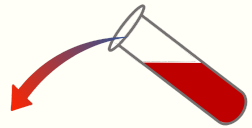
Acute Promyelocytic Leukemia

- ATRA induces differentiation of cells
  - Decreases expression of tissue factor
  - Early treatment is crucial in decreasing mortality
- Aggressive blood product repletion is warranted



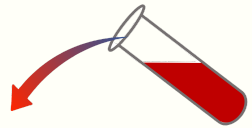
Workup of Coagulopathy

Module: 16



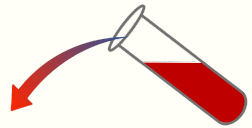
Workup of Coagulopathy

- Mixing Studies
  - With incubation
- Immediate inhibitors:
  - Anticoagulant contamination
  - Anti phospholipid Antibody
  - Fibrin/Fibrinogen Degradation Products
  - Some Paraproteins
- Inhibitors with Incubation
  - Specific Factor Inhibitors/Antibodies



Mixing Studies

- Mix patient and normal plasma 1:1
- Perform PT and/or aPTT immediately and after 1 hour incubation at 37°C
- Looking for “Prolongation of the Normal”
- Specific antibodies require time to bind to the antigen target.
- Common inhibitors: heparin, Lupus Anticoagulant, dysproteins, paraproteins, Fibrin Split Products (DIC), specific factor inhibitors



Mixing Studies

Factor Deficiency

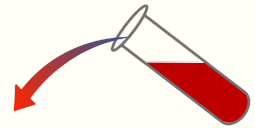
aPTT	Patient	Normal	1:1
Immediate	51”	29”	33”
1 Hour Incubation @ 37°C	52”	29”	32”

Lupus Anticoagulant: antiphospholipid antibody

aPTT	Patient	Normal	1:1
Immediate	51”	29”	48”
1 Hour Incubation @ 37°C	52”	29”	50”

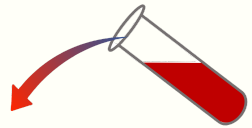
Anti-Factor VIII Antibody

aPTT	Patient	Normal	1:1
Immediate	51”	29”	33”
1 Hour Incubation @ 37°C	52”	29”	50”



A Factor Panel to Differentiate Systemic Coagulopathies

Factor	V	VII	VIII	X
Vitamin K Deficient	NI	↓	NI	↓
Liver Disease	↓	↓	NI or ↑	↓
DIC	↓	↓	↓	↓




Any Questions?