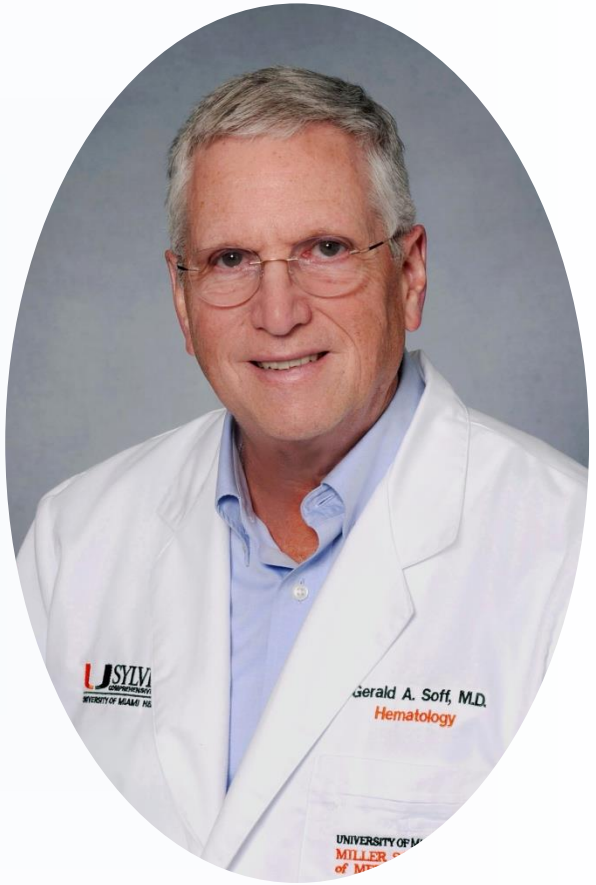
Acquired Bleeding Disorders

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Disclosures

- Research Support (Past 2 years):
  - Amgen
  - Sobi/Dova Pharmaceuticals
  - Anthos Therapeutics
  - Sanofi
  - Novartis

- Data Safety Monitoring Committee
  - Alpine Immune Sciences

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?
- i.e. Elevated aPTT can be from von Willebrand Disease (bleeding), hemophilia (bleeding), Factor XI deficiency (possible risk for post-op bleeding), or Anti-phospholipid antibody syndrome (prothrombotic).



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

We will have additional presentations on related specific topics.

- Thrombocytopenia,
- Platelet function abnormalities,
- Anticoagulation-related bleeding and reversal
- Vascular causes of bleeding.

- Here we will focus on the overall approach to acquired bleeding episodes, and more common disorders.


“You can observe a lot, just by looking.”

Pattern of Bleeding/History:

Clinical Presentation Helps Define Differential Diagnosis.

Mucocutaneous versus deep bleeding?

Immediate versus late bleeding?

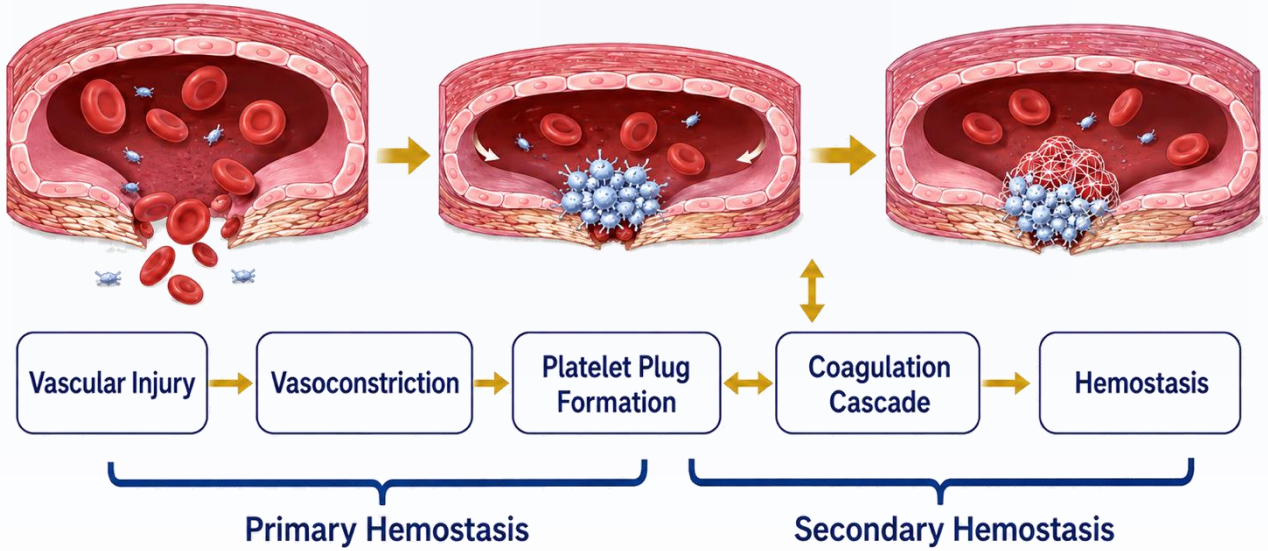
Local versus systemic?

Acquired versus congenital?

Family history?

Clinical Features of Bleeding Disorders

	Defect	Site of Bleeding	Bleeding After Surgery Or Trauma
Primary Hemostasis	Thrombocytopenia Platelet Function Vascular	Skin: (Petechiae/Purpura/Ecchymosis), Mucous membranes: (Epistaxis, gingiva/gum, vaginal, GI)	Immediate, usually mild
Secondary Hemostasis	Coagulation Factor Disorders	Deep: Soft tissues, joints, muscles	Delayed (1-2 days), often severe



Cutaneous Bleeding:
Not Raised, Not Warm, Not Tender, Not Painful!

Petechiae: <3 mm





imagebank.hematology.org

Purpura: 3–10 mm/Ecchymosis: >10 mm



imagebank.hematology.org



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

Hematoma: Raised, Warm, Tender, Painful!

Muscle Hematoma



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



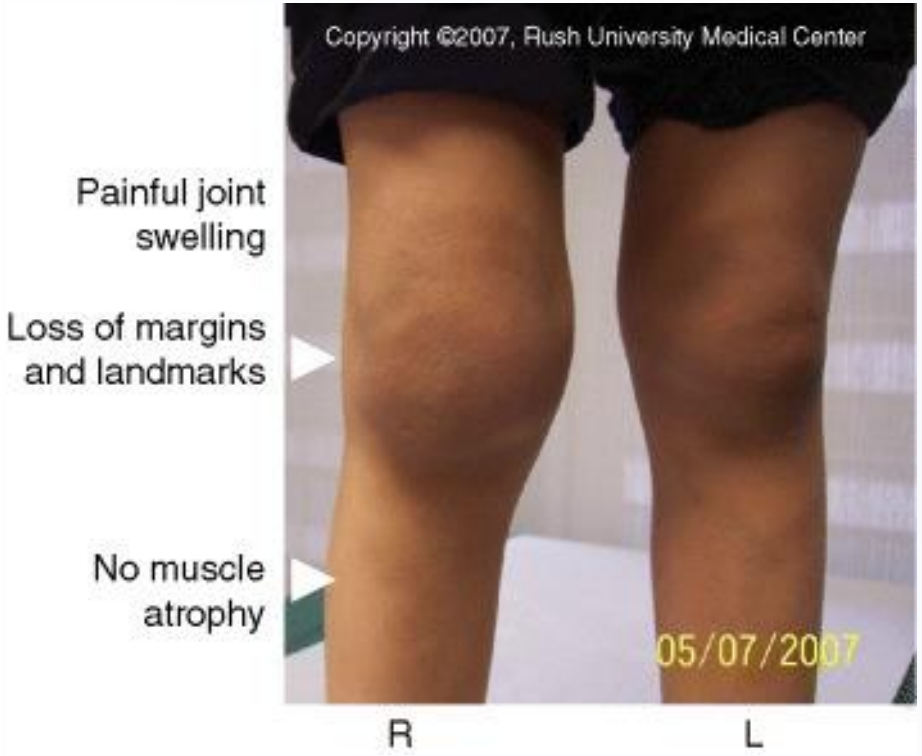
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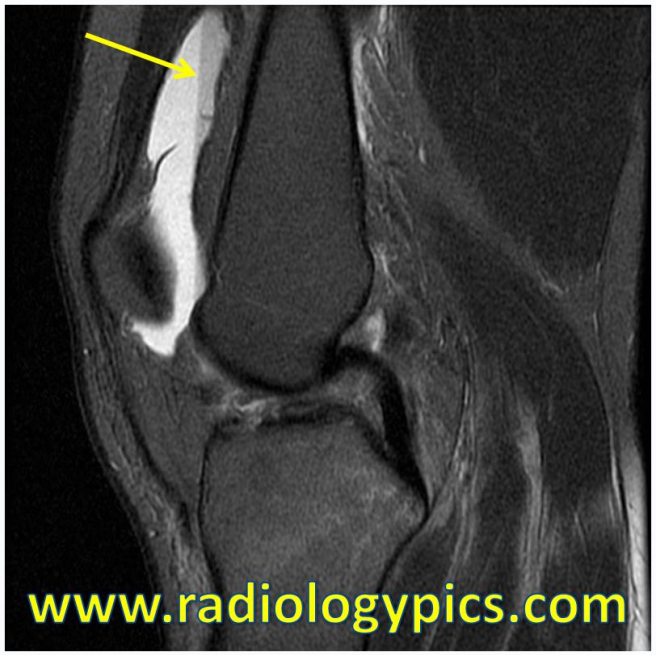
Subcutaneous Hematoma



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

Hemarthrosis: Joint Bleed. (From Severe Factor Deficiency)





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

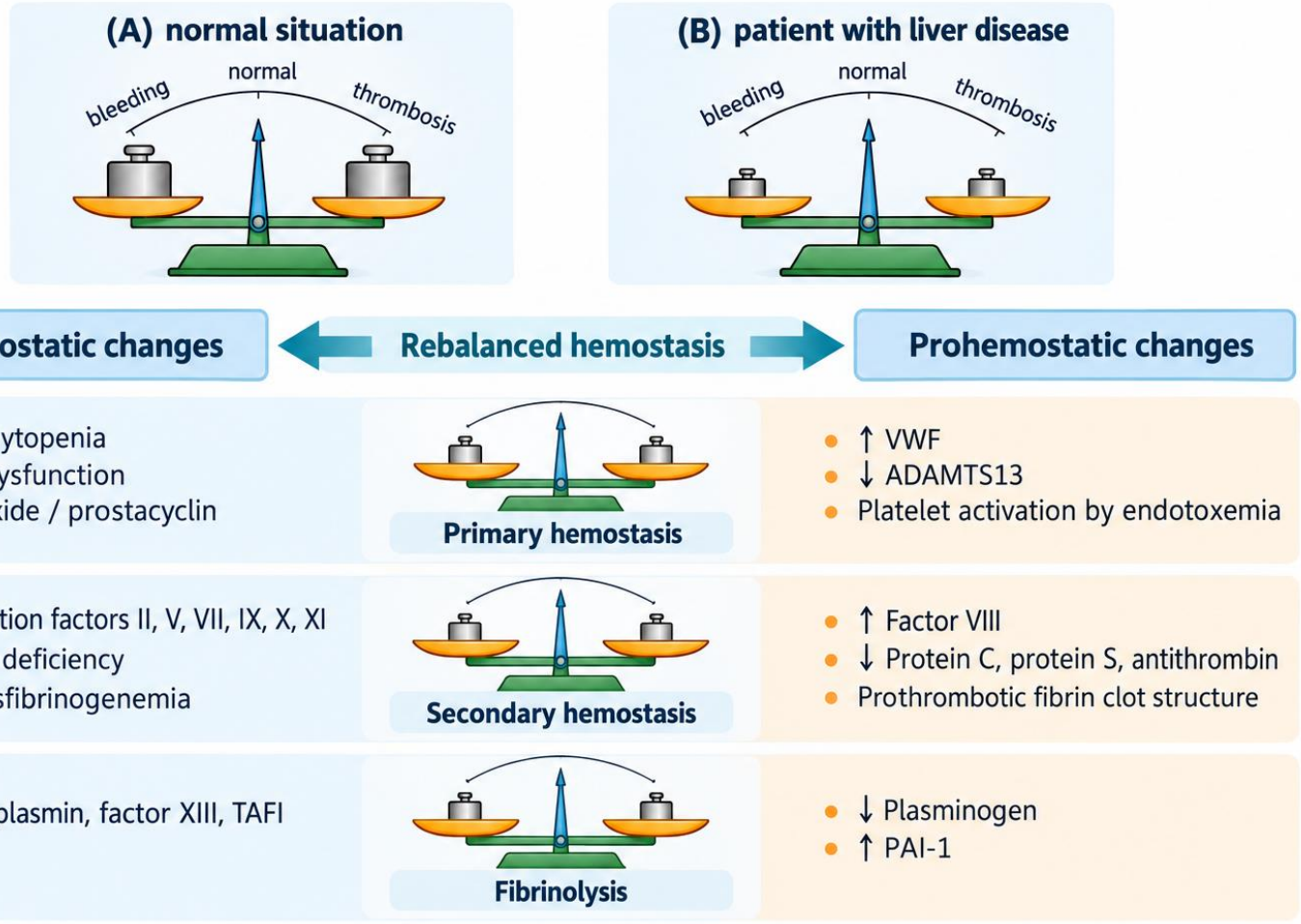
Acquired Bleeding Disorders:

- Liver disease
- Vitamin K deficiency
- Disseminated intravascular coagulation
- Uremic coagulopathy
- Acquired hemophilia
- Acquired von Willebrand disease
- Acute Promyelocytic Leukemia
-
- Anticoagulant Therapy, Thrombocytopenia, and Platelet function disorders to be covered in other lectures.)

Coagulopathy of Liver Disease (I)

- 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 primarily by endothelial cells**, with liver sinusoidal endothelial cells being the predominant source.
  - **von Willebrand factor: Vascular endothelium and megakaryocytes (α-granules of platelets).**
- Decrease in physiologic anticoagulants:
  - Protein C, Protein S, Antithrombin

Rebalanced hemostasis in liver disease



- Redrawn from Tiede A, Susen S, Lisman T. Acquired bleeding disorders. Haemophilia. 2024; 30(Suppl. 3): 29–38. https://doi.org/10.1111/hae.14995.
- Intagliata, NM., et al. (2021). AGA technical review on coagulation in cirrhosis. Gastroenterology, 161(5), 1630-1656

Coagulopathy of Liver Disease (II)

- Often concomitant Vitamin K deficiency
  - Poor nutrition,
  - Malabsorption of fat-soluble vitamins
- Dysfibrinogenemia characterized by an increased content of sialic acid residues that results in delayed fibrin polymerization.
  - Martinez J et al Blood. 1983;61(6):1196.
- Thrombocytopenia
  - Decreased thrombopoietin (TPO)
  - Splenic sequestration (unclear if “still true”).

Laboratory Findings of Coagulopathy of Liver Disease:
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 level shortens the aPTT.
  - "Acute phase reactant"
  - In CLD, this blunts the aPTT prolongation.

Bleeding in Liver Failure is Mostly Anatomically Driven

- The decline in liver-derived procoagulant proteins is matched by a parallel decline in anticoagulant proteins (e.g., activated protein C), so the system remains functional overall."
  - Intagliata, NM., et al. (2021). AGA technical review on coagulation in cirrhosis. Gastroenterology, 161(5), 1630-1656
- The proportionate loss of procoagulants and anticoagulants leaves thrombin generation largely intact, so bleeding in cirrhosis is mostly not a coagulopathy at all **— it is anatomic/hemodynamic.**
- **Portal hypertension is the true driver.**

Variceal Bleeding in CLD



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

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
  - (Factor VIII/vWF, Fibrinogen, Factor XIII)
  - Keep fibrinogen above 100 mg/dl in the acute setting
- Platelet transfusions usually not needed, unless severe thrombocytopenia and bleeding.
  - De Simone & Sarode. Semin Thromb Hemost 2013;39:172–181

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

Management of coagulopathy in chronic liver disease (CLD) rests on the rebalanced-hemostasis paradigm:

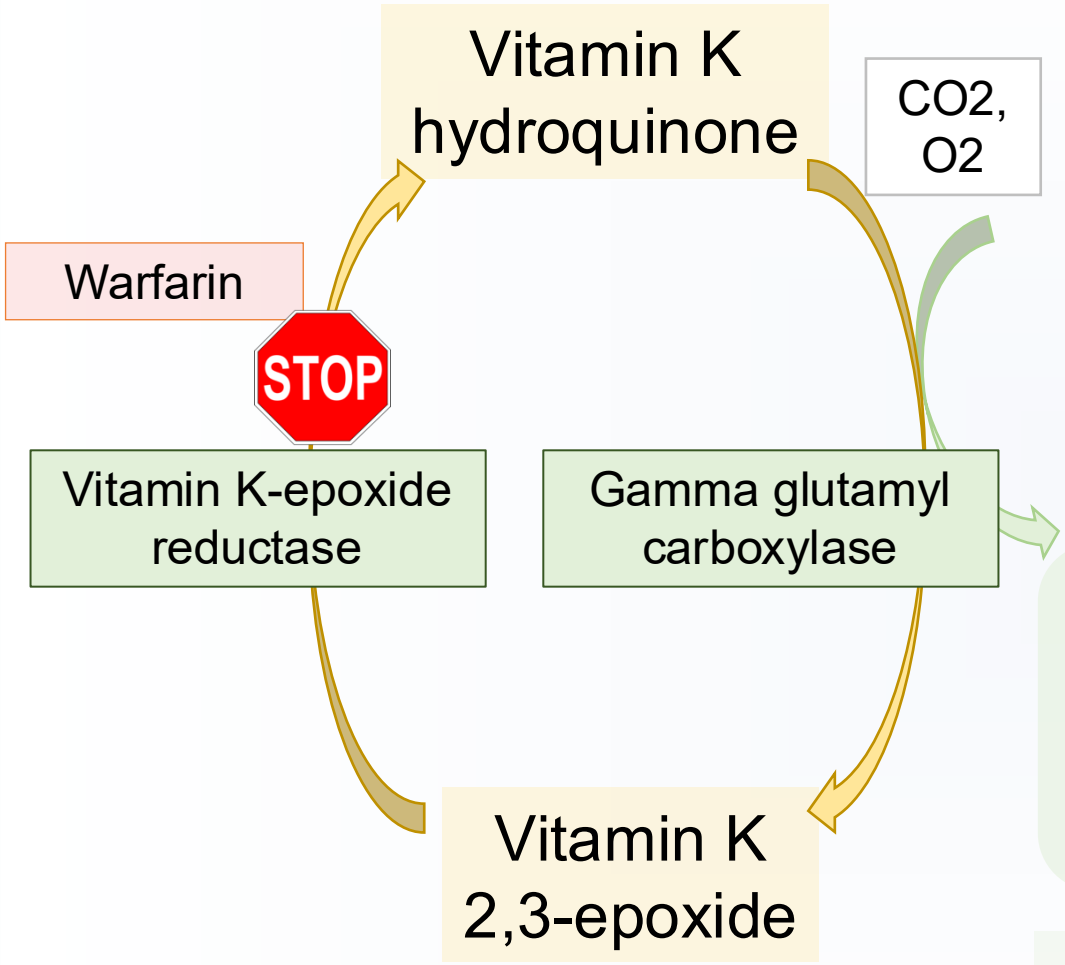
Intervention	Recommendation in CLD	References
Conventional tests (INR, PT, aPTT)	Do not use to gauge bleeding risk or trigger prophylactic correction; INR reflects synthetic function, not hemostatic balance	[1-4]
Viscoelastic testing (TEG/ROTEM)	Preferred to guide transfusion; normal values avoid product use even with elevated INR; RCTs show markedly fewer transfusions with no change in bleeding, rebleeding, or mortality	[1-3, 5]
Fresh frozen plasma (FFP)	Not recommended prophylactically; minimal effect on thrombin generation, raises portal pressure, risk of TACO/TRALI; restrict to hemorrhagic shock/volume replacement	[1, 3, 6-7]
Vitamin K	No measurable INR effect in cirrhosis outside malnutrition or cholestasis; does not reduce bleeding	[3, 5, 8]
Platelet transfusion	No validated threshold; reserve for active clinically significant bleeding or high-risk procedures (commonly <50 $\times 10^9$/L); prophylactic use may paradoxically increase bleeding via portal pressure and poor increment from splenic sequestration	[2-4, 6-7]
TPO-receptor agonists (avatrombopag, lusutrombopag)	Option in ambulatory patients with platelets <50 $\times 10^9$/L before planned procedures to raise count/avoid transfusion; require 2–8 day lead-in; not for acute bleeding; routine use to prevent procedural bleeding not recommended	[3, 6-7]
Fibrinogen / cryoprecipitate	Give for active bleeding with low fibrinogen (commonly <100–120 mg/dL); low-volume cryoprecipitate preferred over FFP	[1-2, 6-8]
Prothrombin complex concentrate (4F-PCC)	Low-volume alternative to FFP for bleeding/procedures when correction needed; efficacy/safety data still limited	[1-3]
Recombinant factor VIIa	Not recommended; no benefit in variceal bleeding; increased arterial thrombosis risk	[3, 6]
Tranexamic acid	Only if documented hyperfibrinolysis; caution if prothrombotic state/PVT present; not routine	[6]
Desmopressin (DDAVP)	Not recommended; VWF already elevated in cirrhosis	[6]
VTE prophylaxis (hospitalized)	Cirrhotic inpatients are at higher VTE risk; pharmacologic prophylaxis (LMWH preferred) generally does not increase bleeding; avoid with recent bleeding or platelets <50 $\times 10^9$/L	[1, 9]
Anticoagulation for PVT / VTE / AF	Treat acute symptomatic PVT and VTE; LMWH, VKA, and DOACs acceptable in Child-Pugh A; LMWH preferred in Child-Pugh B/C; DOACs increasingly first-line; treat PVT ≥6 months	[1, 6, 10]

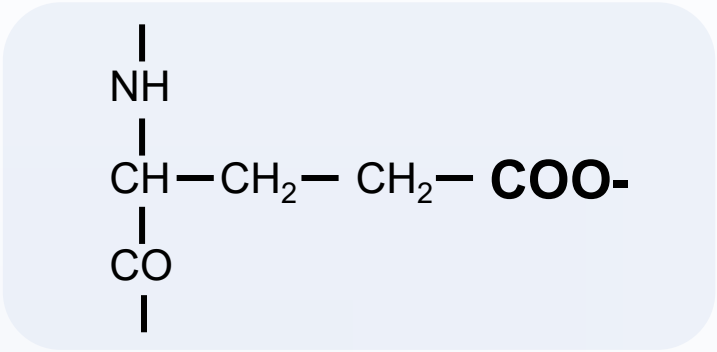
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5. Mahmud N, Fricker ZP, McElroy LM, et al. ACG clinical guideline: perioperative risk assessment and management in patients with cirrhosis. *Am J Gastroenterol.* 2025.
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9. O'Shea RS, Davitkov P, Ko CW, et al. AGA clinical practice guideline on the management of coagulation disorders in patients with cirrhosis. *Gastroenterology.* 2021.
10. Tripodi A, La Mura V, Piscaglia F, et al. Managing coagulation abnormalities, bleeding, and thrombosis in patients with cirrhosis. *J Gen Intern Med.* 2026.

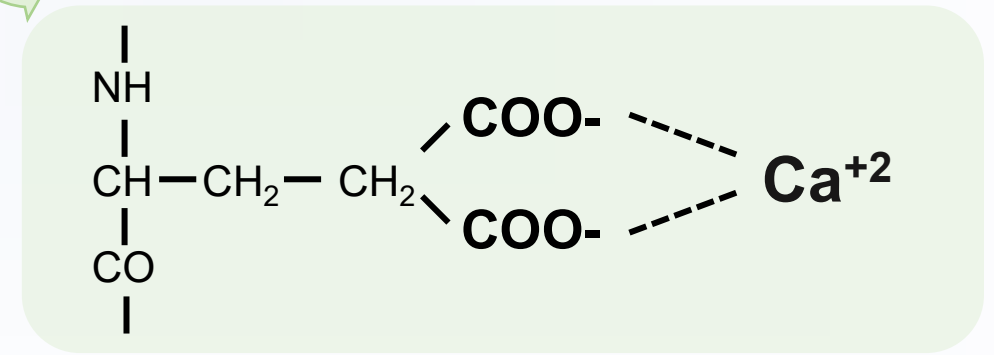
Vitamin K Deficiency

Vitamin K Mediated γ-Carboxylation of Glutamic Acid





Glutamic Acid:
Single negative charge

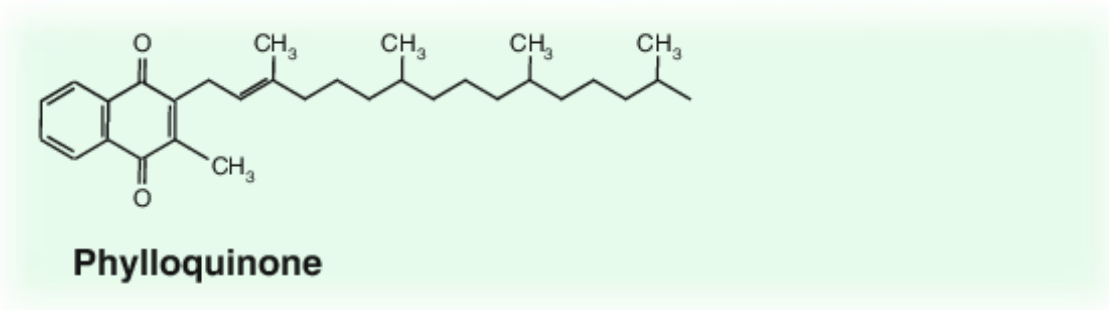


Gamma-Carboxyglutamic Acid (Gla):
Divalent negative charge. Can bind calcium

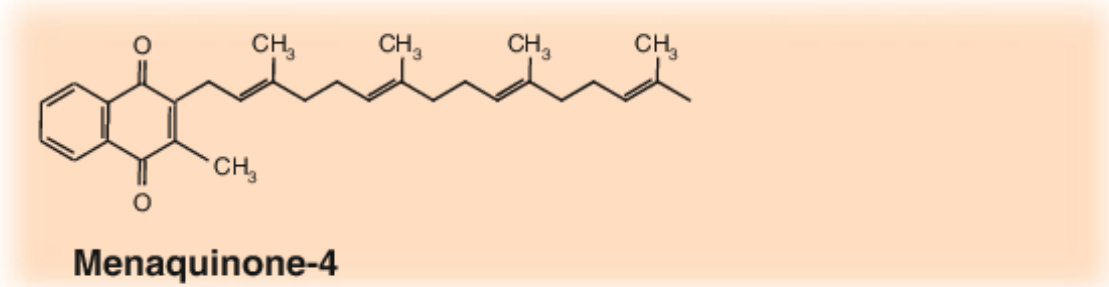
Vitamin K-Dependent Factors

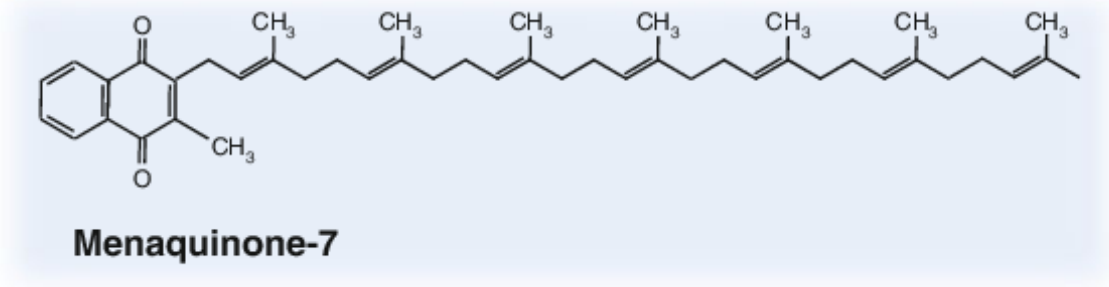
- Factors II (Prothrombin), VII, IX, X
- Protein C, Protein S
- While both procoagulants and anticoagulants are affected, the net effect of vitamin K deficiency or antagonism is anticoagulation.
- Deficiency of vitamin K-dependent factors prolongs both the PT and aPTT, but effect is greater on PT.

Vitamin K



Vitamin K2





- **Vitamin K1 (phylloquinone),** from green leafy vegetables is the primary dietary form.
- **Menaquinones**, have unsaturated side chains of varying length (MK-n)3.
- **Bacteria in the gut** convert K1 to K2 and then into a range of vitamin K forms.

- EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Turck D, et al. Dietary reference values for vitamin K. EFSA Journal. 2017 May;15(5):e04780.

Vitamin K Deficiency

- Common causes:
  - Insufficient dietary intake,
  - Inadequate absorption,
  - Decreased storage of vitamin K due to liver disease,
  - Decreased processing of Vitamin K1 to K2 and 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 K2 production in the intestines.

Mechanisms of Antibiotic-Associated Coagulopathy

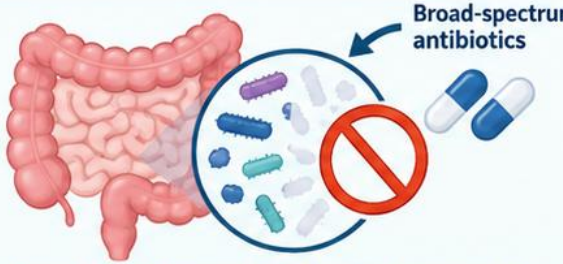
1. Reduced dietary vitamin K1 availability



Illness, poor oral intake, malnutrition, or cholestasis/malabsorption reduce phylloquinone (vitamin K_1) supply.

This often coexists with antibiotic exposure and lowers vitamin K reserve.

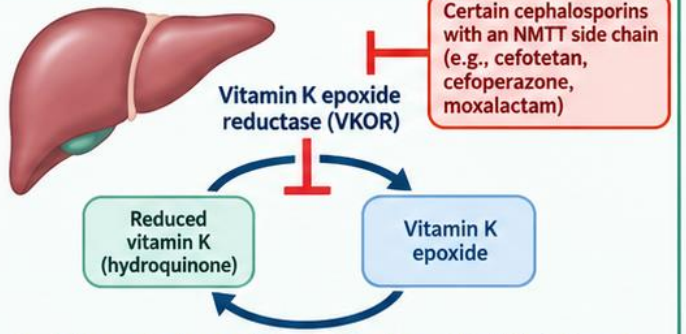
2. Suppression of gut microbiota



Broad-spectrum antibioitics suppress intestinal bacteria that synthesize menaquinones (vitamin K_2).

Contribution of microbiota-derived K_2 to human coagulation homeostasis is variable/uncertain, but loss may contribute, especially when dietary intake is poor.

3. Direct inhibition of the vitamin K cycle



Certain cephalosporins with an N-methylthiotetrazole (NMTT) side chain (e.g., cefotetan, cefoperazone, moxalactam) inhibit vitamin K epoxide reductase.

This impairs recycling of reduced vitamin K.

Common final pathway

Reduced reduced-vitamin K availability/function → impaired gamma-carboxylation of factors II, VII, IX, X (and proteins C/S).

Clinical/laboratory effect

PIVKA accumulation, prolonged PT/INR +/- prolonged aPTT, and possible bleeding.

Risk is greatest when antibiotics are combined with low vitamin K intake, prolonged illness, cholestasis, or malabsorption.

References: Shearer MJ, Bechtold H, Andrassy K, et al. *J Clin Pharmacol*. 1988;28:88-95. PMID: 3350995. Conly JM, Stein K. *Prog Food Nutr Sci*. 1992;16:307-343. PMID: 1492156. Park GH, Kim S, Kim MS, et al. *Int J Environ Res Public Health*. 2019;16:3937. PMID: 31623191.

Vitamin K Deficiency Replacement

- Vit. K (phytonadione (vitamin K1): 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

Disseminated Intravascular Coagulation Is Not A Disease, But a Process

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

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

Why Patients with Fulminant DIC Bleed

Bleeding is multifactorial: consumption of platelets and clotting factors, fibrinogen depletion, and hyperfibrinolysis leave the patient unable to form a stable clot.

Mechanism	Major details / why it causes bleeding	Representative references
Consumption of coagulation factors (consumptive coagulopathy)	Systemic thrombin generation consumes fibrinogen and clotting factors faster than they can be replaced; factors II, V, VIII, and XIII may fall, with prolonged PT and aPTT. The result is inadequate substrate for stable fibrin clot formation.	Levi & Scully 2018; Taylor et al. 2001
Thrombocytopenia from platelet consumption	Ongoing thrombin-driven platelet activation and incorporation into diffuse microthrombi consume platelets faster than they are produced. Low platelet count directly impairs primary hemostasis.	Levi & Scully 2018; Levi 2014
Fibrinogen depletion and hyperfibrinolysis	Secondary fibrinolysis generates excess plasmin, which degrades fibrinogen and can further reduce factors V and VIII. This is especially important in the hemorrhagic / fibrinolytic phenotype of DIC (e.g., trauma, obstetric, APL-related DIC).	Levi 2014; Asakura 2017
Fibrin/fibrinogen degradation products (FDPs) as functional inhibitors	High FDP and D-dimer levels interfere with fibrin polymerization and can impair platelet function, worsening bleeding beyond simple factor depletion.	Levi 2014; Asakura 2017
Acquired platelet dysfunction	Platelets may be qualitatively abnormal because of prior activation, partial degranulation, and proteolytic injury to surface receptors, adding dysfunction to thrombocytopenia.	Levi & Scully 2018; Levi 2014
Consumption of physiologic anticoagulants (indirectly perpetuates bleeding)	Loss of antithrombin, protein C, and TFPI removes physiologic restraint on thrombin generation, sustaining consumption of platelets and coagulation factors and worsening the coagulopathy.	Levi & Scully 2018; Taylor et al. 2001

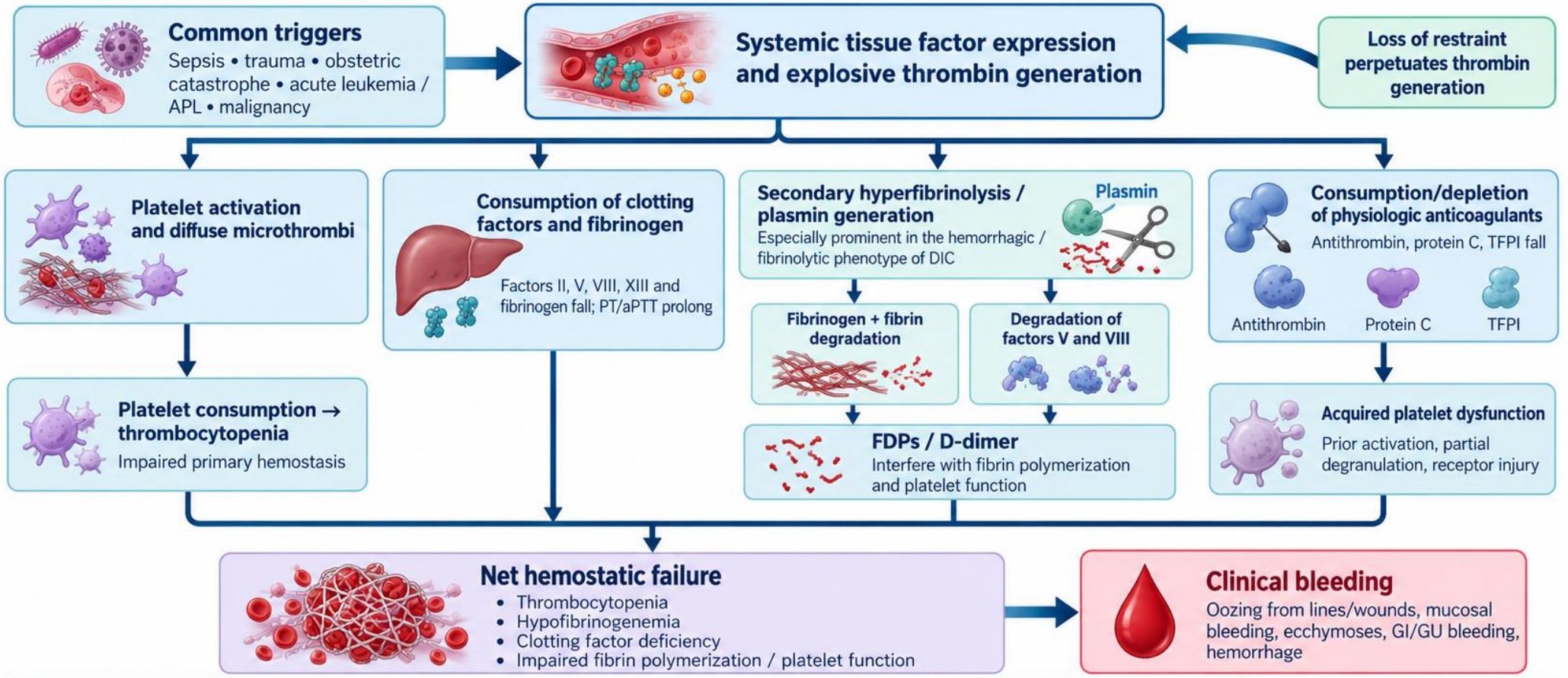


Bottom line: in fulminant DIC, bleeding occurs because ongoing thrombin generation and fibrinolysis consume or degrade the components required for hemostasis: platelets, fibrinogen, and clotting factors.

References: Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. Thromb Haemost. 2001;86:1327-1330. PMID: 11816725. Levi M. *Int J Lab Hematol.* 2014;36:228-236. PMID: 24750668. Levi M, Scully M. *Blood.* 2018;131:845-854. PMID: 29255070. Asakura H. *J Intensive Care.* 2017;5:14. PMID: 28289544.

Pathways Leading to Bleeding in Fulminant DIC

Excess thrombin generation, consumptive coagulopathy, and hyperfibrinolysis converge to produce an unstable hemostatic system.



Bottom line: fulminant DIC bleeds because the body is simultaneously consuming platelets and clotting factors while fibrinolysis degrades fibrinogen and destabilizes clot formation.

References: Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. *Thromb Haemost.* 2001;86:1327-1330. PMID: 11816725. Levi M. *Int J Lab Hematol.* 2014;36:228-236. PMID: 24750668. Levi M, Scully M. *Blood.* 2018;131:845-854. PMID: 29255070. Asakura H. *J Intensive Care.* 2017;5:14. PMID: 28289544.

Disseminated Intravascular Coagulation

Laboratory findings:

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

Treatment:

- ***TREAT UNDERLYING CAUSE***
- ***No specific therapy has been validated.***

- Supportive Care:
- Keep the fibrinogen > 100 mg/dl
  - Cryoprecipitate
- FFP for bleeding or procedures
- Avoid inhibitors of fibrinolysis (EACA, tranexamic acid, aprotinin)

Causes Of Uremic Coagulopathy

Cause	Mechanism
Uremic toxin accumulation	Urea, creatinine, phenolic acid, and guanidinosuccinic acid impair ADP-mediated platelet aggregation and stimulate nitric oxide production, degrading platelet function
Excess nitric oxide / cyclic nucleotides	Elevated NO with increased cAMP and cGMP inhibits platelet activation and aggregation
Dysfunctional von Willebrand factor / GPIb-IIb/IIIa	Impaired platelet–vessel wall and platelet–platelet adhesion; reduced glycoprotein receptor efficacy
Reduced thromboxane A2 and storage-pool defect	Decreased TxA2 synthesis and depleted platelet ADP and serotonin reduce secondary aggregation
Anemia	Loss of laminar red-cell flow reduces peripheral displacement of platelets toward endothelium (prolonging bleeding time); free hemoglobin scavenges less NO, raising unbound NO
Dialysis-related platelet activation	Contact with artificial circuit surfaces and heparinization causes platelet degranulation, receptor loss, and transient exacerbation of bleeding

C. Baaten et al., J Am Soc Nephrol 32, 1583-1598 (2021)., A. D. Kaye et al., Adv Ther 37, 3707-3722 (2020). P. Lutz, P. Jurk, Semin Thromb Hemost 46, 342-356 (2020). M. Noris et al., Kidney Int 44, 445-450 (1993), P. I. Ponchia, R. Ahmed, M. Farag, M. Alkhalil, Cardiovasc Drugs Ther 37, 975-987 (2023). O. A. Simon et al., Sci Rep 15, 3781 (2025).

Uremic Coagulopathy: Treatment

Treatment	Mechanism / notes
Correction of anemia / erythropoietin	**Restores platelet margination toward vessel wall; RBCs also scavenge free NO; shortens bleeding time and reduces bleeding events**
Desmopressin (DDAVP)	Releases factor VIII:vWF multimers from endothelium, enhancing platelet–vessel adhesion; first-line for acute bleeding or pre-procedure. Watch flushing, hypotension, hyponatremia
Conjugated estrogens	Long-lasting hemostasis for recurrent GI/mucosal bleeding or elective surgery; can be combined with DDAVP. Well tolerated
Optimize/initiate dialysis	Removes uremic toxins improving platelet function; peritoneal dialysis particularly beneficial. Avoid over-dialysis (platelet activation/exhaustion)
Cryoprecipitate / pathogen-reduced cryoprecipitated fibrinogen complex	Provides fibrinogen, vWF, FVIII, FXIII; effect on bleeding time inconsistent—not uniformly recommended; infection risk
Tranexamic acid	Inhibits fibrinolysis; small studies show reduced bleeding in dialysis patients; requires renal dose adjustment
Minimize heparin exposure during HD	Reduces iatrogenic bleeding in high-risk patients; alternatives to systemic heparin for ~1–2 months after major hemorrhage

1. Baaten, C., et al., J Am Soc Nephrol, 2021. 32(7): p. 1583-1598. 2.Beverly, A., et al., Cochrane Database Syst Rev, 2023. 2(2): p. CD013649. 3. Galbusera, M., G. et al. Semin Dial, 2009. 22(3): p. 279-86. 4. Kaye, A.D., et al., Adv Ther, 2020. 37(9): p. 3707-3722. 5. Mohinani, A., et al.. Eur J Haematol, 2023. 110(5): p. 470-479. 6. Salani, M. and T. Golper, Semin Dial, 2020. 33(3): p. 263-269.

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 (undetectable to <5%)
  - "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.**

Acquired Hemophilia: Treatment

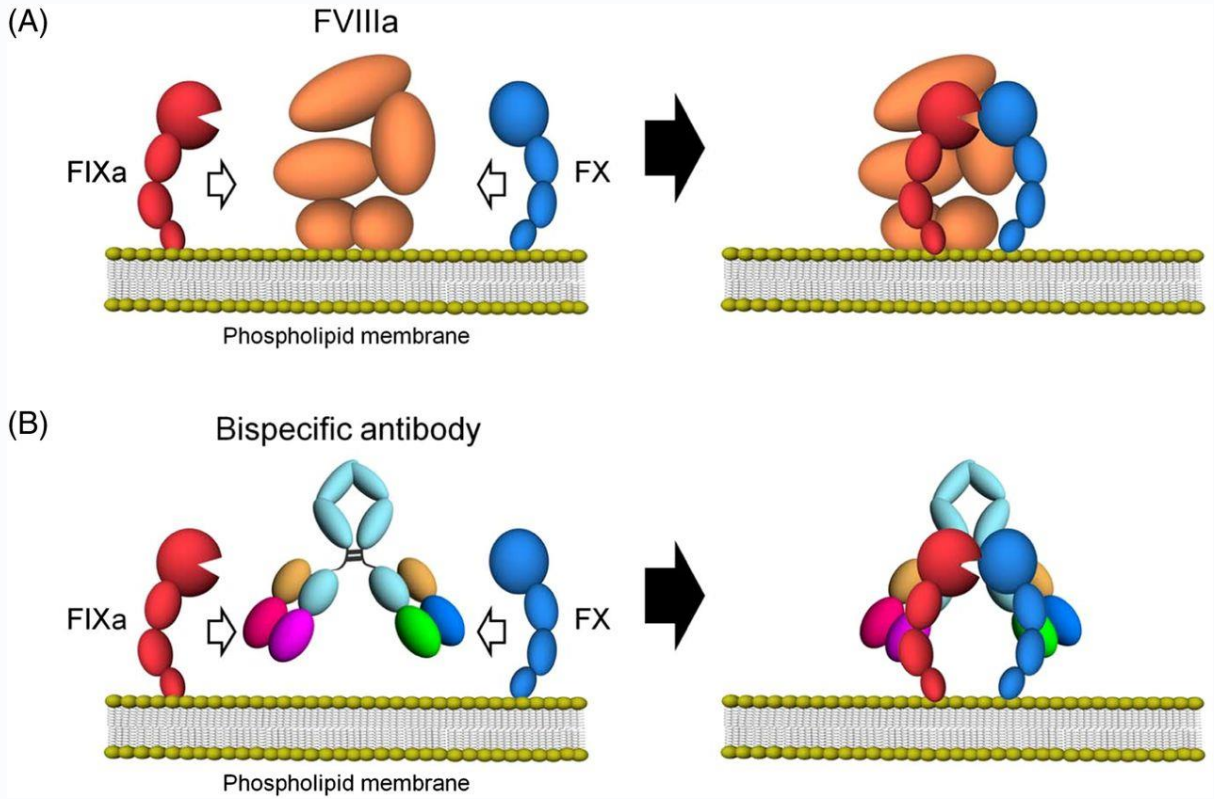
Acute Control of Bleeding

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

Elimination of the inhibitor:

- Prednisone +/- cyclophosphamide
- Rituximab

Emicizumab: A bispecific antibody binds FIXa and FX (replacing the cofactor activity of FVIIIa).



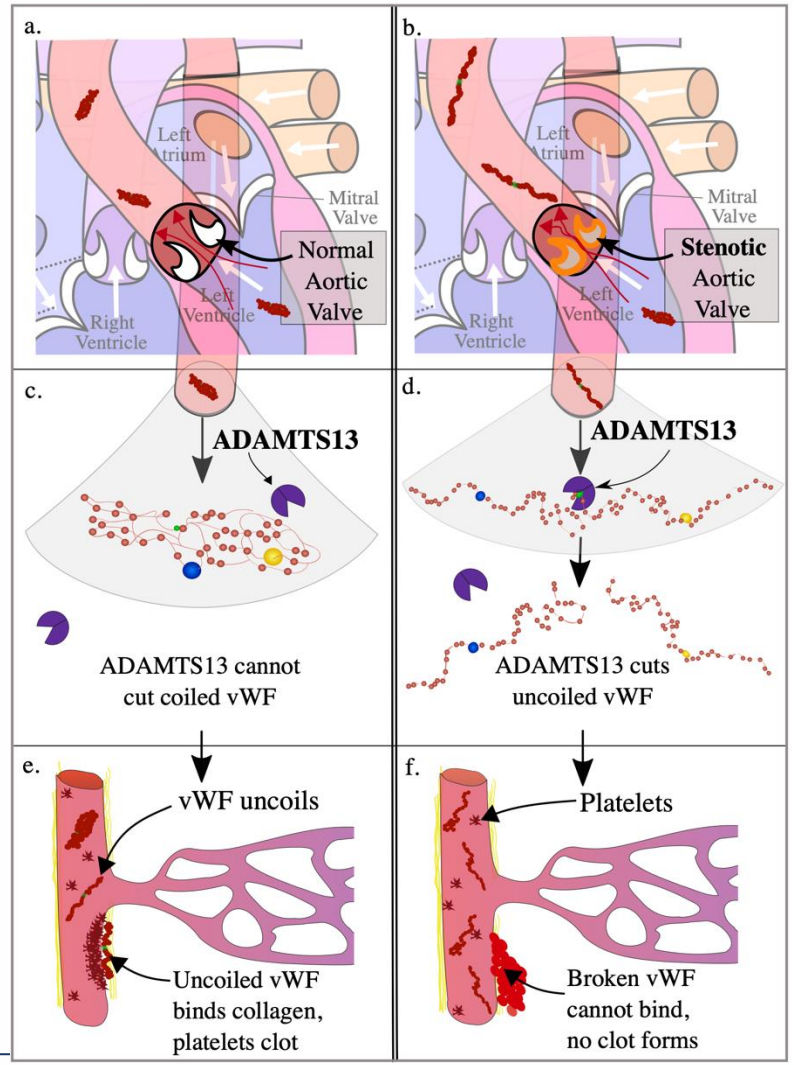
Michael A. Nardi Clin Lab Sci 2020;33:37-47

Acquired von Willebrand Disease

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

Heyde's Syndrome Triad



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

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Acute Promyelocytic Leukemia

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 is 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.

Cause	Brief Mechanism	Ref.
Tissue factor (TF) overexpression	APL blasts constitutively express high levels of TF, activating the extrinsic cascade → thrombin generation and consumption of fibrinogen, factors, and platelets (DIC)	[1-3]
"Cancer procoagulant"	Cysteine protease expressed by blasts directly activates factor X, adding to thrombin generation and consumptive coagulopathy	[1-2]
TF-bearing microparticles	Microparticles shed from APL cells carry active TF into plasma, linking the leukemic cell to systemic coagulation activation	[3]
Annexin A2 / S100A10 (p11) overexpression	Surface co-receptor assembles plasminogen + tPA → accelerated, α2-antiplasmin–protected plasmin generation; upregulated by PML-RARα; high expression on cerebral microvasculature explains ICH predilection	[4-8]
Urokinase (uPA) / uPAR expression	Additional plasminogen activation by blasts, boosting systemic fibrinogenolysis and depletion of fibrinogen/α2-antiplasmin	[9-10]
Functional TAFI deficiency	Normal antigen but reduced activity (plasmin inactivation) removes a brake on fibrinolysis, tipping toward bleeding	[5, 11]
Thrombocytopenia (marrow/consumption)	Marrow replacement and DIC-related consumption lower platelet counts	[12-13]
Podoplanin (PDPN)–CLEC-2 platelet consumption	Aberrant PDPN on APL cells engages platelet CLEC-2 → platelet activation, aggregation, clearance; adds to thrombocytopenia and defective primary hemostasis	[9]
Inflammatory cytokines (IL-1β, TNF-α)	Downregulate endothelial thrombomodulin, upregulate TF → prothrombotic endothelium amplifying consumption	[10]
"ETosis" (extracellular chromatin release)	Promoted by ATRA; increases both thrombin and plasmin generation, may transiently worsen coagulopathy early in therapy	[14-15]

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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

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	Nl	↓	Nl	↓
Liver Disease	↓	↓	Nl or ↑	↓
DIC	↓	↓	↓	↓

Any Questions?

