22/Sep/2019

Approach to the Patients with Bleeding Diathesis

Kosin University Gaspel Hospital
Hematology & Oncology
LEE, EUN MI

Contents

- Overview of Hemostasis
- Approach to patients with bleeding diathesis
  - Patient history
  - Laboratory tests
- Bleeding disorder
  - Disorders of platelets
  - Disorders of coagulation system

Contents

- Overview of Hemostasis

- Approach to patients with bleeding diathesis
  - Patient history
  - Laboratory tests

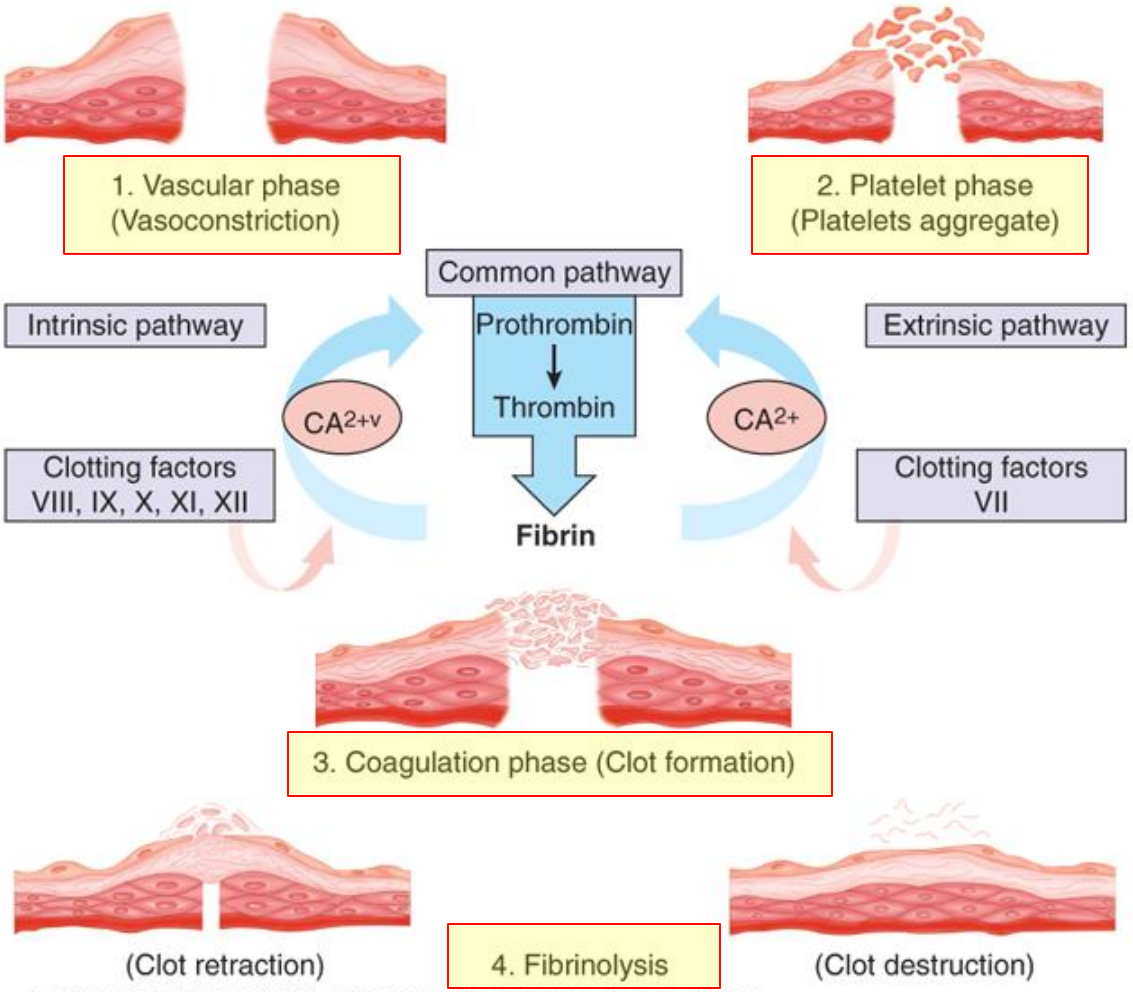
- Bleeding disorder
  - Disorders of platelets
  - Disorders of coagulation system

Hemostasis

- Hemostasis involve a complex interplay among vascular integrity, platelet number and function, coagulation factor and fibrinolysis

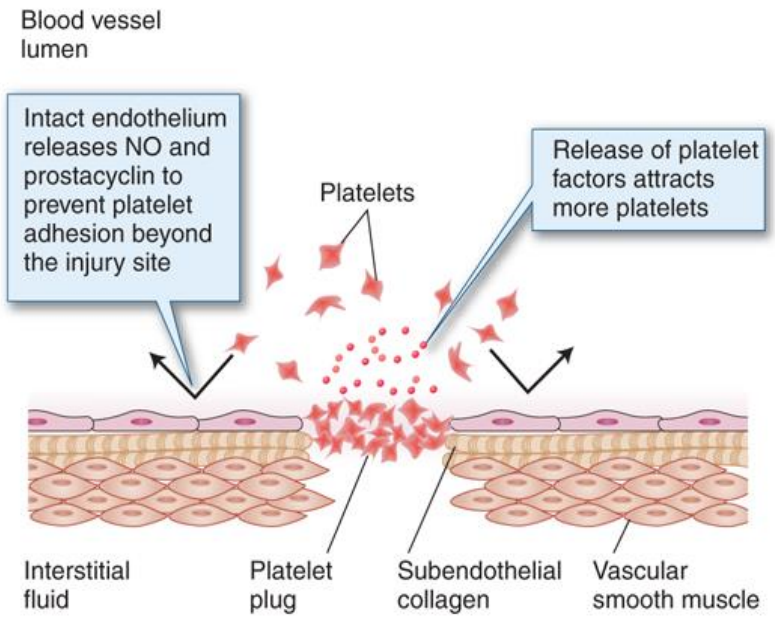
- Phases of the hemostatic process
  1) Endothelial injury and formation of platelet plug
  2) Propagation of the clotting process by the coagulation cascade
  3) Termination of clotting by antithrombin control mechanism
  4) Removal of clot by fibrinolysis

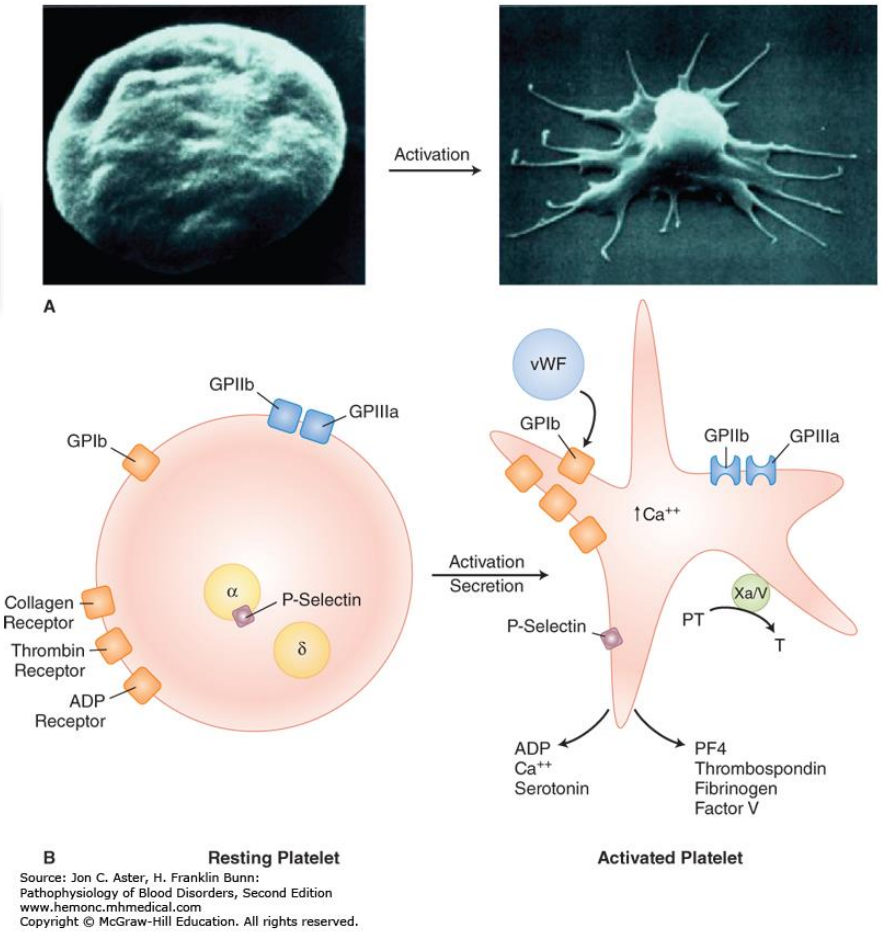
Biology of Hemostasis



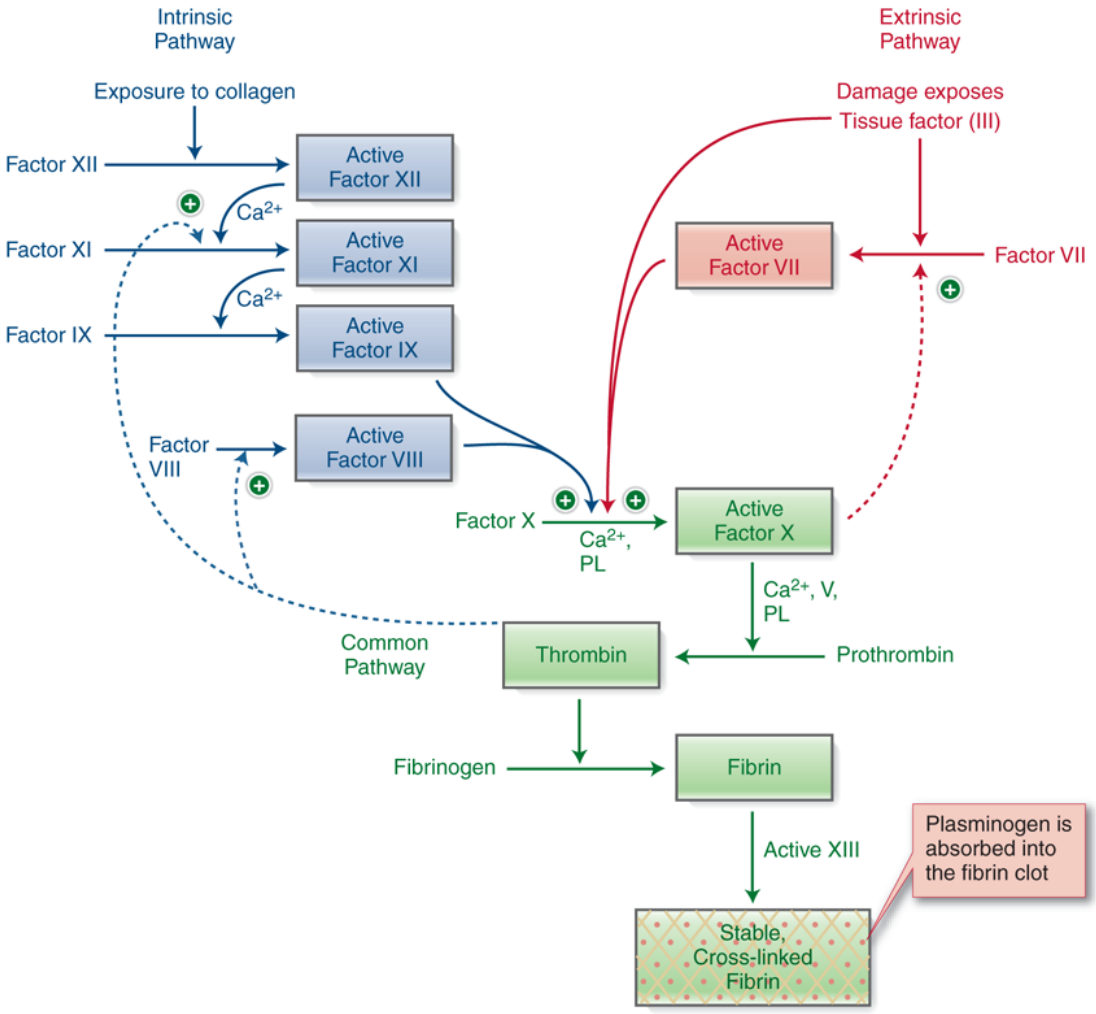
Formation of the Platelet Plug

- Adhesion → Aggregation → Activation of platelets



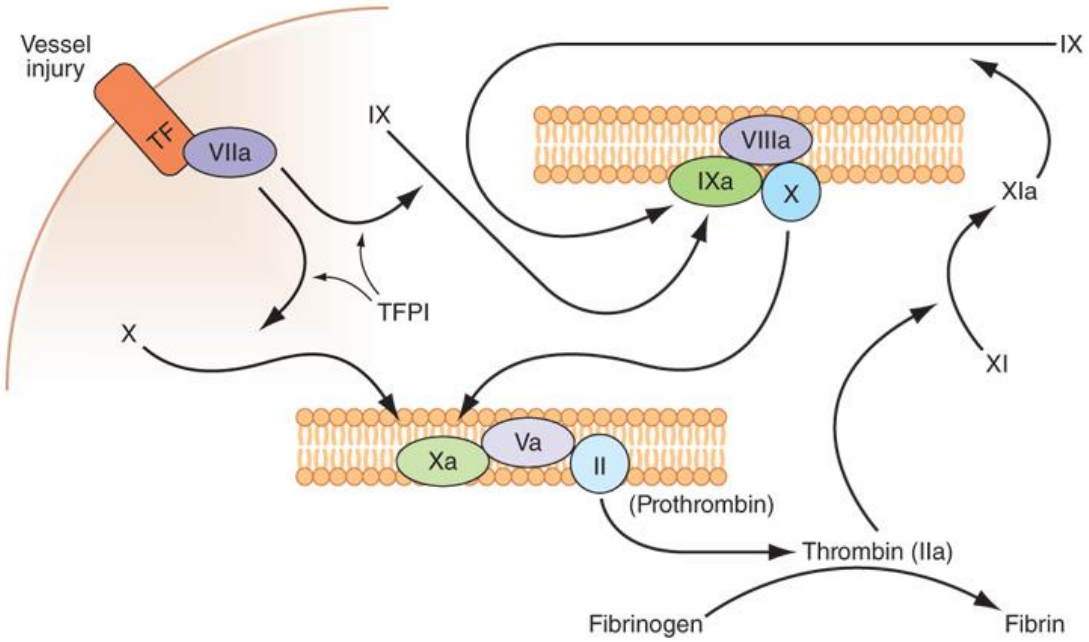


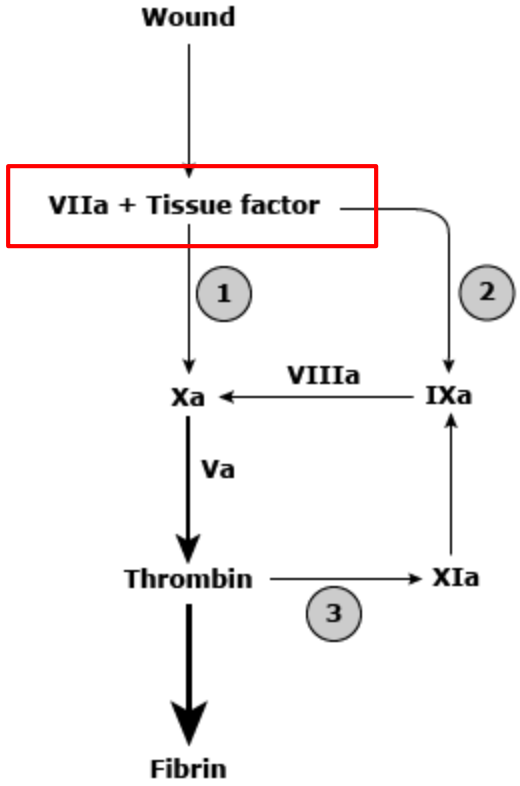
Classic Coagulation Cascade



Overview of Coagulation Cascade

- Coagulation is initiated by **tissue factor** exposure

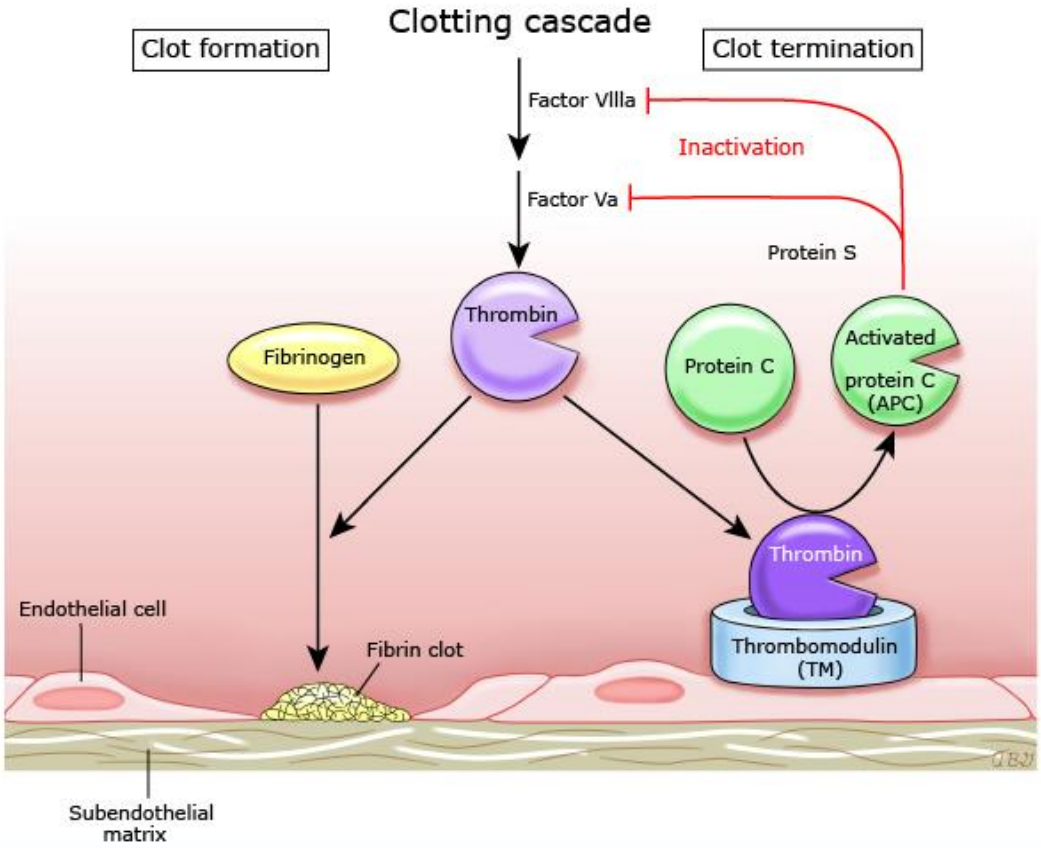




Termination of Clotting

- **Anti-thrombin (AT-III)**
  - The major protease inhibitors of thrombin and other clotting factor in coagulation
- **Tissue factor pathway inhibitor (TFPI)**
  - A plasma protease inhibitors that regulates the tissue factor induced extrinsic pathway of coagulation
- **Protein C**
  - A plasma glycoprotein that becomes an anticoagulant when it is activated by thrombin

Protein C pathway



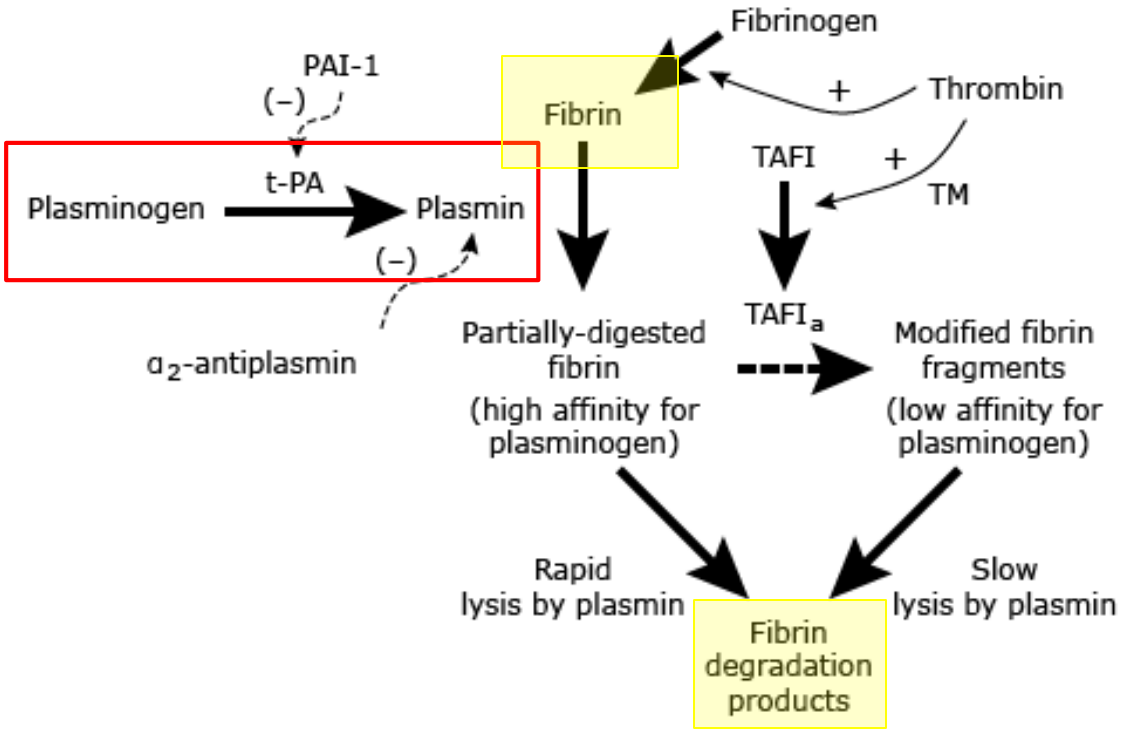
Refer to UpToDate for an overview of hemostasis regulation and the roles of specific procoagulant and anticoagulant factors in clinical thrombosis and hemostasis.

APC: activated protein C; TM: thrombomodulin.

Courtesy of Lawrence LK Leung, MD

Fibrinolysis

- **Plasmin**
  - The major protease enzyme of the fibrinolytic system
  - Activated by tissue-type plasminogen activator (t-PA), urokinase



Classifications of Bleeding Disorders

	Disorder
Vessel	• Acquired: secondary steroid use, vitamin C deficiency • Congenital: hereditary hemorrhagic telangiectasis, Ehlers-Danlos syndrome
Platelets	Thrombocytopenia • Acquired: drug-induced, immune-mediated • Congenital: inherited platelet or BM disorder Disorder of platelet function • Acquired: drug-induced, renal failure • Congenital: secretion defects are the most common von Willebrand syndrome • Acquired • Congenital: von Willebrand disease (vWD)
Coagulation factors	• Acquired: Vitamin K deficiency, liver disease, anticoagulant therapy, massive blood loss (hemodilution), acquired coagulation factor inhibitor • Congenial: hemophilia A, hemophilia B, deficiencies or defects of factors II, V, X, XI, fibrinogen, or XIII
Fibrinolysis	• Acquired: hyperfibrinolytic syndrome, disseminated intravascular coagulation (DIC) • Congenital: α-2 antiplasmin deficiency, plasminogen activator inhibitor-1 deficiency, Quebec platelet disorder
Others	• Acquired bleeding secondary to other disorder such as renal failure, thyroid disease, Cushing syndrome

Contents

- Overview of Hemostasis
- Approach to patients with bleeding diathesis
  - Patient history
  - Laboratory tests
- Bleeding disorders
  - Disorders of platelets
  - Disorders of coagulation system

Patient History

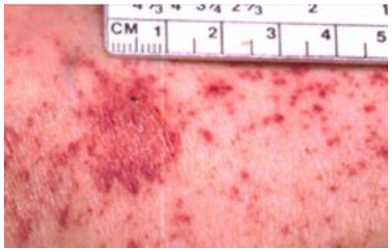
- Underlying medical condition
  - Caner, excess alcohol use, liver disease, kidney disease, connective tissue disorders, hypothyroidism
- Elements of the bleeding history
- Interpretation of bleeding history
- Family history
- Medical use

Elements of Bleeding History

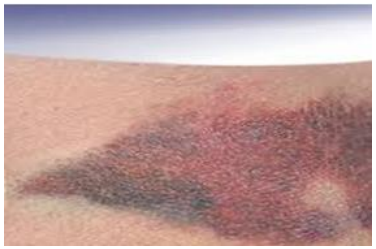
- Questions to consider when evaluating a patient for a possible bleeding disorder
  - What are the patient's bleeding symptoms?
  - Dose the history suggest a congenital or acquired problem?
  - What is the timing of the bleeding?
  - Is the bleeding systemic or local?
  - Are there any aggravating or contributing factors?
  - What is the patient's general medical history?
  - How many times has the patient experienced a significant hemostatic challenge, and how many of these were associated with abnormal bleeding?

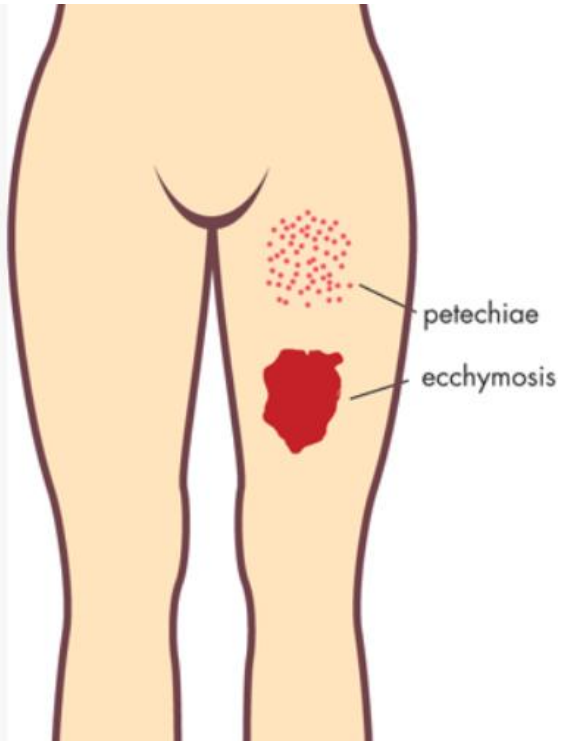
Purpura

- **Petechiae**
  - Small, purpuric lesion up to 2 mm across



- **Ecchymosis** or **bruies**
  - Larger extravasation of blood, more than 2 mm across





Clinical Features of Bleeding

Bleeding Characteristics	Thrombocytopenia or platelet functional defects	Clotting factor defeciencies or inhibitors
Major site of bleeding	Mucocutaneous (mouth, nose, GI tract, Urinary tract, menorrhagia)	Deep tissue (joint, muscles) or soft tissue hematomas
Petechiae	Common	Uncommon
Ecchymosis	Generally small of superficial; may be significant, depending upon the degree of thrombocytopenia	May develop large ecchymosis
Excessive bleeding after minor cut	Yes	Not usually
Excessive bleeding with surgery or invasive procedures	Often immediately; degree varies with severity of the defect	Often during the prodedure. Some individuals may experience delayed bleeding

Family History

- Inherited bleeding disorders
  - von Billebrand disease: dominant inheritance, variable penetrance
  - Hemophilia A & B: sex linked inheritance, high penetrance
  - Other clotting factor deficiencies: recessive inheritrance
- Lack of a family history does not eliminate the possibility
  - 30~40% of individuals with hemophilia A have a de novo germline mutation
- Some individuals may report a family history of severe bleeding requiring medical interventions (surgery, transfusions)

Substances Increase Bleeding Risk

- Bleeding risk is increased with the use of certain medications, herb preparation, and dietary supplements

Drug class	Mechanism
Anticoagulants	Interfere with clot formation
Antiplatelet agents, including NSAIDs	Interfere with platelet function
Glucocorticoids	Interfere with vascular integrity
Antibiotics	Cause vitamin K deficiency, especially with lunger use Some interfere with platelet function
SSRIs	Interfere with platelet function
Alcohol	Complications of liver disease may affect clot formation and may cause thrombocytopenia May cause thrombocytopenia due to direct marrow toxicity
Vitamin E	Interfere with vitamin K metabolism in some individuals
Galic	IInterfere with platelet function in some individuals
Gingko biloba	Unknown

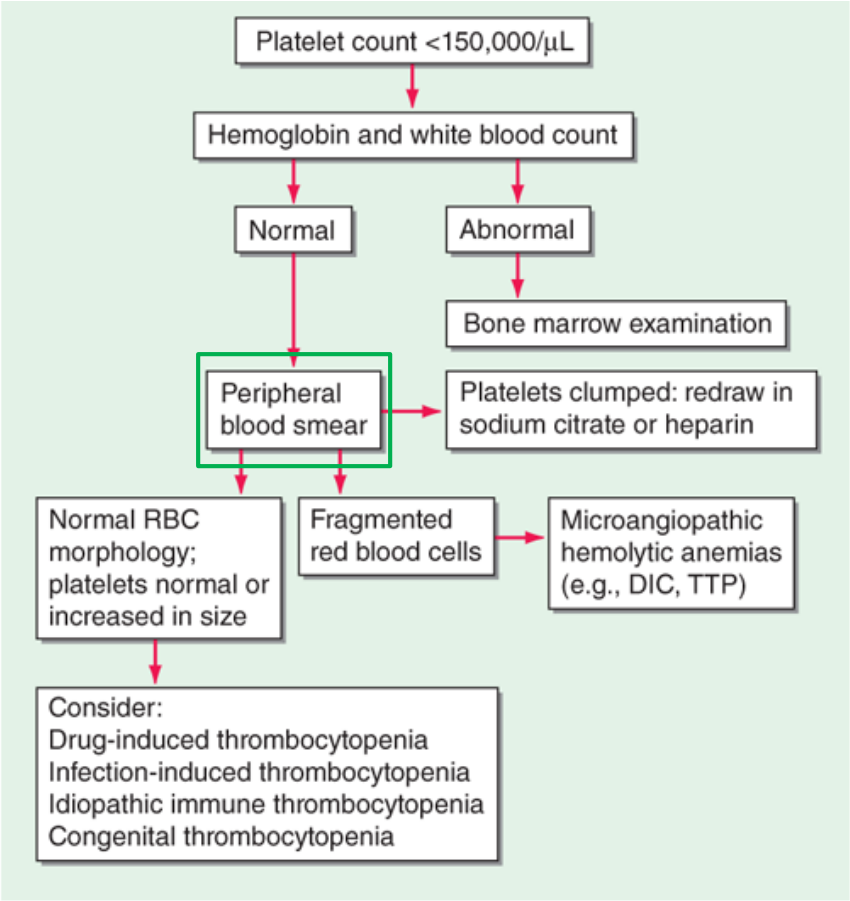
Laboratory Evaluaion

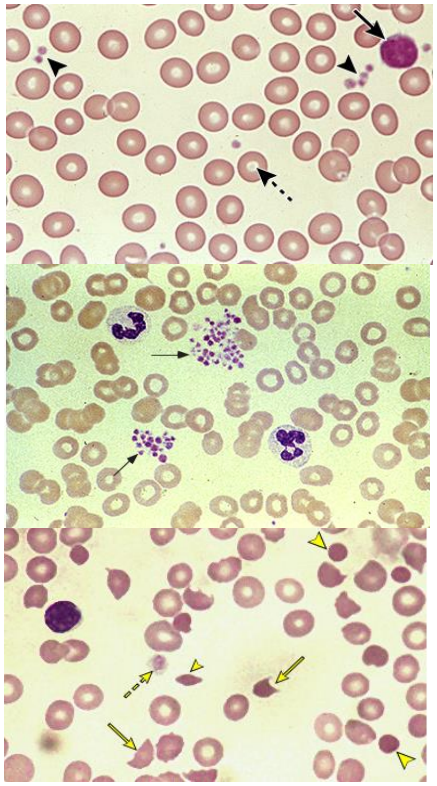
- **Initial testing (screening test)**
  - CBC with platelet count and review of platelet morphology
  - PT and aPTT

- **Specific testing**
  - Test for platelet function defect
  - Test for von Willebrand disease (VWD)
  - Mixing test for PT or aPTT
  - Thrombin time (TT)
  - Specific clotting factor assays
  - Test for increased fibrinolysis

Low Platelet Counts in CBC

- Algorithm for Thrombocytopenia Evaluation



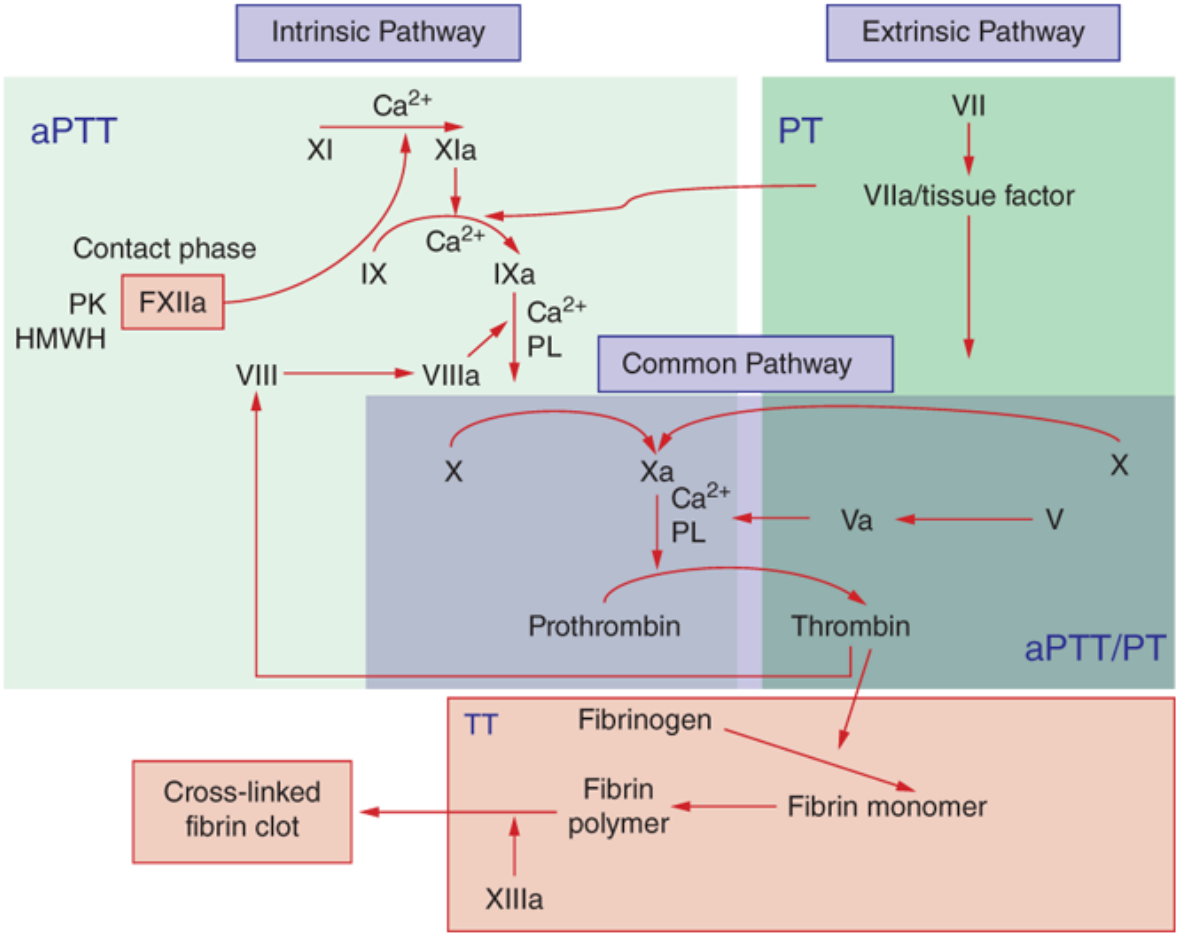


Normal

Platelet clumping

MAHA

PT/aPTT/TT



Causes of prolonged PT/aPTT

Test Result	Cause of test result pattern	
	Inherited	Acquired
Prolonged PT **Normal aPTT**	• Factor VII deficiency	• Mild vitamin K deficiency • Liver disease • Wafarin • DIC
Normal PT **Prolonged aPTT**	• Deficiency of factor VIII, IX, or IX • Deficiency of XII, prekallikrein, or HMW kininogen • Von Willebrand disease	• Heparin, dabigatron, argatroban, direct factor Xa inhibitor • Acquired inhibitors factor VIII, IV, IX or XII • Acquired von Willebrand syndrome • Lupus anticoagulant
Prolonged PT **Prolonged aPTT**	• Deficiency of prothrombin, fibrinogen, factor V, or factor X • Combined factor deficiencies	• Liver disease • DIC • Severe vitamin K deficiency • Anticoagulants • Acquired inhibitor of prothrombin, fibrinogen, factor V, or factor X • Amyloidosis-associated factor X deficiency

Platelet Function Test

- To evaluate congenital and acquired disorders affecting platelet number, platelet function, or both
- Highly operator-dependent, poorly standardized and poorly reproducible
- Platelet aggregation studies
  - Platelet-platelet cohesion: ristosetin, thrombin, collagen, epinephrine, ADP..
- PFA-100 (Platelet function analyzer)
- Classic Bleeding time

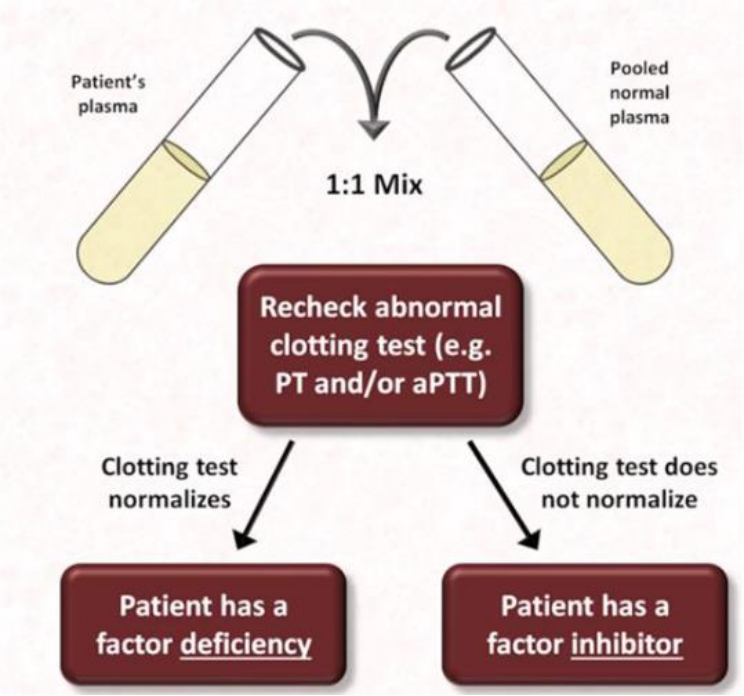
VWD Test

- von Willebrand disease (VWD) is suspected
  - Normal CBC & normal/prolonged aPTT & normal PT
- Von Willebrand Factor (VWF)
  - An adhesive link between platelets and injured vessel wall
  - A carrier for clotting factor VIII
- Testing for VWF
  - Plasma VWF antigen (VWF:Ag)
  - Plasma VWF activity (ristocetin cofactor [VWF:RCo] and collagen binding [VWF:CB])
  - Plasma factor VIII activity (FVIII:C)

Mixing Test for PT/aPTT

- To distinguish between an abnormally prolonged clotting time due to a factor deficiency vs. a factor inhibitor

- Common cause or inhibitors
  - Oral anticoagulants
  - Heparin
  - Antiphospholipid antibodies
  - Acauired coaguation factor inhibitors



Thrombin Time

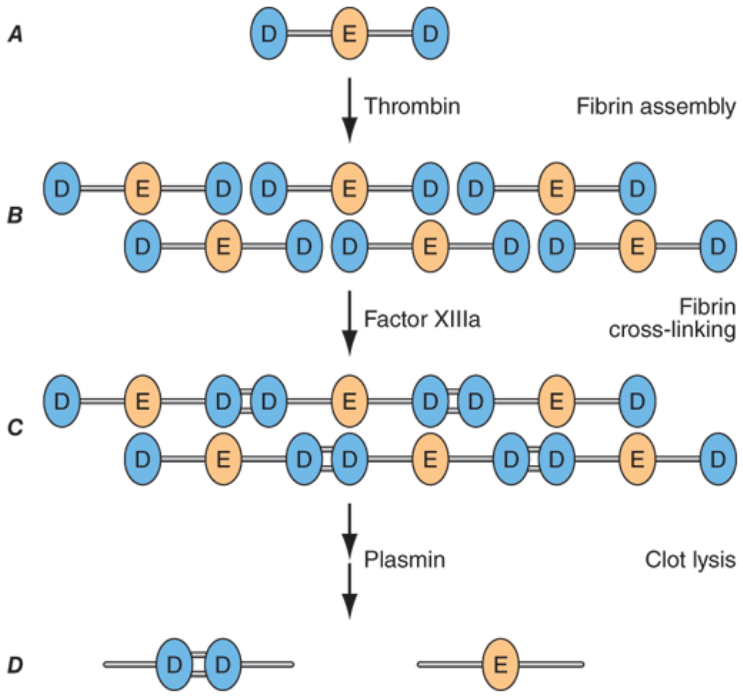
- Measures the final step of coagulation, the conversion of fibrinogen to fibrin

- Useful in the following clinical setting
  - Evaluation of a patient with a prolonged PT and aPTT
  - Evaluation of an inherited fibrinogen disorder
  - Detection of heparin in a sample

- TT prolongation
  - Anticoagulation, acquired fibrinogen disorder, DIC, liver disease, hypoalbuminemia, paraproteinemia, Bovine thrombin exposure

Test for Fibrinolysis

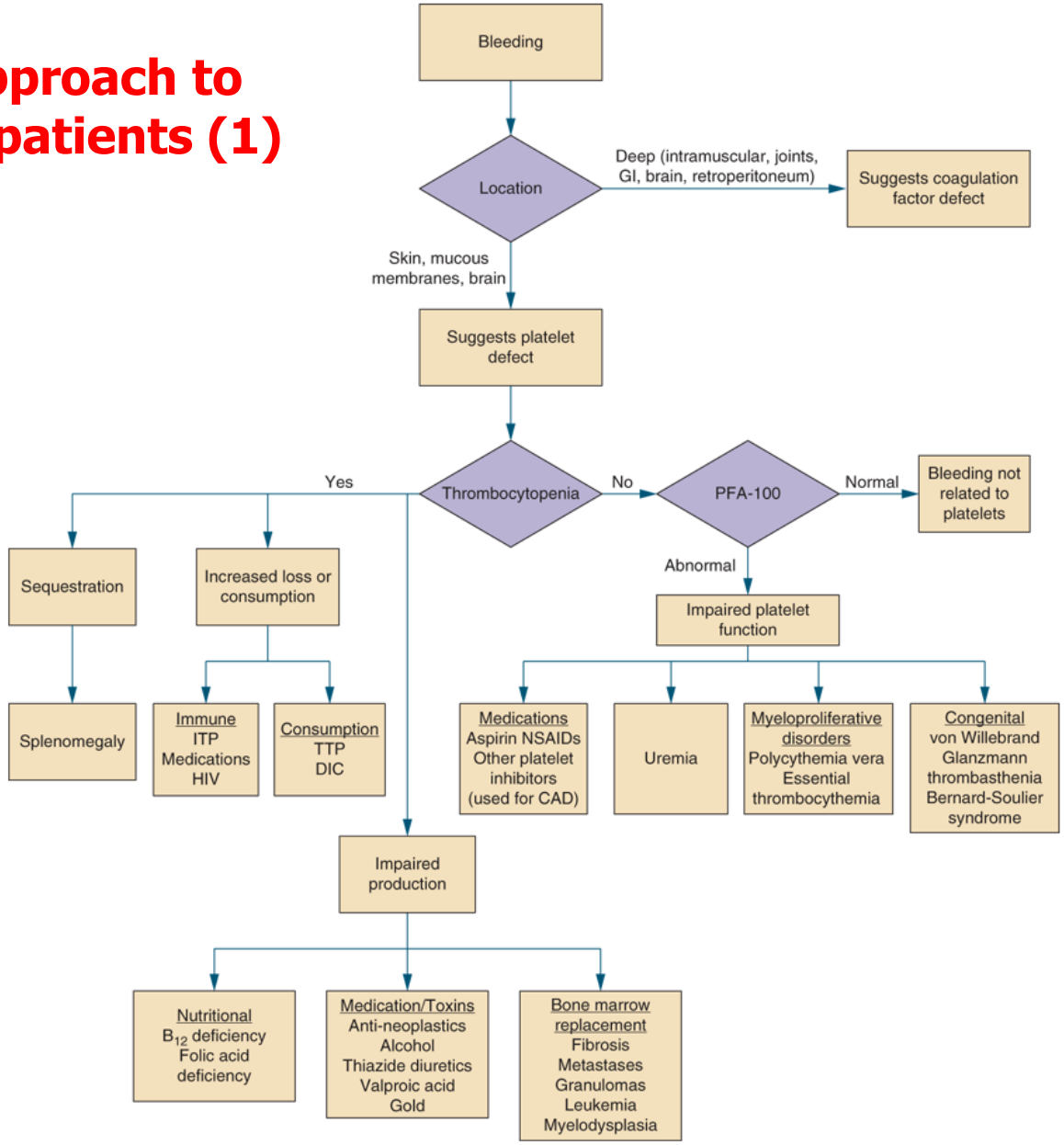
- Eulglobulin lysis time
  - Measure time to clot lysis
  - Not well standardized
  - Defects increased fibrinolysis
    Factor XIII deficiency
- Alpha 2- antiplasmin level
- PAI-1 acitivey



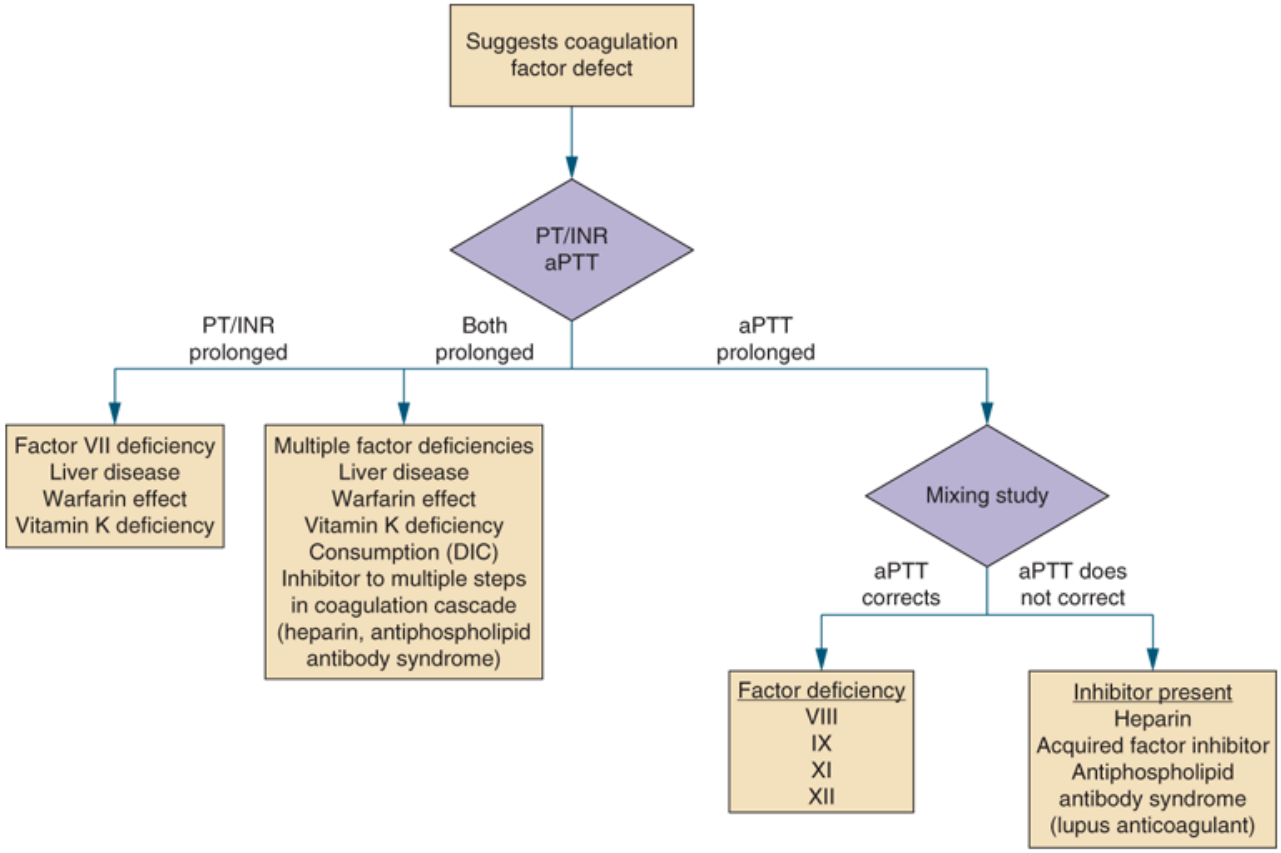
Results of Bleeding Disorders

Disorder	Platelet count	PT	aPTT	TT	Fibrinogen level
Vasculopathies, connective tissue disorder, or collagen disorders affecting skin	Normal	Normal	Normal	Normal	Normal or increased
Thrombocytopenia	Decreased	Normal	Normal	Normal	Normal
Qualitative platelet abnormalities	Normal or decreased	Normal	Normal	Normal	Normal
Hemophilia A or B	Normal	Normal	Prolonged	Normal	Normal
von Wellebrand disease (vWD)	Normal	Normal	Normal or Prolonged	Normal	Normal
Disseminated intravascular coagulation (DIC)	Decreased	Prolonged	Prolonged	Prolonged	Decreased

Diagnostic Approach to the bleeding patients (1)



Diagnostic Approach to the bleeding patients (2)



aPTT, activated partial thromboplastin time; CAD, coronary artery disease; DIC, disseminated intravascular coagulation; GI, gastrointestinal; INR, international normalized ratio; ITP, idiopathic thrombocytopenia purpura; NSAIDs, nonsteroidal antiinflammatory drugs; PT, prothrombin time; TTP, thrombotic thrombocytopenic purpura.

Symptom to Diagnosis: An Evidence-Based Guid, 3e.

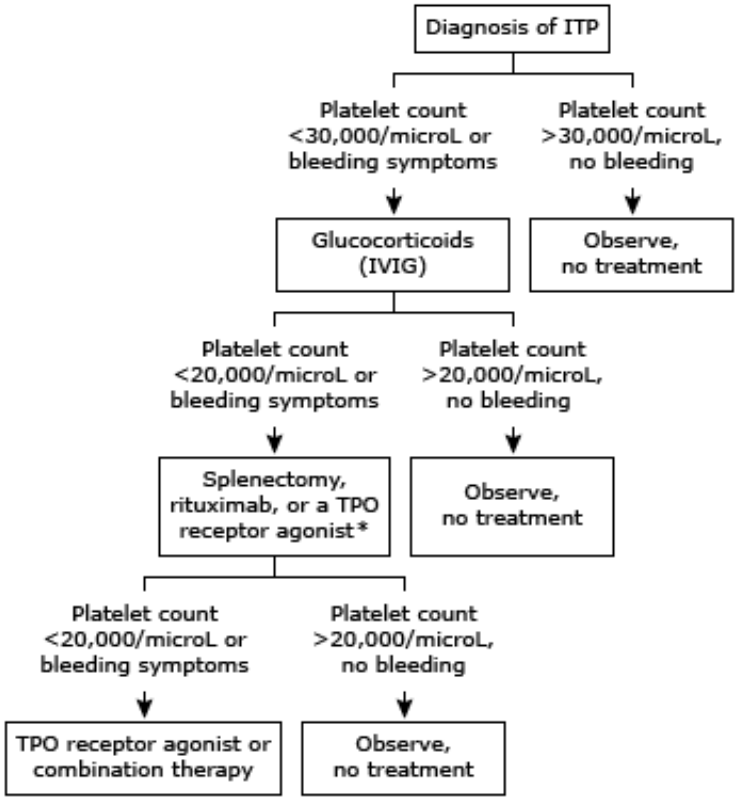
Contents

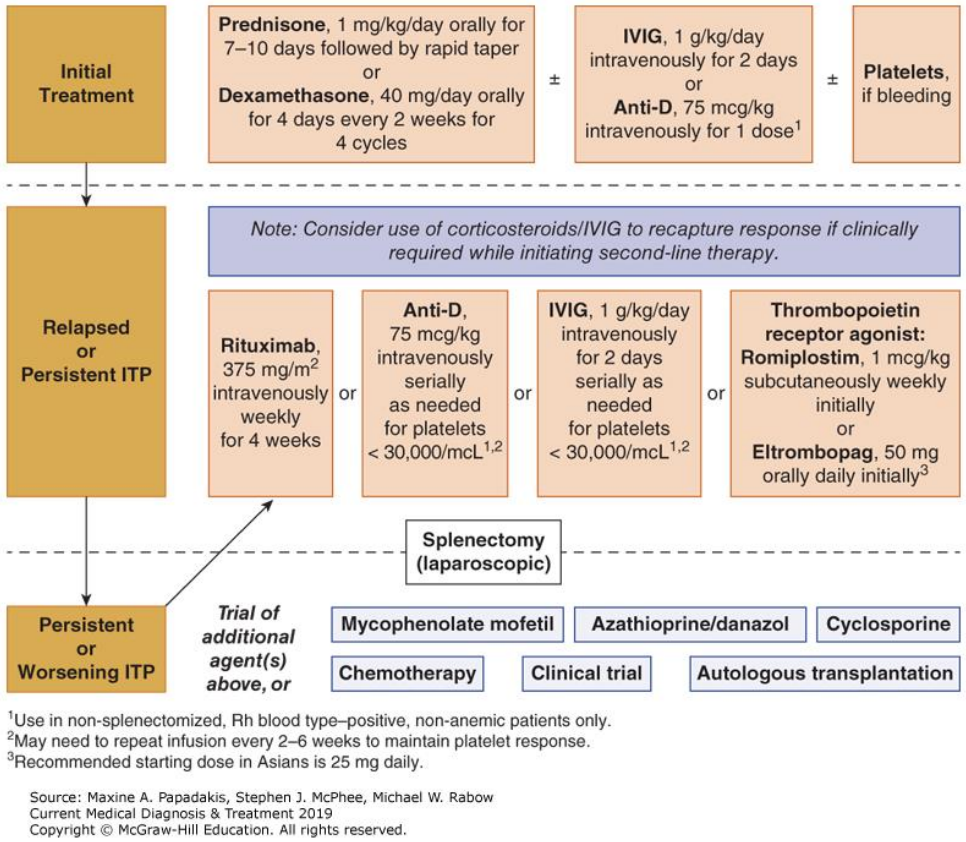
- Overview of Hemostasis
- Approach to patients with bleeding diathesis
  - Patient history
  - Laboratory tests
- Bleeding disorders
  - Disorders of platelets
  - Disorders of coagulation system

Immune Thrombocytopenia (ITP)

- Idiopathic thrombocytopenic purpura
  - An acquired disorder in which there is immune-mediated destruction of platelets and possibly inhibition of platelet release from megakaryocytes
- Secondary ITP
  - Associated with underlying disorder; autoimmune disorder (**SLE**), and infection (**HIV, Hepatitis, and *H.pylori***)
- Laboratory test
  - Thrombocytopenia on CBC with normal morphology
  - BM examination
  - Serology test for antibody (not helpful)

Treatment of ITP





[1]Use in non-splenectomized, Rh blood type–positive, non-anemic patients only.
[2]May need to repeat infusion every 2–6 weeks to maintain platelet response.
[3]Recommended starting dose in Asians is 25 mg daily.

Drug-induced Thrombocytopenia

- Many drugs are associated with thrombocytopenia
- All drugs should be suspect in patient a with thrombocytopenia without a apparent cause and should be stopped, or substituted, if possible
- Thrombocytopenia typically occurs after a period of initial exposure (median, 21 days), and usually resolves in 7~10 days after withdrawal

Drugs Reported as causing DITP

- Drug-induced immune thrombocytopenia
  - Drug-dependent antibodies that react with specific platelet surface antigens and result in thrombocytopenia

"Definite"	"Possible"
Quinidine	Acetaminophen
Qquinine	Amiodarone
TMP/SMX	Ampicillin
Vancomycin	Cephamadole
Penicillin	Cipofloxacin
Rifampin	Diazepam
Carbamazepine	Ethambutol
Ceftriaxone	Furosemide
Ibuprofen	Gold
Mirtazapine	Haloperidol
Oxaliplatin	Lorazepam
Abxicimab	Naproxen
Tirofiban	Pheytoin
Eptifibatide	Piperacillin
	Ranitidine
	Rosiglitazone
	Roxifban
	Sufisoxazole
	Tranilast

Arnold DM et al. *J Thromb Heamost* 2013

von Willebrand Disease

- The most common inherited bleeding disorder
  - Prevalence 1% of general population, but only 0.1~1% of patients are symptomatic
- Three major types
  - Type 1: partial quantitative deficiency
  - Type 2A, 2B, 2N, 2M: qualitative variant
  - Type 3: Severe quantitative deficiency/absence of VWF
- Acquired von Willerand syndrome
  - Reduced production, sequestration, or destruction of VWF
  - Lymphoproliferative disorder, myeloproliferative disorders, autoimmune disease, cardiovascular conditions associated with vessel stress or high flow

Treatment of VWD

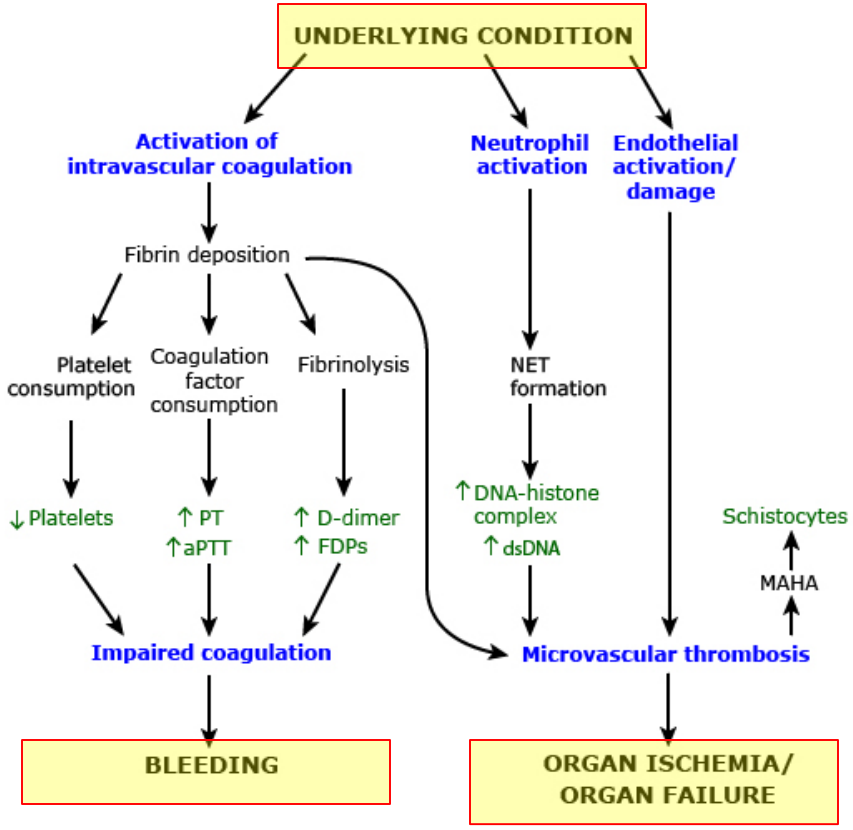
- Desmopresin (DDAVP)
  - Indirectly causes release of VWF & Factor VIII
- VWF-concentrate

Type (%)	Defect	Treatment
1 (70~80)	Normal VWF is present, but in decreased quantity (20~50% of normal level)	Desmopresin
2 (10~15)	Abnormal & dysfuctional VWF	Desmopresin VWF-concentrate (cryoprecipitate)
3 (<10)	Absence of VWF	VWF-concentrate (cryoprecipitate)

- Afibrinolytic agent
  - Aminocapric acid, tranexamic acid

Disseminated Intravascular Coagulation

- The process of coagulation and fibrinolysis become abnormally (and often massively) activated within vasculature, leading to ongoing coagulation and finrinolysis



Common cause of DIC

Sepsis	Immunologic Disorders
Bacteria: staphylococci, streptococci, pneumococci, meningococci, Gram (-) bacilli Viral Parasitic	Acute hemolytic transfusion reaction Oran tissue transplant rejection Immunotherapy Graft-versus-host disease
Trauma & Tissue injury	**Drugs**
Brain injury (gunshot) Extensive burn Fat embolism Rhabdomyolysis	Fibrinolytic agents Aprotinin Wafarin (especially in neonates with protein C deficiency) Prothrombin complex concentrates Recreational drug (amphetamines)
Vascular disorder	**Envenomation**
Giant hemangiomas (Kasabach-Merritt syndrome) Large vessel aneurysms (e.g., aorta)	Snake Inserts
Obstetrical Complication	**Liver disease**
Abruptio placentae Amniotic fluid embolism Dead fetus syndrome Septic abortion	Fulminant hepatic failure Cirrhosis Fatty liver of pregnancy
Cancer	**Miscellaneous**
Adenocarcinoma (prostate, pancreas, etc.) Hematologic malignancies (APL)	Shock Respiratory distress syndrome Massive transfusion

Diagnosis of DIC

- The presence of clinical and/or laboratory coagulation abnormalities or thrombocytopenia

Parameter	Acute (decompensated)	Chronic (compensated)
Platelet count	Reduced	Variable
PT	Prolonged	Normal
aPTT	Prolonged	Normal
Thrombin time	Prolonged	Normal to slightly prolonged
Plasma fibrinogen	Reduced	Normal to elevated
Plasma factor V	Reduced	Normal
Plasma factor VIII	Reduced	Normal
FDP	Elevated	Elevated
D-dimer	Elevated	Elevated

- **Chronic DIC**
  - History of cancer, venous or arterial thromboceomblism

Management of DIC

1. Assess for underlying cause of DIC and treat
2. Establish baseline platelet count, PT, aPTT, D-dimer, fibrinogen
3. Transfusion blood products if ongoing bleeding or high risk of bleeding
   - Platelets: goal > 30,000/mm^3 or 50,000/mm^3 (severe bleeding)
   - Cryoprecipitate: goal fibrinogen level > 80~100 mg/dL
   - Fresh frozen plasma: goal PT & aPTT < 1.5 x normal
   - Packed RBCs: goal Hb > 8 g/dL, or improvement in symptomatic anemia
4. Followed platelets, aPTT, PT, fibrinogen every 4~12 hours as clinically indicated
5. If persistent bleeding due to severe consumption, or consumption that requires blood product use, consider use of heparin
6. Follow laboratory parameters every 4~12 hours as clinically indicated until DIC resolves

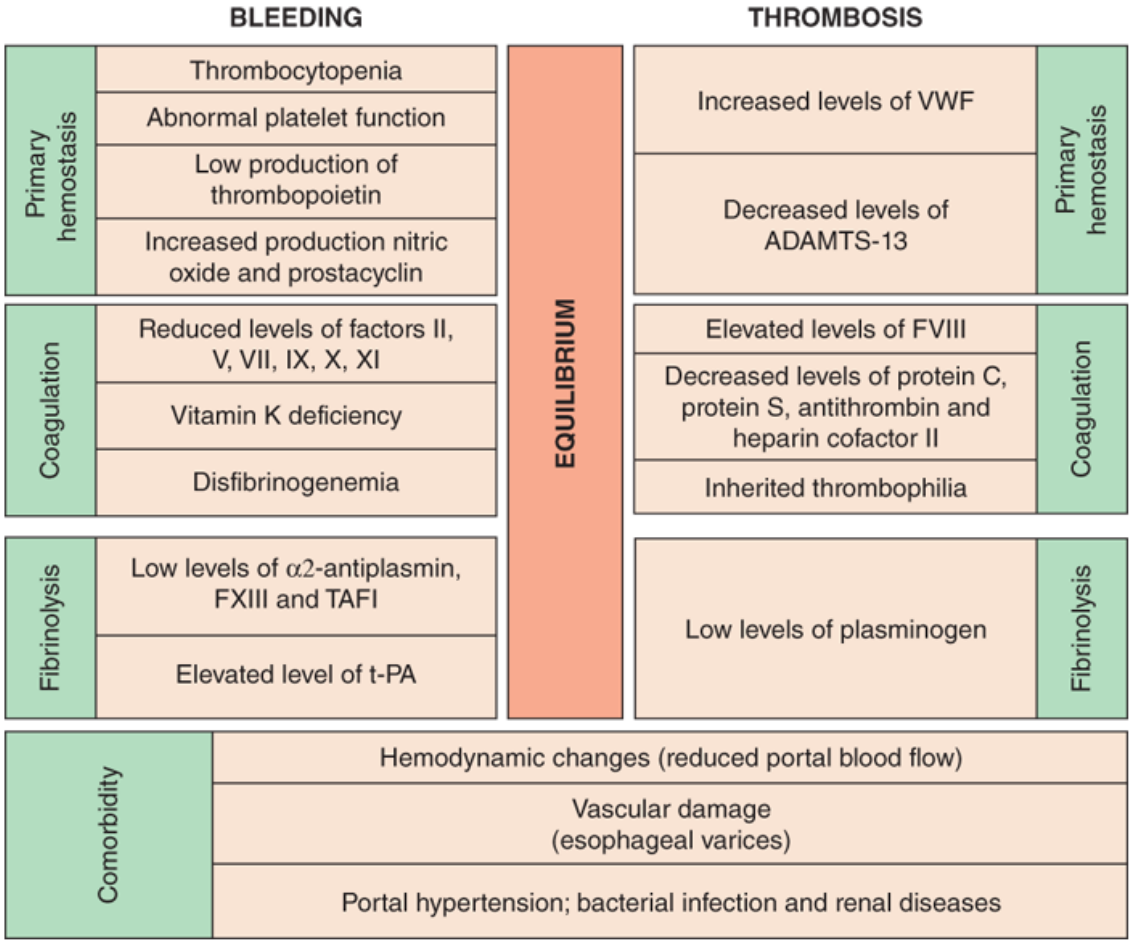
Vitamin K Deficiency

- Vitamin K-dependent proteins
  - A heterogenous group, including coagulation factor proteins (factor II, VII, IV, X, protein C & S)
- Causes of vitamin K deficiency
  - Decreased vitamin K diet intake
  - Decreased production of vitamin by gut flora (antibiotics)
  - Poor absorption: biliary obstruction..
  - Inhibition of vitamin K action: wafarin
- Treatment
  - Vitamin K (oral or parenteral), FFP

Liver Failure

- High risk of bleeding
  - Portal hypertension: esophageal varix
  - Thrombocytopenia: splenomegaly, DIC
  - Decreased synthesis of clotting factor: hepatocyte failure, vitamin K deficiency
  - Systemic fibrinolysis, DIC, disfibrinogemia
- High risk of thrombosis
  - Decreased synthesis of coagulation inhibitors (protein C &S, antithrombin): hepatocyte failure, vitamin K deficiency
  - Failure to clear activated coagulation protein (DIC)
  - Disfibrinogemia

Balance of Hemostasis in Liver Disease



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Acquired Inhibitors of Clotting Factors

- Autoantibody against a specific clotting factors
  - Immune-mediated disease
  - Against Factor VIII (most common), V, IX, X, XI
  - Soft tissue bleeding (common), hemarthrosis (rare)
- Causes of auto-antibody
  - Autoimmune disease, malignancy (lymphoma, prostate cancer), dermatology disease, and pregnancy
- Diagnosis
  - prolonged aPTT on mixing test, normal PT & TT
- No established guideline

Conclusions

- The hemostasis is a dynamic, highly interwoven array of multiple process
  - The platelet plug formation
  - Clotting cascades and propagation of the clot
  - Control mechanisms and termination of clotting
  - Clot dissolution and fibrinolysis
- Careful history taking and physical examination of patients with bleeding diathesis
- A stepwise approach to investigation are needed

A staged assessment to the diagnostic test of bleeding disorders