BLEEDING DISORDERS

Kenneth Alonso, MD, FACP

Clotting mechanism

- The clotting mechanism is a defense mechanism that limits the extension of injury to tissue. It is cell based.
- Tissue factor (CD 142) is a cell receptor for the serine protease, Factor VIIa.
- It is expressed by smooth muscle cells, fibroblasts, platelets, and leukocytes.
- Tissue factor is not expressed by endothelial cells unless damaged.
- Factor VIIa bound to tissue factor (TF) activates factors X and IX.

Clotting mechanism

- Factor Xa (activated by factor VIIa/TF) is assembled into a prothrombinase complex on the surface of the tissue factor bearing cell.
- This process generates a small amount of thrombin.
- After the initial generation of factor Xa on TF-bearing cells, subsequent factor Xa generation on TF-bearing cells is shut down when TF pathway (plasminogen) inhibitor (TFPI) reacts with factor Xa to inactivate the factor VIIa/TF complex.
- Autoregulatory
- TFPI produced by endothelial cells

Clotting mechanism

- The small amount of thrombin generated on the TF-bearing cell
- Activates platelets
- Releases factor V from alpha granules
- Activates factor V
- Activates factor VIII by releasing it from vWF
- Activates factor XI.
- The primary site of activity of factor IXa activated by factor VIIa/TF is on activated platelets in close proximity to the TF-bearing cell.

Clotting mechanism

- Clotting factors produced in liver
- BUT, vWF is produced by endothelial cells and megakaryocytes).
- Circulating vWF exists as multimers.
- VWF acts as a bridge between platelet surface glycoprotein receptors (GpIb) and exposed collagen.
- Promotes adhesion of platelets to the subendothelial matrix.
- This mediation is needed to overcome the high shear force of flowing blood.

Clotting mechanism

- Factor IXa can diffuse to adjacent cell surfaces because it is not inhibited by TFPI
- Is inhibited much more slowly by antithrombin-III (AT) than is factor Xa.
- Factor IXa moves to the primed platelet surface where it binds to factor VIIIa.
- Factor IXa activates factor X on the platelet surface.

Clotting mechanism

- Factor Xa then complexes to factor Va and activates prothrombin.
- Thrombin is generated and cleaves fibrinogen.
- Additional factor IXa is supplied by factor XIa on the platelet surface.

Clotting mechanism

- AT is the main inhibitor of thrombin.
- Also inhibits IXa, Xa, XIa, XIIa
- Enhanced by the presence of heparin
- Levels elevated in the presence of warfarin
- Other anti-thrombins include heparin co-factor-2, α_2-macroglobulin, and α_1-anti-trypsin.

Clotting mechanism

- Protein S enhances the interaction of factor Xa with TFPI in the presence of Calcium and phospholipids.
- Vitamin K dependent
- Formed in liver and endothelial cells
- 40% free
- Co-factor to activated Protein C in the inactivation of Factor Va and Factor VIIIa
- Reversibly inhbits Factor Va-Factor Xa complex
- 60% bound to C4b binding protein
- Inhibits complement pathway
- Upregulated with inflammation

Clotting mechanism

- Protein C is activated by thrombin
- Acts by inhibiting activated factors V and VIII with Protein S and phospholipids acting as cofactors
- Endothelial protein C receptor activates Protein C

Clotting mechanism

- Protein Z inhibitor (PZi) with Calcium inhibits Factor Xa
- Produced in liver
- Thrombomodulin is an endothelial cell receptor that binds to thrombin and prevents clot formation in the undamaged endothelium

Table 3

Nomenclature of the coagulation proteins/clotting factors

Clotting factor number	Clotting factor name	Function	Plasma half-life (h)	Plasma concentration (mg/L)
I	Fibrinogen	Clot formation	90	3000
II	Prothrombin	Activation of I, V, VII, VIII, XI, XIII, protein C, platelets	65	100
III	TF	Co factor of VIIa	-	-
IV	Calcium	Facilitates coagulation factor binding to phospholipids	-	-
V	Proacclerin, labile factor	Co-factor of X-prothrombinase complex	15	10
VI	Unassigned			
VII	Stable factor, proconvertin	Activates factors IX, X	5	0.5
VIII	Antihaemophilic factor A	Co-factor of IX-tenase complex	10	0.1
IX	Antihaemophilic factor B or Christmas factor	Activates X: Forms tenase complex with factor VIII	25	5
X	Stuart-Prower factor	Prothrombinase complex with factor V: Activates factor II	40	10
XI	Plasma thromboplastin antecedent	Activates factor IX	45	5
XII	Hageman factor	Activates factor XI, VII and prekallikrein		-
XIII	Fibrin-stabilising factor	Crosslinks fibrin	200	30
XIV	Prekallikerin (F Fletcher)	Serine protease zymogen	35	
XV	HMWK- (F Fitzgerald)	Co factor	150	
XVI	vWf	Binds to VIII, mediates platelet adhesion	12	10 μg/mL
XVII	Antithrombin III	Inhibits IIa, Xa, and other proteases	72	0.15-0.2 mg/mL
XVIII	Heparin cofactor II	Inhibits IIa	60	-
XIX	Protein C	Inactivates Va and VIIIa	0.4	-
XX	Protein S	Cofactor for activated protein C		-

HMWK – High molecular weight kininogen; vWf – Von Willebrand factor; TF – Tissue factor

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260295/

Table 4

Classification of coagulation factors

Fibrinogen family	Vitamin K dependent	Contact family
Fibrinogen	Factor II	Factor XI
Factor V	Factor VII	Factor XII
Factor VIII	Factor IX	HMWK
Factor XIIII	Factor X	Prekallikerin

HMWK – High molecular weight kininogen

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260295/

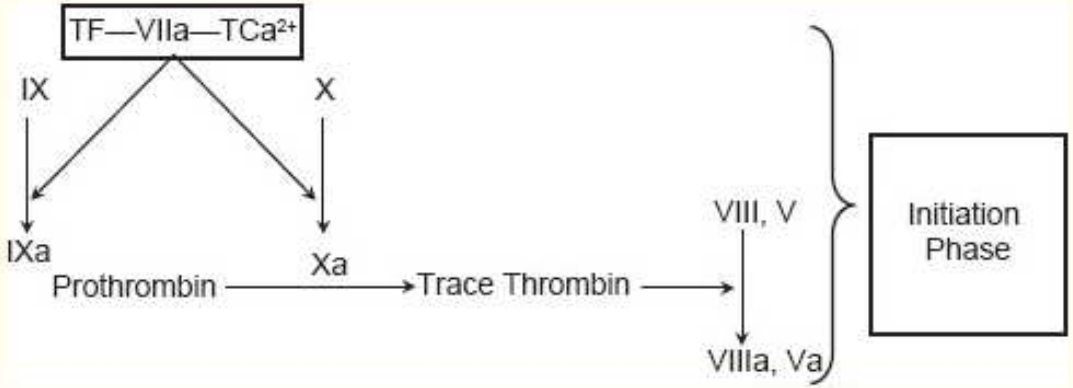

Figure 2

Current concept of coagulation (initiation phase)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260295/

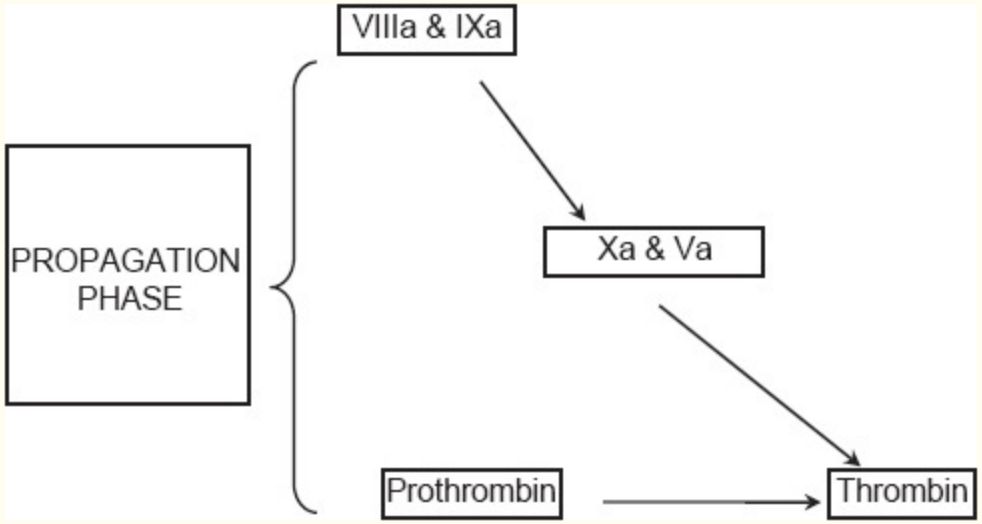

Figure 3

Current concepts of coagulation (propagation phase)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260295/

Cell based model of hemostasis

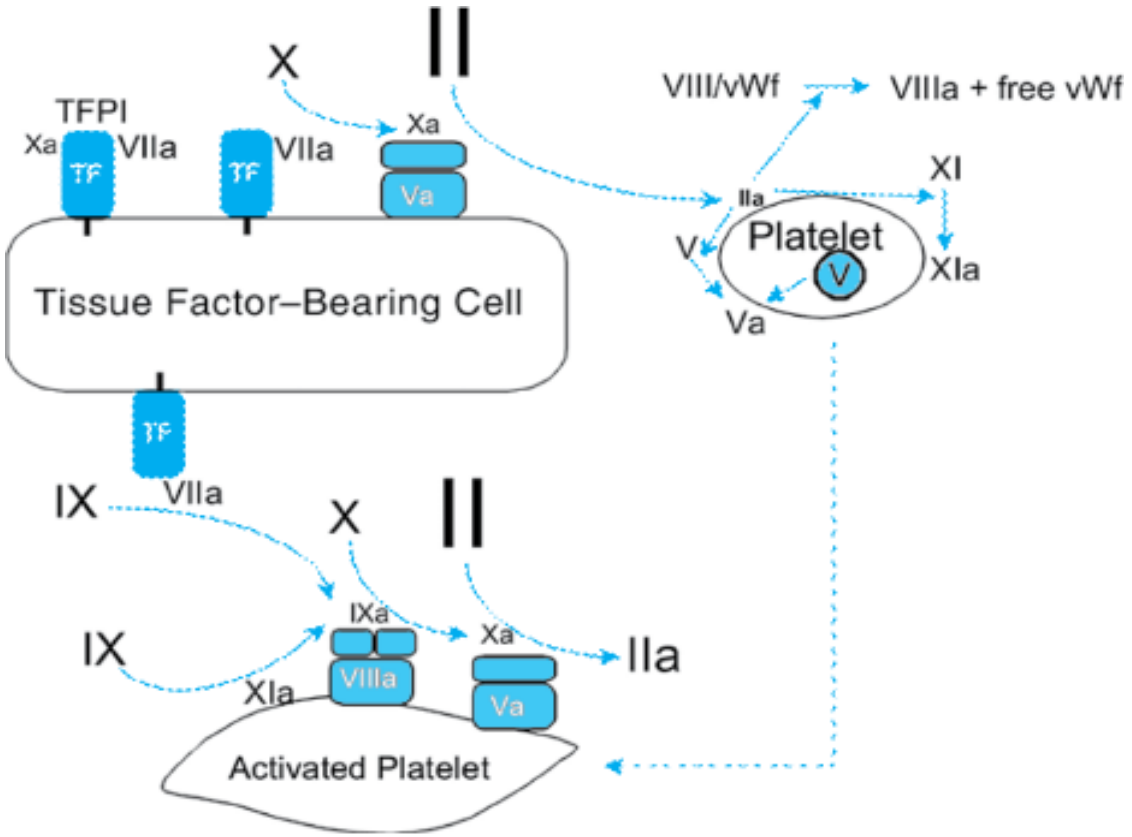

Fig 106-31
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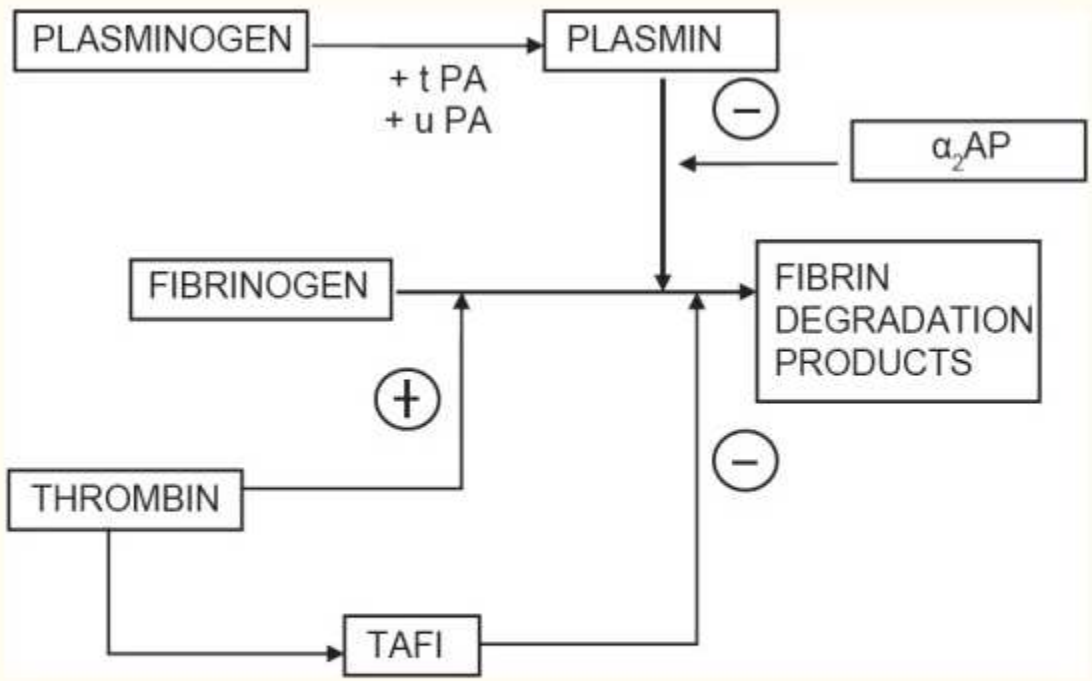


Figure 4

Regulation of the fibrinolytic system

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260295/

Endothelial cell function.

- Activated coagulation proteins generated on platelets localized to the site of an injury must be confined to the site of injury.
- Nitric oxide and prostacyclin generated by endothelial cells impede platelet aggregation.
- Vasodilators.
- ADPase generated by endothelial cells enhances platelet disaggregation.
- Activated coagulation factors that move to an endothelial cell surface are rapidly inhibited by antithrombin (AT III) associated with heparin-like glycosaminoglycans (GAG) on the endothelial surface.

Endothelial cell function.

- Thrombin that reaches the endothelial cell surface binds to thrombomodulin (TM).
- Once bound, thrombin can no longer cleave fibrinogen.
- Instead, thrombin activates protein C and endothelium produced protein S, leading to the formation of activated protein C (APC)/protein S (PS) complexes on the endothelial cell surface.
- APC/PS on the endothelial cell surface inactivates factors Va and VIIIa.

Endothelial cell function.

- Endothelium also produces and tissue factor pathway inhibitor and inactivates factors VIIa and Xa.
- Endothelium also produces the serine protease tissue-type plasminogen activator (t-PA).
- Plasminogen cleaves to form plasmin.
- Plasmin cleaves fibrin to degrade thrombin.
- However, endothelial cells also secrete inhibitors of plasminogen activators that limit fibrinolysis.
- Thrombosis is favored with endothelial cell injury.

Endothelial cell function

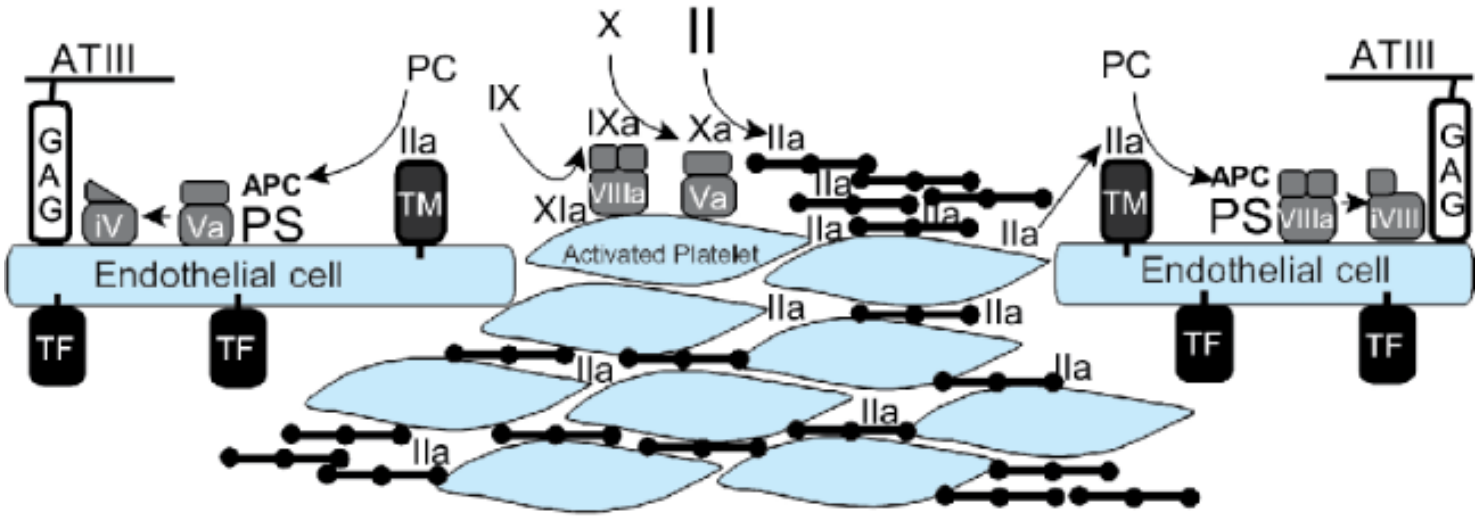


Fig 106-32 Accessed 03/02/2010

Platelet function

- Platelet α granules
- Have P-selectin on their membranes
- Contain:
- Fibrinogen
- Fibrinonectin
- Factor V
- Factor VIII
- Platelet factor 4 (heparin binding)
- Platelet derived growth factor (PDGF
- Transfroming growth factor (TGF-β).

Platelet function

- Platelet adhesion to extracellular matrix underlying endothelium is mediated through endothelium produced von Willebrand factor (VWF).
- VWF acts as a bridge between platelet surface glycoprotein receptors (GpIb) and exposed collagen.
- This mediation is needed to overcome the high shear force of flowing blood.

Platelet function

- Platelets can also adhere to the extracellular matrix through interactions with fibronectin.
- Platelet dense (δ) granules degranulate, releasing Ca^{2+} and ADP, amplifying the aggregation process.
- ADP induces platelet conformational change.
- Fibrinogen bridges GpIIa-IIIa receptors, leading to aggregation.
- Phosphatidylserine (negatively charged) on the platelet surface serves as a Ca^{2+} binding site and nucleus for assembly of coagulation complexes.

Platelet function

- Thrombin stabilizes the platelet plug by binding to a protease activated receptor on the platelet membrane
- In concert with thromboxane (TxA_2), derived from platelets, and ADP, leads to further aggregation and platelet contraction.
- Fibrin split products are also generated as thrombin cleaves fibrinogen.

Preoperative coagulation tests

- Screening preoperative coagulation tests
- For patients with Class I or II physical status
- Only in the presence of
- Hepatic disease
- Renal disease
- Inter-current use of anticoagulants.

Bleeding disorders

- Vascular disorders

  Congenital

  Osler-Weber-Rendu syndrome

  Ehlers-Danlos syndrome

  Osteogenesis imperfecta

  Cavernous hemangioma

  Acquired

  Scurvy

  Immunoglobulin disorders

  Glucocorticoid excess

  Amyloid angiopathy

Bleeding disorders

- Platelet disorders
  - Splenic sequestration (with splenomegaly)
  - Decreased production
  - Decreased survival
    - Immune related (ITP)
    - Non-immune related (TTP, HUS)

Thrombocytopenia

- By definition, a platelet count <100,000/fl
- Platelet counts between 10-50,000/fl may aggravate post-traumatic bleeding
- Platelet counts <10,000/fl may be associated with spontaneous hemorrhage, particularly if patient is on chemotherapy

Table 14-9 Causes of Thrombocytopenia

Decreased Production of Platelets
Selective impairment of platelet production
Drug-induced: alcohol, thiazides, cytotoxic drugs
Infections: measles, human immunodeficiency virus (HIV)
Nutritional deficiencies
B_{12}, folate deficiency (megaloblastic leukemia)
Bone marrow failure
Aplastic anemia (see Table 14-7)
Bone marrow replacement
Leukemia, disseminated cancer, granulomatous disease
Ineffective hematopoiesis
Myelodysplastic syndromes (Chapter 13)
Decreased Platelet Survival
Immunologic destruction
Primary autoimmune
Chronic immune thrombocytopenic purpura
Acute immune thrombocytopenic purpura
Secondary autoimmune
Systemic lupus erythematosus, B-cell lymphoid neoplasms
Alloimmune: posttransfusion and neonatal
Drug-associated: quinidine, heparin, sulfa compounds
Infections: HIV, infectious mononucleosis (transient, mild), dengue fever
Nonimmunologic destruction
Disseminated intravascular coagulation
Thrombotic microangiopathies
Giant hemangiomas
Sequestration
Hypersplenism
Dilution
Transfusions

Thrombocytopenia

- Common agents that affect glycoproteins:
- Quinine or quinidine
- Vancomycin
- Mitomycin
- Platelet-inhibitory drugs
- Antibodies to heparin and platelet factor 4 complex
- Activates platelets
- Heparin (Type II thrombocytopenia)
- Begins shortly after heparin exposure
- Associated with venous and arterial thrombosis
- Type I thrombocytopenia is due to platelet aggregation by heparin and poses no long-term hazard

Thrombocytopenia

- A complication of the post partum period
- Antiphospholipid syndrome.
- HIV related
- CD4 and CXCR4 are found on megakaryocytes
- Infected cells prone to apoptosis
- Glycoprotein antibodies also found
- Increases splenic clearance

Immune thrombocytopenic purpura

- Acute
- Childhood
- Generally follow viral infection
- Self-limited.
- Petechiae, may become confluent
- Chronic
- Women 3:1
- <40 years of age
- History of easy bruising or nosebleeds
- Melena or menorrhagia may be initial presentation

Immune thrombocytopenic purpura

- Pathogenesis
- Antibodies to glycoproteins Ib-IIIa or Ib-IXa.
- Act as opsonins, leading to splenic clearing
- Histopathology
- That of accelerated thrombopoiesis
- Peripheral blood demonstrates the presence of large platelets (macrothrombocytes)
- The bone marrow contains increased numbers of megakaryocytes, many of which are immature
- Therapy
- Glucocorticoids given if very low platelet counts.
- Splenectomy if platelet counts do not recover.

Table 14-10 Thrombotic Microangiopathies: Causes and Associations

Thrombotic Thrombocytopenic Purpura
Deficiency of ADAMTS13
Inherited Acquired (autoantibodies)
Hemolytic Uremic Syndrome
Typical: *Escherichia coli* strain O157:H7 infection
Endothelial damage by Shiga-like toxin
Atypical: alternative complement pathway inhibitor deficiencies
(complement factor H, membrane cofactor protein (CD46), or factor I) Inherited Acquired (autoantibodies)
Miscellaneous associations
Drugs (cyclosporine, chemotherapeutic agents) Radiation, bone marrow transplantation Other infections (HIV, pneumococcal sepsis) Conditions associated with autoimmunity (systemic lupus erythematosus, HIV infection, lymphoid neoplasms)

HIV, Human immunodeficiency virus.

Thrombotic microangiopathies

- Thrombotic thrombocytopenic purpura (TTP)
- Petechiae
- Neurologic involvement prominent
- Non-immune related decreased platelet survival as a result of platelet activation and aggregation.
- Deficient vWF metalloprotease (ADAMTS13)
- permits accumulation of vWF multimers and platelet aggregation.

Thrombotic microangiopathies

- Typical (classical) hemolytic uremic syndrome (HUS)
- Acute bleeding with oliguria, hematuria, thrombocytopenia and microangiopathic hemolytic anemia.
- May have neurologic symptoms.
- E. coli O157:H7 strain related gastroenteritis
- Shiga-like toxin induced endothelial injury
- Increased expression of leukocyte adhesion molecules on epithelial cells and direct binding and activation of platelets.
- Endothelin and TNF-α production as well as diminished NO production induce vasoconstriction.

Thrombotic microangiopathies

- Atypical hemolytic uremic syndrome
- Thrombocytopenia with microangiopathic hemolytic anemia.
- May have neurologic symptoms.
- Uncontrolled complement activation in those with defects in complement factor H (fails to break down C3 convertase).
- A small percentage of patients lack membrane cofactor protein CD46, or complement factor I.

Thrombotic microangiopathies

- Often skin biopsy needed to differentiate.
- TTP responds to plasma exchange.
- Typical HUS ameliorates with treatment of underlying disorder, though progression to chronic renal disease common.
- Atypical HUS has worse prognosis.

Bleeding disorders

- Dilutional disorders

  Type 2B von Willebrand's disease

  Qualitative platelet disorders

  Autosomal recessive

    Bernard-Soulier syndrome

    May present as in von Willebrand's.

    Giant platelets

    Deficiency in the glycoprotein complex Ib-IX (von Willebrand receptor)

      Poor response to ristocetin.

Bleeding disorders

- Glanzmann syndrome
- Mucosal bleeding

  Uremia

  Dysfunction of glycoprotein Iib-IIIa, an integrin that binds fibrinogen and bridges platelets

  Poor response to fibrinogen

  Anti-platelet medications such as NSAIDs aggravate

Anti-platelet agents

- Bleeding is the major complication of anti-platelet agent use.
- Aspirin irreversibly inhibits cyclo-oxygenase.
- Conversion of arachidonic acid to prostaglandins and to thromboxane 2 is blocked.
- Platelet aggregation decreases.
- Clopidogrel and ticlopidine irreversibly block ADP receptors on platelet membranes
- Inhibit platelet aggregation
- Ticlopidine can cause neutropenia.

Anti-platelet agents

- Dipyramidole blocks intra-platelet phosphodiesterase
- Increases cAMP
- Inhibiting adenosine uptake by the platelet.
- Platelet aggregation decreases.
- Abciximab binds to the glycoprotein Iib/Iia receptor on platelets and prevents their interaction with fibrinogen.
- Platelet aggregation decreases.

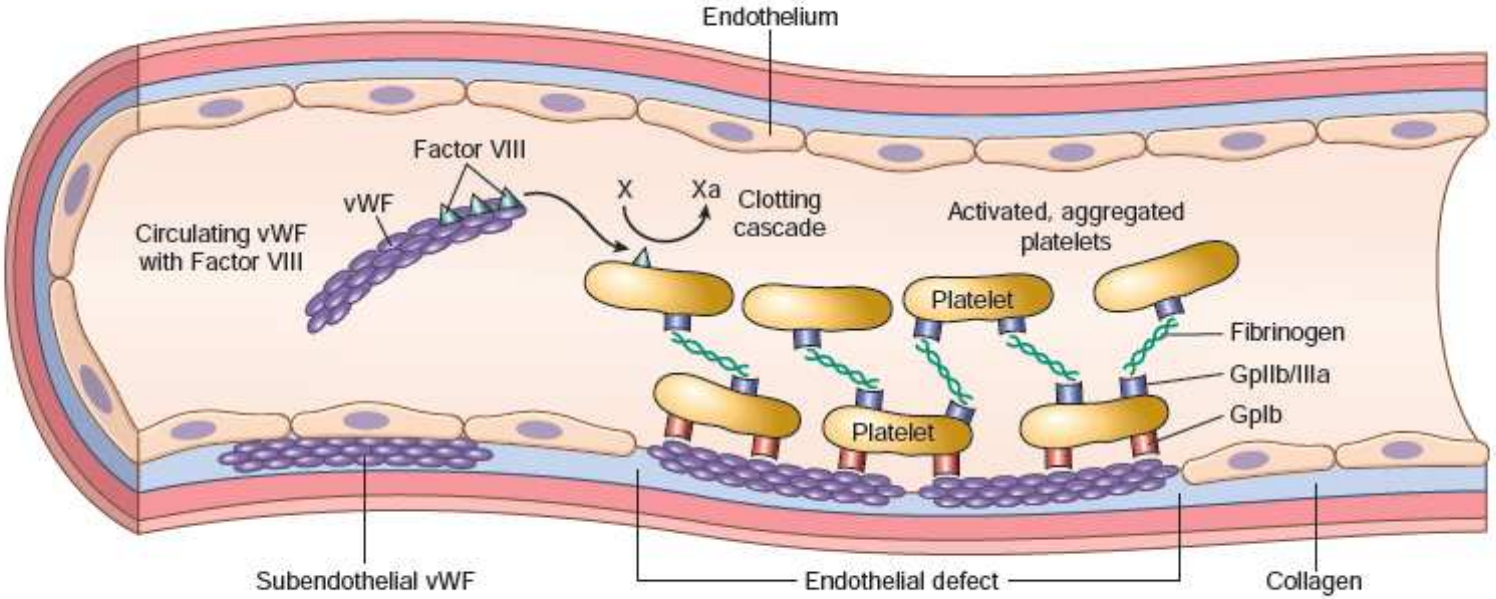


Figure 14-26 Structure and function of factor VIII-von Willebrand factor (vWF) complex. Factor VIII is synthesized in the liver and kidney, and vWF is made in endothelial cells and megakaryocytes. The two associate to form a complex in the circulation. vWF is also present in the subendothelial matrix of normal blood vessels and the α-granules of platelets. Following endothelial injury, exposure of subendothelial vWF causes adhesion of platelets, primarily via the glycoprotein Ib (GpIb) platelet receptor. Circulating vWF and vWF released from the α-granules of activated platelets can bind exposed subendothelial matrix, further contributing to platelet adhesion and activation. Activated platelets form hemostatic aggregates; fibrinogen participates in aggregation through bridging interactions with the glycoprotein IIb/IIIa (GpIIb/IIIa) platelet receptor. Factor VIII takes part in the coagulation cascade as a cofactor in the activation of factor X on the surface of activated platelets.

Bleeding disorders

- Coagulation disorders

  Hereditary

  Afibrinogenemia

  Manifest as subcutaneous or umbilical hematoma at birth

  Dysfibrongenemia

  Factor II deficiency

  Factor VII deficiency

  Hemophilia A (VIII), B (IX), or C (XI)

  Factor XIII deficiency

  von Willebrand's disease

Hemophilia

- Lifelong recurrent bleeding into soft tissues, muscles, weight bearing joints, and closed spaces.
- Hemophilia A
- Deficiency of Factor VIII
- Factor VIII is co-factor for Factor IX to activate Factor X
- 40% of cases of hemophilia A are severe and associated with inversion of intron 22 in the factor VIII gene at Xq28
- Occasionally in women (unfavorable lyonization)
- 30% have no family history of same

Hemophilia

- Hemophilia B
- Christmas disease
- Deficiency of Factor IX
- Factor IX with Factor VIII as cofactor activates Factor X
- F9 gene at Xq27.1
- Occasionally in women (unfavorable lyonization)
- Some mutations associated with sensitivity to warfarin
- Mutations near the beginning of the gene sequence cause Hemophilia B Leyden
- Factor IX production normalizes during puberty

Hemophilia

- Hemophilia C
- PTA deficiency
- Rosenthal syndrome
- Factor XI deficiency
- Factor XI activates Factor IX
- F11 gene at 4q35.2
- Severity related to involvement of both alleles

Thrombin generation

- Thrombin generated early in coagulation converts Factor XI to Factor XIa, which sustains thrombin production through Factor IX activation.
- Factor XI activation during thrombin generation does not require Factor XIIa.
- In the kallikrein-kinin system, artificial or abnormal surfaces facilitate Factor XII autoactivation.

Thrombin generation

- Factor XIIa converts prekallikrein to α-kallikrein, which activates additional FXII and cleaves high molecular–weight kininogen, liberating bradykinin
- Promotes thrombin generation through Factor XIIa-mediated activation of Factor XI.
- Factor XIa, in turn, can activate Factor XII.
- In plasma, prekallikrein and Factor XI circulate as complexes with high molecular weight kininogen, which may serve as a cofactor for prekallikrein and Factor XI activation.

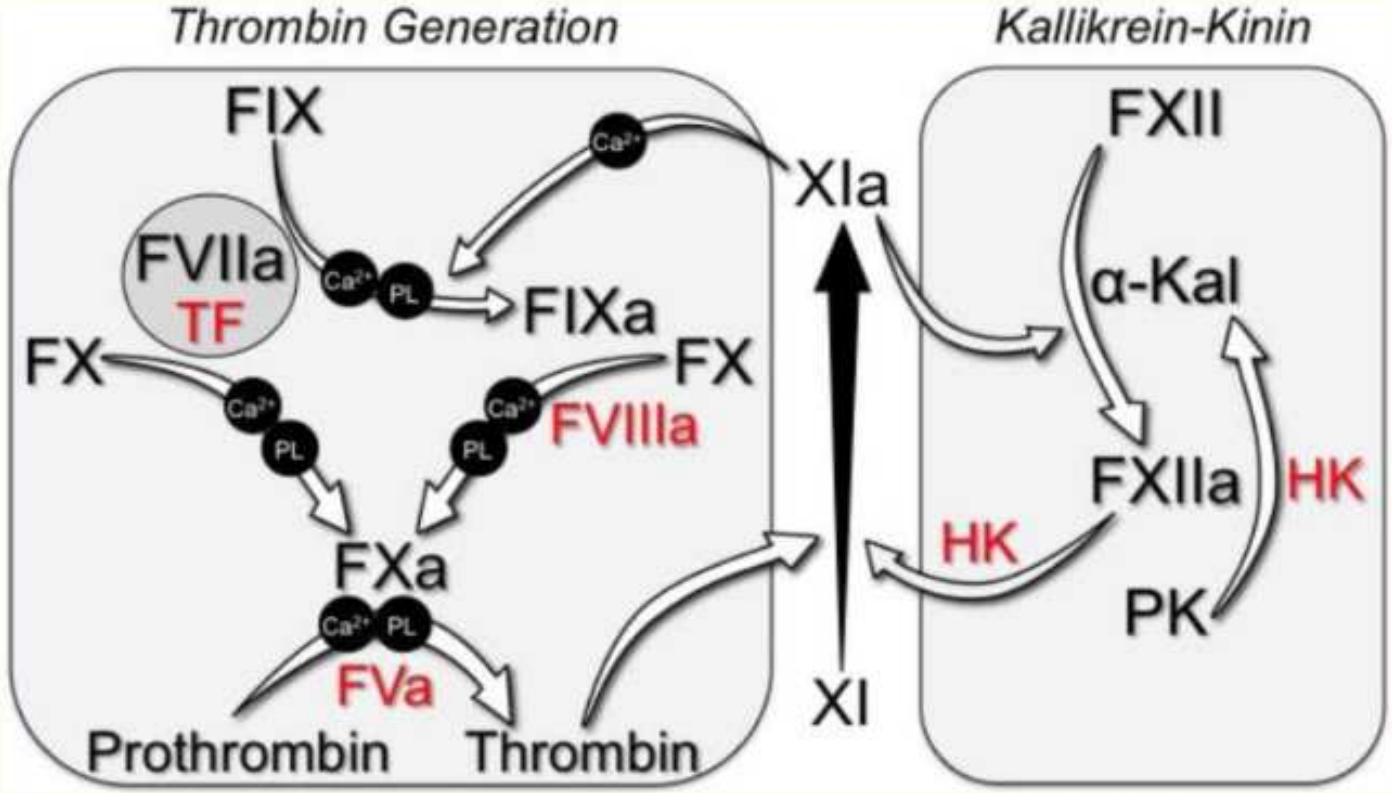


Figure 1

Factor XI, thrombin generation, and the kallikrein-kinin system (KKS)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5776729/

Von Willebrand's disease

- Most common inherited bleeding disorder
- 1% of adults
- Presents with bleeding following a cut, tooth extraction, surgery, or with epistaxis or menorrhagia.
- VWF gene at 12p13.31
- Type I
- 70% of cases
- Autosomal dominant
- Mutations interfere with maturation of vWF or with plasma clearance

Von Willebrand's disease

- Type 2A
- 25% of cases
- Autosomal dominant
- Missense mutations lead to decreased platelet dependent function associated with the absence of intermediate and high molecular weight multimers
- Type 2B
- 5% of cases
- Autosomal dominant
- Increased affinity for Gpib
- Spontaneous binding of high molecular weight VWF multimers to platelets leading to rapid clearance of both from plasma

Von Willebrand's disease

- Type 2M
- Autosomal dominant
- Decreased affinity for platelets and subendothelium not associated with the absence of high molecular weight mutimers
- Type 2N
- Autosomal recessive
- Decreased affinity of vWF for Factor VIII
- Type III
- Autosomal recessive
- Frameshift mutations in both alleles
- Very low levels of vWF
- Presents in neonatal period or in infancy

Test	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3
VWF:Ag	↓	N or ↓	N or ↓	N or ↓	N	0
VWF:RCo	↓	↓↓↓	↓ ou ↓↓	↓↓	N	0
Agglut. high dose low dose	 N or ↓ 0	 ↓↓↓ 0	 N ++	 decreased 0	 N 0	 0 0
F VIII	N or ↓	N or ↓	N or ↓	N or ↓	↓↓	↓↓↓
Multimers	N	IMW & HMW absent	HMW absent	N or ↓	N	0
VWF:CB	↓	↓↓	↓↓	N or ↓	N	0

https://www.stago-us.com/uploads/pics/von-Willebrand-EN_03.jpg

Bleeding disorders

- Coagulation disorders

  Acquired

  Fibrinolysis

  Diffuse intravascular coagulation

  Anticoagulants

  Vitamin K deficiency
- Mixed disorder

  Uremia

  Liver failure

  Hypothermia (<35C, platelet dysfunction; <33C, decreased synthesis of all factors)

Diagnostic approach

- The history and physical exam should focus on identifying the following common causes:

  Liver disease, splenomegaly, uremia

  Anticoagulation, chemotherapy administration

  Recent procedure (surgery, biopsy) that would be a source of bleeding

- Common reasons for initiating a bleeding disorder work-up

  History indicative of more bleeding than expected for a hemostatic challenge

  Spontaneous bleeding

Diagnostic clues

- Epistaxis in the absence of thrombocyopenia suggests von Willebrand's disease.
- (Menorrhagia may also be noted in women.)
- The presence of asymptomatic petechiae in a lower (dependent) limb suggests thrombocytopenia.
- However, palpable petechiae or purpura, whether symptomatic or not, suggest a vasculitis.
- Extensive superficial purpura suggest a plasma coagulation disorder.
- A vascular defect must always be considered in the case of superficial bleeding.

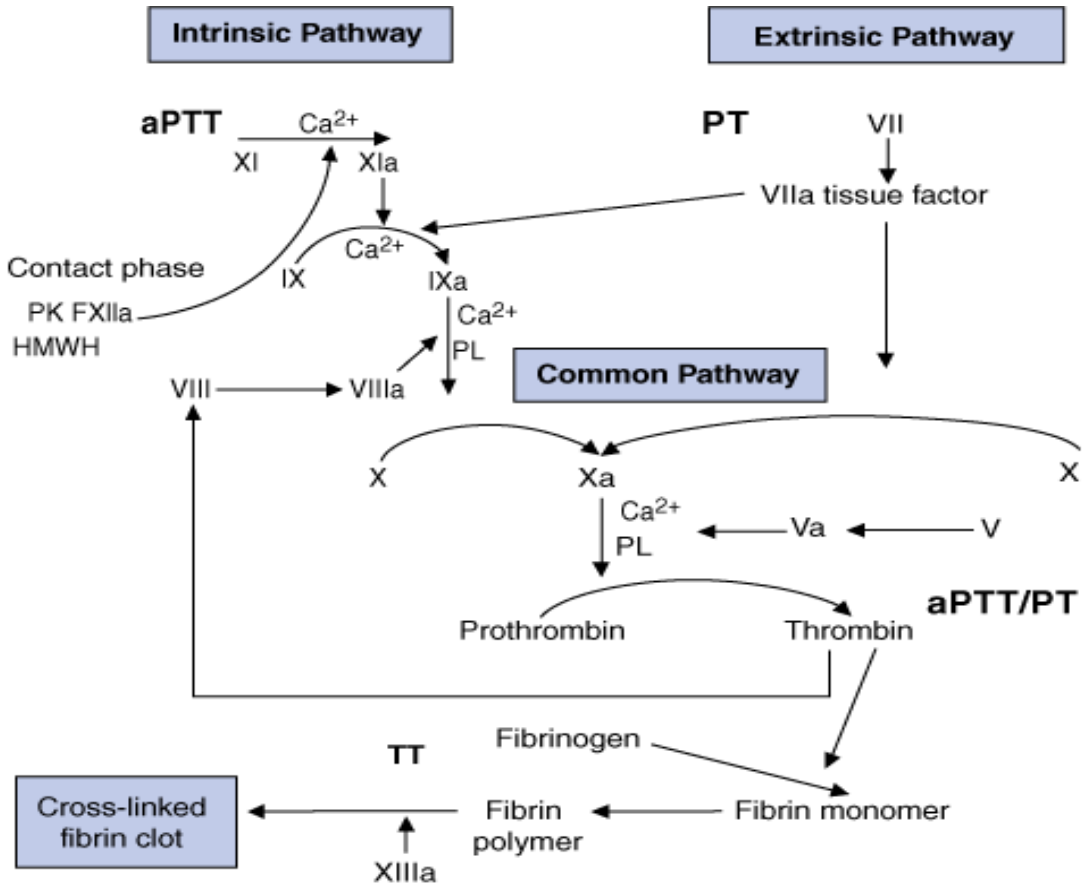
Diagnostic clues

- Recurrent oozing from a surgical site or cut, or deep hematoma formation suggest a plasma coagulation disorder.
- Delayed oozing from a surgical site or cut suggests a Factor XIII deficiency.
- Hemarthrosis is classically associated with the hemophilias.
- Bleeding from any site or in the CNS may reflect a coagulation disorder, though that too is not likely in the absence of other history or signs.
- Coagulopathy is common in severe liver disease.
- Splenomegaly is often associated with platelet sequestration.

Coagulation tests

- The Bleeding Time is a sensitive screening test for platelet dysfunction in presence of normal platelet count.
- Prothrombin, Partial Thromboplastin, and Thrombin Times will be abnormal if fibrinogen levels are low (<100 mg/dl).
- Factor XIII levels of 5% are needed for normal clot retraction.

Clotting cascade



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Fig. 110-1 Accessed 03/01/2010

Prothrombin time

- Prothrombin time measures vitamin K dependent procoagulants II, V, VII, X.
- Levels above 20% are needed for a normal result.
- Factor VII has shortest half-life of procoagulants (3-5 hours)
- Warfarin interferes with vitamin K.
- Heparin does not interfere with assay.
- ISI permits comparison of prothrombin times obtained with various reagent sources.
- The INR is only used to reflect changes in the prothrombin time secondary to anticoagulation

Partial thromboplastin time

- Partial Thromboplastin time measures procoagulants VIII, IX, X.
- Levels above 40% are needed for a normal result.
- If ellagic acid is not used for activation, a prolonged Partial Thromboplastin time may reflect Factor XI deficiency.
- Factor X sensitive to Heparin.

Procoagulant assays

- Patient plasma is mixed 1:1 with normal plasma. The appropriate assay (PT, PTT) is performed.
- If the coagulation time does not correct, an inhibitor (antibody) is present.
- To determine inhibitor in patient plasma
- Patient plasma is mixed in varying proportions with normal.
- The appropriate assay (PT, PTT) is performed.
- Calculate the concentration of the inhibitor

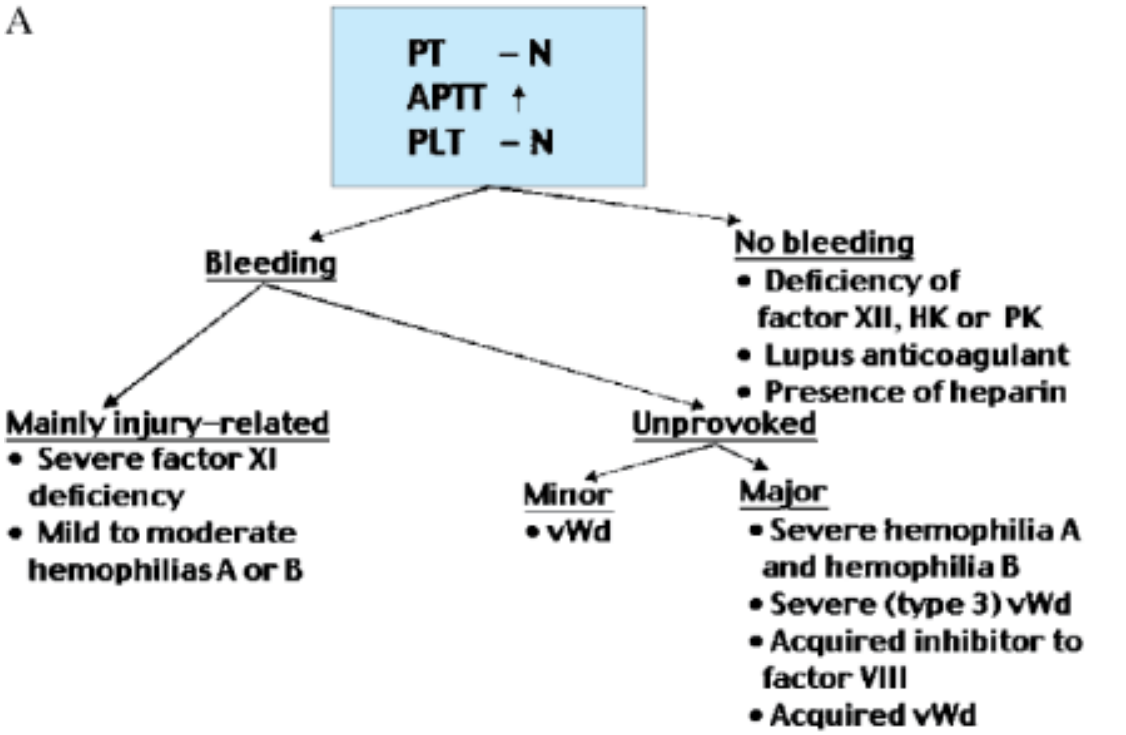
Platelet screen

- Elevated bleeding time
- Normal platelet count
- Aspirin or NSAIDs
- Synthetic penicillins
- If there are skin changes, a biopsy may be needed to distinguish a vascular from a platelet disorder.
- The PTT may be elevated in Factor VIII deficiency (though not necessarily so in von Willibrand's disease).
- Check Factor VIIIc, VWF, and ristocetin co-factor activity (platelet function).

Platelet screen

- Elevated platelet count
- Thrombocythemia with secondary platelet dysfunction
- Low platelet count
- AND platelets are of normal size
- Heparin
- Quinine use
- Splenomegaly with platelet sequestration
- ITP
- TTP (anemia, schistocytes, elevated LDH)
- Bone marrow failure
- DIC (schistocytes).

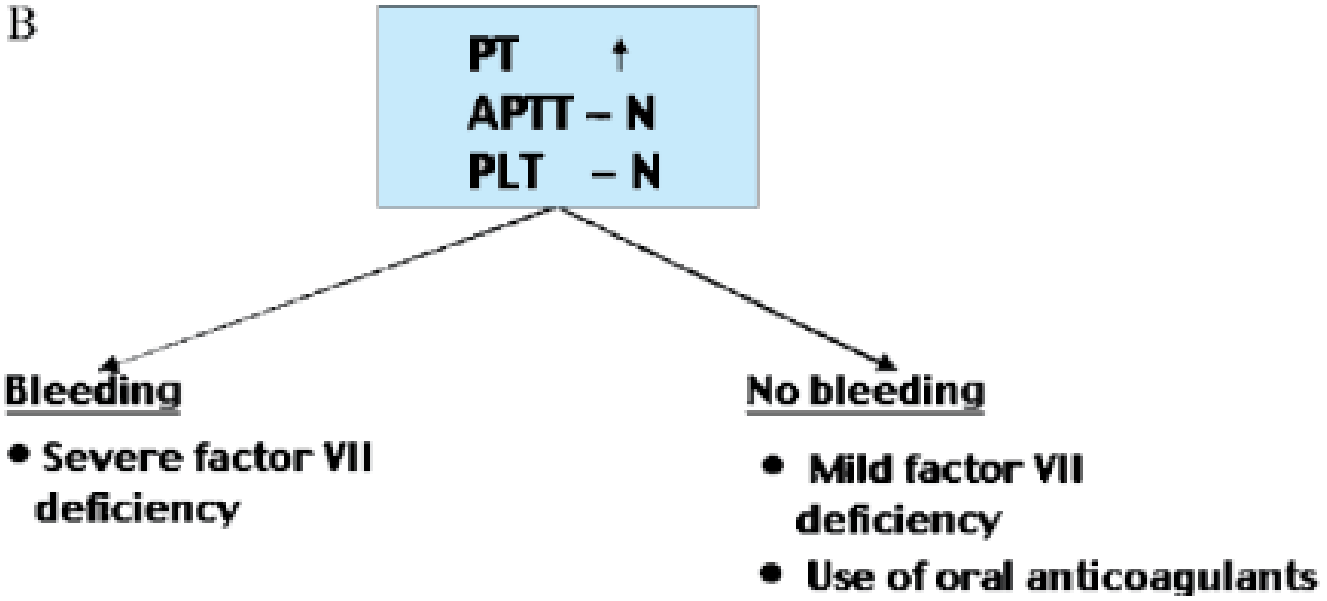
Differential diagnosis



Source: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology*, 7th Edition: http://www.accessmedicine.com

Fig. 109-1 Accessed 03/02/2010

Differential diagnosis



Source: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology*, 7th Edition: http://www.accessmedicine.com

Fig. 109-1 Accessed 03/02/2010

Differential diagnosis

C

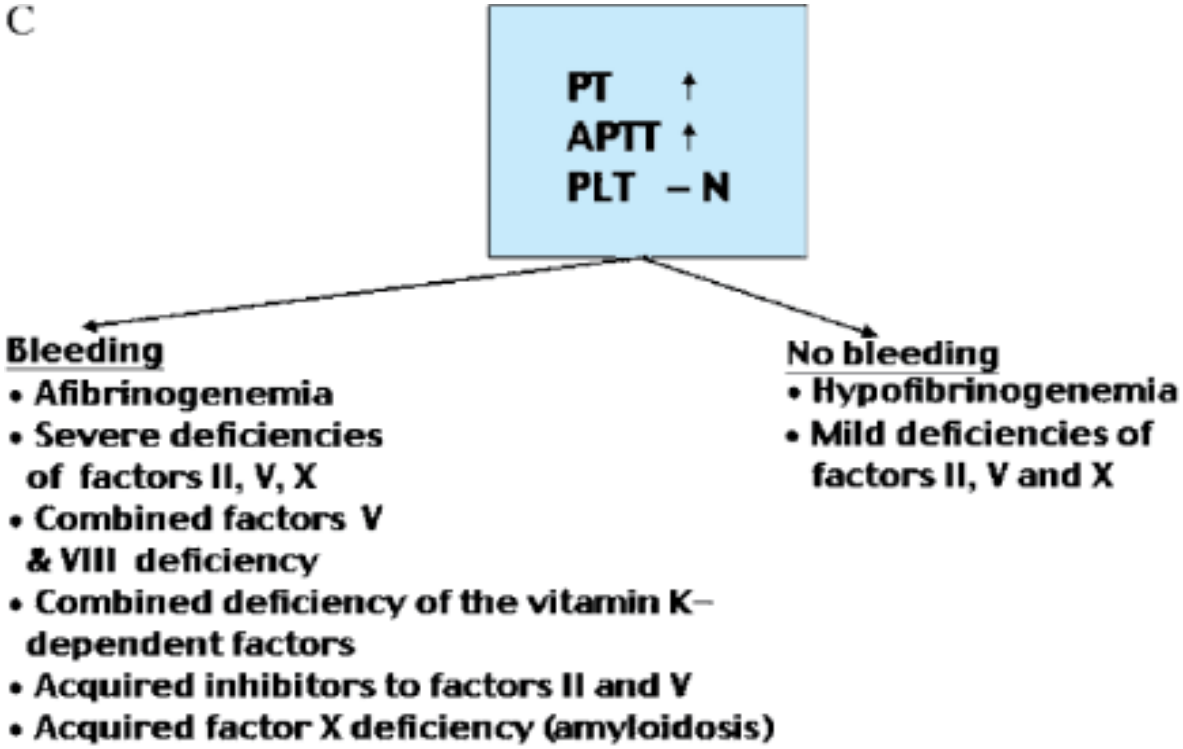


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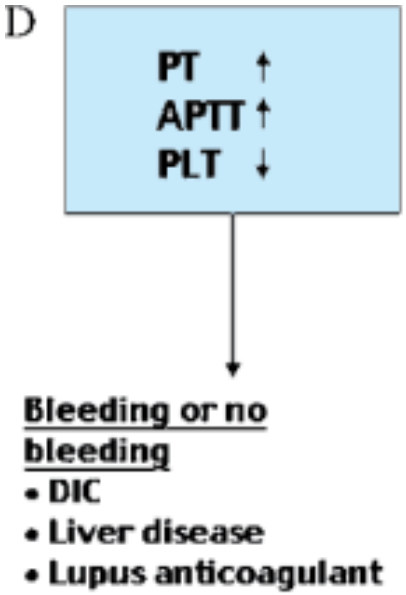
Fig. 109-1 Accessed 03/02/2010

Differential diagnosis



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Differential diagnosis

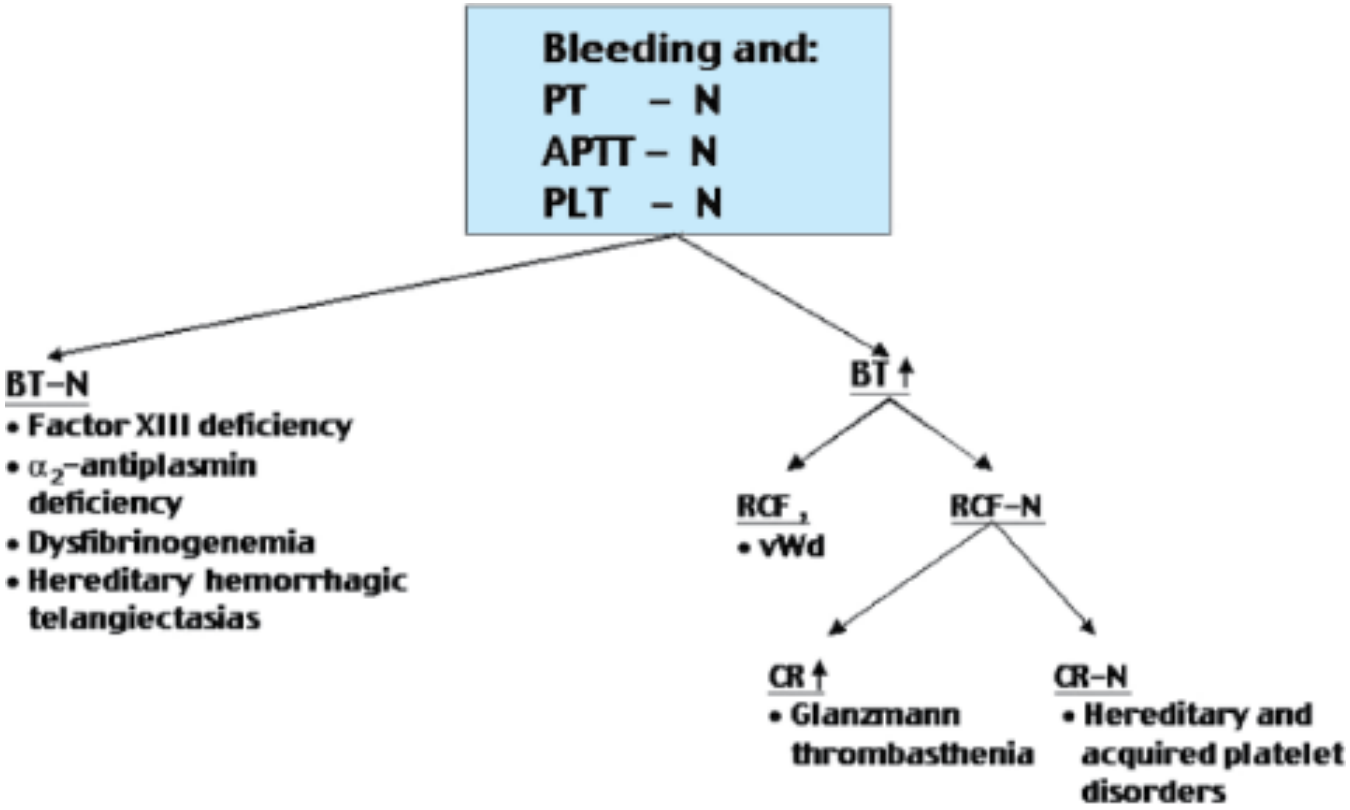

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Fig. 109-1 Accessed 03/02/2010

Platelet aggregation studies

- Abnormal aggregation with adenosine diphosphate or epinephrine
  - Arachidonic acid metabolism (COX inhibition)
  - Storage pool disease
- Abnormal aggregation with collagen (fibrinogen binding)
  - Glanzmann thrombasthenia
- Abnormal aggregation with ristocetin
  - von Willebrand disease
  - Bernard-Soulier syndrome (giant platelets)

Other coagulation tests

- All tests that measure time to clot formation require normal levels of fibrinogen.
- Reptilase time (RT)
- Snake venom that converts fibrinogen to fibrin

  Used to determine if prolonged TT is caused by heparin or a fibrinogen dysfunction or deficiency

  If both TT and RT are prolonged

  Either a quantitative or qualitative deficiency of fibrinogen

  May be acquired or congenital.

  If TT is prolonged but RT is normal

  Heparin.

Therapy of bleeding disorders.

- Fresh frozen plasma is used to correct bleeding problems due to excess of:
- Warfarin
- Vitamin K deficiency
- Liver failure
- Factor XI deficiency
- Replacement of coagulation factors lost following massive transfusion.

Therapy of bleeding disorders.

- Cryoprecipitate is used in the treatment of deficiency of:
- von Willebrand factor
- Factor XIII
- Fibrinogen.
- Recombinant factor VIII or IX are preferred for treatment of hemophilia.
- Tranexamic acid, a plasminogen activator inhibitor, may also be employed to limit acute bleeding in hemophilia.

Therapy of bleeding disorders.

- Mild hemophilia as well as von Willebrand's Disease respond to intranasal desmopressin

- Hemophilia prophylaxis seeks to maintain factor levels in the 3-5% range.
- Treat all bleeds early.
- <u>After 1-3 years of factor therapy, inhibitors develop</u>

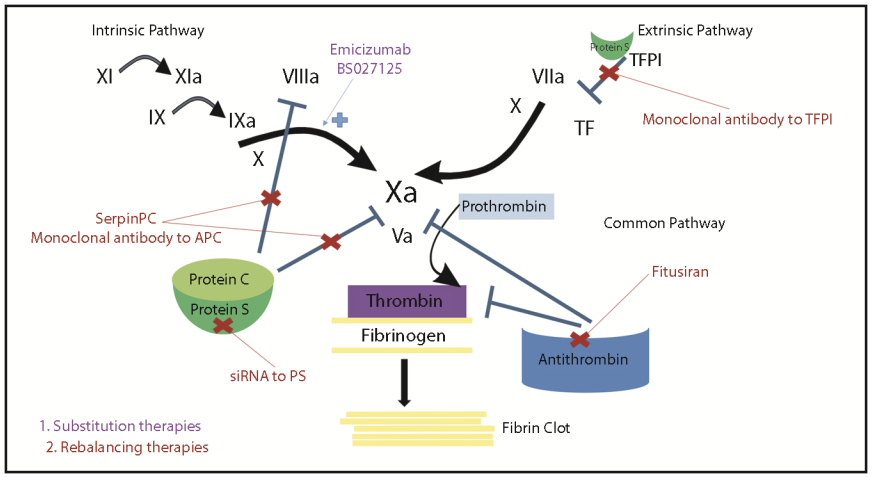
Therapy of severe hemophilia

- Concisumab is an anti-Tissue Factor Inhibitor (TFPI) antibody that binds to the Kunitz-2 domain of TFPI
- Blocks downregulation of coagulation by preventing TFPI from binding to and blocking the factor Xa active site
- Subcutaneous route
- Emicizumab mimics Factor VIII
- Subcutaneous route
- Fitusiran is a small interfering RNA that binds Anti-Thrombin III messenger RNA in the liver, blocking translation and synthesis
- Subcutaneous route
- Effective in those with or without inhibitors

Therapy of severe hemophilia

- SerpinPC is a serine protease that inhibits Activated Protein C (APC), prolonging the activity of prothrombinase, promoting clot formation
- Subcutaneous route
- Emicizumab mimics Factor VIII
- Subcutaneous route
- Fitusiran is a small interfering RNA that binds Anti-Thrombin III messenger RNA in the liver, blocking translation and synthesis
- Subcutaneous route
- Effective in those with or without inhibitors

New therapies for hemophilia



Angela C. Weyand,Steven W. Pipe, New therapies for hemophilia, Blood, 2019, Figure 3.

Therapy of bleeding disorders.

- Platelets are administered to maintain counts >50,000/ul if invasive surgery is planned.
- Spontaneous bleeding unusual if counts >10,000/ul.
- Tranexamic acid is administered empirically in those trauma patients at risk for hemorrhage.

Factor	Name	Function
I	Fibrinogen	Bridges platelets by binding to GpIIB/IIIA surface receptors 90 hour half-life
II	Prothrombin	Activates Factors I, V, VII, VIII, IX, X, Protein C, and platelets 65 hour half-life Vitamin K dependent Calcium activated
III	Thromboplastin (Tissue factor)	Cofactor VIIa
	Thrombin	Activated by Factor Xa Converts Factor XI to Xia, VIII to VIIIa, XIII to XIIIa, Fibrinogen to Fibrin
IV	Calcium	Required for phospholipid binding
V	Factor V	Cofactor for Factor X-prothrombinase complex to activate Factor X 15 hour half-life
VII	Factor VII	Activates IX, X 5 hour half-life Vitamin K dependent Calcium activated

Factor	Name	Function
VIII	Antihemophiliac factor A	Cofactor of IX Only clotting factor that is not a protease (is a transglutaminase)
IX	Antihemophiliac factor B	Activates X 25 hour half-life Vitamin K dependent Calcium activation
X	Factor X	Forms prothrombinase complex with Factor V Activates thrombin 40 hour half-life Vitamin K dependent Calcium activation
XI	Plasma thromboplastin	Activates Factor IX 45 hour half-life
XII	Hageman factor	Activates XI, VII, prekallikrein
XIII	Fibrin stabilizing factor	Crosslinks fibrin 200 hour half-life
	Protein C Protein S	Inactivates Va and VIIIa Cofactor for activated Protein C

Factor	Name	Function
ATIII	Antithrombin III	Inhibits IIa and Xa
	Plasminogen Plasmin	Converts to plasmin Lyses fibrin
vWF	Von Willebrand factor	Binds VIII Mediates platelet adhesion
	Fibronectin	Mediates cell adhesion
	Prekallikrein (Fletcher factor)	Stimulated by Factor XII

Diffuse intravascular coagulopathy

- DIC is an acute, subacute, or chronic thrombo-hemorrhagic disorder characterized by the excessive activation of coagulation and the formation of thrombi in the microvasculature of the body
- The onset can be fulminant, as in endotoxic shock or amniotic fluid embolism
- Insidious and chronic, as in cases of carcinomatosis or retention of a dead fetus.
- 50% of the affected are obstetric patients having complications of pregnancy.
- 33% of the affected patients have carcinomatosis.

Diffuse intravascular coagulopathy

- Two major mechanisms trigger DIC:
- (1) release of tissue factor or other, poorly characterized procoagulants, into the circulation
- (2) widespread injury to the endothelial cells.
- Microangiopathic hemolytic anemia
- An unusual form of DIC occurs in association with giant hemangiomas (Kasabach-Merritt syndrome), in which thrombi form within the neoplasm because of stasis and recurrent trauma to fragile blood vessels.

Diffuse intravascular coagulopathy

- Histopathology
- Thrombi are most often found in the brain, heart, lungs, kidneys, adrenals, spleen, and liver
- Affected kidneys may have small thrombi in the glomeruli that evoke only reactive swelling of endothelial cells or, in severe cases, microinfarcts or even bilateral renal cortical necrosis.
- Numerous fibrin thrombi may be found in alveolar capillaries, sometimes associated with pulmonary edema and fibrin exudation, creating “hyaline membranes”
- Microinfarcts in central nervous system
- Microinfarcts in adrenal gland

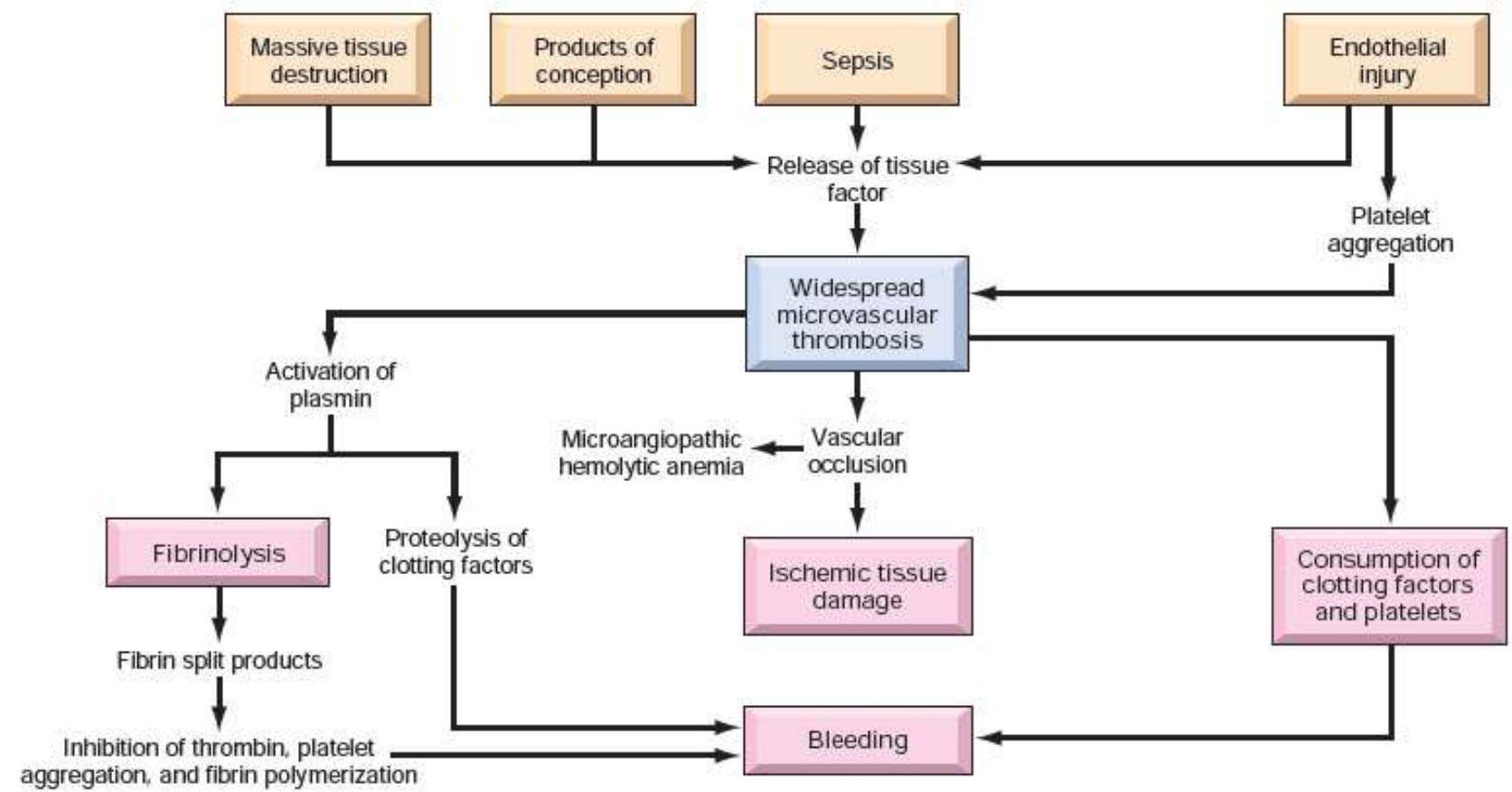


Figure 14-27 Pathophysiology of disseminated intravascular coagulation.