

Bleeding Disorders

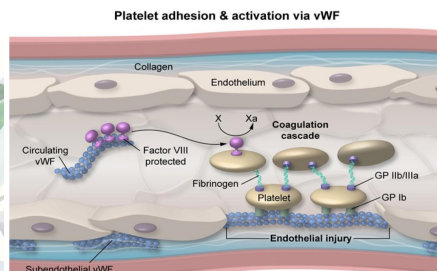
Before we talk about Bleeding Disorders, let's talk about Normal Hemostasis

NORMAL HEMOSTASIS

Hemostasis is the dynamic process of **coagulation** as it occurs in areas of vascular injury, involving the carefully modulated interaction of platelets, vascular wall, and procoagulant and anticoagulant proteins. After an injury to the vascular endothelium, subendothelial collagen induces a conformational change in von Willebrand factor (VWF), an adhesive protein to which platelets bind via their glycoprotein Ib receptor. After adhesion, platelets undergo activation and release numerous intracellular contents, including adenosine diphosphate (ADP). These **activated platelets** subsequently induce aggregation of additional platelets. Simultaneously, tissue factor, collagen, and other matrix proteins in tissue activate the coagulation cascade, leading to the formation of the enzyme **thrombin** (Fig. 151.1). Thrombin causes further aggregation of platelets, a positive feedback activation of factors 5 and 8, the conversion of fibrinogen to fibrin, and the activation of factor 11. A **platelet plug** forms, and bleeding ceases, usually within 3-7 minutes. The generation of thrombin leads to formation of a permanent clot by the activation of factor 13, which cross links fibrin, forming a stable thrombus. Finally, contractile elements within the platelet mediate **clot retraction**. Thrombin also contributes to the eventual limitation of clot size by binding to the protein thrombomodulin on intact endothelial cells, converting protein C into activated protein C. Thrombin contributes to the eventual lysis of the thrombus by activating plasminogen to plasmin. All of the hemostatic processes are closely interwoven and occur on biological surfaces that mediate coagulation by bringing the critical players—platelets, endothelial cells, and subendothelium—into close proximity with pro- and anticoagulant proteins.

• Platelet hemostasis

- Platelet adhesion:** platelets bind to vWF via **platelet GpIb receptor** at the endothelial injury site
 - Ristocetin normally activates vWF to bind to glycoprotein Ib
- Platelet activation:** After binding to vWF, platelets change their shape and release mediators that lead to activation of more platelets (positive feedback). These mediators include:
 - Adenosine diphosphate (ADP):** promotes adhesion of platelets to endothelium
 - Thromboxane A₂ (TXA₂):** activates additional platelets and promotes vasoconstriction
 - Calcium:** required for secondary hemostasis
 - Platelet-activating factor (PAF):** a phospholipid mediator that is produced by platelets and inflammatory cells (e.g., neutrophils, monocytes, macrophages), involved in platelet aggregation and activation and local inflammatory response
- Platelet aggregation**
 - Mediated by **GpIIb/IIIa-receptor** and fibrinogen → formation of a **white thrombus** composed of platelets and fibrinogen
 - A white thrombus is transient, unstable, and easily dislodged. It stabilizes through the process of secondary hemostasis.



Many think of coagulation as having **intrinsic and extrinsic pathways**, but the reality is that these pathways are closely interactive and do not react independently (Fig. 151.2). For ease of use, all coagulation factors are denoted using Arabic rather than Roman numerals to prevent misreading factor VII (7) as factor VIII (8). In vivo, factor 7 autocatalyzes to form small amounts of factor 7a. When tissue is injured, **tissue factor** is released and causes a burst of factor 7a generation. Tissue factor, in combination with calcium and factor 7a, activates factor 9 and factor 10. The activation of factor 9 by factor 7a results in eventual generation of thrombin, which feeds back on factor 11, generating factor 11a and accelerating thrombin formation. This process explains why deficiency of factor 8 or factor 9 leads to severe bleeding disorders, whereas deficiency of factor 11 is usually mild, and deficiency of factor 12 is asymptomatic.

A series of **inhibitory factors** serve to tightly regulate the activation of coagulation. **Antithrombin III** inactivates thrombin and factors 10a, 9a, and 11a. The **protein C and protein S** system inactivates activated factors 5 and 8, which are cofactors localized in the "tenase" and "prothrombinase" complexes. The **tissue factor pathway inhibitor**, an anticoagulant protein, limits activation of the coagulation cascade by factor 7a and factor 10a. **Fibrinolysis** is initiated by the action of tissue plasminogen activator on plasminogen, producing plasmin, the active enzyme that degrades fibrin into split products. Fibrinolysis eventually dissolves the clot and allows normal flow to resume.

Deficiencies of anticoagulant proteins may predispose to thrombosis.

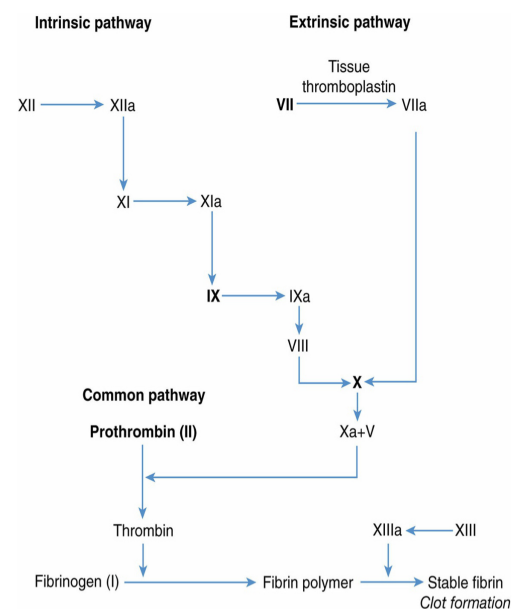


FIGURE 13.2 Coagulation cascade. Activated partial thromboplastin time measures the function of the intrinsic pathway and the extrinsic pathway, except for factor VII; the prothrombin time measures the function of the extrinsic pathway (factors VII, X, and V), fibrinogen, and prothrombin (factor II). Factors in bold type are vitamin K-dependent coagulation factors.

Hemostasis is the mechanisms of stoppage of bleeding after injury of a blood vessel; different factors are involved:

1- Vascular factor :

Role: - Reflex vasoconstriction at the site of bleeding.

- Damaged endothelium activate F XII

Assessment

1- Bleeding time → normal = 4-8 min.

2- Hess test (capillary fragility test) → cuff of sphygmomanometer is inflated between systole & diastole for 5 min. → if > 5 petechiae appear within 5 cm circle in the forearm → +ve test.

2- Platelets:

Role

1- Adhesion to exposed collagen fibers (Von Willbrand factor is essential).

2- Aggregation; platelets accumulate at injured site helped by adenosine diphosphate (ADP) & thromboxane A₂

3- Release of: - Thromboxane A₂ → ↑ platelet aggregation.

- Serotinine → ↑ vasoconstriction

- Platelet factor 3 (PF₃) → enhance clotting

- Thrombasthinine → ↑ clot retraction.

4- Platelet plug formation

Assessment:

1- Bleeding time.

2- Hess test.

3- Platelet count (N = 150 – 400.000 /mm³)

4- Platelet function tests: → assess platelet adhesiveness.

→ assess aggregation by aggregometer

→ assay of PF₃ level.

→ clot retraction test.

3- Coagulation factors:

Names

I	Fibrinogen	II	Prothrombin
III	Tissue thromboplastin	IV	Calcium
V	Labile factor	VII	Stable factor
VIII	Antihemophilic factor	IX	Christmas factor
X	Stuart prower factor	XI	Plasma thromboplastin antecedent
XII	Hageman factor	XIII	Fibrin stabilizing factor

Criteria

- Most coagulation factors are formed in the liver except F VIII is formed by endothelial cells.

- Vitamin K dependent factors → II, VII, IX, X.

- Factor VIII is composed of clotting part = F VIIIc & antigenic part = F VIIIa,

normally → $\frac{F\ VIIIc}{F\ VIIIa} = 1$

Overview of coagulation factors

Factor number	Descriptive name	Activated by	Involvement in pathways			Function
			Common	Intrinsic	Extrinsic	
I†	- Fibrinogen* - Active form (Ia): fibrin	Thrombin	✓			Stabilization of the platelet plug
II	- Prothrombin* - Active form (IIa): thrombin	Factor Xa/Va complex	✓	✓	✓	- Cleaves fibrinogen to fibrin - Activates numerous other coagulation factors
III†	Tissue factor* (TF)	Endothelial injury			✓	- Activates factor VII - Tissue factor and factor VIIa form a complex that activates factor X.
IV†	Calcium* (Ca²⁺)	Released by platelets and fibrocytes	✓	✓	✓	Required for complex formation and other reactions in the coagulation cascade
V*	Proaccelerin†	Thrombin	✓			Factors Va and Xa form a complex that cleaves prothrombin to thrombin.
VII*	Proconvertin†	Tissue factor			✓	Factor VIIa and tissue factor form a complex that activates factor X.
VIII*	Antihemophilic factor (AHF)	Thrombin		✓		Factors VIIIa and IXa form a complex that activates factor X.
IX*	- Plasma thromboplastin component (PTC) - Christmas factor	Factor XIa		✓		
X*	Stuart factor	Complexes TF-VIIa and VIIIa-IXa	✓			Factors Xa and Va form a complex that cleaves prothrombin to thrombin.
XI*	Plasma thromboplastin antecedent (PTA)	- Factor XII - Thrombin		✓		Activates factor IX
XII*	Hageman factor	- Exposed collagen - Kallikrein - Kininogen (HMWK)		✓		- Activation of: - Factor XI - Kallikrein system: leads to the production of bradykinin
XIII*	Fibrin-stabilizing factor	Thrombin	✓			Stabilizes the fibrin network by introducing crosslinks

* = preferred term [3]
† = rarely used term

Control of coagulation factors:

- 1- Fibrinolytic system: Plasmin splits fibrin network into fibrin degradation products.
- 2- Natural coagulation inhibitors (Antithrombin III, Protein C & Protein S).

Assessment:

- 1- Clotting time ➡ normal = 8-12 min.
rough test → prolonged with defects in any phase
- 2- Thrombin time (TT) ➡ normal = 15-20 Sec.
 - time needed to plasma to clot after addition of bovine thrombin
 - prolonged in fibrinogen deficiency.
- 3- Prothrombin time (PT) ➡ normal = 12-14 Sec.
 - time needed to plasma to clot after addition of thromboplastin & Ca.
 - Test extrinsic & common pathways.
- 4- Partial thromboplastin time (PTT) ➡ normal = 25-40 Sec.
 - time needed for plasma to clot after addition of kaolin, Ca & platelets.
 - Test intrinsic & common pathways.

Let's Now talk about Bleeding Disorders

Summary

Bleeding disorders are a group of heterogeneous conditions characterized by defects in hemostasis that lead to an increased susceptibility to bleeding (also known as hemorrhagic diathesis). They are classified into disorders of primary hemostasis (when caused by a platelet abnormality), disorders of secondary hemostasis (when caused by defects in the extrinsic and/or intrinsic pathway of the coagulation cascade), and hyperfibrinolysis (when there is increased clot degradation). Although clinical features may overlap, mucocutaneous bleeding (e.g., epistaxis, petechiae, gastrointestinal bleeding) is associated with disorders of primary hemostasis, and bleeding into potential spaces (e.g., hemarthrosis, muscular bleeding) is characteristic of disorders of secondary hemostasis. The diagnostic workup of a bleeding disorder begins with a detailed clinical assessment, the CBC, and a coagulation panel. This typically allows the disorder to be classified as one of primary or secondary hemostasis. Specialized studies are then required to determine the specific etiology so that treatment can be initiated. Treatment may include transfusion of blood products, replacement of specific coagulation factors, or administration of adjuvant medications (e.g., tranexamic acid or desmopressin).

Evaluation of Bleeding Disorders

- History provides the most useful information.
 - von Willebrand disease (vWD) or platelet dysfunction → mucous membrane bleeding, petechiae, small ecchymoses
 - Clotting factors—deep bleeding with more extensive ecchymoses and hematomas
- Laboratory studies
 - Obtain platelets, bleeding time, PT, PTT
 - If normal, von Willebrand factor (vWF) testing and thrombin time
 - If abnormal, further clotting factor workup
 - Bleeding time—platelet function and interaction with vessel walls; qualitative platelet defects or vWD (platelet function analyzer)
 - Platelet count—thrombocytopenia is the most common acquired cause of bleeding disorders in children

- PTT—**intrinsic pathway**: from initiation of clotting at level of factor XII through the final clot (prolonged with factor VIII, IX, XI, XII deficiency)
- PT—measures **extrinsic pathway** after activation of clotting by thromboplastin in the presence of Ca^{2+} ; **prolonged by deficiency of factors VII, XIII or anticoagulants**; standardized values using the **International Normalized Ratio (INR)**
- Thrombin time—measures the **final step: fibrinogen → fibrin**; if prolonged: **decreased fibrin or abnormal fibrin** or substances that interfere with fibrin polymerization (**heparin or fibrin split products**)
- Mixing studies
 - If there is a prolongation of PT, PTT, or thrombin time, then add normal plasma to the patient's and repeat labs:
 - ▶ **Correction of lab prolongation suggests deficiency of clotting factor.**
 - ▶ **If not or only partially corrected, then it is due to an inhibitor (most common on inpatient basis is heparin).**
 - ▶ **If it becomes more prolonged with clinical bleeding, there is an antibody directed against a clotting factor (mostly factors VIII, IX, or XI).**
 - ▶ **If there is no clinical bleeding but both the PTT and mixing study are prolonged, consider lupus anticoagulant (predisposition to excessive clotting).**
- Clotting factor assays—each can be measured; severe deficiency of factors VIII or IX = <1% of normal; moderate = 1–5%; mild = >5%
- Platelet aggregation studies—if suspect a **qualitative platelet dysfunction, ristocetin**

Table 19-3. Clinical Findings in Coagulopathies

	Factor VIII	Factor IX	vWF
Platelet	Normal	Normal	Normal
PT	Normal	Normal	Normal
PTT	↑	↑	↑
Bleeding time	Normal	Normal	↑
Factor VIII	↓	Normal	Normal
Factor IX	Normal	↓	Normal
vWF	Normal	Normal	↓
Sex	Male	Male	Male/female
Treatment	Factor VIII, DDAVP	Factor IX	Fresh frozen plasma, cryotherapy, DDAVP

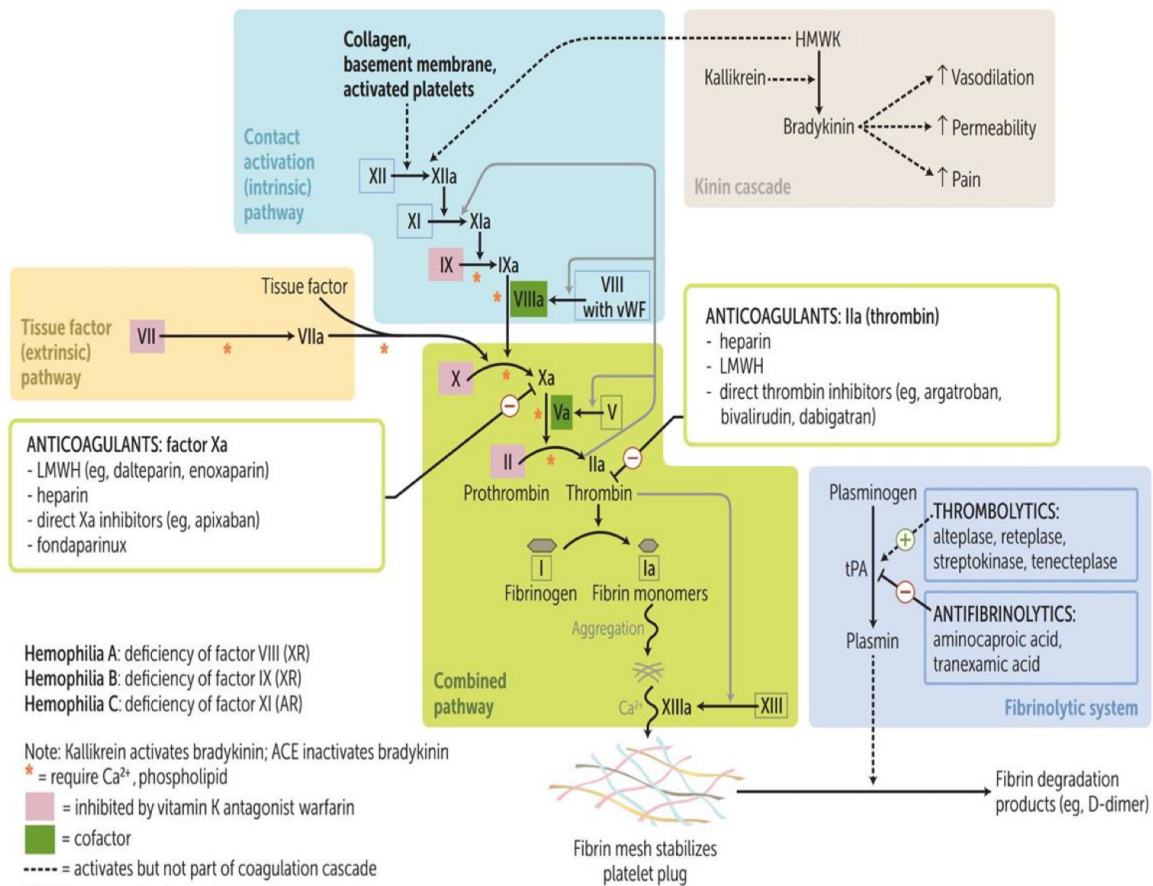
Definition of abbreviations: DDAVP, Desmopressin; PT, prothrombin time; PTT, partial thromboplastin time; vWF, von Willebrand factor.

Interpretation

Defect in	PT	PTT	Specific
Common pathway (X, V, II, I)	Prolonged	Prolonged	} Specific factor assay
Extrinsic pathway (VII)	Prolonged	Normal	
Intrinsic pathway (XII, XI, IX, VIII)	Normal	Prolonged	

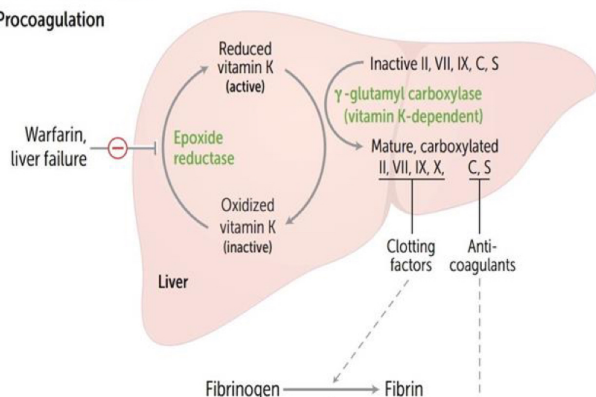
N.B.: Prolonged both PT & PTT also occur in multiple factors deficiency e.g. liver cell failure, vitamin K deficiency & DIC.

Coagulation and kinin pathways



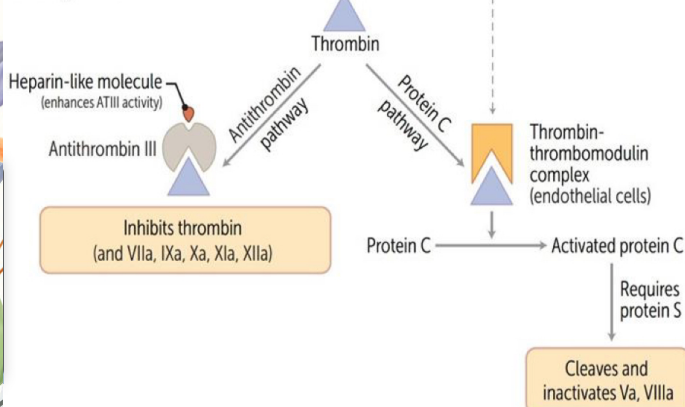
Procoagulation

Procoagulation



Anticoagulation

Anticoagulation



Vitamin K deficiency: ↓ synthesis of factors II, VII, IX, X, protein C, protein S.

Warfarin inhibits vitamin K epoxide reductase. Vitamin K administration can potentially reverse inhibitory effect of warfarin on clotting factor synthesis (delayed). FFP or PCC administration reverses action of warfarin immediately and can be given with vitamin K in cases of severe bleeding.

Neonates lack enteric bacteria, which produce vitamin K. Early administration of vitamin K overcomes neonatal deficiency/coagulopathy.

Factor VII (Seven)—Shortest half life.

Factor II (Two)—Longest (Tallest) half life.

Antithrombin inhibits thrombin (factor IIa) and factors VIIa, IXa, Xa, XIa, XIIa.

Heparin enhances the activity of antithrombin. Principal targets of antithrombin: thrombin and factor Xa.

Factor V Leiden mutation produces a factor V resistant to inhibition by activated protein C. tPA is used clinically as a thrombolytic.

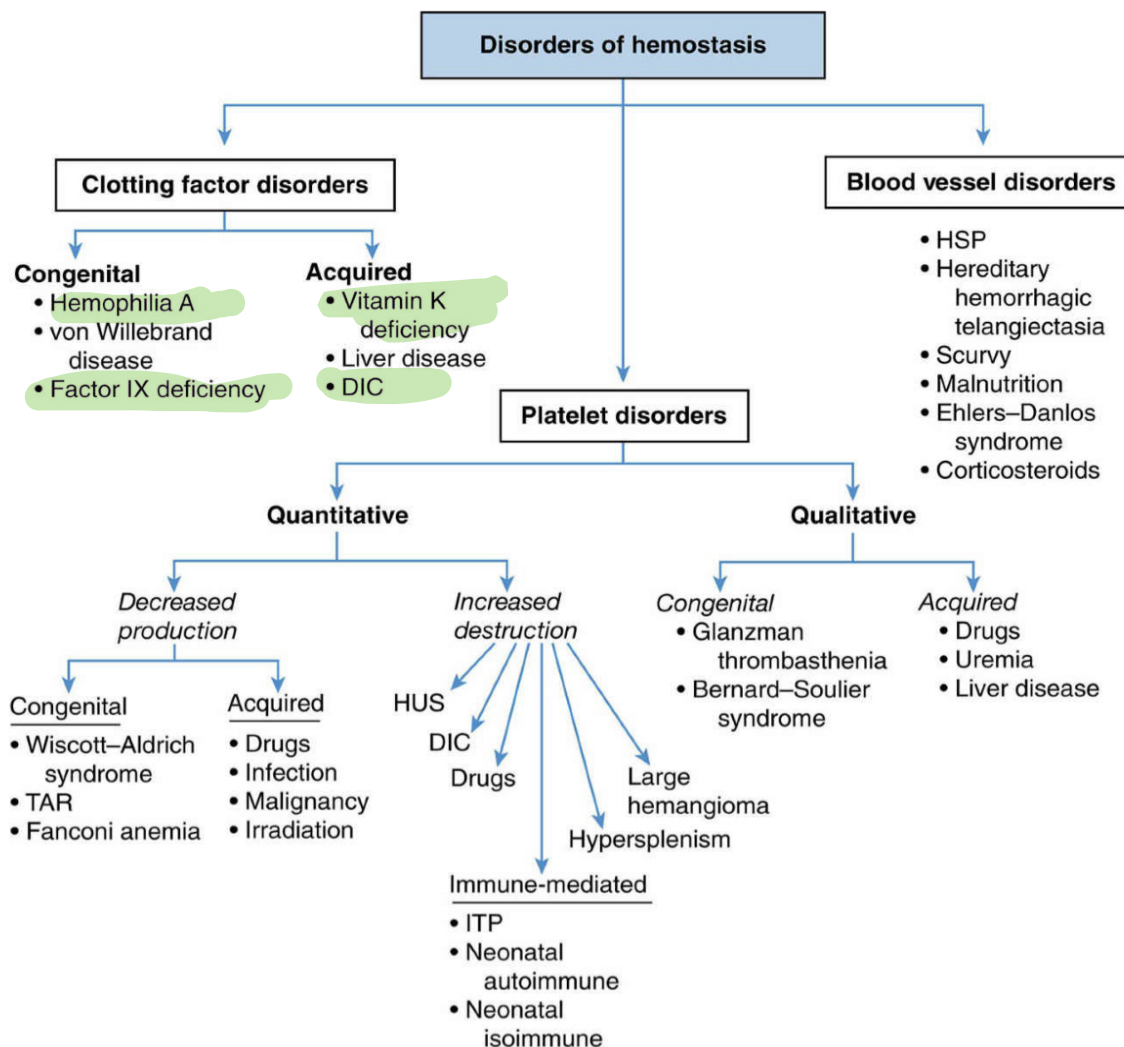


FIGURE 13.3 Overview of the differential diagnosis of disorders of hemostasis. *DIC* = disseminated intravascular coagulation; *HUS* = hemolytic uremic syndrome; *HSP* = Henoch-Schönlein purpura; *TAR* = thrombocytopenia-absent radius syndrome; *ITP* = immune thrombocytopenic purpura.

First/Platelet Disorders

- **Platelet dysfunction** (thrombocytopathy): disorders that lead to dysfunctional adhesion or aggregation of platelets

- Inherited
 - Von Willebrand disease *VWD is mixed plt and CF disorder*
 - Bernard-Soulier syndrome
 - Glanzmann thrombasthenia
- Acquired
 - Drug-induced: e.g., aspirin, NSAID, clopidogrel
 - Immune thrombocytopenic purpura
 - Chronic kidney disease
 - Cardiopulmonary bypass [10]

Von Willebrand Disease

Summary

Von Willebrand disease (vWD) is a bleeding disorder characterized by a deficiency or dysfunction of von Willebrand factor (vWF). In the vast majority of cases, vWD is an inherited disorder caused by mutations in the vWF gene. vWF is involved in platelet adhesion and prevents degradation of factor VIII. Therefore, vWF deficiency or dysfunction impairs primary hemostasis as well as the intrinsic pathway of secondary hemostasis. vWD is often asymptomatic, but mucocutaneous bleeding, GI bleeding, and menorrhagia may occur. Diagnosis is based on patient history and laboratory studies such as quantitative measurement of vWF and ristocetin cofactor assay. Treatment is indicated for symptomatic patients; prophylaxis is indicated for surgical candidates and involves desmopressin and concentrates containing vWF and factor VIII.

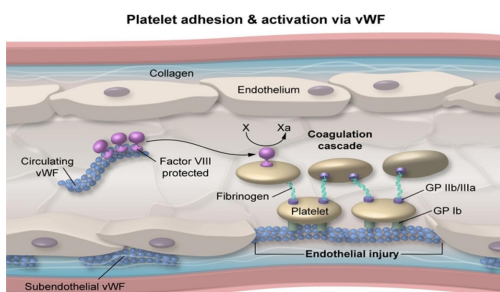
Definition:

- **VWD is the most common inherited bleeding disorder with a decrease in the level or functioning of von Willebrand factor (VWF).** It is autosomal dominant.
 - vWF serves as a **carrier for factor VIII and prolongs its half-life**. The half-life of factor VIII bound to vWF is 12 hours, while the half-life of free factor VIII is 2 hours. Decreased levels of vWF, therefore, lead to functional deficiency of factor VIII.
- The most common hereditary bleeding disorder
 - VWD is inherited autosomally(AD>AR)
 - VWD is classified on :
 1. protein is quantitatively reduced, but not absent (type 1)- The most common form.
 2. qualitatively abnormal (type 2)
 3. absent (type 3)
 - functions of VWD:
 1. platelets adhere to VWF through their glycoprotein IB (GPIb) receptor.
 2. VWF serves as the carrier protein for plasma factor VIII.

Pathophysiology

Deficiency or dysfunction of vWF leads to:

- Dysfunctional platelet adhesion → impaired primary hemostasis
- Reduced binding of factor VIII → increased degradation → ↓ factor VIII activity → impaired intrinsic pathway of secondary hemostasis



CLINICAL MANIFESTATIONS

- symptoms of **mucocutaneous hemorrhage**, including excessive bruising, epistaxis, menorrhagia, and postoperative hemorrhage, particularly after mucosal surgery.
- because others in the family may be affected with the same disorder, teenager's menstrual history is usually recognized as being abnormal,
- VWF is an acute-phase protein, stress will increase its level, patients not bleed with major stress, such childbirth, but may bleed excessively with mucosal surgery.
- Bruising symptoms may diminish during pregnancy because VWF levels may double or triple during pregnancy
- patients with VWD may have gastrointestinal telangiectasia
- type 3, or homozygous, VWD, bleeding symptoms are much more profound. may have joint hemorrhages or spontaneous CNS hemorrhages.

Variants of von Willebrand disease ^[2]			
Type	Description	Etiology	Mechanism
Inherited von Willebrand disease ^[1]	Type 1 (80-85%)	• Autosomal dominant inheritance	• Mild to moderate deficiency of vWF and factor VIII
	Type 2 (15-20%)	• VWD caused by mutations in the vWF gene	• Dysfunctional vWF
	Type 3 (~3%)	• Autosomal recessive inheritance	• Complete absence of vWF and factor VIII
Acquired von Willebrand disease (aVWD)	• VWF deficiency that occurs secondary to other medical conditions ^[3]	• Lymphoproliferative and myeloproliferative diseases (e.g., multiple myeloma, monoclonal gammopathies, lymphoma, essential thrombocythemia) • Autoimmune diseases (e.g., SLE) • Cardiovascular defects (e.g., ventricular septal defect, aortic stenosis) • Hypothyroidism • Side effects of certain drugs (e.g., valproic acid)	• Unknown

▪ "What Is the Most Likely Diagnosis?"

- Look for bleeding related to platelets (epistaxis, gingival, gums) **with a normal platelet count**. VWD is markedly **worsened after the use of aspirin**.

LABORATORY FINDINGS

- if history is suggestive of a mucocutaneous bleeding disorder, testing should including:
 1. quantitative assay for VWF antigen
 2. testing for VWF activity (ristocetin cofactor activity)
 3. testing for plasma factor VIII activity
 4. determination of VWF structure (VWF multimers)
 5. platelet count.
- bleeding time and a long partial thromboplastin time are normal in type 1 VWD.
- type 2B disease("hyperactive" VWF=rapid clearance of VWF and platelets) or platelet-type disease (pseudo-VWD=abnormality of the GPIb receptor on platelets) may have lifelong thrombocytopenia
- Levels of VWF vary with blood type (type O < A < B < AB)

• ↑ **Bleeding time**

- **Normal or ↑ aPTT** (may be prolonged as a result of factor VIII deficiency)

• Normal PT and platelet count

• ↓ Factor VIII

• ↓ VWF antigen levels

• Ristocetin cofactor assay: failure of platelet aggregation or a ristocetin cofactor level < 30 IU/dL

• Further qualitative assessment by collagen binding assay

TREATMENT

- increasing the plasma level of VWF and factor VIII
- In type 1 & some patients with type 2 , the synthetic drug DDAVP induces the release of VWF from endothelial cells.
- replacement therapy(**HUMATE P**):
 - ✓ type 3 and some variants of type 2
 - ✓ plasma-derived VWF containing concentrates contain factor VIII
 - ✓ 1 U/kg will increase the plasma level by 1.5%.
 - ✓ The plasma half-life of both factor VIII and VWF is 12 hr
- Avoid aspirin

.To Sum up:

☆ Von Willbrand factor (VWF) is essential for:

- 1- Platelet adhesion.
- 2- Carrier for F VIII protecting it from proteolysis

☆ Deficiency of Von Willbrand factor result in: Platelet dysfunction and decrease plasma F VIII.

☆ In Von Willbrand disease: Von Willbrand factor may be low or abnormal or absent.

Clinical picture

- Inherited mainly as autosomal dominant disorder
- The commonest hereditary bleeding disoredr (3-4 out of 100.000)
- Mild bleeding:
 - Commonly epistaxis, gum bleeding &menorrhagia.
 - May be post operative bleeding
 - Very rarely purpura or hemarthrosis

Investigations

1- Coagulation profile

Prolonged
Clotting time

Prolonged
PTT

Normal
PT

Prolonged
Bleeding time

↓

Impaired platelet adhesion

2- F VIII assay → low (both F VIIIa & F VIIIc are decreased)

3- VWF assay → low (type 1) or abnormal (type 2) or absent (type 3).

Treatment

1. Desmopressin (i.v. or intranasal)→ effective especially in type 1 & some of type 2.
 2. Factor VIII concentrate (contain F VIII & VWF):
 - For severe bleeding episodes.
 - The only effective treatment in type 3.
 3. Cryoprecipitate & fresh frozen plasma may be used.
 4. Antifibrinolytics (e.g EACA) → as adjuvant treatment in oral bleeding.
- N.B. VWF is formed & stored in endothelial cells & platelets.

🦋 Bernard -Soulier Syndrome

- ✓ inherited as an autosomal recessive disorder.
- ✓ absence or severe deficiency of the VWF receptor (GPIb complex) on the platelet.
- ✓ This syndrome is characterized by thrombocytopenia, with giant platelets and markedly prolonged bleeding time (>20 min).
- ✓ Platelet aggregation by ristocetin-induced test is absent as it induces the binding of VWF to platelets, but other agonists aggregation are normal.

🦋 Glanzmann thrombasthenia

- ✓ this disorder is inherited in an autosomal recessive manner.
- ✓ caused by deficiency of the platelet fibrinogen receptor GPIIb-IIIa
- ✓ Prolonged bleeding time and normal platelet count.
- ✓ Platelets have normal size and morphologic features on the peripheral blood smear.
- ✓ Aggregation studies show abnormal or absent aggregation with all agonists used except ristocetin because ristocetin does not require a metabolically active platelet.

🦋 Disseminated Intravascular coagulation (Mixed)

Summary

Disseminated intravascular coagulation (DIC) is a disorder characterized by systemic activation of the extrinsic clotting cascade with microthrombi formation, platelet consumption, and subsequent exhaustion of all clotting factors. Common causes of DIC include sepsis, trauma, and malignancy. Depending on the underlying pathophysiological processes and subtype, patients present with signs of bleeding (e.g., purpura, petechiae, ecchymoses) and/or multiorgan failure. Laboratory studies can be highly variable. However, typical findings in overt decompensated DIC include thrombocytopenia, prolonged PT and aPTT, decreased fibrinogen levels, and elevated D-dimer levels. Treatment involves identification of the underlying cause and supportive therapy with transfusions of blood products (pRBCs, platelet concentrates, FFP, and/or cryoprecipitate) and, in select cases, anticoagulants (e.g., heparin) or antifibrinolytic therapy (tranexamic acid). Close monitoring and specialist consultation (e.g., critical care and hematology) are typically required.

Definition: Wide spread activation of clotting factors all over the body resulting in:

- 1- Thrombosis and ischaemia of different vessels.
- 2- Consumption of coagulation factors → bleeding.
- 3- Microangiopathic hemolytic anemia & thrombocytopenia.

- consumption of clotting factors, platelets, and anticoagulant proteins.
- Consequences include widespread intravascular deposition of fibrin → TISSUE ISCHEMIA AND NECROSIS+ generalized HEMORRHAGIC STATE AND HEMOLYTIC ANEMIA.
- Any life-threatening pathologic process associated with hypoxia, acidosis, tissue necrosis, shock, and/or endothelial damage may trigger DIC including:
 1. septic shock (especially meningococemia)
 2. incompatible blood transfusion
 3. rickettsial infection
 4. snakebite
 5. giant hemangioma
 6. acute promyelocytic leukemia

NOTE:

for activation of coagulation and fibrinolysis.

- ✓ The D-dimer = FDP test in sensitivity
- ✓ D-dimer more specific

Predisposing factors

- 1- Severe tissue damage in → shock, dehydration, burn, hyperthermia.
- 2- Sepsis : meningococcal, rickettsia, malaria, viral
- 3- Tumors e.g. AML, dissiminated malignancy e.g. neuroblastoma
- 4- Incompatible blood transfusion.
- 5- Severe hepatitis , pancreatitis or severe collagen vascular disease
- 6- Snake bites , insect bites.

Mechanisms

- Underlying disease → ↑ release of procoagulants (e.g., **tissue factor**) → ↑ activation of the extrinsic coagulation cascade and platelets → ↑ **activation of thrombin** → ↑ generation of fibrin → ↑ **generation of microthrombi rich in fibrin and platelets** → ↑ activation of fibrinolysis and other anticoagulant pathways that break down thrombi → ↑ **fibrin degradation** and consumption of natural anticoagulants → further clinical course and resulting type of DIC is determined by the dominance of hyperfibrinolysis and/or hypercoagulopathy
 - Nonsymptomatic type DIC: **low-grade fibrinolysis and/or hypercoagulation**
 - Bleeding type DIC: **hyperfibrinolysis** due to excessive plasmin activity → increased fibrin degradation → thrombi becoming unstable and dissolving shortly after formation
 - Massive bleeding type DIC: **hypercoagulation and hyperfibrinolysis** → consumption of platelets and all coagulation factors → bleeding diathesis
 - Organ failure type DIC: ↑ cytokines → ↑ plasminogen activator inhibitor-I (PAI-I) and ↑ neutrophil extracellular traps (NETs) → **hypercoagulation with suppressed fibrinolysis** → platelet and fibrin-rich microthrombi → impaired perfusion and tissue necrosis

CLINICAL MANIFESTATIONS

- Bleeding frequently first occurs from sites of venipuncture or surgical incision.
- The skin may show petechiae and ecchymoses.
- Tissue necrosis most seen as infarction of skin, subcutaneous tissue, or kidneys.
- Anemia caused by hemolysis owing to microangiopathic hemolytic anemia.

1- Manifestations of the cause.

2- Hemorrhagic manifestations: (bleeding from puncture sites, ecchymosis , purpura).

3- Thrombotic manifestations: gangrene in the skin, subcutaneous tissues, extremities or infarction of the kidney.

4- Uncontrollable severe bleeding and severe anemia → Shock

Routine laboratory tests

- Coagulation panel: Monitor frequently (e.g., every 6–8 hours or until stable or improving).
 - ↑ aPTT, ↑ PT
 - ↓ Fibrinogen: indicative of associated hyperfibrinolysis
 - Markers of fibrin breakdown: ↑ D-dimer or other FDPs
 - ↑ Bleeding time
 - Coagulation factors: ↓ factor V and ↓ factor VIII
 - CBC and blood smear
 - ↓ Platelet count: due to consumption and/or bleeding
 - ↓ Hct: occurs with bleeding
 - Schistocytes: indicative of microangiopathic hemolytic anemia
 - Other tests of organ function (e.g., renal function tests, liver chemistries): Order depending on clinical picture and underlying conditions.
- 1- Investigations for the cause.

2- Consumption of coagulation factors (defective all phases of coagulation esp. prolonged PT , PTT, thrombin time, and low fibrinogen).

3- ↑ Fibrin degradation products (FDPs) & D-dimer assay.

4- Anemia → ↓ Hb%, ↓ RBCs count & fragmented RBCs (schistocytes).

5- Thrombocytopenia → ↓ platelet count & ↑ bleeding time.

! The diagnosis of DIC is not based on a single marker but on a combination of laboratory findings. Thrombocytopenia, elevated D-dimer, increased PT and aPTT, and low fibrinogen should immediately raise suspicion for DIC. [9]

TREATMENT

- The first 2 steps in the treatment of DIC are the most critical:
 1. treat the trigger that caused DIC and
 2. restore normal homeostasis by correcting the shock, acidosis, and hypoxia that usually complicate DIC.
- If the underlying problem can be controlled, bleeding quickly ceases and abnormal laboratory findings improve.
- Blood components are used for replacement therapy in patients with hemorrhage.
 - ✓ platelet infusions (for thrombocytopenia)
 - ✓ cryo-precipitate (for hypofibrinogenemia)
 - ✓ fresh frozen plasma (for replacement of other coagulation factors and natural inhibitors).
- heparin in DIC is limited to patients who have vascular thrombosis in association with DIC

Treatment

- 1- Aggressive management of the cause.
- 2- Plasma or whole blood transfusion.
- 3- Heparin used only in:
 - AML.
 - Purpura fulminans.
 - Severe ischemic manifestations.

Prognosis

- Generally bad ,depending on the cause and the extent of spread of coagulations.

👉 .To Sum Up:

Differential diagnosis of platelet disorders						
	HUS	TTP	Disseminated intravascular coagulation (DIC)	Immune thrombocytopenic purpura (ITP)	Bernard-Soulier syndrome	Glanzmann thrombasthenia
Pathophysiology	• Endothelial cell dysfunction due to bacterial toxins	• ADAMTS13 deficiency	• Systemic coagulation activation • Platelet and coagulation factor consumption (mixed disorder)	• Antiplatelet antibodies (Anti-GpIIb/IIIa)	• Adhesion disorder: deficient platelet GPIb-IX • Autosomal recessive	• Aggregation disorder: deficient platelet GPIIb-IIIa • Autosomal recessive
Typical presentation	• Toddler or preschooler with history of diarrheal illness • Presents with petechiae, jaundice, and oliguria	• Previously healthy adult, sometimes associated with triggers (e.g., infection, surgery, pregnancy) • Presents with mental status changes, fever, petechiae, fatigue, and pallor	• Patient with a history of serious underlying illness (e.g., sepsis, trauma, malignancy) • Presents with thrombosis, embolism, organ dysfunction, and/or bleeding	• Asymptomatic or presenting with petechiae, purpura, epistaxis, menorrhagia, gingival bleeding		
Peripheral smear	• + Schistocytes • ↓ Platelets	• + Schistocytes • ↓ Platelets	• +/- Schistocytes • ↓ Platelets	• Normal platelet morphology • ↓ Platelets	• Giant platelets • ↓ Platelets • Abnormal ristocetin cofactor assay	• Normal platelets • Abnormal results on platelet aggregation testing confirm the diagnosis.
PT (INR) and aPTT	• Normal/increased		• Increased	• Normal		
D-dimer, fibrin degradation products	• Normal/increased		• Increased	• Normal		

Second/ Clotting Factor Dysfunction

Disorders of secondary hemostasis (disorders of the coagulation cascade)

- **Intrinsic pathway**
 - Factor VIII deficiency (hemophilia A)
 - Factor IX deficiency (hemophilia B)
 - Factor XI deficiency (hemophilia C)
- **Extrinsic pathway: factor VII deficiency** (autosomal recessive bleeding disorder caused by mutation of the F7 gene)
- **Both pathways**
 - Deficiency or inhibition of vitamin K-dependent coagulation factors II, VII, IX, and X
 - Vitamin K deficiency: e.g., malabsorption syndrome, depletion of gut flora (e.g., following antibiotic administration), vitamin K deficiency bleeding of the newborn
 - Vitamin K antagonist therapy (e.g., warfarin)
 - Inhibition of coagulation factors by autoantibodies (most commonly anti-factor VIII) ^[11]
 - Disseminated intravascular coagulation (DIC)
 - Impaired hepatic production of coagulation factors (e.g., cirrhosis)
 - Fibrinogen deficiency
 - Anticoagulant treatment

🦋. Hemophilia A, B, C

Hemophilia A (Classic hemophilia)

Definition

- Sex-linked recessive coagulation defect due to deficiency of F VIIIc
- 20% of cases are new mutations.
- Hemophilia A represents 85% of all hemophilias

Pattern of deficiency

- Hemostatic level of factor VIII is >30-40U/L(30-40%); below this level bleeding occur
- Plasma level of Factor VIII in carrier females is between 40-60%

Hemophilia B (Christmas disease)

- Factor IX deficiency.
- Incidence: 1 out of 50,000 (in contrast to hemophilia A which is 1 out of 10,000)
- Sex-linked recessive disorder.
- As hemophilia A. **but** milder.
- Treated by: Recombinant factor IX or factor IX concentrate given/24 hours.

Hemophilia C

- Factor XI deficiency.
- Autosomal recessive disorder so can affect both sexes.
- Very mild disease.
- Treated by fresh frozen plasma given / 48 hours.

Clinical picture

The severity of bleeding depends on plasma level of factor VIII & severity of trauma .

	Severe	Moderate	Mild
F VIIIc	< 1%	1-5%	6-30%
Bleeding	spontaneously	with mild trauma	with severe trauma

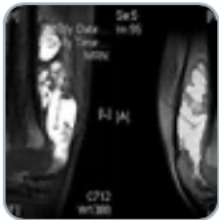
1- **At birth** : unusual bleeding from the umbilicus or circumcision site

2- **Later:**

- ✧ External bleeding : epistaxis, dental bleeding ,hematuria, gastrointestinal
- ✧ Internal bleeding e.g.: intracranial hemorrhage, muscle hematoma
- ✧ Skin → ecchymosis & hematoma (no petechiae)
- ✧ Hemarthrosis → mainly in big joints of lower limbs:
 - Joint become swollen, red, hot, tender with limited mobility.
 - Later on → fibrosis & ankylosis

CLINICAL MANIFESTATIONS

- Neither factor VIII nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus
- 2% of neonates with hemophilia sustain intracranial hemorrhages and 30% of male infants bleed with circumcision
- With severe hemophilia, only 90% have evidence of increased bleeding by 1 yr of age
- hemophilia has a high rate of spontaneous mutation and so may go undiagnosed in the newborn.
- Obvious symptoms of easy bruising, intramuscular hematomas, and hemarthroses begin when the child "begins to cruise
- Bleeding from minor traumatic lacerations of the mouth (a torn frenulum) may persist for hr or days and may cause the parents to seek medical evaluation
- The hallmark of hemophilia is **hemarthrosis**. . The earliest joint hemorrhages appear most commonly in the ankle.
- Complain of a warm, tingling sensation in the joint as the first sign of an early joint hemorrhage.
- Repeated bleeding episodes into the same joint develop a "target" joint.
- Recurrent bleeding may then become spontaneous because of the underlying pathologic changes in the joint.
- Most muscular hemorrhages are clinically evident owing to localized pain or swelling, bleeding into the iliopsoas muscle requires specific mention.
- ✓ Patients may lose large blood volumes into **iliopsoas muscle** → hypovolemic shock
- ✓ vague area of referred pain in the groin.
- ✓ The hip is held in a flexed, internally rotated position due to irritation of the iliopsoas.
- ✓ The diagnosis is made clinically by the inability to extend the hip
- Life-threatening bleeding is by bleeding into vital structures (central nervous system, upper airway) or by exsanguination (external, gastrointestinal, or iliopsoas hemorrhage).
- Life-threatening hemorrhages require replacement therapy to achieve a level equal to that of normal plasma (100 IU/dL, or 100%).
- Patients with mild hemophilia who have factor VIII or factor IX levels of >5 IU/dL usually do not have spontaneous hemorrhages= prolonged bleeding after surgery **OR** moderate trauma.



Severity	Clinical signs	Factor VIII or IX activity
Mild hemophilia	Hematomas following severe trauma	> 5% to < 50%
Moderate hemophilia	Hematomas following mild trauma	≥ 1% to 5%
Severe hemophilia	Spontaneous hematomas	< 1%



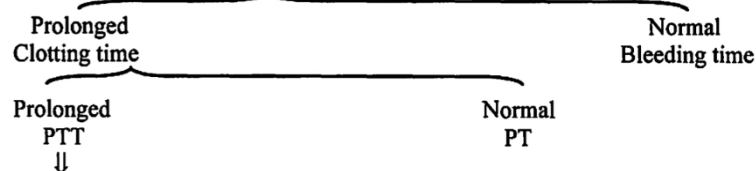
Petechial bleeding is a common sign of platelet disorders, but **NOT** of coagulation disorders such as hemophilia.

LABORATORY FINDINGS AND DIAGNOSIS

- reduced level of factor VIII or factor IX is PTT.
- In severe hemophilia, PTT is usually 2-3 times the upper limit of normal. platelet count, bleeding time, prothrombin time, and thrombin time are normal.
- Unless the patient has an inhibitor (ATB, heparin) to factor VIII or IX, the mixing of normal plasma with patient plasma results in correction of PTT.
- The specific assay for factors VIII and IX will confirm the diagnosis of hemophilia
- quantitative Bethesda assay for inhibitors to measure the antibody titer as 25-35% of hemophilia patients who receive infusions of factor VIII or factor IX, a factor-specific antibody may develop, termed *inhibitors*

1. Diagnostic:

1- Coagulation profile



Time is corrected by barium sulphate adsorbed plasma (contain F8 & F11) not by serum (contain F9 & F11)

2- F VIIIc assay → low

2. Carrier detection by:

- Direct gene mutation analysis
- F VIII/vWF ratio (<1.0)

3. Prenatal diagnosis:

- CVS or amniocentesis & DNA analysis.
- Fetal blood sample at 18-20 weeks

GENETICS AND CLASSIFICATION

- Hemophilia occurs in approximately 1:5,000 males, with 85% having factor VIII deficiency and 10-15% having factor IX deficiency.
- mL of normal plasma has 100 IU/dL (100% activity) of each factor. term % activity = percentage found in normal plasma.
- The hemostatic level for factor VIII is >30-40%, and for factor IX, it is >25-30%.
- The lower limit of levels for factors VIII and IX in normal individuals is approximately 50%.
- **TYPES:**
 1. **SEVERE HEMOPHILIA** <1% activity of the specific clotting factor, and bleeding is spontaneous.
 2. **MODERATE HEMOPHILIA** levels of 1-5% and require mild trauma to induce bleeding.
 3. **MILD HEMOPHILIA** have levels of >5%, may go many years before diagnosed, and require significant trauma to cause bleeding
- cause lyonization of the X chromosome = **some female carriers** of hemophilia A or B have sufficient reduction of factor VIII or factor IX to produce mild bleeding disorders.

TREATMENT

- mild to moderate bleeding occurs, levels of factor VIII or factor IX must be raised to hemostatic levels in the 35-50% range.
- For life-threatening or major hemorrhages, the dose should aim to achieve levels of 100% activity.
- Calculation of the dose of recombinant factor VIII (FVIII) or recombinant factor IX (FIX) is as follows:

$$\text{Dose of FVIII (IU)} = \% \text{ desired (rise in FVIII)} \times \text{Body weight (kg)} \times 0.5$$

$$\text{Dose of FIX (IU)} = \% \text{ desired (rise in plasma FIX)} \times \text{Body weight (kg)} \times 1.4$$

- A concentrated intranasal form of **DESMOPRESSIN ACETATE (STIMATE)** can also be used to treat patients with mild hemophilia A. (synthetic vasopressin ↑ factor 8 by 4 times)

Treatment

1- Prophylactic treatment

- Regular F VIII replacement 20 unit/kg 3 times a week.
- Hepatitis B vaccine.
- Avoid trauma, I.M. injections & aspirin.

2- During bleeding attacks

A. Factor VIII replacement:

- 1- Recombinant factor VIII $\Rightarrow$ dose = 25-50 unit/kg according to severity.
Calculated dose(IU) = % desired (rise in F VIII) $\times$ Body weight(kg) $\times$ 0.5
- 2- Others: - Fresh frozen plasma.
 - Cryoprecipitate
 - Factor VIII concentrate.

B. Adjuvant drugs:

- 1- Desmopressin (DDAVP) $\rightarrow$ $\uparrow$ plasma F VIII by 4 folds.
- 2- Antifibrinolytics $\rightarrow$ inhibit fibrinolysis $\rightarrow$ stabilize the clot e.g. .
 - * Tranexamic acid.
 - * ξ -AminoCaproic Acid (EACA).
 - Indications: - Mucosal bleeding(oral bleeding, epistaxis).
 - Menorrhagia
- 3- Prednisone (short course) in hemarthrosis & hematuria (minimize fibrosis).

C. Special cases:

- 1- Intracranial Hemorrhage: High dose of F VIII (50–75 unit/kg) for 2 weeks.
- 2- Hemarthrosis: - Local $\rightarrow$ cold compresses.
 - F VIII replacement + prednisone (short course)
 - Rest for 48 hr then physiotherapy to avoid ankylosis

Complications

a. Of bleeding:

- Severe blood loss $\rightarrow$ hypovolemic shock
- Severe intracranial hemorrhage.
- Hemophilic arthropathy $\rightarrow$ joint stiffness(joint MRI show $\uparrow$ iron deposition)
- Muscle atrophy

b. Of treatment:

- 1- Complications of transfusion (See page 245)
- 2- Factor VIII inhibitors:
 - ✧ About 5-10 % of hemophiliacs develop antibodies against factor VIII. So, become refractory to treatment. Antibody titre is measured by Bethesda units
 - ✧ Treatment options:
 - High dose of factor VIII(100-200 unit/kg)
 - Activated prothrombin complex concentrate(aPCC)
 - Recombinant activated F VII (Novo Seven) $\rightarrow$ activate extrinsic pathway.
 - Others : Desensitization , Rituximab

.To Sum Up:

1. It occurs due to recurrent hemarthroses
2. Hemosiderin deposition in the joint
 - a. Triggers synovial inflammation
 - b. Inflammation leads to fibrosis
 - c. Destruction of cartilage and bone
3. Diagnosis
 - a. Severe hemophilic arthropathy can be visualized on X-ray
 - b. Earlier detection can be done by MRI
4. Prophylaxis
 - a. Factor concentrates

- Initial screening test for hemophilia is Coagulation studies and CBC



Hemophilia A & B	
Inheritance	• X-linked recessive
Clinical features	• Delayed/prolonged bleeding after mild trauma ◦ Hemarthrosis, intramuscular hematomas ◦ Gastrointestinal or genitourinary tract bleeding ◦ Intracranial hemorrhage • Complications: hemophilic arthropathy
Laboratory findings	• $\uparrow$ Activated PTT • Normal platelet count & PT • Absent or $\downarrow$ factor VIII (hemophilia A) or factor IX (hemophilia B) activity
Treatment	• Factor replacement • Desmopressin for mild hemophilia A

.Vit K deficiency

Summary

Vitamin D deficiency is characterized by low serum vitamin D levels, although there is significant debate among professional societies over what level constitutes a deficiency. Causes include decreased cutaneous production of vitamin D, insufficient dietary intake, inadequate gastrointestinal absorption, impaired vitamin D metabolism (i.e., decreased activation, increased deactivation), and excessive losses. Patients are typically asymptomatic unless the deficiency is severe, in which case symptoms of complications (e.g., rickets, osteomalacia, hypocalcemia) may develop. Screening for vitamin D deficiency should be performed in individuals with conditions placing them at increased risk (e.g., those causing impaired metabolism or absorption of vitamin D), and may be considered in certain population groups (e.g., individuals with obesity, who are pregnant and/or lactating, or who have darker skin pigmentation). 25-hydroxyvitamin D (25-OHD) is the best diagnostic marker for vitamin D deficiency. Additional diagnostic studies are performed if complications or underlying conditions are suspected. Management involves the administration of vitamin D in addition to treatment of any associated complications and/or underlying conditions. Ensuring adequate daily vitamin D intake, especially in patients at increased risk for vitamin D deficiency, can help prevent associated complications.

- The deficiency of vitamin K resulting in decreased production of factors II, VII, IX, and X.
- **Etiology:**
 - The body obtains vitamin K exogenously from intestinal absorption of dietary Vitamin K and endogenously from bacterial production of vitamin K in the intestine.
 - Vitamin K deficiency is most commonly due to inadequate dietary intake, intestinal malabsorption, or hepatocellular disease-causing loss of storage sites.
 - An acutely ill patient with underlying liver disease can become vitamin K deficient in 7-10 days.
 - Deficiency in newborns is the result of poor placental transfer, absent gut flora, immature liver function, and inadequate levels in breast milk. All newborns should receive a vitamin K injection to prevent vitamin K-deficient bleeding.
- **Clinical Presentation:**
 - Bleeding may mimic that of hemophilia and may occur at any site. Look for oozing at venipuncture sites.
- **Diagnosis:**
 - Both the PT and PTT are elevated. The PT usually elevates first and more severely.
 - A correction of the PT and PTT in response to giving vitamin K is the most common method of confirming the diagnosis.
- **Treatment:**
 - Severe bleeding is treated with infusions of fresh frozen plasma.
 - Vitamin K is given at the same time to correct the underlying production defect.

.To Sum up:

VITAMIN K DEFICIENCY

- Vitamin K deficiency is the most common hemorrhagic disease
- It is recommended to give 0.5-1 mg IV Vitamin K at birth
- Neonates who are breast fed with no prophylactic vit. K are in the highest risk for hemorrhagic dz.
- Incidence 2-10 days of life.
- ICH, GI bleeding, bleeding from umbilical stump, generalized echymoses.
- Lab: ↑PT, ↑PTT, may ↓VII
- after the neonatal period is usually secondary to:
 1. a lack of oral intake of vitamin K
 2. alterations in the gut flora due to the long-term use of broad-spectrum antibiotics
 3. malabsorption of vitamin K accompany cystic fibrosis or biliary atresia reduced synthesis of vitamin K-dependent clotting factors (factors II, VII, IX, and X, and protein C and protein S).
- ✓ Prophylactic administration of water-soluble vitamin K orally is indicated in these cases (2-3 mg/24 hr for children / 5-10 mg/24 hr for adolescents and adults), or 1-2 mg IV.
- Advanced cirrhosis, synthesis of many of the clotting factors reduced so vitamin K is ineffective.
- warfarin (Coumadin) and related anticoagulants depend on interference with vitamin K, with a concomitant reduction of factors II, VII, IX, and X.
- Rat poison (superwarfarin); is a specific vitamin K antidote.
- TTT: correct nutritional disorder and malabsorption. In severe bleeding give: FFP + prothrombin complex concentrate (II, VII, IX, X)

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Interpretation of laboratory findings in bleeding disorders [18][20][28]					
Defective pathway	Disorders	Platelet count	PFA or bleeding time	PT/INR	aPTT
Disorders of primary hemostasis	Thrombocytopenia	• ↓	• ↑	• Normal	• Normal
	Platelet dysfunction (e.g., aspirin therapy, chronic kidney disease)	• Normal	• ↑	• Normal	• Normal
Disorders of secondary hemostasis	Extrinsic pathway (e.g., factor VII deficiency)	• Normal	• Normal	• ↑	• Normal
	Intrinsic pathway (e.g., hemophilia, heparin therapy)	• Normal	• Normal	• Normal	• ↑
	Intrinsic and extrinsic pathways (e.g., deficiency of vitamin K-dependent coagulation factors)	• Normal	• Normal	• ↑	• ↑
Disorders of primary AND secondary hemostasis	Von Willebrand disease	• Normal	• ↑	• Normal	• Normal/↑ [27]
	Disseminated intravascular coagulation (DIC)	• ↓	• ↑	• ↑	• ↑

Laboratory and Clinical Findings in Coagulation Disorders

Disorder	aPTT	PT	Platelet Function Assay	Platelet Count	Petechiae	Hemarthroses
Factor VIII, IX deficiency	Prolonged	Normal	Normal	Normal	No	Yes
von Willebrand	Prolonged	Normal	Abnormal	Normal	No	Rare
Thrombocytopenia	Normal	Normal	*	Low	Yes	No
Platelet function defect	Normal	Normal	Abnormal	Normal	Yes	No
Vitamin K deficiency	Prolonged	Prolonged	Normal	Normal	Yes	Yes
DIC	Prolonged	Prolonged	Abnormal	Low	Yes	Sometimes

*Platelet function assays may be unreliable with thrombocytopenia and therefore are typically not indicated.

aPTT = activated partial thromboplastin time; PT = prothrombin time; DIC = disseminated intravascular coagulation.

