🩸 HEMATOLOGY AND ONCOLOGY FOR USMLE 🩸

COAGULATION

PLATELET PLUG FORMATION (PRIMARY HEMOSTASIS)

Primary hemostasis is the rapid formation of a temporary platelet plug at the site of vascular injury. It is fast, platelet-driven, and unstable until reinforced by fibrin (secondary hemostasis).

🔹 OVERVIEW FLOWCHART — Primary Hemostasis

Endothelial Injury →

i) Reflex vasoconstriction → ↓ blood flow

ii) → Exposure of subendothelial collagen → vWF binds collagen → Platelet adhesion via GpIb receptor → Platelet activation (ADP, TXA_2 release) → GpIIb/IIIa expression ↑ → Fibrinogen bridges platelets → Platelet aggregation → Temporary platelet plug 🩸

1️⃣ Injury Phase

🔎 What Happens?

Endothelial damage leads to:

- Exposure of subendothelial collagen
- Release of von Willebrand factor (vWF) from:
  - Weibel-Palade bodies (endothelial cells)
  - Platelet α-granules
- Reflex vasoconstriction

🧠 Key Concept

Endothelium normally produces:

- Prostacyclin (PGI_2)
- Nitric oxide (NO)

Both are anti-aggregation factors 🚫

When injured → this inhibition is lost → platelets can adhere.

2️⃣ Adhesion Phase

🔬 Mechanism

Subendothelial collagen → vWF binds collagen → Platelet GpIb receptor binds vWF → Platelet attaches to vessel wall

📌 Important Receptor

- GpIb = adhesion receptor
- Connects platelet to vWF

📊 High-Yield Table: Adhesion Disorders

Disorder	Defect	Mechanism	Lab Finding
von Willebrand Disease	↓ vWF	Impaired platelet adhesion	↑ Bleeding time, ↑ PTT (sometimes)
Bernard-Soulier Syndrome	↓ GpIb	Cannot bind vWF	↑ Bleeding time, giant platelets

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🧪 Ristocetin Test (VERY HIGH-YIELD)

Ristocetin → Causes vWF to bind GpIb → Platelet agglutination occurs

If no aggregation:

- Add normal plasma:
  - If corrected → vWF deficiency/vWD (Normal plasma provides vWF)

- If NOT corrected → GpIb defect/Bernard-Soulier (Even if you add normal vWF, platelets lack functional GpIb → no binding → no clumping.)

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3 Activation Phase

After adhesion:

Platelet shape change (becomes spiky) → Degranulation → ADP release → TXA_2 synthesis → Increased GpIIb/IIIa expression

🧬 What Do Platelets Release?

Granule Type	Contents
α-granules	vWF, fibrinogen, Factor V
Dense granules	ADP, Ca^{2+}, serotonin

🔬 ADP Function

- Binds $P2Y_{1\ \ 2}$ receptor
- Increases GpIIb/IIIa expression
- Promotes aggregation

🔬 TXA_2 Function

- Origin: Arachidonic acid (via COX enzyme)
- Vasoconstriction + platelet aggregation

💊 Antiplatelet Drugs

Drug	Mechanism	Effect
Aspirin	Irreversibly inhibits COX	↓ TXA_2

Clopidogrel / Prasugrel / Ticagrelor	Inhibit $P2Y_{1,2}$ receptor	↓ GpIIb/IIIa expression
Eptifibatide / Tirofiban	Block GpIIb/IIIa	Prevent fibrinogen bridging
Abciximab	Monoclonal Ab vs GpIIb/IIIa	Blocks aggregation

🧠 USMLE Tip: Aspirin works for the lifespan of platelets (7–10 days) because platelets cannot synthesize new COX.

4️⃣ Aggregation Phase

🔬 Mechanism

ADP stimulation → GpIIb/IIIa receptor insertion → Fibrinogen binds between platelets → Platelets cross-link → Platelet plug formation

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🔎 Important Receptor

- GpIIb/IIIa = aggregation receptor
- Binds fibrinogen (NOT vWF)

📊 Aggregation Disorder

Disorder	Defect	Result
Glanzmann Thrombasthenia	↓ GpIIb/IIIa	No platelet aggregation

Lab:

- ↑ Bleeding time
- Normal platelet count
- Normal ristocetin test

🔥 Integrated Flowchart (Primary Hemostasis)

Endothelial injury → vWF released → vWF binds collagen → Platelet GpIb binds vWF → Platelet adhesion → ADP release → $P2Y_{1\ \ 2}$ activation → GpIIb/IIIa expression → Fibrinogen bridging → Platelet aggregation → Temporary platelet plug (unstable)

🧠 Primary vs Secondary Hemostasis

Feature	Primary	Secondary
Main Component	Platelets	Clotting factors
Time	Seconds	Minutes
Stability	Weak	Strong
Key Product	Platelet plug	Fibrin mesh

Lab test	Bleeding time	PT / PTT

🩸 Transition to Secondary Hemostasis

Temporary platelet plug → Activation of coagulation cascade → Thrombin formation → Fibrin production → Stable clot formation 🧵

🚨 Clinical Correlations

vWF protects Factor VIII

Mnemonic:
"von Willebrand protects VIII"

If vWF ↓ → Factor VIII ↓ → PTT may increase

Desmopressin (DDAVP)

Desmopressin → Releases vWF from endothelial cells →

Used in:

- vWD
- Mild Hemophilia A

⚠️ USMLE Traps

1. GpIb = adhesion (vWF binding)
2. GpIIb/IIIa = aggregation (fibrinogen binding)
3. Ristocetin tests vWF function
4. Aspirin does NOT affect ADP pathway
5. Platelet disorders = ↑ bleeding time
6. Coagulation factor disorders = ↑ PT/PTT

🎯 Exam Pearls

- Mucosal bleeding → think platelet disorder
- Deep tissue bleeding → think coagulation disorder

- Giant platelets → Bernard-Soulier
- Normal platelet count + bleeding → qualitative defect
- Alcoholics may have platelet dysfunction

🏁 Memory Hook

Adhesion = vWF + GpIb

Activation = ADP + TXA_2

Aggregation = GpIIb/IIIa + fibrinogen

🧬 COAGULATION & KININ PATHWAYS (SECONDARY HEMOSTASIS)

Secondary hemostasis reinforces the unstable platelet plug by forming a stable fibrin mesh 🧵.

🔹 BIG PICTURE

Vascular injury → Tissue factor exposure → Activation of coagulation cascade → Thrombin formation → Fibrin production → Fibrin cross-linking → Stable clot formation 🩸

🧠 Pathways Overview

There are 3 pathways:

1️⃣ Extrinsic (Tissue factor pathway)
2️⃣ Intrinsic (Contact activation pathway)
3️⃣ Common pathway

All converge at Factor X.

🔴 EXTRINSIC PATHWAY (Fast pathway)

Trigger:

Tissue injury exposes Tissue Factor (Factor III).

Flowchart

Tissue injury → Tissue Factor (III) released → Activates Factor VII to VIIa → VIIa activates Factor X → Common pathway begins

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🧪 Lab Test

PT (Prothrombin Time) monitors:

- VII (most sensitive)
- X
- V
- II (prothrombin)
- I (fibrinogen)

🧠 High-Yield:

- First factor to drop in warfarin therapy = Factor VII
- Therefore PT rises first

🔵 INTRINSIC PATHWAY (Contact activation)

Triggered by exposure to:

- Collagen
- Negatively charged surfaces

Flowchart

Collagen exposure
→ XII → XIIa
→ XI → XIa
→ IX → IXa
→ IXa + VIIIa
→ Activate X
→ Common pathway

🧪 Lab Test

PTT (Partial Thromboplastin Time) monitors:
All factors EXCEPT:

- VII

- XIII

So it tests:

XII, XI, IX, VIII, X, V, II, I

📊 Hemophilia Table

Disorder	Factor Deficiency	Lab Finding
Hemophilia A	VIII	↑ PTT
Hemophilia B	IX	↑ PTT
vWD	↓ vWF (↓ VIII stability)	↑ Bleeding time ± ↑ PTT

🧠 vWF protects Factor VIII from degradation.

🟢 COMMON PATHWAY

All pathways converge at Factor X.

Flowchart

X → Xa
→ Xa + Va
→ Prothrombin (II) → Thrombin (IIa)
→ Fibrinogen (I) → Fibrin
→ XIII → XIIIa
→ Cross-linked fibrin mesh 🧵

🧠 Why Thrombin Is So Important

Thrombin:

- Converts fibrinogen → fibrin
- Activates XIII
- Activates V, VIII, XI (positive feedback 🔥)
- Activates platelets

Thrombin = central amplifier of clotting

🧪 PT vs PTT Quick Comparison

Test	Pathway	Key Factor	Clinical Use
PT	Extrinsic + common	VII	Warfarin monitoring
PTT	Intrinsic + common	VIII, IX	Heparin monitoring

💊 ANTICOAGULANTS

Heparin

Mechanism:

Heparin

→ Activates antithrombin III

→ Inhibits:

- IIa (thrombin)
- Xa

- IXa
- XIa
- XIIa

Monitoring: ↑ PTT

LMWH mainly inhibits Xa.

Warfarin

Inhibits:

- Vitamin K epoxide reductase
- ↓ Factors II, VII, IX, X
- ↓ Protein C & S

Monitoring: PT/INR

🧠 Early warfarin → hypercoagulable (Protein C drops first)

Direct Xa inhibitors

- Rivaroxaban
- Apixaban

Block Xa directly.

Direct Thrombin Inhibitors

- Dabigatran
- Argatroban
- Bivalirudin

Block thrombin directly.

🧬 Regulatory Anticoagulant Proteins

Protein C → Inactivates Va & VIIIa

Protein S → Cofactor for Protein C

Antithrombin III → Inhibits thrombin & Xa

⚡ KININ SYSTEM

Triggered by Factor XII.

Flowchart

Factor XII activation
→ Prekallikrein → Kallikrein
→ HMWK → Bradykinin
→ Bradykinin causes:

- Vasodilation
- Increased vascular permeability
- Pain

🔥 ACE Inhibitor Mechanism

ACE normally:

- Breaks down bradykinin

ACE inhibitor → ↑ Bradykinin

→ Cough

→ Angioedema

🧠 C1 Esterase Inhibitor Deficiency

↓ C1 esterase inhibitor → Uncontrolled kallikrein activity

→ ↑ Bradykinin → Hereditary angioedema

🔁 FIBRINOLYTIC SYSTEM

Clot must eventually be removed.

Flowchart

Plasminogen

→ (tPA) → Plasmin

→ Fibrin breakdown

→ Fibrin degradation products (D-dimer)

💊 Thrombolytics

- tPA
- Alteplase
- Reteplase
- Tenecteplase

Increase plasmin.

🚫 Antifibrinolytics

- Aminocaproic acid
- Tranexamic acid

Block plasmin activation.

📊 Complete Integrated Flow

Vessel injury

→ Extrinsic pathway (TF + VII) OR Intrinsic pathway (XII → XI → IX → VIII)

→ X activation

→ Prothrombin → Thrombin

→ Fibrinogen → Fibrin

→ XIII cross-links

→ Stable clot 🧵

→ tPA activates plasmin

→ Clot breakdown

→ D-dimer formed

🚨 Clinical Correlations

DIC

Widespread clotting → Consumption of factors → ↑ PT → ↑ PTT → ↑ D-dimer → ↓ Platelets

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Liver Disease

Liver makes clotting factors → Prolonged PT first (Factor VII short half-life)

Vitamin K Deficiency

Affects:

II, VII, IX, X

Protein C & S

PT prolonged first.

⚠️ Exam Traps

- XII deficiency → ↑ PTT but NO bleeding
- PT normal, PTT high → think intrinsic problem
- PTT normal, PT high → think Factor VII issue
- D-dimer = fibrin breakdown, not just clot presence
- Thrombin activates upstream factors (positive feedback)

🎯 Memory Grid

Extrinsic = 7

Intrinsic = 12 → 11 → 9 → 8

Common = 10 → 5 → 2 → 1 → 13

🧪 Vitamin K–Dependent Coagulation

Vitamin K is essential for proper activation of several clotting factors. Without it, coagulation factors are synthesized but nonfunctional.

🔬 Why Vitamin K Is Important

Vitamin K enables γ-carboxylation of glutamate residues on certain clotting factors.

This modification allows factors to: → Bind calcium (Ca^{2+}) → Attach to phospholipid surfaces → Participate in coagulation

Without γ-carboxylation → factors cannot bind calcium → cannot function.

🟢 Vitamin K-Dependent Factors

Mnemonic: I_0972 + C & S

- II (Prothrombin)
- VII
- IX
- X
- Protein C
- Protein S

🔁 Vitamin K Cycle (VERY HIGH-YIELD)

Reduced Vitamin K (active form) → Used by γ-glutamyl carboxylase → Carboxylates factors II, VII, IX, X, C, S → Vitamin K becomes oxidized → Vitamin K epoxide reductase converts it back to reduced form

This recycling is critical 🔁

💊 Warfarin Mechanism

Warfarin → Inhibits Vitamin K epoxide reductase → Prevents regeneration of reduced vitamin K → ↓ γ-carboxylation → Produces inactive clotting factors

Monitoring: PT/INR (because Factor VII is affected first)

🧠 Why PT Rises First

Factor VII has:

- Shortest half-life (~6 hours)

So warfarin or vitamin K deficiency → Factor VII drops first → PT prolongs before PTT

🔥 Warfarin-Induced Hypercoagulability

Warfarin decreases:

- Clotting factors
- Protein C (natural anticoagulant)

Protein C has short half-life.

Warfarin initiation
→ Protein C drops quickly
→ Temporary hypercoagulable state
→ Risk of skin necrosis ⚠️

That's why we "bridge" with heparin initially.

🧠 Vitamin K Deficiency Causes

→ ↓ II, VII, IX, X
→ ↓ Protein C & S
→ ↑ PT (first)
→ Later ↑ PTT

Causes:

- Newborns (sterile gut, low stores)
- Broad-spectrum antibiotics
- Fat malabsorption
- Liver disease
- Warfarin overdose

👶 Neonatal Vitamin K Deficiency

Newborns:

- Sterile gut (no bacteria producing vitamin K)
- Poor placental transfer
- Low hepatic stores

→ Risk of hemorrhagic disease of newborn

Prevention:

IM Vitamin K at birth 💉

🟡 Anticoagulation Pathways (Regulatory Proteins)

Protein C Pathway

Thrombin → Activates Protein C → Activated Protein C (APC) + Protein S → Inactivates Va & VIIIa → Decreases clot formation

So Protein C is a natural anticoagulant.

🧬 Factor V Leiden

Mutation in Factor V → Resistant to activated Protein C → Cannot be inactivated → Increased clot risk

Most common inherited thrombophilia.

🔵 Antithrombin III System

Antithrombin III inhibits:

- Thrombin (IIa)
- IXa
- Xa
- XIa
- XIIa

Heparin enhances antithrombin activity.

Flowchart:

Heparin → Binds antithrombin III → Conformational change → Strong inhibition of Xa & IIa

LMWH mainly inhibits Xa.

🧵 Fibrin Formation Review

Prothrombin (II) → Thrombin (IIa) → Fibrinogen (I) → Fibrin → XIIIa cross-links → Stable clot

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🧠 Integrated Flowchart (Procoagulation vs Anticoagulation Balance)

Vessel injury → Vitamin K-dependent factors activated → Thrombin generated → Fibrin formed

Simultaneously:

Thrombin → Activates Protein C → APC + Protein S → Inactivates Va & VIIIa → Limits clot extension

And:

Antithrombin III → Inhibits thrombin & Xa

Balance determines clot formation ⚖️

📊 Comparison Table

Condition	PT	PTT	Key Feature

Early Vitamin K deficiency	↑	Normal	VII affected first
Severe deficiency	↑	↑	All vitamin K factors reduced
Warfarin therapy	↑	± ↑	Monitor INR
Liver disease	↑	↑	All factors reduced
Factor V Leiden	Normal	Normal	Hypercoagulable

🚨 USMLE Traps

- Vitamin K deficiency → PT rises first
- Warfarin initially pro-thrombotic
- Factor V Leiden = thrombosis, NOT bleeding
- Neonates need vitamin K injection
- Antibiotics can cause coagulopathy
- tPA increases plasmin (thrombolysis)

🎯 Memory Hook

Vitamin K = makes factors "sticky" (via calcium binding)

Warfarin = blocks recycling

Heparin = boosts antithrombin

Protein C = brakes system

Factor V Leiden = brake failure

🩸 Bleeding Time, PT, PTT Table

🔥 Patterns

- ↑ Bleeding Time Only → Platelet problem
- ↑ PT Only → Extrinsic pathway problem → Factor VII issue
- ↑ PTT Only → Intrinsic pathway defect (VIII, IX, XI, XII) or heparin

- ↑ PT First → Vitamin K deficiency or Warfarin
- ↑ PT + ↑ PTT → Severe vitamin K deficiency, liver disease, DIC
- ↑ Everything (BT, PT, PTT) → DIC

Condition	Bleeding Time	PT	PTT	Rationale / Mechanism
ITP	↑	Normal	Normal	↓ Platelet count → impaired primary hemostasis
TTP / HUS	↑	Normal	Normal	Platelet consumption in microthrombi
Aplastic anemia	↑	Normal	Normal	Bone marrow failure → ↓ platelets
Uremia	↑	Normal	Normal	Platelet dysfunction (toxic metabolites impair adhesion)

Aspirin	↑	Normal	Normal	COX inhibition → ↓ TXA_2 → ↓ platelet aggregation
Bernard-Soulier syndrome	↑	Normal	Normal	Defective GpIb → impaired vWF-mediated adhesion
Glanzmann thrombasthenia	↑	Normal	Normal	Defective GpIIb/IIIa → impaired fibrinogen-mediated aggregation
von Willebrand disease	↑	Normal	↑ (sometimes normal)	↓ vWF → ↓ platelet adhesion + ↓ Factor VIII stabilization
Hemophilia A	Normal	Normal	↑	Intrinsic pathway defect (Factor VIII)
Hemophilia B	Normal	Normal	↑	Intrinsic pathway defect (Factor IX)
Heparin therapy	Normal	Normal	↑	Activates antithrombin → inhibits IIa & Xa → intrinsic pathway prolonged

Warfarin therapy	Normal	↑	↑ (later)	↓ Vitamin K–dependent factors (II, VII, IX, X); PT rises first (Factor VII shortest t½)
Vitamin K deficiency	Normal	↑	↑ (late)	↓ γ-carboxylation of II, VII, IX, X
Liver disease	Normal or ↑	↑	↑	↓ synthesis of clotting factors (II, VII, IX, X, V)
DIC	↑	↑	↑	Consumption of platelets + clotting factors
Factor XII deficiency	Normal	Normal	↑	Intrinsic lab abnormality but does NOT cause bleeding
Antiphospholipid syndrome	Normal	Normal	↑	Lupus anticoagulant interferes with phospholipid in test tube (lab artifact) but causes thrombosis in vivo

-> The End <-