

🩸 HEMATOLOGY AND ONCOLOGY FOR USMLE 🩸

Coagulation Disorders

📌 Prothrombin Time (PT)

🔍 What does PT test?

Evaluates the Extrinsic + Common pathway

Factors tested:

- VII (Extrinsic)
- X, V, II (prothrombin), I (fibrinogen) → Common pathway

🧠 Mnemonic:

"Play Tennis outside" → PT = Extrinsic pathway

📊 When is PT prolonged?

- Factor VII deficiency (earliest in Vit K deficiency ⚠)
 - Warfarin therapy
 - Liver disease
 - DIC
 - Severe vitamin K deficiency
-

INR (International Normalized Ratio)

$$\text{INR} = \text{Patient PT} / \text{Control PT}$$

- Normal = 1
- > 1 = prolonged PT
- Used to monitor warfarin therapy

Warfarin inhibits:

- Factors II, VII, IX, X
- Protein C and Protein S

⚠ Step 1 Trap:

Factor VII has the shortest half-life → PT prolongs first in vitamin K deficiency and warfarin therapy.

📌 Partial Thromboplastin Time (PTT)

🔍 What does PTT test?

Evaluates Intrinsic + Common pathway

Factors tested:

- XII, XI, IX, VIII → Intrinsic
- X, V, II, I → Common
- (NOT VII, NOT XIII)

🧠 Mnemonic:

"Play Table Tennis inside" → PTT = Intrinsic pathway

📊 When is PTT prolonged?

- Hemophilia A (VIII)

- Hemophilia B (IX)
 - Hemophilia C (XI)
 - Heparin therapy
 - Factor inhibitors (e.g., anti-VIII antibodies)
 - DIC
 - Severe liver disease
-

Thrombin Time (TT)

 What does TT measure?

Conversion of:

Fibrinogen → Fibrin

 TT is prolonged in:

- Anticoagulants (especially heparin)
- Hypofibrinogenemia
- DIC

- Advanced liver disease

 Think: TT checks the final step of coagulation.

Factor XIII

Neither PT nor PTT measures

 Why?

Factor XIII (Fibrin-stabilizing factor) acts after fibrin is already formed.

Sequence:

Fibrinogen → (Thrombin) → Fibrin → Factor XIII
cross-links fibrin

So XIII works after the clot has formed, stabilizing it.

 What measures Factor XIII?

Clot solubility test (most classic test)

Also called:

- SM urea clot solubility test
- Or acetic acid clot solubility test

👉 In Factor XIII deficiency, the fibrin clot forms normally
BUT it dissolves in SM urea within 24 hours.

Because:

Factor XIII is needed to cross-link fibrin strands and stabilize the clot.

② Specific Factor XIII activity assay

Used for confirmation in modern labs.

Mixing Study — Differentiating Deficiency vs Inhibitor

 Principle:

Patient plasma + Normal plasma → Repeat PT/PTT

Result	Interpretation
✓ Corrects	Clotting factor deficiency
✗ Does NOT correct	Factor inhibitor present

🧠 Why?

If a factor is missing → normal plasma supplies it → clotting normalizes.

If an inhibitor (antibody) is present → it also inactivates factors in normal plasma → no correction.

📌 Most common acquired inhibitor = Factor VIII inhibitor

🩸 Hemophilias

All are intrinsic pathway defects → ↑ PTT, normal PT

Hemophilia A

- Factor VIII deficiency
- X-linked recessive
- Most common hemophilia
- Think: "Hemophilia ATE (VIII)" 

Labs:

- ↑ PTT
- Normal PT
- Normal bleeding time

Clinical Features:

- Hemarthroses (bleeding into joints 🦵)
- Easy bruising
- Bleeding after trauma/dental procedures

Treatment:

- Desmopressin (\uparrow vWF \rightarrow stabilizes VIII)
 - Factor VIII concentrate
 - Efficizumab (bispecific antibody mimics VIII function)
-

Hemophilia B (Christmas Disease)

- Factor IX deficiency
- X-linked recessive

Labs:

- \uparrow PTT
- Normal PT

Treatment:

- Factor IX concentrate
-

Hemophilia C

- Factor XI deficiency
- Autosomal recessive

 Labs:

- ↑ PTT
- Normal PT

 Treatment:

- Factor XI concentrate

 Hemophilia Comparison Table

Feature	Hemophilia A	Hemophilia B	Hemophilia C
Factor	VIII	IX	XI
Inheritance	X-linked	X-linked	Autosomal recessive
PT	Normal	Normal	Normal

PTT	↑	↑	↑
Hemarthroses	Yes	Yes	Mild/Variable

Vitamin K Deficiency

Mechanism

Vitamin K is required for γ -carboxylation of:

- II
- VII
- IX
- X
- Protein C
- Protein S

This modification allows calcium binding → activation of clotting factors.

Without vitamin K → Factors produced but nonfunctional

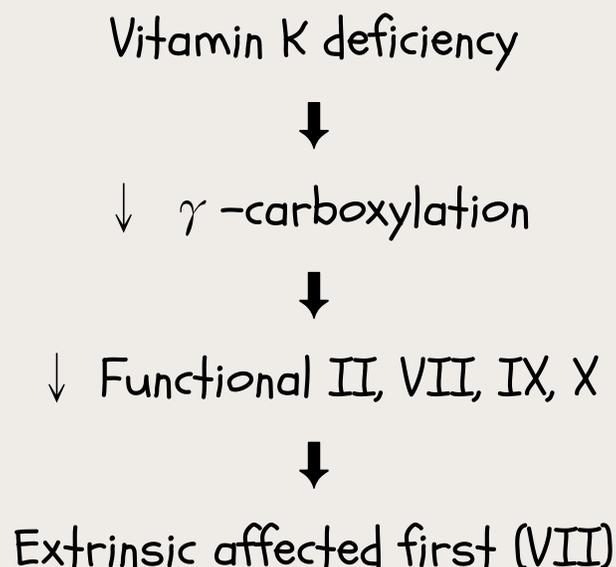
Lab Findings

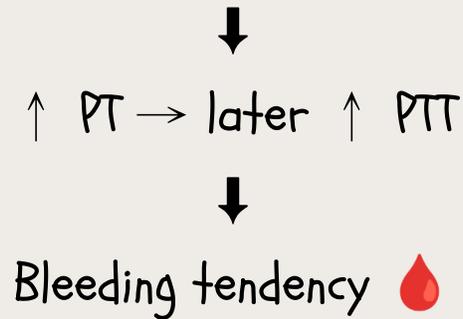
- ↑ PT (earliest)
- ↑ PTT (later)
- Normal bleeding time

⚠ Why PT increases first?

Factor VII has shortest half-life.

Flowchart — Vitamin K Deficiency





🎯 USMLE Points

- Isolated ↑ PT → think Factor VII or early Vit K deficiency
 - Isolated ↑ PTT → think Hemophilia
 - Both PT & PTT ↑ → think DIC, liver disease, severe Vit K deficiency
 - Mixing study correction = deficiency
 - No correction = inhibitor
-

🩸 Platelet Disorders

Core Concept: Primary Hemostasis

Primary hemostasis = Platelet plug formation

Steps:

1.  Adhesion → Platelets bind exposed collagen via vWF
2.  Activation → Shape change + granule release
3.  Aggregation → Platelets bind each other via GpIIb/IIIa

 All platelet disorders affect primary hemostasis

Hallmark Clinical Features of Platelet Disorders

- ↑ Bleeding Time (BT)
- Mucosal bleeding (epistaxis, gum bleeding)
- Petechiae
- Easy bruising
- Immediate bleeding after trauma

 Contrast:

- Platelet disorders → superficial bleeding
- Coagulation factor disorders → deep bleeding (hemarthroses)

Lab Patterns in Platelet Disorders

Parameter	Finding
Bleeding Time	↑
PT	Normal
PTT	Normal
Platelet Count	Usually ↓ (except qualitative disorders)

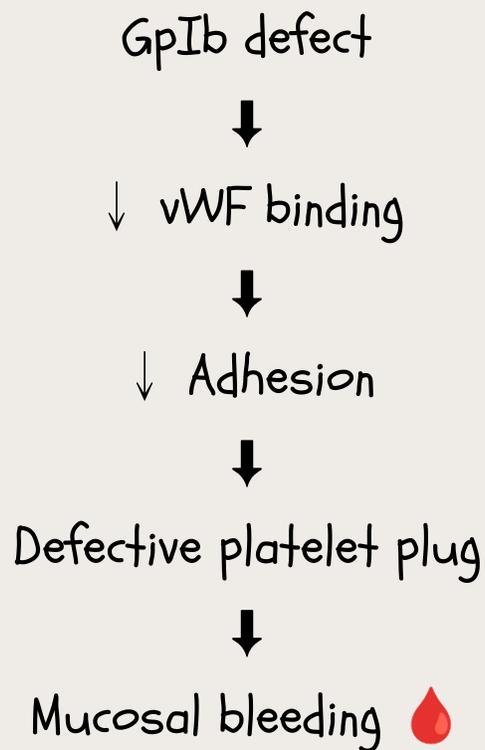
Bernard-Soulier Syndrome

Mechanism

Autosomal recessive defect in platelet adhesion

- ↓ GpIb receptor
 - ↓ Platelet binding to vWF
 - ↓ Adhesion to damaged endothelium
-

Pathway Flow



Labs

- ↓ Platelet aggregation
 - ↑ Bleeding time
 - Large platelets (giant platelets)
 - Platelet count: ↓ or normal
-

USMLE Clue

“Big platelets” + adhesion defect = Bernard-Soulier

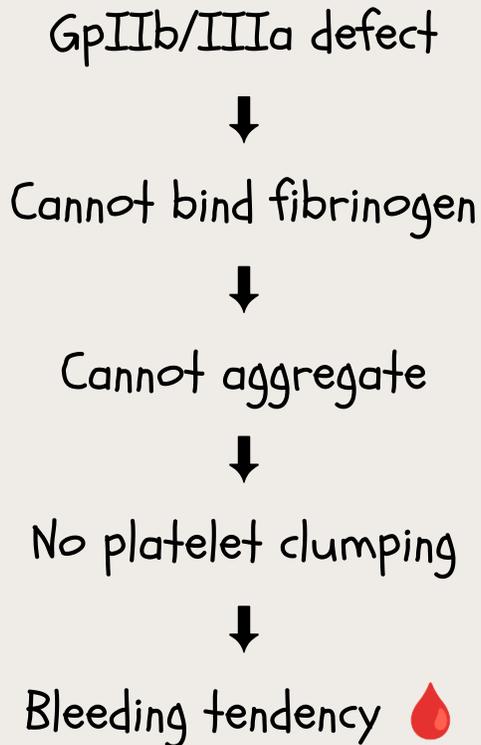
Glanzmann Thrombasthenia

Mechanism

Autosomal recessive defect in platelet aggregation

- ↓ GpIIb/IIIa (integrin α IIb β 3)
 - ↓ Platelet-to-platelet binding (via fibrinogen)
-

Pathway Flow



Labs

- ↑ Bleeding time
 - Normal PT/PTT
 - Platelet count: normal
 - Peripheral smear: no platelet clumping
-

Comparison

Feature	Bernard-Soulier	Glanzmann
Defect	Adhesion	Aggregation
Receptor	GpIb	GpIIb/IIIa
Platelet size	Large	Normal
Clumping	Reduced	Absent

Immune Thrombocytopenia (ITP)

Mechanism

Autoantibodies (usually IgG) against GpIIb/IIIa



Opsonized platelets



Splenic macrophage destruction



↓ Platelet count

Labs

- ↓ Platelet count
 - ↑ Bleeding time
 - Normal PT/PTT
 - ↑ Megakaryocytes in bone marrow
-

Causes

- Idiopathic
 - Autoimmune diseases (eg, SLE)
 - Viral infections (HIV, HCV)
 - Malignancy (CLL)
 - Drug-induced
-

Treatment

- Glucocorticoids
 - IVIG
 - Rituximab
 - TPO receptor agonists (eltrombopag, romiplostim)
 - Splenectomy (refractory cases)
-

USMLE Pearls

- Anti-GpIIb/IIIa antibodies
 - Increased megakaryocytes = bone marrow trying to compensate
 - Normal PT/PTT differentiates from DIC
-

Uremic Platelet Dysfunction

Mechanism

Renal failure



Accumulation of uremic toxins



Impaired platelet adhesion & aggregation

 Labs

- Normal platelet count
 - ↑ Bleeding time
 - Normal PT/PTT
-

 Key Point

Qualitative defect — platelets present but dysfunctional

 Thrombotic Microangiopathies (TMA)

These disorders:

- Form microthrombi in small vessels
- Cause thrombocytopenia
- Cause microangiopathic hemolytic anemia (MAHA)

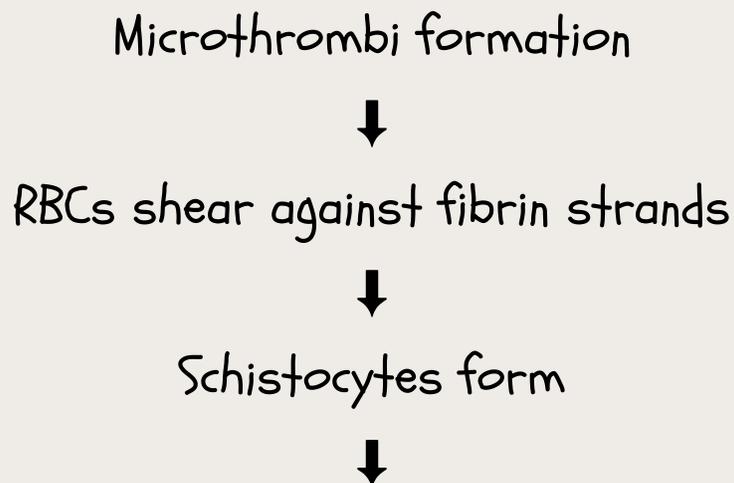
⚠ IMPORTANT:

Unlike DIC → coagulation cascade is NOT activated

So:

- PT normal
 - PTT normal
 - Fibrinogen normal
-

🧠 Pathophysiology Overview



Hemolysis



↑ LDH, ↓ Hb



Thrombotic Thrombocytopenic Purpura (TTP)



Epidemiology

Typically adult females



Mechanism

Deficiency or inhibition of ADAMTS13

ADAMTS13 normally cleaves large vWF multimers.



Flowchart

↓ ADAMTS13



Large vWF multimers accumulate



Excess platelet aggregation



Microvascular thrombosis



MAHA + Thrombocytopenia

Presentation

Classic pentad:

- Thrombocytopenia
 - MAHA (schistocytes, ↑ LDH)
 - Acute kidney injury
 - Fever
 - Neurologic symptoms
-

Labs

- ↓ Platelets
 - ↓ Hb
 - Schistocytes
 - ↑ LDH
 - Normal PT/PTT
-

 Treatment

 Emergency!

- Plasma exchange (removes antibodies + replaces ADAMTS13)
 - Glucocorticoids
 - Rituximab
-

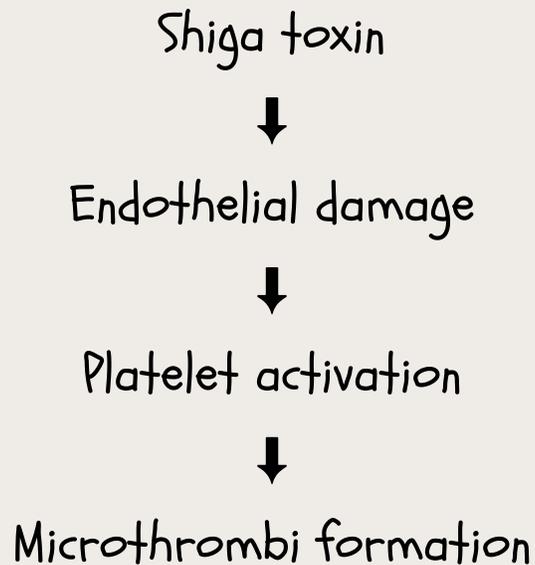
Hemolytic Uremic Syndrome (HUS)

 Epidemiology

Typically children

Mechanism

Shiga toxin-producing E. coli (O157:H7)



Presentation

Triad:

- Thrombocytopenia
- MAHA
- Acute kidney injury

Distinguishing feature:

- Bloody diarrhea
-

Labs

- ↓ Platelets
 - Schistocytes
 - ↑ LDH
 - Normal PT/PTT
-

Treatment

Supportive care

(Antibiotics may worsen toxin release ⚠)

VS TTP vs HUS vs DIC Comparison Table

Feature	TTP	HUS	DIC
ADAMTS13	↓	Normal	Normal
Trigger	Autoimmune	Shiga toxin	Sepsis, trauma, malignancy
PT/PTT	Normal	Normal	↑
Fibrinogen	Normal	Normal	↓
Neuro symptoms	Prominent	Mild	Variable
Bloody diarrhea	No	Yes	No
Treatment	Plasma exchange	Supportive	Treat underlying cause

Exam Points

- Normal PT/PTT + MAHA = Think TTP or HUS
 - Schistocytes = microangiopathic process
 - If PT/PTT prolonged → think DIC instead
 - Neurologic symptoms prominent → TTP
 - Child with bloody diarrhea → HUS
-

Mixed Platelet & Coagulation Disorders

These disorders affect both primary and secondary hemostasis, so lab patterns get more interesting.

von Willebrand Disease (vWD)

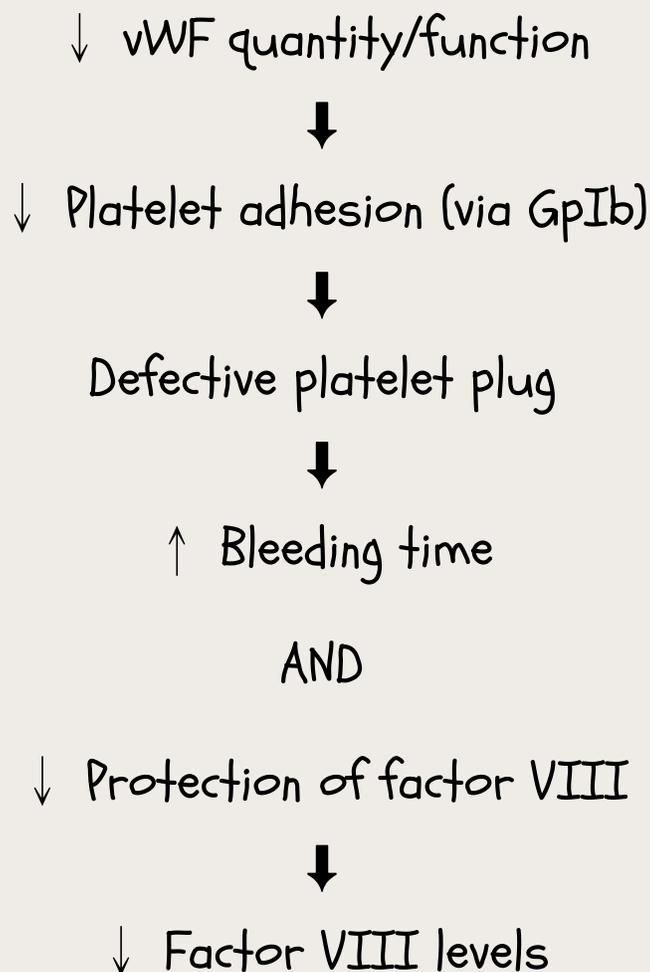
Core Concept

vWF has two major roles:

- 1] Platelet adhesion (primary hemostasis)
- 2] Stabilizes factor VIII (secondary hemostasis)

So deficiency affects both platelet function AND intrinsic pathway.

Pathophysiology Flow



↓
↑ PTT

Lab Pattern

Parameter	Finding
Platelet Count	Normal
Bleeding Time	↑
PT	Normal
PTT	Normal or ↑

 PTT increases because vWF carries factor VIII.

Genetics

- Most common inherited bleeding disorder

- Usually autosomal dominant
 - Typically mild
-

Clinical Presentation

- Menorrhagia
- Epistaxis
- Easy bruising
- Prolonged bleeding after dental procedures

 Think: mucosal bleeding + prolonged PTT + normal platelets.

Treatment

- Desmopressin (DDAVP) → releases vWF from endothelium
 - vWF concentrates (severe cases)
-

⚡ Disseminated Intravascular Coagulation (DIC)

📌 Core Concept

Widespread clotting factor activation → consumption → bleeding

You clot everywhere

Then you bleed everywhere

🧠 Mechanism Flowchart

Trigger (sepsis, trauma, etc.)



Massive tissue factor activation, factor III (it initiates extrinsic pathway by activating VII → VIIa)



Widespread thrombin generation



Microthrombi formation



Consumption of platelets + clotting factors



Bleeding + organ ischemia



Lab Pattern

Parameter	Finding
Platelet Count	↓
Bleeding Time	↑
PT	↑
PTT	↑
Fibrinogen	↓
D-dimer	↑

Smear	Schistocytes
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 Factor V and VIII levels decrease.

Clinical Clues

- Oozing from IV sites
 - Bleeding + thrombosis
 - Acute organ failure
-

Causes Mnemonic: SSSSTOP Making New Thrombi

- Sepsis (gram negative common)
- Snake bites
- Shock/Heat stroke
- Trauma
- Obstetric complications
- Pancreatitis
- Malignancy

- Nephrotic syndrome
 - Transfusion
-

Acute vs Chronic DIC

Type	Characteristics
Acute	Rapid consumption → life-threatening bleeding
Chronic	Compensated by liver → more thrombosis

USMLE Pearl

Normal PT/PTT = TTP/HUS

Prolonged PT/PTT = DIC

Hereditary Thrombophilias

Autosomal dominant disorders causing hypercoagulable states.

Primary problem: too much clotting, not bleeding.

Antithrombin Deficiency

Mechanism

Antithrombin normally inhibits:

- Thrombin (IIa)
- Factor Xa

Deficiency → reduced inhibition → thrombosis

Lab Pattern

- PT normal
- PTT normal

- Heparin response blunted (heparin requires antithrombin)

⚠ Key exam point:

Heparin ineffective because it works by activating antithrombin.

🧠 Acquired Causes

- Nephrotic syndrome → loss in urine
 - Renal failure
-

🧬 Factor V Leiden

📌 Most Common Inherited Thrombophilia

- ◆ What does Factor V do?

Once activated:

- Factor V \rightarrow Factor Va
- Factor Xa + Factor Va + Ca^{2+} + phospholipids = Prothrombinase complex

 Function of the Prothrombinase Complex:

Converts:

Prothrombin (Factor II) \rightarrow Thrombin (Factor IIa)

And thrombin then:

- Converts fibrinogen \rightarrow fibrin
- Activates Factors V, VIII, XI (positive feedback)
- Activates XIII \rightarrow stabilizes fibrin

 Pathophysiology

Point mutation: Arg506Gln

Factor V becomes resistant to degradation by activated protein C (APC)

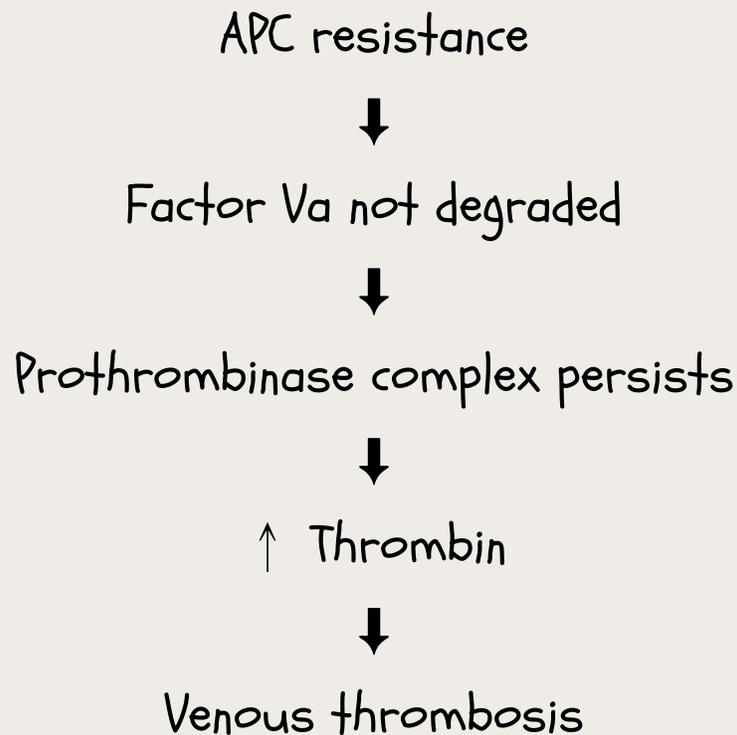
Normally:

Protein C inactivates Va and VIIIa

With mutation:

Factor V persists → excessive clotting

 Flow



 Clinical Clues

- DVT at young age
- Cerebral vein thrombosis

- Recurrent pregnancy loss
-

Protein C or Protein S Deficiency

Function

Protein C + S:

Inactivate factors Va and VIIIa

“Protein C Cancels, Protein S Stops” coagulation.

Mechanism

↓ Protein C/S



Va and VIIIa remain active



Excess thrombin formation



Thrombosis

! Warfarin-Induced Skin Necrosis

Warfarin initially decreases Protein C faster than procoagulant factors



Temporary hypercoagulable state



Skin necrosis

Prothrombin G20210A Mutation

Mechanism

Mutation in 3' untranslated region



↑ Prothrombin production



↑ Plasma thrombin



Venous clots



Hereditary Thrombophilia Comparison Table

Disorder	Mechanism	Key Clue
Antithrombin deficiency	↓ inhibition of IIa & Xa	Heparin resistance
Factor V Leiden	APC resistance	Most common inherited thrombophilia
Protein C deficiency	↓ Va, VIIIa inactivation	Warfarin skin necrosis
Protein S deficiency	↓ Protein C function	Similar to Protein C deficiency

Prothrombin mutation	↑ Prothrombin levels	Venous thrombosis
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 Integration Table — DIC vs vWD vs Thrombophilia

Feature	vWD	DIC	Thrombophilia (hypercoagulable states)
Bleeding	Yes	Yes + clots	No
Thrombosis	Rare	Yes	Yes
PT	Normal	↑	Normal
PTT	↑	↑	Normal
Platelets	Normal	↓	Normal

D-dimer	Normal	↑	Normal
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Exam Tricks

If question shows:

- Mucosal bleeding + ↑ PTT + normal platelets → vWD
 - Bleeding + thrombosis + ↑ PT/PTT + ↓ fibrinogen → DIC
 - Recurrent DVT in young patient → think inherited thrombophilia
 - Heparin not working → antithrombin deficiency
 - Warfarin skin necrosis → protein C deficiency
-

Blood Transfusion Therapy

Packed Red Blood Cells (PRBCs)

Dose Effect

- ↑ Hemoglobin \approx 1 g/dL per unit
- ↑ Hematocrit \approx 3% per unit
- Improves oxygen-carrying capacity

Clinical Use

- Acute blood loss
- Severe symptomatic anemia
- Hemodynamic instability due to anemia

Important

- Does NOT provide clotting factors
 - Does NOT significantly correct coagulopathy
-

Platelets

Dose Effect

- ↑ Platelet count \approx 30,000/ μ L per apheresis unit
- (\approx 5,000/ mm^3 per random donor unit)

Clinical Use

- Active significant bleeding + thrombocytopenia
- Platelet count <10,000 (prophylaxis)
- Qualitative platelet dysfunction
- Before invasive procedures (if low platelets)

! Not useful in:

- Immune destruction (e.g., ITP) unless life-threatening bleed
-

③ Fresh Frozen Plasma (FFP)

 Contains:

- All coagulation factors
- All plasma proteins

Clinical Use

- Liver failure (cirrhosis)
- DIC

- Multiple factor deficiencies
 - Immediate warfarin reversal (if PCC unavailable)
-

4 Prothrombin Complex Concentrate (PCC)

 Contains:

- Factors II, VII, IX, X
- Protein C & S

 Clinical Use

- Rapid warfarin reversal
- Major bleeding with elevated INR

 Faster and requires less volume than FFP.

5 Cryoprecipitate

 Contains:

- Fibrinogen

- Factor VIII
- Factor XIII
- vWF
- Fibronectin

Clinical Use

- Hypofibrinogenemia
 - DIC with low fibrinogen
 - Massive transfusion protocol
 - Factor VIII deficiency (if specific concentrates unavailable)
-

6 Albumin

Effect

- ↑ Intravascular oncotic pressure
- Volume expansion

Clinical Use

- Post large-volume paracentesis
 - Therapeutic plasmapheresis
 - Severe hypoalbuminemia
-

Blood Transfusion Complications

1) Infection Transmission

- Very low risk (screening is advanced)
-

2) Transfusion Reactions

- Acute hemolytic (ABO mismatch)
 - Febrile non-hemolytic
 - Allergic
 - Anaphylactic
-

3) TACO (Transfusion-Associated Circulatory Overload)

- Volume overload
- Pulmonary edema
- Hypertension
- Common in elderly or heart failure patients

👉 Cardiogenic pulmonary edema

④ TRALI (Transfusion-Related Acute Lung Injury)

- Hypoxia
- Inflammation
- Noncardiogenic pulmonary edema
- Hypotension

👉 Occurs within 6 hours

👉 Immune-mediated (anti-HLA and anti HNA antibodies)

⑤ Iron Overload

- Chronic transfusions

- May lead to secondary hemochromatosis
-

6 Hypocalcemia

- Citrate in stored blood chelates Ca^{2+}
 - Seen in massive transfusion
-

7 Hyperkalemia

- Old RBC units \rightarrow cell lysis \rightarrow \uparrow K^+
-

Exam Pearls

Clinical Scenario	Give
Hb 6 g/dL	PRBC

INR 6 with bleeding (warfarin)	PCC
Low fibrinogen in DIC	Cryoprecipitate
Platelets 8,000	Platelets
Post-paracentesis	Albumin

 Coagulation Cascade — Factor Lists

 Extrinsic Pathway

(Measured by PT)

- Factor VII
- Tissue Factor (Factor III)

Mnemonic:

 "7 is outside" (Extrinsic = short pathway)

● Intrinsic Pathway

(Measured by PTT)

- Factor XII
- Factor XI
- Factor IX
- Factor VIII

Mnemonic:

👉 "TENET" = 12, 11, 9, 8

● Common Pathway

(Affects both PT & PTT)

- Factor X
- Factor V
- Factor II (Prothrombin)
- Factor I (Fibrinogen)
- Factor XIII (stabilizes fibrin)

Mnemonic:

👉 "10 → 5 → 2 → 1 → 13"

🟡 Vitamin K-Dependent Factors

- Factor II
- Factor VII
- Factor IX
- Factor X
- Protein C
- Protein S

Mnemonic:

👉 "1972 + C, S"

(Important: 1972 refers to 10, 9, 7, 2 — NOT factor I)

🟢 Factors Produced by the Liver

👉 All clotting factors except vWF

So:

- I
- II
- V
- VII
- VIII
- IX
- X
- XI
- XII
- XIII
- Protein C
- Protein S
- Antithrombin

⚠ Note:

- Factor VIII is produced by liver sinusoidal endothelial cells
- vWF is produced by endothelial cells & megakaryocytes

◆ Positive Feedback Targets of Thrombin

1. Factor V \rightarrow Va

- Enhances the common pathway (Xa + Va \rightarrow more thrombin)

2. Factor VIII \rightarrow VIIIa

- Boosts the intrinsic pathway (IXa + VIIIa \rightarrow more Xa \rightarrow more thrombin)

3. Factor XI \rightarrow XIa

- Activates intrinsic pathway earlier (XII \rightarrow XI \rightarrow IX \rightarrow VIII \rightarrow X \rightarrow thrombin)

4. Platelets

- Activates platelets \rightarrow more PL surface for coagulation
- Releases ADP and thromboxane A₂ \rightarrow recruits more platelets

Mnemonic: P-5811

Warfarin Inhibits

Warfarin inhibits Vitamin K epoxide reductase

→ ↓ Gamma-carboxylation of:

- II
- VII
- IX
- X
- Protein C
- Protein S

 Step 1 favorite:

- Protein C falls first → transient hypercoagulability
→ skin necrosis

Heparin Inhibits

Heparin activates Antithrombin III

Antithrombin inhibits:

- Factor IIa (Thrombin)
- Factor Xa
- Also inhibits IXa, XIa, XIIa (less emphasized)

High-yield:

- Unfractionated heparin → inhibits IIa & Xa
 - LMWH (e.g., enoxaparin) → mainly inhibits Xa
-

Acute Phase Reactants

- Fibrinogen (Factor I)
- Factor VIII
- vWF

(↑ in inflammation, pregnancy, OCP use)

Contact Factors (Intrinsic Initiators)

- Factor XII
- High molecular weight kininogen
- Prekallikrein

 Factor XII deficiency:

- ↑ PTT
- NO bleeding

 Natural Anticoagulants

- Protein C (inhibits Va and VIIIa)
- Protein S (cofactor for protein C)
- Antithrombin III
- TFPI (Tissue factor pathway inhibitor)

 Lab Associations

Condition	PT	PTT
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Hemophilia A (Factor VIII)	Normal	↑
Hemophilia B (Factor IX)	Normal	↑
Factor VII deficiency	↑	Normal
DIC	↑	↑
Vitamin K deficiency	↑ first	↑ later

Coagulopathies — Inheritance Patterns

Disorder	Inheritance
Hemophilia A	X-linked recessive
Hemophilia B	X-linked recessive

Hemophilia C	Autosomal recessive
von Willebrand disease (Type 1 & 2)	Autosomal dominant
von Willebrand disease (Type 3)	Autosomal recessive
Factor V Leiden	Autosomal dominant
Prothrombin gene mutation (G20210A)	Autosomal dominant
Protein C deficiency	Autosomal dominant
Protein S deficiency	Autosomal dominant
Antithrombin III deficiency	Autosomal dominant
Factor XIII deficiency	Autosomal recessive
Afibrinogenemia	Autosomal recessive

Dysfibrinogenemia	Autosomal dominant
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Platelet Disorders — Inheritance Only

Disorder	Inheritance
Glanzmann thrombasthenia	Autosomal recessive
Bernard-Soulier syndrome	Autosomal recessive
Storage pool disease	Usually autosomal recessive

<- The End ->