MEDICINE

432 Team

30

Bleeding Disorders

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

NO OBJECTIVES

❖ Normal Hemostasis

A protective mechanism that has evolved to maintain physiological Haemostasis. Blood coagulation is complex and finely balanced system of activating & inhibitory feed-back or feed-forward pathways with integration & coordination of its five major components i.e.,

- Blood Vessels
- Blood Platelets.
- Coagulation factors
- Coagulation inhibitors
- Fibrinolytic system

(Links with immune system)

Blood Vessels: First line of defense in haemostasis. Vascular endothelium synthesizes & releases a variety of factors and also has receptors for large no. of molecules. Endothelium is usually activated by trauma, or stimulated by thrombin, cytokines or shear stress:

- Leucocyte & Platelet adhesion
- Inflammation
- Phagocytosis
- Vascular Permeahbity

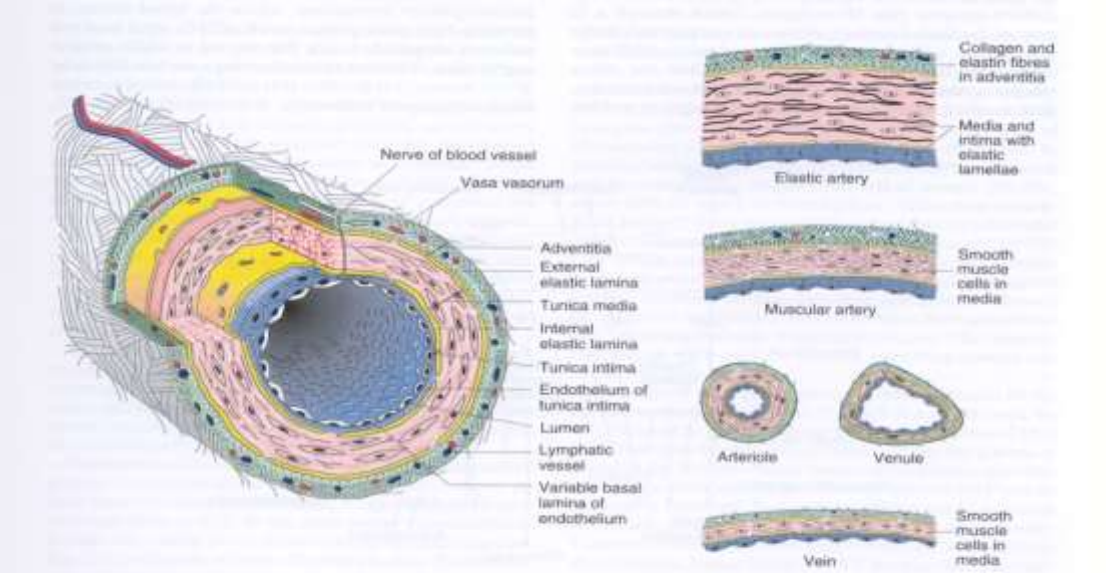


Figure 26.2 Structure of blood vessels. The muscularity and elasticity of vessels vary in different regions of the circulation, but all are lined by antithrombogenic endothelium and surrounded by adventitia expressing tissue factor (from *Gray's Anatomy*, by permission of the publisher).

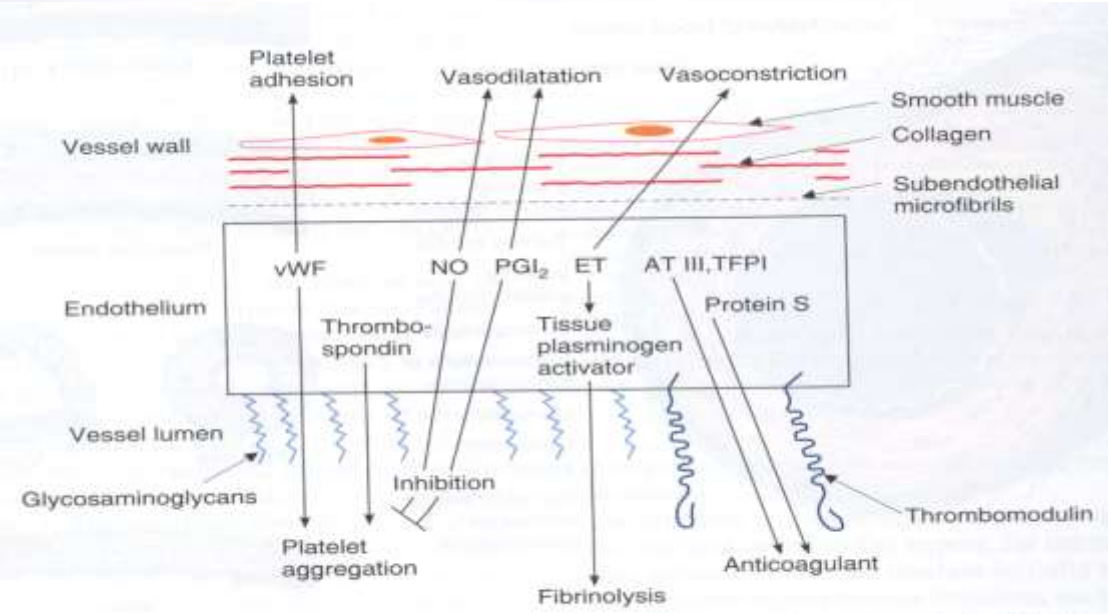
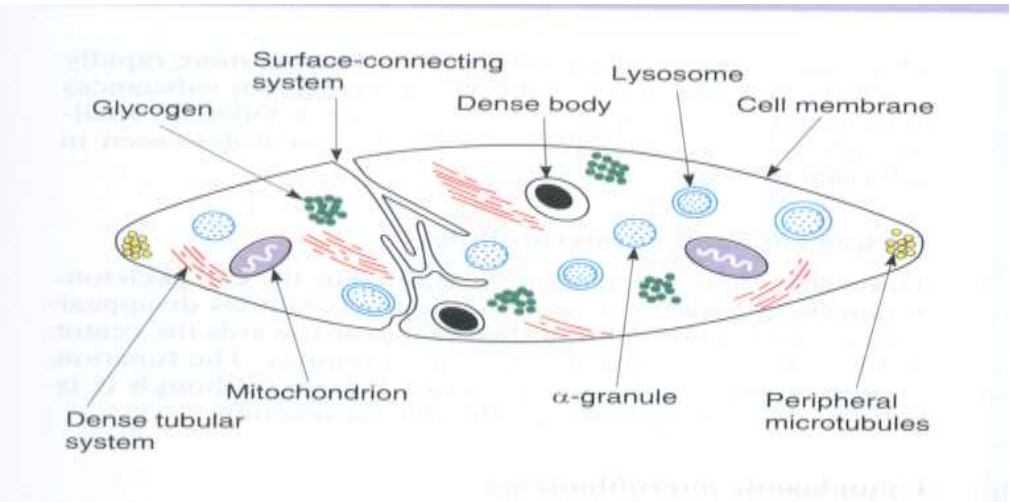


Figure 26.3 Haemostatic and vasculoregulatory factors expressed by endothelial cells. NO = nitrous oxide; ET = endothelin; vWF = von Willebrand factor; PG = prostaglandin; AT III = antithrombin III; TFPI = tissue factor pathway inhibitor.

- Most of the heparin that we are using comes from Chinese pigs.
- Heparin stick to the endothelium by charge , so the charge is on the endothelium.
- Endothelium is responsible to repel the protein.
- Sub-endothelium is highly charged but with the opposite, so when you injure endothelium you will expose yourself to the opposite charge which will attract the protein in.
- Endothelial cell will produce Vwf :Von Willebrand factor " essential protein

- **Platelets:**

Platelets are fragments of the cytoplasm of megakaryocytes formed in the bone marrow and are non-nucleated. Many substances can induce platelet aggregation e.g., ADP, TXA_2, adrenaline, 5HT, vasopressin and platelet activating factor. This helps in forming a platelet plug at the site of injury & stop bleeding.



- Platelets are not cells. They are fragments "very active" of megakaryocytes.
- Life span of platelet:-5-7 days "disturb very quickly and the moment you shake them little bit they get activated ".
- Platelets are full of granules (α granules (or called δ granule)) which play a major role on attracting coagulation (coagulation is not allowed to happen in circulation but happens at the site of injury)
- They have connected tubules to increase surface area when platelet gets activated it looks like star "the connected tubule flip to the other way"

Table 26.3 Some important platelet dense body and α-granule contents

Dense bodies	
ADP	Aggregation, vasoconstriction
ATP	Degrades to ADP
5-HT	Vasoconstriction, aggregation
Calcium	?
Pyrophosphate	?
Alpha-granules	
PF4	Heparinoid neutralization
Beta-thromboglobulin	? Chemotaxis
Thrombospondin	? Aggregation
PDGF	Mitogenesis, vessel repair
vWF	Adhesion, aggregation
Fibrinogen	Aggregation, coagulation
Factor V	? Prothrombinase activity
Fibronectin	Fibroblast and platelet adhesion
PAI-1	Inhibition of fibrinolysis
α_2-antiplasmin	Inhibition of fibrinolysis

Coagulation Factors

Table 26.4 Some characteristics of clotting factors in man

Traditional name	Preferred nomenclature	Mol. wt	Plasma conc. (μg/ml)	Half-life (h)	Gene size; location*	Product†
Fibrinogen	Factor I	340 000	2–4 × 10^3	90	50kb; C4q26–q28	3026
Aα-chain		56 000				
Bβ-chain		52 000				
	γ-chain	46 000				
Prothrombin	Factor II	72 000	120	65	24 kb; 11p11	579
Tissue factor	Factor III	45 000	0	–	12.6 kb; 1p21	263
Calcium	Factor IV	40	100	–	–	–
Proaccelerin	Factor V	330 000	10	15	6.8 kb; 1q21–25	2224
Proconvertin	Factor VII	48 000	1	5	12.8 kb; 13q34	406
Antihaemophilic factor	Factor VIII	360 000	0.05	10	190 kb; Xq28	2332
Christmas factor	Factor IX	57 500	4	25	35 kb; Xq26	415
Stuart–Prower factor	Factor X	55 000	12	40	25 kb; 13q34	445
Plasma thromboplastin antecedent	Factor XI	160 000	6	45	25 kb; 4q35	1214
Hageman factor	Factor XII	85 000	40	50	13.5 kb; 5q33	536
Fibrin stabilizing factor	Factor XIII	320 000	20	200	a 160 kb; 6 p ter; b 28 kb; 1q31	a = 731 b = 641
Fletcher factor	Prekallikrein	90 000	40	35	?	619
Fitzgerald factor‡	High mol. wt Kininogen	120 000	70	150	27 kb; C3q26	626

* Chromosome number and band location.
† Number of amino acids.
‡ Also known as Williams, Flaujeac or Reid factors.

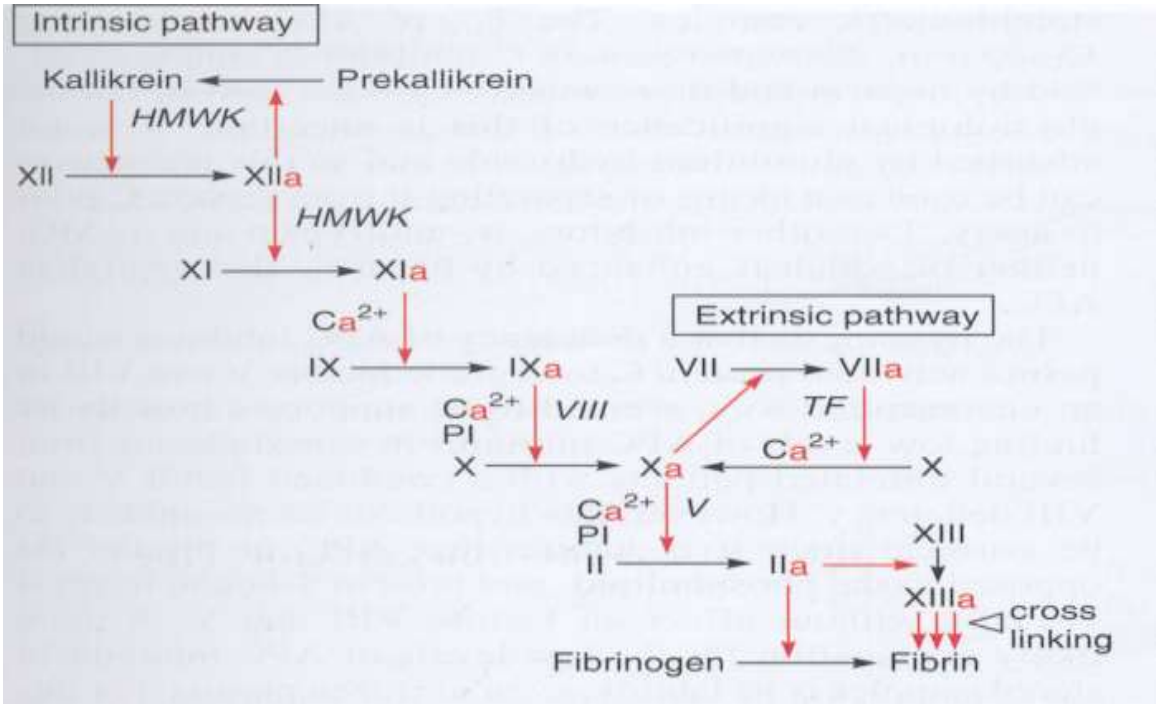
Naturally Occurring Anticoagulants in Blood

Table 26.5 Some characteristics of inhibitors of procoagulant serine proteases

Inhibitor	Mol. wt (kDa)	Plasma conc. μg/ml	Plasma conc. μmol/l	T1/2 (h)	Chromosomal position	Major substrate	Other substrates
Antithrombin	58	125	2.5	60	1q23–q25	IIa, Xa	IXa, XIa, XIIa
Heparin cofactor II	66	80	1.2	?	22q11	IIa	–
α_1-antitrypsin	55	1500	20–30	96	14q31–q32	XIa, Xa	Plasmin
C_1 esterase inhibitor	105	180	2.8	40	11p11–q13	KK, XIa	XIa
α_2-antiplasmin	70	70	1.0	60	18p11–q11	Plasmin	KK, XIIa, XIa
α_2-macroglobulin	725	2500	3.0	240	?	KK	IIa
Tissue factor pathway inhibitor	32	0.1	0.003	?	2q31–q32	TF–VIIa	Xa

KK = kallikrein

Traditional Coagulation Pathway



❖ **Intrinsic Pathway:**

•The trigger is the activation of factor XII by contact with foreign surface, injured blood vessel, and glass.

•Activated factor XII will activate factor XI

•Activated factor Xl will activate IX

•Activated factor IX + factor VIII + platelet phospholipid factor (PF3)+ Ca activate factor X.

❖ **Extrinsic Pathway:**

•Triggered by material released from damaged tissues (tissue thromboplastin)

•Tissue thromboplastin + VII + Ca >> activate X

❖ **Common pathway for both intrinsic and extrinsic pathways:**

•Activated factor X + factor V +PF3 + Ca activate prothrombin activator; a proteolytic enzyme which activates prothrombin.

•Activated prothrombin activates thrombin

•Thrombin acts on fibrinogen and change it into insoluble thread like fibrin.

• Factor XIII + Calcium strong fibrin (strong clot)

The coagulation intrinsic &extrinsic pathways have been invented to monitor warfarin and heparin. Extrinsic pathway which we really need to initiate the clot.

- Extrinsic pathway measures warfarin , intrinsic pathway measures heparin
- TF:-tissue factor.
- X –> Xa (a:-activated).
- Factor VIII is a cofactor , so you don't need it much "who are the patent who defiant factor VIII? Hemophilia A
- In intrinsic pathway you need kallikrein or HMWK (High-molecular-weight kininogen)
- Why patients with hemophilia A bleed (you can live your daily life with just the extrinsic pathway) -> we need factor VIII to sustain the propagation of the cascade
- Thromboplastin is the strongest ever clotting insult that you can give to the circulation. You need just a micromole and the whole system will clot.

Problems with traditional coagulation pathway

- No explanation why FVIII or FIX deficiency causes clinically severe bleeding, since the extrinsic pathway ought to bypass the need for FVIII and FIX.
- No explanation for less severe bleeding in FXI deficiency
- No explanation for absent bleeding in FXII deficiency
- No explanation for the lag phase followed by explosively rapid thrombin generation observed experimentally

New Concept of Blood Coagulation

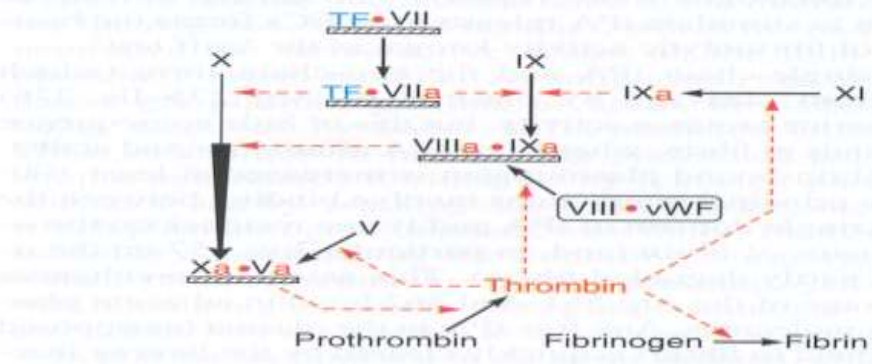


Figure 26.12 Thrombin generation network initiated by TF–VIIa. Symbols as in Figure 26–1. The activator complexes Xa–Va and IXa–VIII, assemble on the surface of an activated platelet. Factor VIII bound to vWF is inactive. Direct activation of X by TF–VIIa allows a small amount of thrombin to be generated, which feeds back to activate the cofactors V and VIII, leading to an explosive burst of further thrombin generation.

• Christmas disease — also called hemophilia B or factor IX hemophilia (Christmas was the patient name)
• New concept of blood coagulation:- crossover between the intrinsic and extrinsic pathway which happen in the surface of the platelets (not in the plasma)
• Platelet surface has phospholipids
• All clotting should appear at the surface of the cell membrane and cannot appear in the plasma

Approach to a Patient with Bleeding Tendency

History:

- Type of Bleeding:
  - Mucosal & Skin
  - Joint & Muscles

-Past Surgical History
-Family History: If +ve family history, pattern of inheritance
- Drugs

-Examination:

- Skin & oral mucosa
- Joints
- Associated abnormalities

-Investigations:

- Prothrombin time
- Partial thomboplastin time
- Platelet count
- Bleeding time
- Thrombin time

Note(s):

• Patient who have low platelet will have epistaxis whereas hemophilia patient their joint is destroyed.
• Coagulation factors is a major source in preventing bleeding in high stress areas (joints(e.g. knee)) while platelets are a major source in preventing bleeding in low stress areas (e.g. mouth , nose)
• prothrombin time: - when you standardize it-> it will become international normalized ratio (INR)
• Bleeding time: - Bleeding time is a crude test of hemostasis (the arrest or stopping of bleeding). It indicates how well platelets interact with blood vessel walls to form blood clots.-> can be used for low platelets. Cannot be used for hemophilia
• Thrombin time :- measures the clotting factors on the common pathway->suppose you have a patient with prolonged INR with normal thrombin time where do you think the problem ?->factor V & factor VII .patient with growing APTT with normal thrombin time where is the problem? Intrinsic pathway->factors XII,XI,IX and VIII

VERY IMPORTANT!!

First-line tests used in investigating acute haemostatic failure				
test			Platelet count	condition
PT	APTT	TT		
N	N	N	N	Disorder of platelet function. Factor XIII deficiency. Disorder of vascular haemostasis. Normal haemostasis.
Long	N	N	N	Factor VII deficiency. Early oral anticoagulation.
N	Long	N	N	Factors VIII: C, IX, XI, XII, prekallikrein, HMWK deficiency. Von willebrand's disease. Circulating anticoagulant
Long	Long	N	N	Vitamin K deficiency. Oral anticoagulants. Factors V, VII, X, II deficiency
Long	Long	Long	N	Heparin. Liver disease. Fibrinogen deficiency. Hyperfibrinolysis
N	N	N	Low	Thrombocytopenia
Long	Long	N	Low	Massive transfusion. Liver disease
Long	Long	Long	Low	DIC. Acute liver disease
N= Normal				

Notes:

- Warfarin affects clotting factors (II, VII, IX,X)
- Why in early Oral anticoagulation, PT looks prolong and TT is normal ? because VII
- has the shortest half-life "PT long", IX is normal "TT is normal"
- Factor VII is the shortest living factor (2 hours only)
- subendothelium is highly charged it cannot attract the simple coagulation factorsa
- needs vWF which will attract the platelets and in the surface of the platelets the
- coagulation factors will stick around
- vWF is essential in making a link between platelets and coagulation cascade
- vWF protect factor VIII
- Commonest coagulation defect is von willebrand disease

Inherited Platelet disorders

Thrombocythopathy	Molecular abnormality	Functional abnormality
Defect of adhesion		
Bernard–Soulier syndrome	↓GPIb, GPV, GPIX	F V:VWF binding to platelets ↓ Platelet adhesion to microfibrils ↓
von Willebrand platelet syndrome	↑GPIb	V:VWF binding to platelets ↑ Plasmatic FV:VWF level ↓ Platelet adhesion to subendothelium ↓ (?)
Defect of reactivity to collagen	↓GPIa	Platelet adhesion to collagen ↓
Defect of activation		
Abnormality in intracellular Ca^{++} fluxes	?	Defect in enzymatic reactions and metabolic events responsible for activation. Platelet release and aggregation ↓
Abnormality in prostaglandin pathway	Cyclooxygenase or thromboxane synthetase deficiency	Platelet release and aggregation ↓
Defect of reactivity to ADP	Receptors number ↓	Defect in activation and aggregation to ADP
Defective response to epinephrine	Decrease in platelet alpha$_2$–adrenergic receptors	Defective activation induced by epinephrine
Montreal platelet syndrome	Decrease of calpain	Spontaneous aggregation by increased exposure of binding sites for adhesive proteins ?
Defect of secretion of adhesive proteins		
Grey platelet syndrome	α-granule content and typical α-granules number ↓	Release of adhesive proteins ↓ Adhesion (?) and aggregation ↓
Defect of secretion of dense granules		
δ-storage pool disease	Dense bodies number ↓ and function ↓	Release of ADP ↓ Aggregation ↓
Defect of aggregation		
Glanzmann disease	↓GPIIb and GPIIIa	Fibrinogen binding ↓ Aggregation ↓
Variant thrombasthenia	Abnormal ↓GPIIb–GPIIIa complex	Idem
Defect of procoagulant activity		
Platelet factor 3 deficiency	Abnormality in phospholipids involved in binding of factors Va and Xa	Defect of activation in situ of plasmatic factors

Inherited Thrombocytopenias

A. May-Hegglin thrombocytopenia. :- have large platelets
B. Thrombocytopenia with absent radii (TAR).
C. Wiskott-Aldrich syndrome.
D. Epstein's Syndrome.

Notes:

• Treatment of platelet defect is to transfuse platelet except in von willebrand disease we use cryoprecipitate

• patient who don't want to receive any blood

Product -> (DDAVP) desmopressin is an alternative for them -> increase vWF

• desmopressin can cause hyponatremia

Treatment of platelet disorders

A. Avoid antiplatelet drugs & trauma
B. Local measures
C. DDAVP infusion
D. Platelet transfusion (HLA compatible)
E. Recombinant activated factor VII
F. Bone marrow transplantation (rarely required)

Inherited Bleeding disorders

Focus on the 1st and 2nd

Disorder	Screening tests				Specific assays* (u/dl)
	PT	PTTK	TCT	BT	
Haemophilia A	N	↑	N	N	Factor VIII <50 vWF:Ag N Ricof N
von Willebrand's disease	N	↑ or N	N	↑ or N	Factor VIII <50 vWF:Ag <50 or N Ricof <50 or N
Haemophilia B	N	↑	N	N	Factor IX <50
Factor XI deficiency	N	↑	N	N	Factor XI <35
Factor X deficiency	↑	↑	N	N	Factor X <50
Factor V deficiency	↑	↑	N	N or ↑	Factor V <50
Factor VII	↑	N	N	N	Factor VII <50
Factor II	↑	↑	N	N	Factor II <50
Afibrinogenaemia	↑	↑	↑	↑	Fibrinogen undetectable
Dysifibrinogenaemia	↑	↑	↑	↑	Fibrinogen N or ↓
Factor XIII deficiency	N	N	N	N	Fibrin solubility ↑ Factor XIII <5%
Factor V plus VIII deficiency	↑	↑	N	N	Factor V <50 Factor VIII <50
Hyperplasminaemia	N	N	N	N	Euglobulin clot lysis time short (α_2-antiplasmin absent)

PT = prothrombin Time; PTTK = activated partial thromboplastin time; TCT = thrombin clotting time; BT = bleeding time; ↑ = increased, ↓ = decreased; N = normal.
* Factor VIII (formerly VIII:c); vWF:Ag, von Willebrand factor antigen (formerly VIIIR: Ag); Ricof, ristocetin cofactor.

Types of Bleeding	
Platelet bleeding	**Factor bleeding**
Superficial	Deep
Epistaxis, gingival, petechiae, purpura, mucosal surfaces such as the gums, vaginal bleeding	Joints and muscles

Hemophilia

Look for delayed joint or muscle bleeding in a male child, since the condition is X-linked recessive. Bleeding is delayed because the primary hemostatic plug is with platelets. The prothrombin time (PT) is normal and the aPTT is prolonged. Mixing studies with normal plasma will correct the aPTT to normal. The most accurate test is a specific assay for factor VIII or IX. Treat mild cases with DDAVP. Severe bleeding with very low levels of factor VIII or IX is treated with replacement of the specific factor.

Hemophilia – A

- X-Linked recessive disorder
- Males are affected and females are carriers.
- Deficiency of FVIII due to gene mutations or deletions:

A. Severe (< 1%)
B. Moderate (1-5%)
C. Mild (5-40%)

Clinical Features:

- Severe spontaneous recurrent bleeding
- Usually muscle & joints
- Internal organ bleeds also occur
- Recurrent bleeds lead to joint & muscle damage.
- Family history or new mutation

Severity of Hemophilia

Severity	Factor VIII or IX level	Clinical Presentation
Severe	<1%	Spontaneous hemarthrosis & muscle hematomas
Moderate	2 – 5 %	Mild trauma or surgery cause hematomas
Mild	5 - 50 %	Major injury or surgery result in excess bleeding

Findings on investigation Hematology

❖ ***Hematology***

- CBC: normal
- clotting studies:
  PT normal
  Bleeding time N
- APTT
- VIII: C
- vWF: Ag normal

❖ ***Diagnostic imaging:***

- Joint X-ray -> 2^{nry} osteoarthritic changes

- U/S, CT in loin pain (psoas bleeds, renal capsule bleeds, retroperitoneal bleeds)

Notes:
Patient with very severe hemophilia and the gene is completely deleted from him and you are trying your best you give him all the plasma product and the Recombinant:
Antibodies development because he will see protein that he haven't seen it in his life

Treatment of Hemophilia

1) Factor concentrates for acute bleed:

❖ **Sources of FVIII conc. :**

a) Donated human blood (plasma)
b) Recombinant DNA technology (transforming non-human, mammalian cell lines to express human FVIII)
c) Cloning of the normal FVIII gene and production of synthetic FVIII

❖ **Dosage guidelines:** "Dosage is for your own"

*Based on the patient's body weight.
- Rule of thumb:-
* FVIII levels will be increased 2% for every 1 unit/kg infused, thus 50 units/kg IV bolus will rise FVIII to 100%

* FIX levels will be increased 1% for every 1 unit/kg infused, thus 50 units/kg IV bolus will rise FIX to 50%

❖ **Example of dosage calculation for Hemophilia A:**

- Patient:14 y/o boy with a knee bleed
- Weight: 55 kg
- Goal: raise factor VIII level to 50% of normal
- Calculate: 25 units x 55kg= 1375 units
- Or 50 x 55/2 = 1375 units

2) DDAVP (synthetic vasopressin):

- Used either IV or intra-nasaly to Rx pt with mild hemophilia A with the FVIII levels>10% -The drug releases FVIII stored in the endothelial cells, it can double or triple the body's plasma level of FVIII.
- Not all pts respond to DDAVP
- Dose (0.3 microgram/kg) it can be repeated 6-8 hourly
- Response to the second dose is less due to tachyphylaxis

3) Gene Therapy:

It involves taking normal clotting factor genes and placing them into the body of a person with hemophilia, with the hope that patients' body will begin to make clotting factors on its own. However this approach is still investigational and not yet applicable clinically.

➢ Complications: "Contamination with viruses"

Factor concentrates, like many blood products, are made from pooled plasma. It can take up to 30,000 donations of blood to make one batch of factor concentrate and blood products have always been susceptible to contamination by viruses. (Hep A, B, C, HIV and others)

➢ Development of inhibitors:

- ✓ 10-20% have IgG antibodies to FVIII (mostly in severe cases) in Patient Rx w/F concentrate
- ✓ High doses of FVIII may not produce a rise in the plasma level of FVIII
  - How do we deal with pts who develop inhibitors ?
- ✓ Purified procine FVIII may not cross-react with patient's antibodies.
- ✓ Prothrombin complex (Feiba, autoplex)
- ✓ Recombinant F VIIa also "bypass" FVIII
- ✓ Immunosuppression/immunoabsorption .
- ✓ Indication of factor VII :- anyone who develop inhibitors against factor VIII

➢ Clinical management of bleeding:

- As soon as bleeding is suspected treatment should be given according to its severity
- Minor bleeding: (e.g laceration,dental extraction,early joint or muscle bleeding) the FVIII level should be raised to 30-50%
- Moderate bleeding: (e.g major joint or muscle bleeds) FVIII raised to at least 50-70%
- Severe bleeding: (e.g CNS, GI bleed, postoperative, major trauma) FVIII raised to 80- 120% for 7-10 days. And 100% preoperatively and maintained above 50% until healing.

Acquired hemophilia

- Due to the development of an inhibitor (antibody) against factor VIII in a previously normal individual.
-

"Indication of factor VII:- anyone who develop inhibitors against factor VIII"

- It is rare, and affects both males and females.
- It is sometimes associated with cancer, auto- immune conditions and pregnancy but most cases arise spontaneously
- Severe and often life threatening
- Treatment includes factor raVIIa, prothrombin complex, immunosuppression and rituximab (anti CD20 antibody)

Surgery in hemophiliacs

❖ Minor surgery:

- DDAVP with Tranexamic acid may suffice (mild haemophilia). Need to check response beforehand Raise FVIII level 50-70%

❖ Intermediate & major surgery:

- FVIII raised to 80- 120% for 7-10 days and 100% preoperatively and maintained above 50% until healing.
- Twelve hourly boluses or continuous infusion

von Willebrand's disease (vWD)

Definition

VWD is the most common inherited bleeding disorder with a decrease in the level or functioning ofvon Willebrand factor (VWF). It is autosomal dominant.

"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. The aPTT may be elevated in half of patients.

❖ vWD-investigations:

- ✓ Ristocetin Induced Platelet Agglutination
- ✓ VIII:C
- ✓ vWF:Ag
- ✓ vWF multimeric analysis.

Diagnostic Tests

- **VWF (antigen) level may be decreased**
- **Ristocetin cofactor assay:** detects VWF dysfunction, also called VWF activity
- **Factor VIII activity**
- **Bleeding time:** increased duration of bleeding (rarely done)

❖ Types:

1 - Partial deficiency of vWF

2A- Absence of large and intermediate multimers
2B- Absence of large multimers
2M- multimers normal, platelets function ↓
2N - ↓ affinity for FVIII

3 - Severe deficiency of vWF

❖ Treatment of bleeding and surgery in vWD:

- DDAVP for minor bleeding and surgery in type 1 & type 2A
- Intermediate purity FVIII (8Y, Hemate P)
- If above measures fail:
  - # Cryoprecipitate
  - # Platelet transfusion
- Purified vW factor is available but needs to be given along with FVIII

Treatment

The **best initial therapy is DDAVP (desmopressin)**, which releases subendothelial stores of VWF. If there is no response, use factor **VIII replacement** or **VWF concentrate.**

❖ Blood components:

1. RBC's: leukocyte reduced by filtration (LRF)
2. Autologous blood
3. Platelets: (LRF)
4. Platelets, apheresis (LRF)
5. Fresh frozen plasma (FFP)
6. Plasma, apheresis
7. Cryosupernatant plasma (CSP)
8. Cryoprecipitate (Cryo)
9. Serum albumin
10. IV immune globulin (IVIG)
11. Rh immune globulin (Anti-D)
12. Other immune globulins
13. Factor VIII, Factor VII, Factor IX
14. Factor XIII
15. Fibrinogen
16. Zoster immune globulin

❖ Fresh Frozen Plasma:

a. single donor, infection risks
b. ABO typing recommended
c. should be used within 2 hours of thawing
d. unit contains all factors and activity of (250 ml) ~ 8% plasma volume

❖ Cryoprecipitate:

- Pooled
- Factors VIII, I, XIII, vWF, Fibrinogen
- Each unit provides 80 - 100 units of factor VIII

❖ Prothrombin Complex (FEIBA, Autoplex):

Pooled plasma preparation
Treated to inactivate hepatitis viruses & HIV
Reconstituted vial 30 ml = 500 FFP
Substantial quantities of II, VII, IX, X
Tx of Hemophilia A & B with inhibitors, warfarin overdose, severe liver disease

Acquired Thrombocytopenias

Immune Thrombocytopenias

❖ Allo-immune:

- Neonatal allo-immune thrombocytopenia
- Post-transfusion purpura
- Refractions to platelet transfusion

❖ **Auto-immune:**

A) Immune thrombocytopenia (ITP) (previously called Idiopathic thrombocytopenic Purpura) **B)** Secondary immune thrombocytopenia (e.g SLE) **C)** Acute (post viral) thrombocytopenia

❖ **Drug induced immune:**

- Drug-dependent - Drug-independent (auto-immune)

Idiopathic Thrombocytopenic Purpura (ITP)

———	Acute	Chronic
Peak age	**2-8**	**20-40**
Sex incidence	**F=M**	**3F=M**
Ouset	**Sudden**	**insidious**
Duration	**< 6 months**	**> 6 months**
Associated Disorder	**Preceding viral infection**	**1 Idiopathic 2 Secondary**

❖ Clinical Features:

- Main feature is bleeding (muco-cutaneous) and severity depends on the degree of thrombocytopenia.
- Risk of serious bleeding when Platelets < 10x 10^9 /L
- Splenomegaly is not a feature.
- Features of secondary disease

❖ Lab Diagnosis:

- Isolated thrombocytopenia
- Normal or increased no. of megakaryocytes in the bone marrow
- ↑ Mean Platelet volume
- Other causes of thrombocytopenia should be ruled out
- Pseudo-thrombocytopenia
- SLE tests
- CT

❖ Pathogenesis:

- Production of antibodies
- Coating of Platelets
- Removal by RE system (Spleen & Liver)
- AB may be directed against megakaryocytes.
- Drug Induced Thrombocytopenia
- Drug history: Quinine, Quinidine, Sulphonamides, trimethroprim, Gold, Heparin

❖ Management:

- Steroids
- Splenectomy
- Intravenous immunoglobulin (IVIG)
- **Refectory patients (20%):**
- Immunosuperssion: Azathioprine, Cyclophosphamide &Cyclosporine
- Danazol
- Rituximab (anti CD-20 antibody)
- Thrombopoietic stimulating agents: Romiplostim & Eltrombopag
- Platelet transfusion should be avoided unless active bleeding

Treatment	
Presentation	**Management**
No bleeding, count >30,000	No treatment
Mild bleeding, count <30,000	Glucocorticoids
Severe bleeding (GI/CNS), count <10,000	IVIG, Anti-Rho (anti-D)
Recurrent episodes, steroid dependent	Splenectomy
Splenectomy or steroids not effective	Romiplostim or eltrombopag, rituximab, azathioprine, cyclosporine, mycophenolate

Acquired defects of Clotting

❖ Massive transfusion:

- ➢ Dilution of coagulation factors:
  - Crystalloids
  - Packed red cells
- ➢ Activation of clotting factors
- ➢ Breakdown of Platelet, WBC & RBC in stored blood releasing thromboplastins (DIC)
- ➢ Risk maximum with one blood volume equivalent (8-10 units) transfusion

❖ Management:

- Do not use blood components indiscriminately.
- Look for signs of bleeding (mucosal, wounds, puncture sites)
- If Platelet count ≤ 50 transfuse platelet 6-10 units
- If PT & APTT significantly prolonged give plasma (FFP)
- If ↓ fibrinogen < 1g/dL, consider giving cryoprecipitate

Liver Disease

- All the coagulation factors except vWF,are synthesized by the liver.
- Liver also synthesizes AT III, Protein C & S, α2 antiplasmin & Plasminogen
- Hepatocellular damage is accompanied by complex disturbances of hemostasis
- Low Plt count (Splenic or liver sequestration, Platelet dysfunction)
- DIC may occur

- Fibrinogen well preserved till late but may be abnormal.

❖ Management of coagulopathy in liver disease:

- Try vitamin K (as deficiency is common)
- PT & APTT should be corrected to within 5 seconds of normal by giving FFP for liver biopsy & other procedures.
- Platelet transfusion if low count

Renal Failure

- Significant bleeding may occur
- Defect in platelet function & platelet vessel wall interaction
- Uremic toxins seem to impair platelet function.
- Bleeding time is prolonged & Platelet aggregation impaired.
- Peritoneal or hemodialysis partially corrects the defect.
- Anemia should be corrected
- DDAVP reduces BT & minor surgery can be performed.
- Conjugate estrogens.

Coagulopathy in Cancer

Thrombocytopenia

➢ **Decreased production:**

- Chemo/radiotherapy
- Marrow infiltration

➢ **Accelerated destruction:**

- Hypersplenism

- DIC
- Immune thrombocytopenia

Functional Platelet abnormalities

- Myeloproliferative disorders
- Myeloma (Paraprotein)

Coagulation changes

- DIC
- Circulating anticoagulants

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

❖ **DEFINITION:** **"No consensus"**

DIC is an acquired syndrome characterized by activation of intravascular coagulation up to intravascular fibrin formation. The process may be accompanied by secondary fibrinolysis or inhibited fibrinolysis (Muller-Bergaus et al 1995).

Disseminated intravascular coagulation (DIC) does not occur in otherwise healthy people.

❖ **CLINICAL CONDITIONS ASSOCIATED WITH DIC:**

INFECTIONS (Severe sepsis)

- Bacterial (30-50 %)
- Viral
- Parasitic

SEVERE TRAUMA (50-70 %)

- General
- Head trauma

CANCER

- Solid tumours
- Haem. Malignancies (15-20 %)
- APML " Acute Promyelocytic Leukemia"

OBSTETRIC CONDITIONS

- Placental abruption
- Amniotic fluid embolism
- Retained dead foetus

VASCULAR DISORDERS

- Giant haemangiomas
- (Kasabach-Merrit syndrome)
- Large aortic aneurysm (1 %)

SEVERE ALLERGIC/TOXIC REACTIONS

- ABO mismatched transfusion
- Snake bite

❖ Pathogenesis of DIC:

Several lines of evidence suggest that DIC contributes to multiple organ failure due to fibrin deposition in the small and medium- sized vessels of various organs leading to ischaemia and necrosis.

- Entry of tissue thromboplastin into blood stream:
  - Extensive tissue trauma/surgery
  - Disseminated Cancer
  - Following incompatible blood transfusion reaction.
- Direct activation of factor X or factor II (snake venom)
- Severe vascular endothelial injury in gram negative sepsis
- Direct platelet activation in infections, endothelial damage & following thrombin generation.

❖ Lab Diagnosis of Acute DIC:

- ↑ PT
- ↑ APTT
- ↑ Thrombin time
- ↓ Platelets
- ↓ Fibrinogen < 1.0 g/dl (Normal 2.0-4.0 g/dl)
- ↑ FDP & D-Dimer

❖ Management of DIC:

A. <u>Patient resuscitation:</u>

- Fluids for shock
- Antibiotics
- Blood transfusion if low Hb
- Inotropic support

B. <u>Treat the Cause:</u>

- In obstetric situations rapid complete evacuation of uterus may be life saving
- Specific antibiotics for sepsis
- Anti-snake venom

C. <u>Blood Product Replacement:</u>

- FFP in case of bleeding
- Platelet transfusion
- Cryoprecipitate if fibrnogen < 1.0
- Heparin

- Protein-C concentrate in refractory cases (benefit doubtful)

PT, APTT, TT, PLT – Normal in:

A. Factor XIII deficiency

B. Thrombasthenia

- congenital
- drug induced

C. Disorders of vascular hemostasis

D. Scurvy

E. Clot solubility

F. Platelet function

- BT
- Clot retraction
- Platelet aggregation
- Plt glycoprotein analysis

G. Tourniquet test

H. Serum ascorbate level

❖ PT - ↑ & APTT, TT, PLT – N in:

1) Factor VII deficiency

2) Anticoagulant therapy

❖ APTT - ↑ & PT, TT, PLT – N in:

- Factor deficiency
- Inhibitors
- vWD
- Heparin therapy

❖ Prolonged APTT, BT in:

Von Willebrand's disease:

Ristocetin Induced Platelet Agglutination:

VIII: C

vWF:Ag

vWF multimeric analysis

Type 1 - Partial deficiency of vWF

2A - Absence of large and interm. multimers

2B - Absence of large multimers

2M- multimers normal, pl. function ↓

2N - ↓ affinity for FVIII

3 - severe deficiency of vWF

❖ PT, APTT - ↑ & TT, PLT – N in:

- Common Pathway Factor deficiency
- Oral anticoagulant therapy
- Vitamin K deficiency
- Liver disease

❖ PT, APTT, TT - ↑ & PLT – N in:

- Hypo / dysfibrinogenemia
- Liver disease
- Heparin
- Systemic hyperfibrinolysis

❖ APTT, PT,TT all ↑ & PLT – low in:

DIC: FDP, D-dimer, Fibrinogen

SUMMARY

- **Normal Hemostasis:** A protective mechanism that has evolved to maintain physiological Hemostasis.
- **Major components of blood coagulation:**

1- Blood Vessels. 2- Blood platelets. 3- Coagulation factors.
4- Coagulation inhibitors. 5- Fibrinolytic system.

- **Platelets:** are fragments of the cytoplasm of megakaryocytes formed in the bone marrow and are non-nucleated. Activation of the platelets helps in forming a platelet plug at the site of injury & stop bleeding.
- **Traditional coagulation pathway: (IMPORTANT)**
- **Approach to a patient with bleeding tendency:**

✓ **History:**

- Type of bleeding: Mucosal& skin, Joints and Muscles.
- Past surgical history. -Family History. -Drugs

✓ **Examination:**

- Skin and oral mucosa - Joints - Associated abnormalities

✓ **Investigation:**

- Prothrombin time - Partial Thromboplastin time
- Platelet count - Bleeding time - Thrombin time

◎ **Inherited bleeding disorders:**

- Haemophilia A - Von-Willebrand's disease - Haemophilia B

Haemophilia A: X-Linked recessive disorder, deficiency of FVIII, males are affected & females are carriers.

- **Severity of Hemophilia "go back to the table"**
- **Diagnosis**: Prolonged PTT, Low FVIII and normal levels of vWF.
- **Treatment**: factor concentrate for acute bleed, DDAVP, gene thrapy.

◎ **Acquired haemophilia:** due to the development of antibody against FVIII in previously normal person.

- **Von-Willebrand's disease:** Autosomal dominant, deficiency of FVIII-related antigen.
- **Types**:

Type 1 - Partial deficiency of vWF
2A- Absence of large and interm. multimers
2B- Absence of large multimers
2M- multimers normal, pl. function ↓
2N- ↓ affinity for FVIII
3- severe deficiency of vWF

- **Diagnosis:**

- Ristocetin induced platelet agglutination - FVIII
- vWF - vWF multimeric analysis.

- **Treatment:** DDAVP for minor bleeding and surgery in type 1 & 2A, Intermediate purity FVIII. If fail: cryoprecipitate, platelet transfusion.

You got lost, here is your Approach

Bleeding Diathesis

DIFFERENTIAL DIAGNOSIS

PVC **Platelets, Vessels, Coagulopathy** (Always remember them as PVC)

EXTRINSIC PATHWAY (isolated PT ")

- FACTOR DEFICIENCY OR INHIBITOR VIIr
- VITAMIN K DEFICIENCY malnutrition, pancreatic
- insufficiency, recent antibiotic use, warfarin use (early stage)
- LIVER DISEASE
- EARLY DIC

INTRINSIC PATHWAY (isolated PTT ")

- FACTOR DEFICIENCY X linked deficiency of factor VIII (hemophilia A) or factor IX (haemophilia B).
- Autosomal deficiency of factor XI, especially among Ashkenazi Jews (8% are carriers)
- VON WILLEBRAND DISEASE
- FACTOR INHIBITORS lupus anticoagulant due to APA; acquired hemophilia due to an inhibitor to factor VIII
- HEPARIN USE

COMMON PATHWAY (PT ", PTT ")

- FACTOR DEFICIENCY X, V, II, I
- SEVERE VITAMIN K DEFICIENCY malnutrition, pancreatic insufficiency, recent antibiotic use, long term warfarin use
- SEVERE LIVER DISEASE
- SEVERE DIC

PLATELET DYSFUNCTION (normal PT and PTT, platelet >90_103/mL, bleeding time ")

- ***INHERITED*** Bernard Soulier syndrome, Glanzmann's thrombasthenia, storage pool disease
- ***ACQUIRED*** renal failure, liver failure, myeloproliferative disorders, paraproteinemias, autoantibodies, DIC, acquired storage pool disease

VESSELS collagen vascular disease, scurvy

NOTE: INR=international normalized ratio, helps to standardize interpretation of PT

CLINICAL FEATURES

BLEEDING SYNDROMES

- **PLATELET DYSFUNCTION** skin/mucous membrane (petechiae, purpura, small/superficial ecchymosis, epistaxis, gingival bleed, menorrhagia), immediate bleed
- **COAGULATION FACTORS** joints/muscles (hemar throses, muscle hematomas, large/palpable ecchy mosis), delayed bleed

INVESTIGATIONS

BASIC

LABS: LABS CBCD, peripheral smear, AST, ALT, ALP, bilirubin, albumin, INR, PTT, D dimer, fibrinogen

SPECIAL: Depends on each disease.

MANAGEMENT

ACUTE ABC, O2, IV, transfusion 2 U PRBC IV over 2 h, transfusion platelets 6 U, FFP 15 mL/kg, cryoprecipitate 10 15 U q48h for fibrinogen deficiency

TREAT UNDERLYING CAUSE avoid heparin, LMWH, warfarin. Vitamin K deficiency (vitamin K 10 mg PO/SC daily _3 days). vWD type I (DDAVP 0.3 mg/kg SC, intermediate purity factor VIII)

Questions

1) A 25-year-old woman complains of persistent bleeding for 5 days after a dental extraction. She has noticed easy bruisability since childhood, and was given a blood transfusion at age 17 because of prolonged bleeding after an apparently minor cut. She denies ecchymoses or bleeding into joints. Her father has noticed similar symptoms but has not sought medical care. Physical examination is normal except for mild oozing from the dental site. She does not have splenomegaly or enlarged lymph nodes. Her CBC is normal, with a platelet count of 230,000. Her prothrombin time is normal but the partial thromboplastin time is mildly prolonged. The bleeding time is 12 minutes (normal 3-9 minutes). What is most appropriate way to control her bleeding?

a. Factor VIII concentrate
b. Fresh frozen plasma
c. Desmopressin (DDAVP)
d. Whole blood transfusion
e. Single donor platelets

2) A 32-year-old woman presents to the emer- gency department with edema and pain of the right lower extremity that began after a 6-hour car ride. A Doppler ultrasound was completed in which a deep vein thrombosis (DVT) was noted. The patient has no prior history of DVT or pulmonary emboli. The patient has been taking oral contraceptive pills for the past 2 years and is currently compliant with her med- ication. Her family history is significant for a maternal grandmother, mother, and sister with recurrent DVT. Her temperature is 36.2°C (97.2°F), blood pressure is 112/78 mm Hg, heart rate is 86/min, and respiratory rate is 14/min. There is no clinical evidence indicating a pulmonary embolism. Which of the following is the most likely cause of her DVT?

(A) Antithrombin deficiency
(B) Coagulation factor V gene mutation (C) Protein C excess
(D) Protein S deficiency
(E) Prothrombin gene mutation

A 7-year-old boy presents to his pediatrician because of increased gingival bleeding after brush- ing his teeth. The patient's mother denies a his- tory of easy bruising or prolonged bleeding. The boy also reports an episode of prolonged and painful knee swelling after a fall in which he hit his knee. The patient's family history is significant for a maternal grandfather who died of a massive hemorrhage after a minor surgical procedure. On examination there are no ecchymoses or pete- chiae. His conjunctivae are pink and a full physical examination is noncontributory. His activated partial thromboplastin time is 63 sec, prothrom- bin time is 12 sec, bleeding time is 4 min, and coagulation time is prolonged. Which of the fol- lowing additional laboratory results is most likely to be seen in this patient?

(A) Decreased factor VIII concentrations
(B) Decreased platelet concentrations
(C) Decreased WBC count
(D) Increased factor V concentrations
(E) Increased hemoglobin

432 Medicine Team Leaders

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Answers:

1st Questions:C

2nd Questions:B

3rd Questions:A