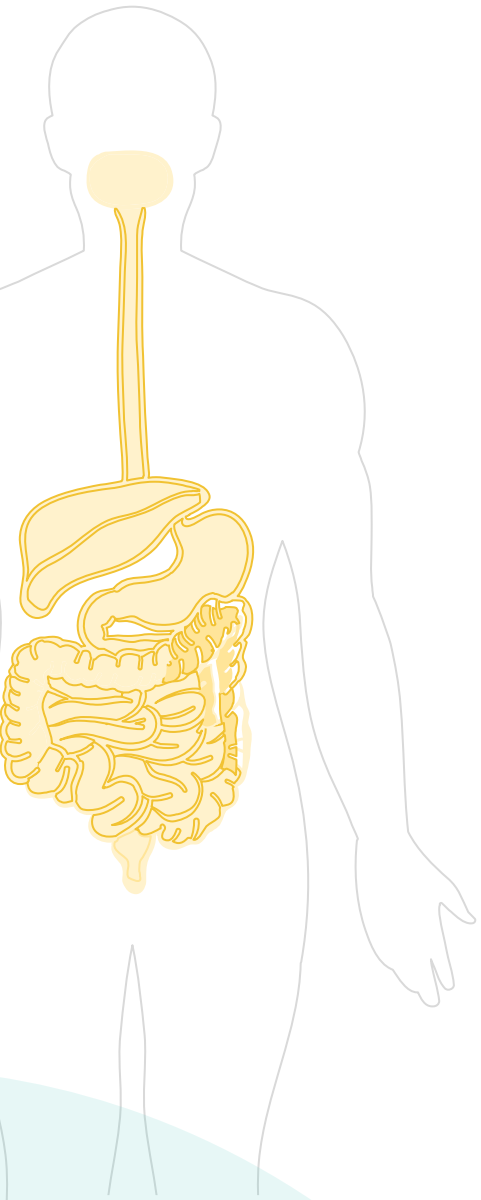
L7



Coagulation Mechanism

GNT Physiology

This lecture was presented by:
Dr. Shahid & Dr. Nervana Mostafa

Color Index:

- Main text
- Important
- Female Slides
- Male Slides
- Notes
- Extra

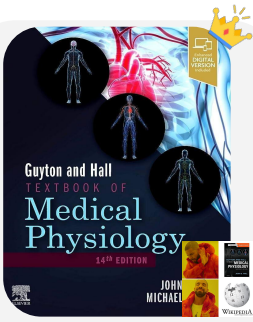
Editing file

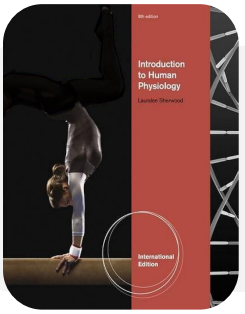
Objectives

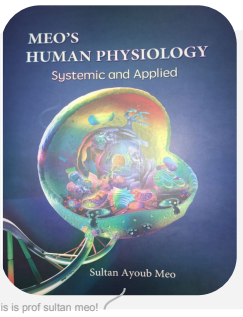
1. Recognize different stages of haemostasis
2. Explain the role of platelet in haemostasis
3. Recognize different clotting factors and cascade of clotting
4. Describe the intrinsic, extrinsic and common pathway
5. Recognize the role of thrombin in coagulation
6. The role of anticoagulants and their mechanism of action

Resources

Only GI chapters included







This is prof sultan meo!

Click Here for the MOST important points mentioned by Dr.Shahid

يقول ابن تيمية - رحمه الله - : إن المسألة **لتغلق عليّ، فاستغفر الله** ألف مرة أو أكثر أو أقل، **فيفتحها** الله علي وإن من أسباب راحة البال، استغفار ذي الجلال.

Haemostasis

Hemostasis:

The spontaneous arrest or stoppage of bleeding from ruptured blood vessels to prevent blood loss.

Antithrombogenic (Favors fluid blood) *Bleeding Tendency* ⟷ Vessel injury Risk Factors ⟷ Thrombogenic (Favors clotting) *Coagulation*

Primary vs secondary Haemostasis:

Dr.shahid: you should know difference between primary and secondary Haemostasis (phase1,2 is primary, phase 3,4 is secondary

-***Primary hemostasis***, which results in the formation of a <u>soft platelet plug</u> involves <u>vasoconstriction, platelet adhesion, platelet activation, and platelet aggregation</u>.
-***Secondary hemostasis*** is primarily defined as the formation of <u>fibrinogen into fibrin</u>, which ultimately evolves the soft platelet plug into a <u>hard</u>, <u>insoluble</u> fibrin clot.

<u>Four</u> steps of "Haemostasis" (Mechanism)

1 Vascular phase

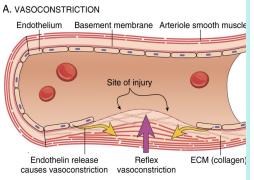
Vascular spasm (Vascular Constriction)

Dr.shahid: know the THREE causative factors of vasocons.

Immediately After injury there is <u>localized</u> Vasoconstriction.
-Importance:
Crushing injuries → Intense spasm -› No lethal loss of blood.
Check end of this page [1]

-Causative Factors are three:

1. Nervous reflexes *(sympathetic stim.)*
2. Local myogenic spasm
3. Local humoral factors

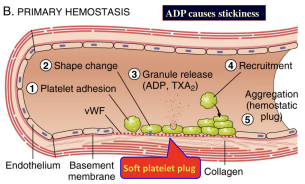


If this phase was enough to stop bleeding, process stops here, If not, 2nd phase will start

2 Platelets Phase

Platelet production & activation → platelets plug formation

Formation of Platelet plug.
Vascular injury results in the exposure of subendothelial collagen and von Willebrand factor (VWF). VWF is a glycoprotein that serves as the initial stationary foundation on which a clot forms.
-Importance
enough to stop bleeding from small vascular damage.

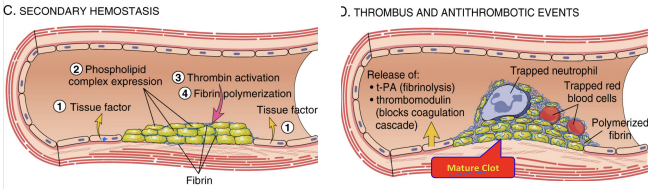


►Primary hemostatic plug (platelet plug)
- Platte adhesion
- Platelet activation
- Platelet aggregation

3 Coagulation phase

Clot formation (IP, EP, common pathway) and clot retraction, and blood coagulation

Blood clotting is the transformation of blood (soluble fibrinogen) from a liquid into a solid gel form (insoluble fibrin strands)
-Pathways: Intrinsic, Extrinsic
Begins to develop in
1-2 min -> Minor trauma
15-20 sec -> Severe trauma
#CLOT is a meshwork of fibrin fibers running in all directions entrapping blood cells, platelets and plasma.



4 Fibrinolytic phase (Fibrinolysis)

[1] Can intensity of spasm change?
بمعنى هل اذا الجرح صار اكبر يكون انقباض blood vessel أقوى؟ نعم.. وهذا اللي يفسر انه الجرح الصغير (مثل السكين او طرف حاد) ينزف بسرعه وبعدها يخف، بينما crushing injuries يكون اقوى بكثير it's like a protective mechanism.

Mechanism of Clotting-steps-

1. **Formation of Prothrombin activator complex (Xa+Ca+PF3*+V) by Extrinsic & Intrinsic Pathways leading to Common Pathway.**
   * (PF3)=Platelet factor 3
2. **Conversion of prothrombin into thrombin**
3. **Conversion of fibrinogen into fibrin**
4. **Fibrin converts to stable fibrin polymer**

Clotting Factors

TABLE 31–5 System for naming blood-clotting factors.

Factor[a]	Names
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Calcium
V	Proaccelerin, labile factor, accelerator globulin
VII	Proconvertin, SPCA, stable factor
VIII	Antihemophilic factor (AHF), antihemophilic factor A, antihemophilic globulin (AHG)
IX	Plasma thromboplastic component (PTC), Christmas factor, antihemophilic factor B
X	Stuart–Prower factor
XI	Plasma thromboplastin antecedent (PTA), antihemophilic factor C
XII	Hageman factor, glass factor
XIII	Fibrin-stabilizing factor, Laki–Lorand factor
HMW-K	High-molecular-weight kininogen, Fitzgerald factor
Pre-Ka	Prekallikrein, Fletcher factor
Ka	Kallikrein
PL	Platelet phospholipid

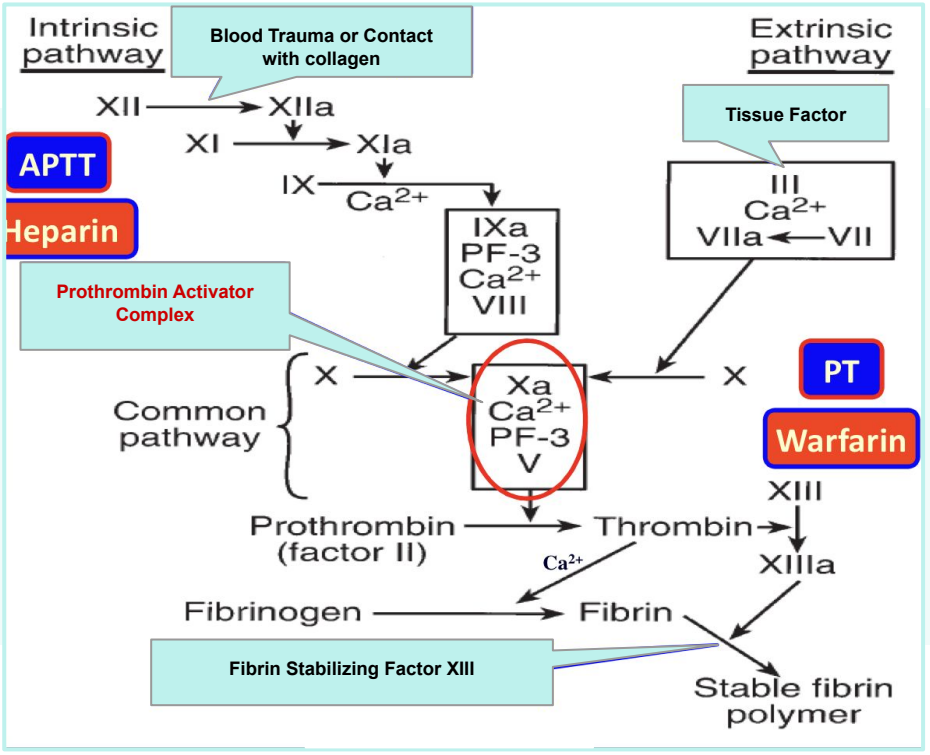
[a]Factor VI is not a separate entity and has been dropped.

Red=Mentioned by Dr.Shahid

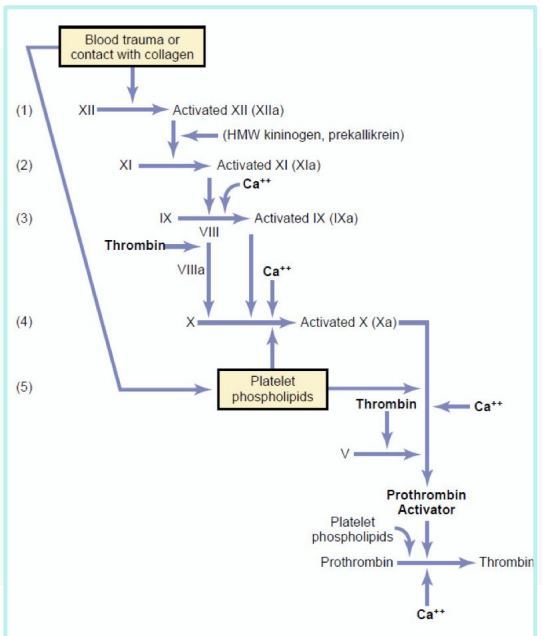
Fibrinogen (factor I):
- A high-molecular-weight plasma protein.
- formed by the liver.
- low levels or no fibrinogen leads to blood leak from vessels.

Fibrin-stabilizing factor (XIII):
- A plasma protein.
- also released from platelets that is entrapped in the clot.
- it must be activated before it affects the fibrin fibers.
- activated XIII factor operates as an enzyme causing additional strength of fibrin meshwork.

Clotting cascade

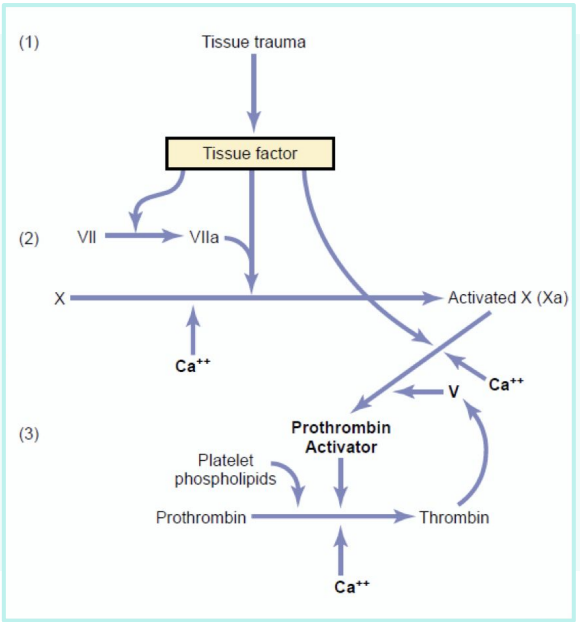


INTRINSIC MECHANISMS FOR INITIATING CLOTTING



Trauma to the blood itself or exposure of the blood to collagen (from a traumatized blood vessel wall), foreign surface/glass

EXTRINSIC MECHANISMS FOR INITIATING CLOTTING



TF or tissue thromboplastin; includes phospholipids from the membranes of the tissue plus a lipoprotein complex that functions mainly as a proteolytic enzyme.

Important points to Remember!

Dr.shahid: If you know this slide, U can solve almost every MCQ!

IMPORTANT

- The intrinsic pathway responds to spontaneous, internal damage of the vascular endothelium whereas the extrinsic pathway becomes activated secondary to external trauma.
- Clotting factors involved in the intrinsic pathway include factors XII, XI, IX, and VIII mainly
- Clotting factors involved in the extrinsic pathway include factors VII, and III. Mainly
- The common pathway includes clotting factors X, V, II, I, and XIII.
- Clotting factor IV is a calcium ion that plays an important role in all 3 pathways

Hepatocytes are responsible for providing the body with clotting factors XIII, XII, XI, X, IX, VII, V, II, and I.

Megakaryocytes produce the body's platelets and also contribute to the production of factor V

Partial thromboplastin time (PTI) measures coagulation throughout the intrinsic pathway and common pathway (25 to 40 seconds)

Clotting factors VIII (antihemophilic factor A), and III (tissue factor) originate from endothelial cells

Extrinsic (VII) vs Intrinsic Pathway Proteases (XII, XI & IX)
Prothrombin time (PT) measures coagulation throughout the extrinsic pathway and common pathway, (11 to 15 seconds)

MCQs

So much MCQs

MCQs

MCQs

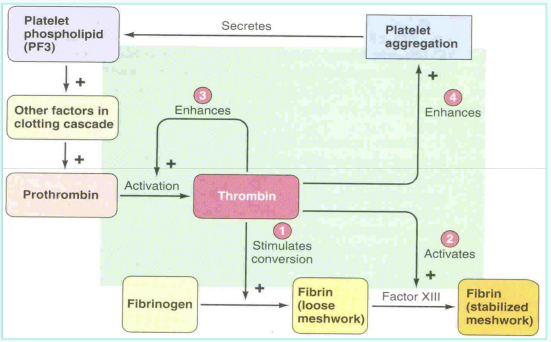
MCQs

This page is MCQs

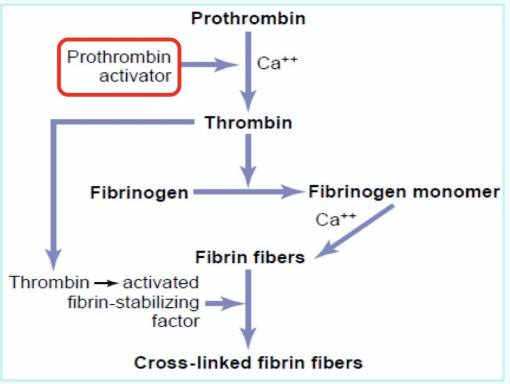
Thrombin

- plasma protein, formed by the liver. - unstable protein that can be split easily into thrombin
- Vitamin K is important for normal production of prothrombin by the liver (so as factors ???).
- Lack of vit K or liver disease can decrease prothrombin, formation to a very low level >>>> bleeding.it's protein enzyme with proteolytic capabilities. - acts on fibrinogen to form one molecule of fibrin monomer, which polymerize with one another to form fibrin fibers.- activates factor XIII (to stabilize fibrin).

Roles of Thrombin in Haemostasis:



Action of Thrombin on fibrinogen to form fibrin:



Procoagulant actions of thrombin enzyme:

I- Cleaves fibrinogen into fibrin.
2- Activates clotting factors:
- XIII to cross link fibrin.
- Intrinsic pathway via factor XI.
- Cofactor of the activation of factors V & VIII.
3- Stimulates platelet activation
- essential in platelet morphological changes to form primary plug.
- stimulates platelets to release ADP & thromboxane A2; both stimulate further platelets aggregation.

Clot Retraction

Male slides

- When clot retracts (contracts), it expresses most of the fluid from the clot within 20-60 min called -> Serum
- Serum cannot clot
- Role of platelets in clot formation & retraction.... they are contractile.

Fate of Clot: Lysis or Fibrous tissue Formation (platelet derived growth factor)

Lysis of Blood clots by "plasmin"

·plasmin is present in the blood in an inactive form plasminogen.
· activated by tissue plasminogen activators (t-PA) in blood.
· Digests intra & extra vascular deposits of Fibrin → fibrin degradation products (FDP e.g. D dimer).
· Unwanted effect of plasmin is the digestion of clotting Factors, is controlled by:
– Tissue Plasminogen Activator Inhibitor (T-PAI).
– Antiplasmin from the liver.

Formed blood clot can either become fibrous or dissolve.
·Fibrinolysis (dissolving) means
Breaking down of fibrin by naturally occurring enzyme plasmin → prevent intravascular blocking.

Plasminogen circulates in blood as a zymogen and can be activated to the protease <u>plasmin</u> by two activators.

Plasminogen (Profibrinolysin)

↓ **Antiplasmin from the liver**

T-PA (Tissue Plasminogen Activator)
U-PA (Urokinase-type plasminogen activator)

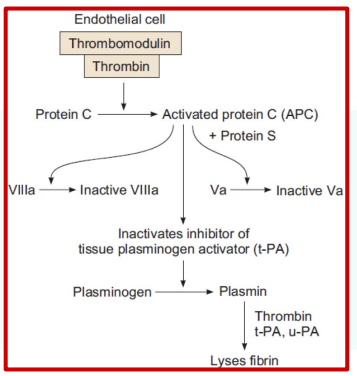
Plasmin (Fibrinolysin)

Lysis of clot

TPA is used to activate plasminogen to dissolve coronary and cerebral clots.

Fibrinolytic system

"The Fibrinolytic system and its regulation by protein C"



Fibrinolysis

- Formed blood clot can either become fibrous or dissolved.
- Fibrinolysis (dissolving), break down of fibrin by naturally occurring enzyme plasmin, therefore prevent intravascular blocking.
- There is a balance between clotting & fibrinolysis:
  - Excess clotting → blocking of Blood Vessels.
  - Excess fibrinolysis → tendency for bleeding

Anticoagulants

Used in Vivo

Parenteral

Heparin

Combines with antithrombin III and I its effectiveness by 100-1000 fold, Also remove Factors XII, XI, X, and IX (Monitored by PTT time) → CANNOT BE TAKEN ORALLY; WHY?

Oral

Warfarin

↓ production of Vit K dependent clotting factors (II, VII, IX and X) by liver (Monitored by PT time) - IS ALWAYS TAKEN ORALLY

Used in Vitro

No Ca^{++} → No Clotting (Needed in many steps)

Heparin → Binds to AT III

Citrate ions → Deionization of Ca^{++}

Oxalate ions → Precipitate the Ca^{++}

EDTA -> chelates (binds) calcium ions

Natural Intravascular Anticoagulants

Antithrombin action of Fibrin and Antithrombin III

85-90 % Thrombin binds with Fibrin
10-15 % Thrombin binds with Antithrombin III
Antithrombin III is a circulating protease blocking clot factors

Alpha$_2$-Macrogobulin

Synthesized mainly in liver and acts as a binding agent for several coagulation factors and inhibits thrombin

Endothelial Surface Factors

~ Smoothness of Endothelium
~ Glycocalyx Layers
Thrombomodulin Protein binds to thrombin > Activates Protein C (with ProtS) - inactivates factors V & VIII and inactivates an inhibitor of tPA-> increasing the formation of plasmin.

Heparin

- vely charged conjugated polysaccharide

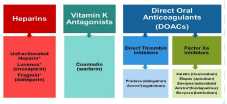
Increase the effectiveness of Antithrombin III

Produced by Mast cells Basophil cells

Most widely used anticoagulant clinically e.g. in stroke.

Anticoagulants

A- Substances that remove calcium ions from blood:
1- Citrate ---------- blood banks.
2- Oxalate & EDTA ------ laboratories.
B- Heparin: duration of action = 6 - 8 hours
(direct antithrombin & prevents conversion of prothrombin to thrombin)
C- Warfarin: (duration of action = 2 -3 days)
⇩synthesis of vitamin K dependent clotting factors by the liver.
D- New oral anticoagulants (NOAC) e.g. apixaban



Prevention of blood clotting in the normal vascular system & Anticoagulants

- Fibrin fibers, adsorbs ~90% of thrombin to removes it from
- circulating blood.
- Heparin, combines with Antithrombin III & quickly removes thrombin
- from blood (endothelial cells Liver, lungs, mast cells, basophils)
- Antithrombin III, removes the remaining thrombin from blood.
- Natural anticoagulant Proteins: - Protein C - Protein S

Bleeding and clotting Disorders

Hemophilia

- ◇ ↑ Bleeding tendency.
- ◇ X-linked disease → occurs exclusively in males (females are carriers) very rarely expressed in females.
- ◇ Hem A & B are inherited in X linked recessive pattern.
- ◇ Hem C is autosomal recessive.
- ◇ Von willebrand disease (VWD) is autosomal dominant.

❖ Types:

- ◇ Hemophilia A (Classic Hemophilia) due to factor VIII deficiency (85%).
- ◇ Small Component → Hemophilia A → ↑Partial thromboplastin time.
- ◇ Large Component → Von-Willebrand's disease → ↑Partial thromboplastin time & bleeding time.
- ◇ Hemophilia B (Christmas disease) due to factor IX (aka christmas factor) deficiency (15%).
- ◇ Hemophilia C (Rosenthal syndrome) due to factor XI deficiency and it affects both sexes.

❖ Clinical Features:

- ◇ Easy bruising, massive bleeding after trauma or operation, hemorrhages in joints.

Thrombocytopenia

- ❖ Very low number of platelets in blood (<50,000/µl) may cause spontaneous bleeding and (less than 10,000) is fatal
- ❖ Pseudothrombocytopenia: 1- Partial clotting of specimen. 2- EDTA-platelet clumping. 3- Platelet satellitism around WBCs. 4- Cold agglutinins. 5- Giant platelets.
- ❖ Etiology:
- ❖ Idiopathic thrombocytopenia: unknown cause.
- ❖ Decreased production : such as: aplastic anemia, leukemia, drugs, infections (HIV , Measles).
- ❖ Increased destruction: Immune Thrombocytopenia purpura (ITP) which is hemorrhages throughout all the body tissues, drugs, Infections (HIV)
- ❖ Clinical features include:
- ❖ Easy bruising, epistaxis Nosebleed, gum bleeding, hemorrhage after minor trauma, petechiae/ecchymosis.
- ❖ Diagnosis:
  - ◇ Platelets (PLT) count decreased.
  - ◇ Bleeding time (B.T) increased.
- ❖ Treatment:
- ❖ Treatment of the underlying cause, platelets concentrates, fresh whole blood transfusion, Splenectomy.

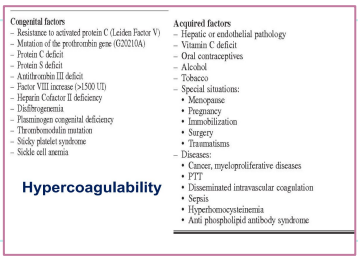
Liver disease & Vitamin K deficiency

- ◇ Fat soluble vitamin
- ◇ Sources: diet, synthesized in the intestinal tract by bacteria.
- ◇ Required by liver for synthesis of 4 clotting factor prothrombin (II), factor VII factor IX, and factor X.
- ◇ leads to: decreased formation of clotting factors → increased clotting time.

❖ Deficiency is rare but maybe seen in GIT or liver disease:

- ◇ hepatitis, cirrhosis → Decreased formation of clotting factors, increased clotting time
- ◇ Malabsorption syndromes, biliary obstruction, broad spectrum antibiotics, dietary deficiency (neonates).
- ◇ Treated by treating the underlying cause → vit K injections

Hypercoagulability
Increased risk of thromboembolism.
Causes:
1- Primary (genetic; Thrombophilia)
2- Secondary (acquired)



Screening test & Treatment

	Mechanism Tested	Normal Value	Disorder
Prothrombin time (PT)	Extrinsic and common pathway.	<12s beyond neonate, 12-18s in-term neonate.	Liver disease, defect in vitamin K-dependent factors, disseminated intravascular coagulation (DIC).
Activated partial thromboplastin time (aPTT)	Intrinsic and common pathway.	25-40s beyond neonate, 70s in-term neonate.	DIC, von Willebrand disease, hemophilia.
Platelet count	Platelet number.	150000-450000 cells per millimeter cubed.	Thrombocytopenia.
Bleeding time (BT)	Hemostasis, capillary and platelet function.	3-7 minutes beyond neonate.	Thrombocytopenia, on Willebrand disease.

IMPORTANT

#Possible SAQ

	Haemophilia A	Haemophilia B	VW disease
Bleeding time	Normal	Normal	Prolonged
Prothrombin time	Normal	Normal	Normal
APTT	Prolonged	Prolonged	Prolonged
Factor VIII	Low	Normal	Low or normal
Factor IX	Normal	Low	Normal
VWF	Normal	Normal	Low

PHYSIOLOGY

GNT Block

Team 443

The BEST

Team Leaders

EVER..

Rafan Alhazzani

Fahad Almughaiseeb

Ghaida Aldossary

Faisal Alzuhairy

Team Members

- Sarah Alshahrani
- Melaf Alotaibi
- Raghad Almuslih
- Layla Alfrhan
- Aroub Almahmoud
- Remas Aljeaidi
- Hamad Alziyadi
- Nazmi A Alqutub
- Nazmi M Alqutub
- khalid Alanezi
- Abdulaziz abahussain
- Yousof Badoghaish
- mansour Alotaibi
- Layan aldosary
- Norah alhazzani
- Jouri Almaymoni
- Salma Alkhlassi
- Shoug Alkhalifa