MED439
KING SAUD UNIVERSITY

Bleeding Disorders

Dr.osama's note :
The lecture is full of informations, however I'm gonna focus on some points which I think you're going to be asked about in the Exam .

Dr's notes
Important
Extra notes
** Only in girls slide
** Only in boys slide

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Editing file

From slide 2-7 the doctor read it quickly

Hemostasis **

Hemostasis is a dynamic process whereby blood coagulation is initiated and terminated in a rapid and tightly regulated fashion which is followed by fibrinolysis and tissue remodeling (**healing**).

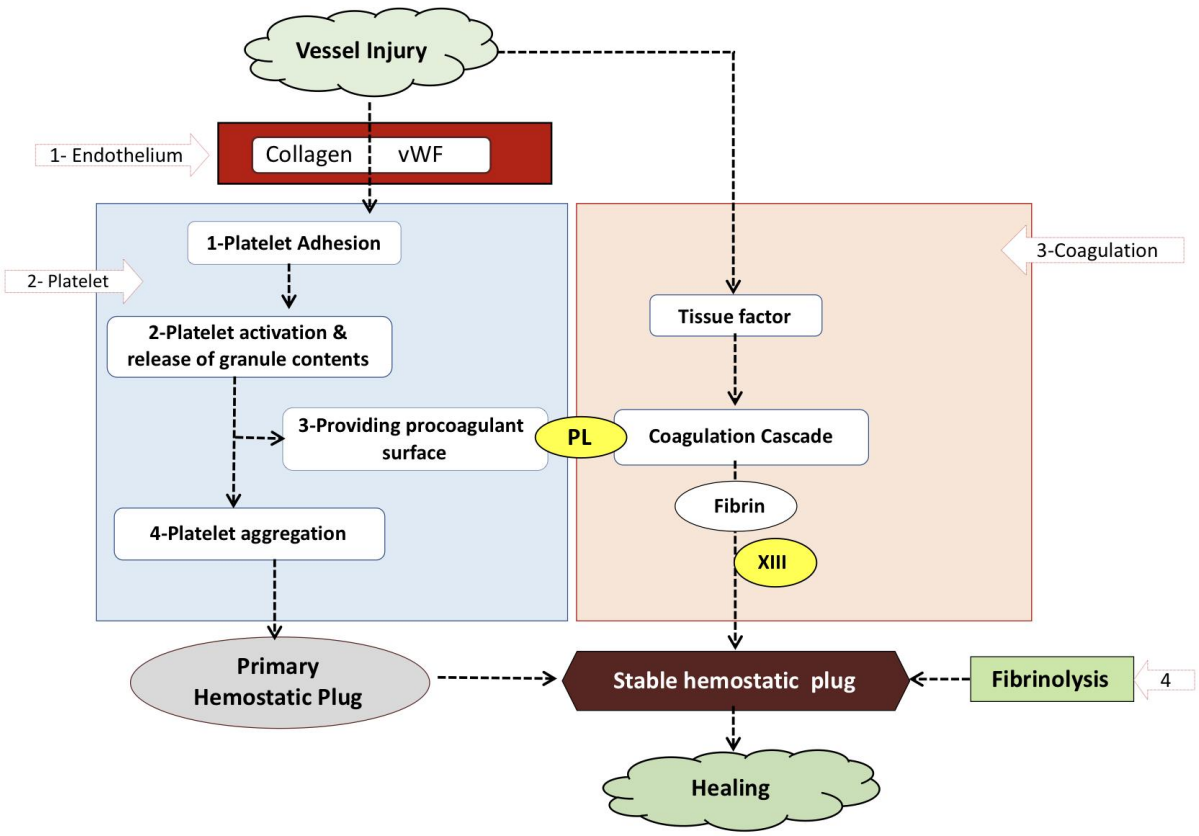
Functions of hemostasis

- Maintain blood in a fluid and clot-free state
- Induce rapid & localized plug at the site of injury
- Rapid removal of the plug once hemostasis is maintained

Component of hemostasis

- Platelets
- Endothelial cells
- Blood vessels
- Coagulation proteins :

Coagulation Factors , Natural Anticoagulants , Fibrinolytic system



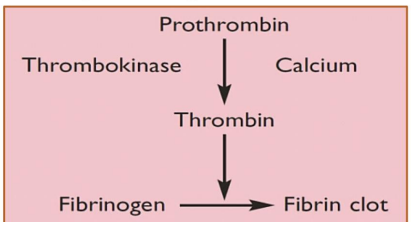
Coagulations Factors **

Are plasma proteins undergo a series of progresive stepwise reactions (**Coagulation Cascade**) in order to form coagulation clot.
They are synthesized in the **liver** as:

- Serine proteases. **The majority**
- Glycoproteins : (**FII , FV and FVIII**)
- Transglutaminase : (**FXIII**)

Coagulations theories

❑ The classic theory of coagulation was described by Paul Morawitz in 1905. He assembled 4 coagulation factors in which the prothrombin, by calcium activation, yielded thrombin converting fibrinogen to fibrin.



❖ **Cascade and waterfall hypotheses:**

❑ In 1964, the Cascade and Waterfall hypotheses was introduced by Macfarlane and Ratnoff respectively
❑ They suggested that the coagulation could be initiated via :

- **Intrinsic pathway** : so named because all the components were present in blood.
- **Extrinsic pathway** : in which the tissue factor (TF) was required in addition to circulating components.
- The initiation of either pathway resulted in activation of FX and the eventual generation of a fibrin clot through a **common pathway**

Homeostasis **

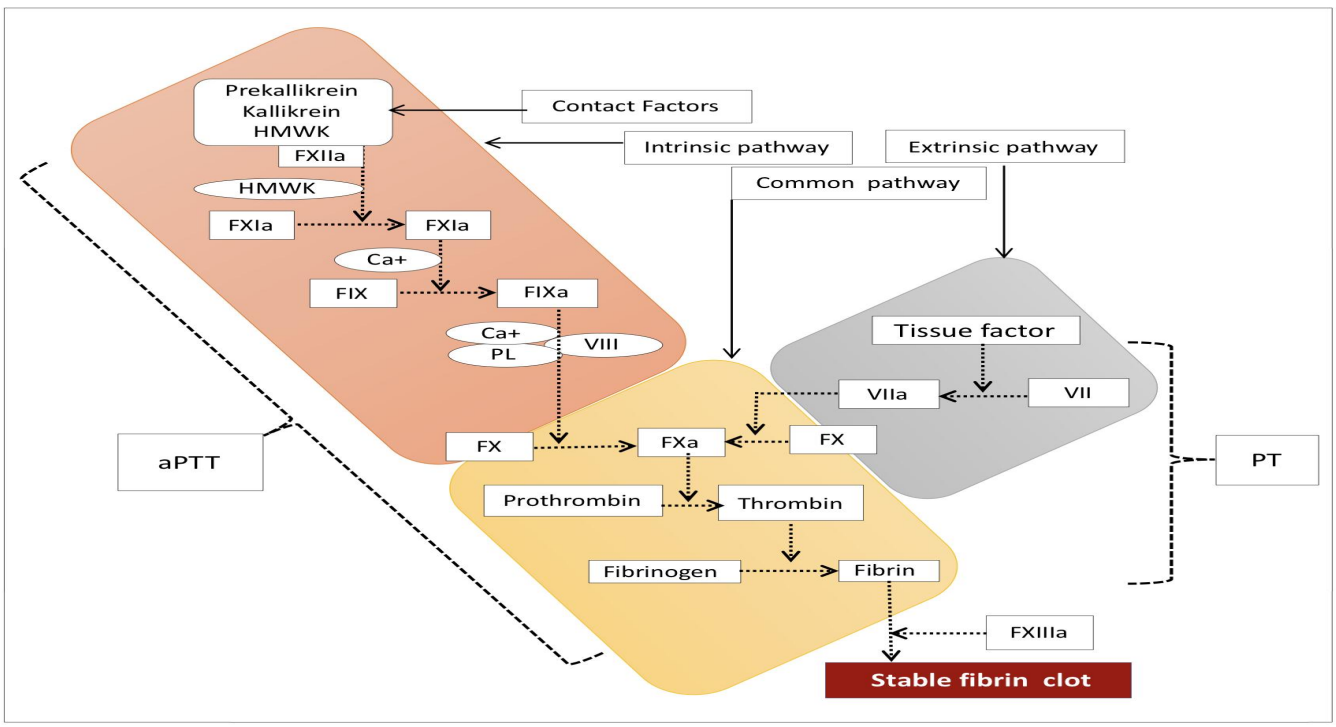
- Pitfalls of Waterfall hypothesis:

- ❑ Coagulation cascade has been widely accepted by physicians and coagulation specialists . Prothrombin time (PT) and activated partial thrombin test (aPTT) were used to test for the adequacy of the extrinsic pathway and intrinsic pathway respectively and are often treated as though they are predictive of clinical bleeding.
- ❑ As researches evolved, many unanswered questions has emerged :

1-Why FVIII &FIX deficiencies are associated with severe bleeding while others not?
2- Why an intact extrinsic pathway could not compensate for the lack of FIX or VIII in hemophilia?
3- What is the role of TF expressing cell & Platelets?
4- TF-VIIa is able to activate FIX which is an intrinsic factor !!

❖ The new concept on homeostasis :

- ❑ Thrombin generation is a complex net work of interactions with positive and negative feed back loops in order to ensure that fibrin clot is limited and localized .
- ❑ In vivo, the whole system of hemostasis is highly integrated and the subsystem of hemostasis do not operate independently.
- ❑ Normal hemostasis is not possible in the absence of platelets (as procoagulant surface and source of phospholipids) and tissue factor (TF) as the sole initiator for coagulation.
- ❑ TF is an integral membrane protein expressed on smooth muscle cells and fibroblasts and released constitutively at biological boundaries such as skin, organ surfaces and vascular adventitia where it functions as a haemostatic envelope.
- ❑ The primary control of haemostasis is the anatomical segregation of cells expressing functional TF from other components of the coagulation network present in blood.



The Cell Based Coagulation Cascade **

Step 1: Initiation of Coagulation on TF-bearing Cells:

- ❑ Following vascular damage blood coagulation is initiated by exposure of FVII to TF expressing cell . Once bound to TF, zymogen FVII is rapidly converted to FVIIa forming TF-FVIIa complex which is able to activate FX and FIX.
- ❑ In the absence of its activated cofactor FVa, FXa generates only trace amounts of thrombin. Although insufficient to clot fibrinogen, this amount of thrombin is able to activate the amplification phase through activation of FV,VIII and FIX.
- ❑ The initiation phase is rapidly inhibited by tissue factor pathway inhibitor (TFPI) released from endothelial cells or activated platelets.

Step 2: Amplification of the initial stimulus

❑ The small amount of thrombin generated during the initiation phase activates the amplification phase through activation of :

1. Platelets :exposing receptors for activated clotting factors and releasing FV form alpha granules onto platelet surfaces
2. Factor XI : which activates factor IX subsequently.
3. Tenase complex (VIIIa-FIXa) : that activate sufficient amount of FXa
4. Prothrombinase complex (FXa– FVa) : this result **in explosive generation of thrombin** that ultimately leads to generation of fibrin clot.

❑ This step is tightly regulated by:

1. Anti-thrombin (AT): serine protease inhibitor synthesized in the liver. AT forms a stable 1 : 1 complex with several coagulation factors, predominantly thrombin but also to some extent FIXa, FXIa and FXIIIa. Heparin induces > 2000 folds increase in the action of AT.
2. Protein C (PC) and Protein S (PS) : vitamin K–dependent inhibitors that inactivate factors Va and VIIIa. PC is activated by the binding of thrombin to thrombomodulin on endothelial cell receptors for PC (EPCR).Protein S is a cofactor that enhances the action of PC.
3. Fibrinolysis: hemostatic system that generate plasmin at the site of injury in order to limit the extent of the evolving thrombus. It includes plasminogen, plasmin and several activators and inhibitors

Remember : Congenital deficiency of natural anticoagulants (TFPI, AT, PC or PS) predispose the patients to risk of thrombosis

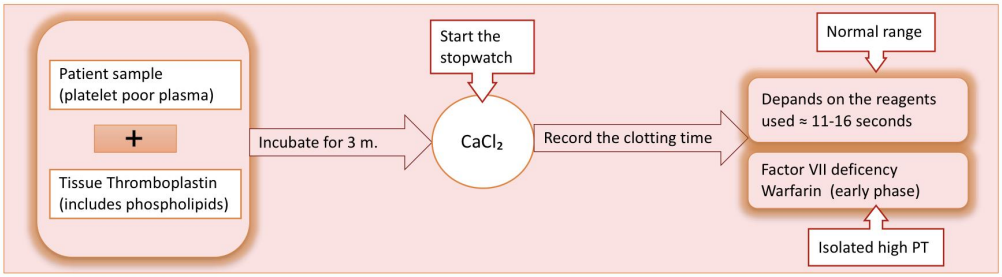
Laboratory investigations of homeostasis **

Blood Sample

- ❑ Patient should be relaxed and not on physical or emotional stress .The sample should not be taken from a running line, especially if heparin is being used to keep the line open.
- ❑ The only specimen acceptable for routine coagulation testing is blood anticoagulated with sodium citrate. the tube must be properly filled (not overfilled and not underfilled) .When hematocrit is abnormal with either sever anemia (<25) or polycythemia (>55), the blood citrate ratio should be adjusted.
- ❑ Samples should be delivered as quickly as possible to prevent deterioration of the labile coagulation factors (FV and VIII). The testing should preferably completed within 2hours. However, If the sample is not urgent , It can be stored at -40˚C after proper centrifugation in order to remove platelets (platelet-poor plasma).

Prothrombin Time PT

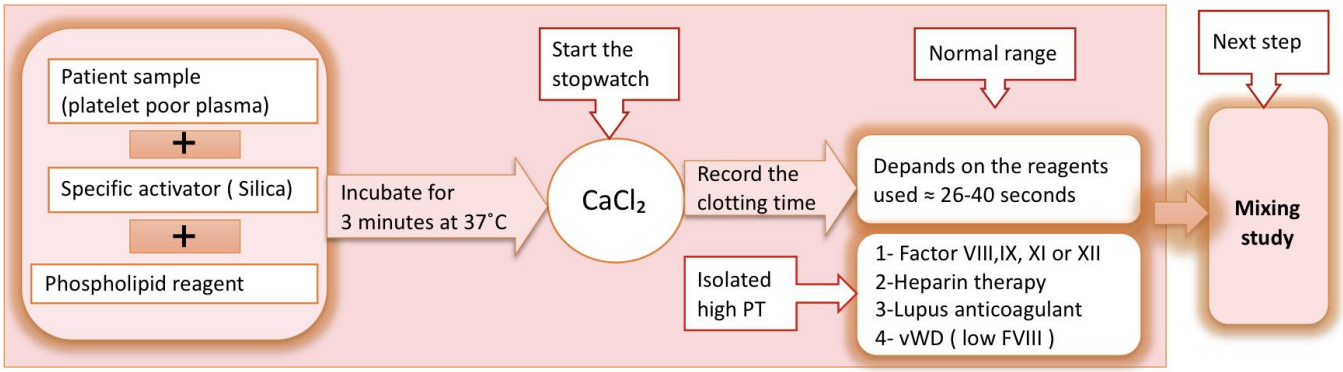
An essential coagulation study that tests the extrinsic and common pathways



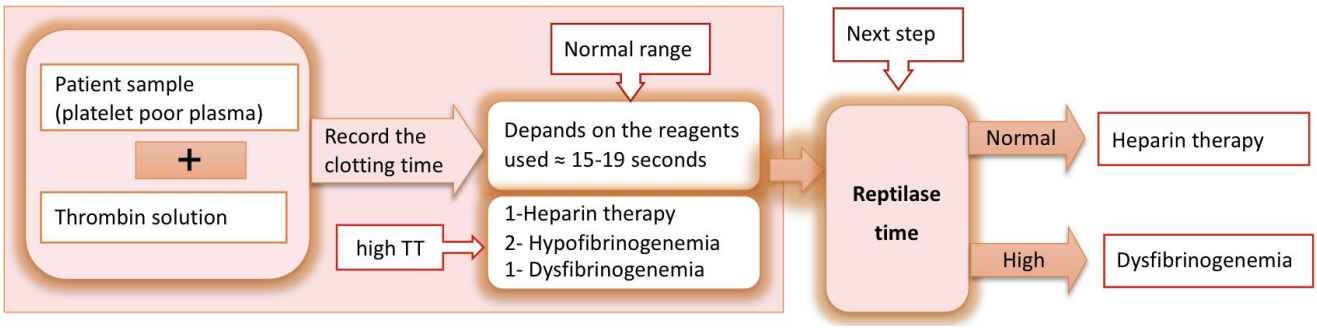
Laboratory investigations of homeostasis **

Activated Partial Thromboplastin time (aPTT)

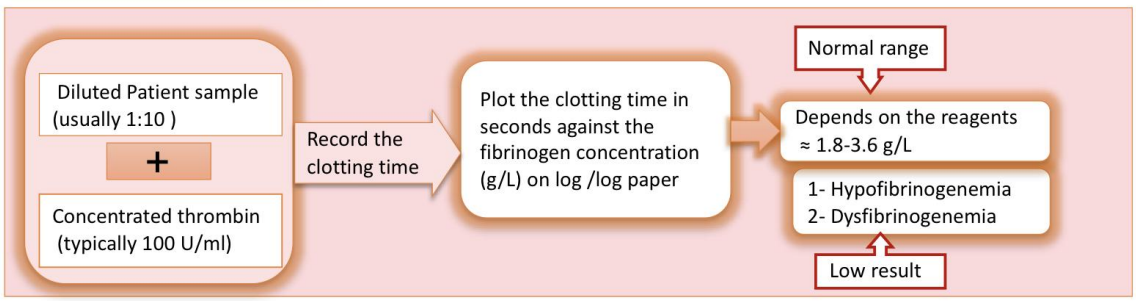
An essential coagulation study that tests the intrinsic and common pathways



Thrombin Time (TT)

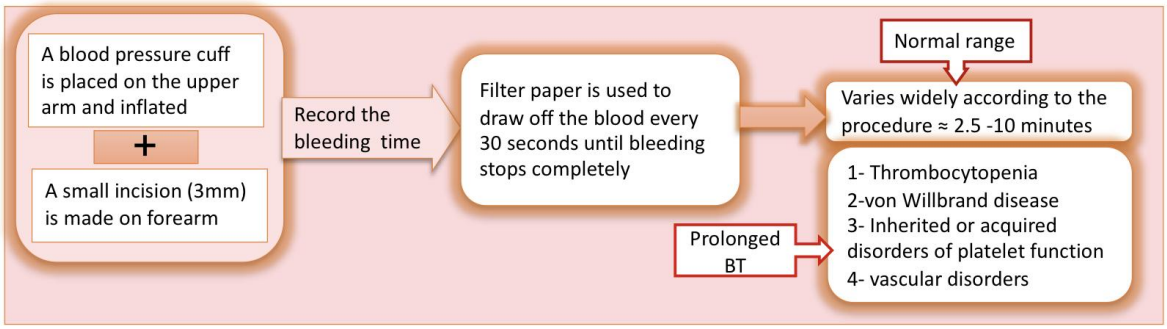


Fibrinogen (Claus method)



Bleeding Time (BT)

Bleeding time is a crude test of hemostasis. It indicates how well platelets interact with blood vessel walls and vWD to form blood clots. The BT tests the function of platelets , vWF, the integrity of skin and blood vessel walls. It is usually normal or minimally prolonged with coagulation factor deficiencies . In general, BT has poor sensitivity and reproducibility and rarely used .



Bleeding disorders results from:

- Vascular disorders
- Thrombocytopenia (Low levels of platelets)
- Defective platelet function. (Such as: Bernard Soulier Syndrome and Glanzmann Thrombasthenia)
- Defective coagulation

Vascular Bleeding Disorders

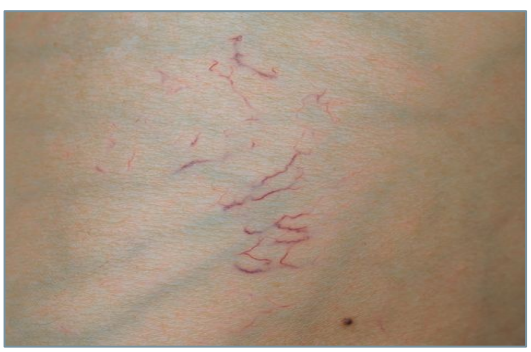
Overview

- **Vascular Bleeding Disorders** are Heterogeneous group of conditions characterized by easy bruising and spontaneous bleeding from the small vessels
- The underlying abnormality is either:
  - In the **vessels themselves**
  - In the **perivascular connective tissues**
- Coagulation tests are **normal**.

Inherited vascular disorders

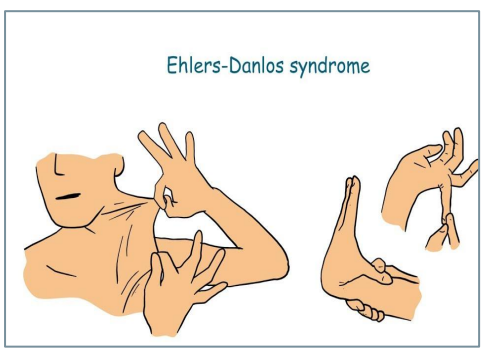
Hereditary hemorrhagic telangiectasia:
AD, Rare condition characterized by dilation of the capillaries, which causes them to appear as small red or purple clusters, often spidery in appearance, on the skin or the surface of an organ

Extra



Connective tissue disorders e.g.: Ehlers–Danlos syndromes:
In the EDS there are hereditary collagen abnormalities with purpura resulting from defective platelet adhesion. EDS can make your joints loose and your skin thin and easily bruised. It also can weaken blood vessels

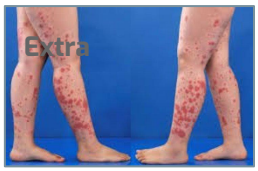
Extra



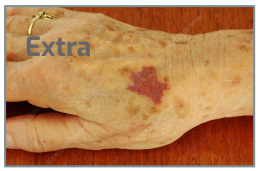
Vascular Bleeding Disorders

Acquired Vascular Disorders

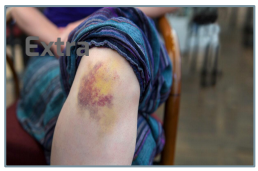
Henoch –Schönlein syndrome: usually seen in children and often follows an acute upper respiratory tract infection



Senile purpura : caused by atrophy of the supporting tissues of cutaneous blood vessels



Simple easy bruising : common benign disorder which occurs in otherwise healthy women, especially those of child-bearing age.



Introduction to Hemostasis Disorders

In this lecture bleeding disorders have been classified based on if they were inherited or acquired. They can also be classified based on their defects in hemostasis which causes their increased susceptibility to bleeding. We recommend you read it before beginning the lecture.

	Disorders of Primary Hemostasis	Disorders of Secondary Hemostasis
Normal function	To make a platelet plug	To make fibrin mesh by coagulation cascade to stabilize platelet plug
Disorder	Due to platelet deficiency or dysfunction	Due to factor abnormalities. (coagulation cascade)
Clinical presentation	**Mucosal and skin bleeding;** with severe thrombocytopenia (low platelet)	**Deep bleeding in muscles and joints**, rebleeding after surgical procedures
Lab tests	• Platelet count (normal is 150k-400k per microliter of blood) • Bleeding time (normal is 2-7 min) • Blood smear and Bone marrow biopsy	• PT (extrinsic pathway) • aPTT (intrinsic pathway)
Conditions	• Von willebrand disease	• Hemophilia A (factor VIII) • Hemophilia B (factor IX)

Congenital Coagulation Disorders

Pathoma

Congenital bleeding disorders discussed in this lecture:

- Haemophilia A (factor VIII deficiency) Prolonged aPTT , Normal PT
- Haemophilia B (factor IX deficiency) Prolonged aPTT , Normal PT
- Von willebrand disease (VWD) (von willebrand factor deficiency) , prolonged bleeding time

HOW TO DIFFERENTIATE BETWEEN VWD AND HEMOPHILIA A ?

By using platelets aggregation test

Deficiency of clotting factors

- Single deficiencies of factors **other than VIII, IX, and vW are rare.**
- All factors deficiency except contact factor (e.g. factor XII) give rise to bleeding disorders of varying degrees of severity.

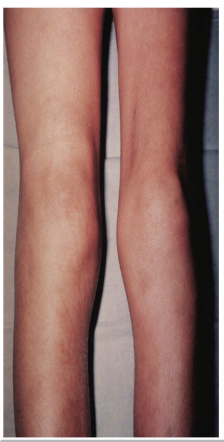
Hemophilia A

Overview

- **Deficiency of factor VIII** (8) results from an abnormality in the factor VIII gene, which lies at the the **long arm of the X-chromosome,** Ranging form single-point mutations to large deletions.
- The prevalence of this disorder is about one per 10,000 **males**. (As it is primarily an X-linked recessive disease)
- Females with haemophilia have been observed extremely rarely and these are either homozygotes for the abnormal gene or are heterozygotes in whom the normal X-chromosome has not produced sufficient quantities of factor VIII due to lyonization.

Clinical features

- **Infants** may develop profuse post-circumcision(ختان) haemorrhage or joint and soft tissue bleeds and excessive bruising.
- Recurrent painful haemarthroses and muscle haematomas dominate the clinical course of severely affected patients
- If inadequately treated, lead to progressive joint deformity and disability.
- **Intracranial bleeding** is the most common cause of death from the disease itself.



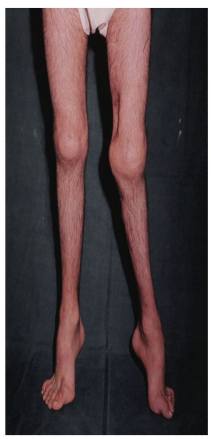


Figure 26.3 Haemophilia A: acute haemarthrosis of the right knee joint with swelling of the suprapatellar region. There is wasting of the quadriceps muscles, particularly on the left.

Figure 26.4 Haemophilia A showing severe disability. The left knee is swollen with posterior subluxation of the tibia on the femur. The ankles and feet show residual deformities of talipes equinus, with some cavus and associated toe clawing. There is generalized muscle wasting. The scar on the medial side of the left lower thigh is the site of a previously excised pseudotumour.

Congenital Coagulation Disorders

Pathoma

Hemophilia A contd..

Diagnosis

- The possibility of haemophilia is suggested by the finding of a **normal PT and a prolonged APTT.** PT : prothrombin time aPTT : Activated partial thromboplastin time
- Confirmation is by a **specific assay of factor VIII coagulant activity with normal VWF.**
- In the plasma, factor VIII is only found complexed with VWF, which acts as a carrier and prolongs its plasma half-life.
- Prenatal diagnosis of haemophilia can be made by analysis of fetal DNA, which can be obtained either by chorionic villus sampling between 11 1/2 and 14 weeks of gestation or by amniocentesis after 16 weeks.
- Genetic mutational analysis allows carriers to be identified with accuracy and is the method of choice.

Treatment

Female's dr: Just read them and know the **major** treatment :)

- Treatment should be given at the earliest sign of spontaneous or post-traumatic bleeding, which consists of **intravenous injections of factor VIII concentrate.**
- Guidelines exist for the plasma level to be achieved for different types of haemorrhage.
- A controlled trial has proven that regular prophylaxis is far superior to on-demand treatment. Approximately 25% of patients with haemophilia, usually after **treatment with factor VIII** on 10-20 occasions, develop **antibodies that inhibit its functional activity.**
- **Haemorrhage** in patients with high-titre inhibitors may require treatment with '**bypassing agents' such as recombinant factor VIIa or FEIBA** (factor eight inhibitor bypassing activity; that is, a plasma-derived activated prothrombin complex concentrate), which activate the coagulation cascade below the level of factor VIII.
- The administration of factor VIII may be avoided in **mild to moderate haemophilia** by using the vasopressin analogue **desmopressin (DDAVP)**, which causes a temporary increase in factor VIII and VWF by provoking the release of these factors from endothelial cells. DDAVP is used intravenously, subcutaneously or intranasally.

Congenital Coagulation Disorders

Pathoma

Hemophilia B

Overview

- Hemophilia B (Also referred to as **Christmas Disease**) develops as a result of **Factor IX deficiency**
- The factor IX gene is located on the long arm of the **X-chromosome.**
- Factor IX deficiency affects about 1 in every 50,000 males.
- The clinical features and inheritance of factor IX deficiency are **identical to those in factor VIII deficiency.**

Diagnosis

- **The APTT is prolonged and the PT normal**.
- The **diagnosis** can be made by **assay of the factor IX level.**

Treatment

Doctor should we know all the treatment ?
Female's dr: Just read them and know the major treatment

- Plasma-derived factor IX concentrate or recombinant factor IX is available and should be **administered intravenously** as soon as spontaneous or post-traumatic bleeding starts.
- Factor IX has a longer half-life in the plasma (18-24 hours) than factor VIII and hence can be given at less frequent intervals.

Correlation of coagulation factor activity and disease severity in haemophilia A or B

Coagulation factor activity (percentage of normal)	Clinical manifestations
<1	**Severe disease** with Frequent spontaneous bleeding into joints, muscles, internal organs from early life Joint deformity and crippling if not adequately prevented or treated.
1–5	**Moderate disease**, Bleeding after minor trauma, Occasional spontaneous episodes.
>5	**Mild disease**, Bleeding only after significant trauma, surgery.

Congenital Coagulation Disorders

Von Willebrand Disease

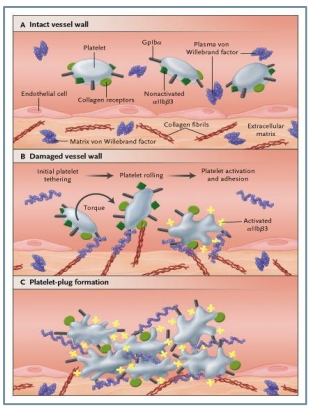
Overview

- It is an **autosomal disorder** characterized by mild (most are undiagnosed), moderate or severe bleeding.
- The bleeding results from **either a qualitative abnormality or a quantitative deficiency of Von Willebrand Factor**
- It's the **most common inherited bleeding disorder** with prevalence of up to 1%

Extra

What are the functions of VWF?

- Binds platelets to subendothelial tissues.
- It acts as a carrier for factor VIII.



The reduction in VWF results in a reduction in factor VIII concentration (can be misdiagnosed as hemophilia A)

Types

AD = Autosomal dominant
AR = Autosomal Recessive

1. Types 1 (most frequent) partial reduction, AD
2. Type 2 there are qualitative abnormalities, AD or AR
3. Type 3 there is nearly complete absence of VWF molecules,

- Spontaneous bleeding is usually confined to **mucous membranes and skin most commonly epistaxis and ecchymoses**.
- Bleeding into joints and muscles is rare except in type 3 disease.

Diagnosis

The laboratory findings include:

- Prolonged PFA closure time.
- Usually a prolonged APTT.
- Reduced factor VIII clotting activity
- **Reduced levels of VWF antigen or activity.**
- **Impaired** ristocetin-induced **platelet aggregation**

Treatment

Doctor should we know all the treatment ?
Female's dr: Just read them and know the major treatment

- For type 1 disease, **desmopressin** (DDAVP) is the first line treatment. DDAVP increases plasma levels of both VWF and factor VIII.
- Very high purity VWF concentrate may be used.
- The antifibrinolytic drug (**tranexamic acid**) may be used for treating epistaxis or menorrhagia.

Acquired Bleeding Disorders

Pathoma

Acquired coagulation disorders are more common than the inherited disorders. Unlike the inherited disorders, multiple clotting factor deficiencies are usual. Some examples:

Acquired Bleeding disorders

- Liver disease
- **Acquired hemophilia**
- **Vitamin K deficiency**
- **DIC**
- Drugs (heparin, warfarin, tPA, rivaroxaban, dabigatran)
  "Anti-coagulants"

Vitamin K Deficiency

Fat-soluble vitamin obtained from green vegetables and bacterial synthesis in the gut.

Hemorrhagic disease of the newborn:

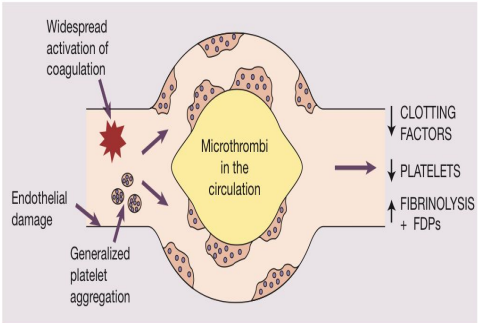
- Caused by liver cell immaturity, lack of gut bacterial synthesis of the vitamin and low quantities in breast milk.
- usually on the second to fourth day of life, but occasionally during the first 2 months.
- **PT and APTT are both prolonged.**

Disseminated Intravascular Coagulation (DIC)

- It is a process in which there is generalized **activation** of the **clotting system** followed by marked activation of the **fibrinolytic system.**
- It is a common complication following intravascular haemolysis of red cells after a mismatched transfusion.

Pathogenesis

- Clotting cascade is activated in various ways (tissue damage, collagen exposure, release of TF and other procoagulants).
- Activation of the cascade leads to the generation and dissemination of large amounts of thrombin in the circulation, the activation of platelets and the formation of intravascular microthrombi.
- As a consequence of the fibrin formation, the fibrinolytic mechanism is activated, resulting in high concentrations of FDPs, including D-dimers.



Acquired Bleeding Disorders

Pathoma

Disseminated Intravascular Coagulation (DIC)

Causes

Female's dr: Just read them

Males' doctor read them quickly

Pathoma: Remember that you don't get DIC, you get DIC because of something else (secondary to another disease)

Miscellaneous:
- Liver failure
- Pancreatitis
- Snake and invertebrate venoms
- Hypothermia
- Heat stroke
- Acute hypoxia
- Massive blood loss

Malignancy:
- Widespread mucin-secreting adenocarcinoma
- **Acute promyelocytic leukaemia**

Obstetric complications:
- Amniotic fluid embolism
- Premature separation of placenta
- Eclampsia; retained placenta
- Septic abortion

Hypersensitivity reactions:
- Anaphylaxis
- Incompatible blood transfusion

Widespread tissue damage:
- Following surgery or trauma
- After severe burns

Vascular abnormalities:
- Kasabach–Merritt syndrome
- Leaking prosthetic valves
- Cardiac bypass surgery
- Vascular aneurysms

Infections:
- Gram-negative and meningococcal septicaemia
- Clostridium welchii septicaemia
- Severe falciparum malaria
- Viral infection – varicella, HIV, hepatitis, cytomegalovirus

Diagnosis

The diagnosis of DIC is not based on a single marker but on a combination of laboratory findings.

- The platelet count is low, thrombocytopenia, due to high consumption
- Fibrinogen concentration is low.
- **High levels of fibrin degradation products (D-dimer),** that correlates with activity of coagulation and fibrinolysis
- The PT and APTT are **prolonged**.
- **RBCs fragments in blood smear (Schistocytes)**
- Compensation by the liver may render some of the coagulation tests normal.

Acquired Bleeding Disorders

Pathoma

Disseminated Intravascular Coagulation (DIC)

Treatment

Female's dr: Just read them and **know the major treatment**

- Treatment is aimed at preventing further coagulation by removal of the initiating cause.
- Supported with transfusions of blood, fresh-frozen plasma and platelet concentrates in order to restore blood volume and replace clotting factors and platelets.

Types

Acute DIC	Chronic DIC
• The haemorrhagic manifestations may be so severe in acute DIC as to lead to death. • Acute DIC may be associated many serious/life threatening diseases.	• In chronic DIC, the haemorrhagic tendency may be mild or moderate. • Some patients with chronic DIC are asymptomatic because the activation of the clotting and fibrinolytic systems is finely balanced and the production of clotting factors and platelets is sufficiently increased to compensate for their increased consumption.

Acquired Hemophilia

- Acquired hemophilia is a rare but life-threatening condition.
- Caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors, most frequently factor VIII (FVIII).
- Could be idiopathic or secondary to underlying condition (autoimmune disease,infection, malignancy,...).
- More common in the elderly.
- Treated with 'bypassing agents' such as recombinant factor VIIa or FEIBA and immune suppression.

Massive Transfusion Syndrome

- Blood loss results in reduced levels of platelets, coagulation factors and inhibitors.
- Further dilution of these factors occurs during replacement with red cells.
- Some protocols include 1 : 1 : 1 for red cells, platelet packs and FFP.

"How lucky we are to have something that makes saying goodbye so hard." A.A. Milne (Winnie-the-Pooh)

Till we meet again ان شاء الله

Summary

	Disorders		Characteristics	Symptoms	Diagnosis	Treatment
Congenital/inherited Bleeding disorders ★	**Hemophilia A (factor VIII deficiency)**		★ an abnormality in the factor **VIII** gene on X-chromosome. Factor VIII is only found complexed with VWF	post-circumcision hemorrhage hemarthroses and muscle hematomas. joint deformity and disability **Intracranial bleeding**	**normal PT and prolonged APTT. (Suggestive test)** **factor VIII coagulant activity assay with normal VWF. (Confirmatory test).**	**IV injections of the deficient factor**
	Hemophilia B (factor IX deficiency)		★an abnormality in the factor **IX** gene on X-chromosome		**normal PT and prolonged APTT.** Factor IX level assay.	
	VWB	**Type 1 partial reduction (AD)** **Type 2 qualitative abnormalities (AD or AR)** **Type 3 absence of VWF (AR)**	binds platelets to subendothelial tissues It acts as a **carrier for factor VIII** **The reduction in VWF results in a reduction in factor VIII concentration (can be misdiagnosed as hemophilia A)**		**Prolonged PFA** closure time **prolonged APTT** ★↓ **factor VIII** ★↓**VWF** antigen or activity **Impaired** ristocetin-induced platelet **aggregation**	
Acquired Bleeding disorders	**DIC**		Activation of coagulation cascade ★↑ **D-dimers, a product of fibrin degradation**		Thrombocytopenia ↓Fibrinogen Schistocytes	
	Vitamin K Deficiency **Infant / neonatal** **1972**		**PT and APTT are both prolonged**			
	Acquired hemophilia					
	Liver diseases					

Correlation of coagulation factor activity and disease severity in haemophilia **A** or **B**

Coagulation factor activity (percentage of normal)	Clinical manifestations
<1	• **Severe disease with Frequent spontaneous bleeding.**
1–5	• **Moderate disease, Bleeding after minor trauma.**
>5	• **Mild disease, Bleeding only after significant trauma, surgery.**

Quiz

Q1) The deficiency in which of the following causes a rare bleeding disorder:							
A	VWF	B	VIII	C	IX	D	XII
Q2) Acute promyelocytic leukemia is a cause of which of the following:							
A	DIC	B	Hemophilia A	C	Acquired vascular defects	D	Hemorrhagic disease of the newborn
Q3) Which of the following is suggestive of Hemophilia A:							
A	Prolonged PT	B	Normal APTT	C	Prolonged APTT	D	Both APTT and PT are prolonged
Q4) Acquired hemophilia is caused due to:							
A	Activation of clotting system followed by activation of fibrinolytic system	B	Deficiency of factor VIII	C	Development of autoantibodies against coagulation factors	D	Vit K deficiency
Q5) Which of the following is **not** a cause of bleeding disorders:							
A	Vascular disorders	B	Defective coagulation	C	anemia	D	thrombocytopenia
Q6) which of the following is true:							
A	<1% activity of factor VIII cause bleeding at minor trauma.	B	Mild hemophilia A patient bleeds at anytime.	C	>5% activity of factor VIII cause bleeding after surgery.	D	Moderate hemophilia A patient mainly bleeds spontaneously.
Q7) Which of the following combinations best describe type 3 of VWD:							
A	Partial reduction of VWF and is AD	B	Complete absence of VWF and is AR	C	complete absence of VWF and is AD	D	Qualitative abnormalities in VWF and is AD
Q8) mild/moderate hemophilia is treated by							
A	iv. With factor 8 concentrate	B	vasopressin analogue desmopressin	C	FEIBA	D	factor 7a
Q9) Which of the following lab tests differentiate between hemophilia A and von willebrand disease?							
A	Platelet aggregation test	B	Both PT & APTT normal	C	Prothrombin time	D	factor VIII deficiency
Q10) The most common acquired deficiency of coagulation factors is:							
A	liver disease	B	DIC	C	hemophilia	D	A&B

Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
D	A	C	C	C	C	B	B	A	D

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