Bleeding Disorders

By:

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Related Physiology

By: Ali Al-Omari

Hemostasis

- Hemostasis: Is the prevention of blood loss while maintaining blood in a fluid state within the vascular system.

- **Primary hemostasis** (is the formation of a weak platelet plug): vasoconstriction, platelet adhesion, platelet activation, and platelet aggregation.
- **Secondary hemostasis** (coagulation cascade): is the cascade of enzymatic reactions that ultimately results in the conversion of fibrinogen to fibrin monomers
- **Tertiary hemostasis** (breakdown of the clot): is defined as the formation of plasmin, which is the main enzyme responsible for fibrinolysis

Primary hemostasis

(Ends with platelets plug formation)

Vascular Constriction:

-Is due to, local myogenic spasm, local autacoid factors (from traumatized tissues and blood platelets) and nervous reflexes

- Endothelin, Thromboxane A2 and Serotonin (vasoconstrictor substances) are the main factor cause vasoconstriction

*The amount of dilating autacoids, such as nitric oxide (NO), prostaglandins will also be decreased after a trauma to the blood vessels

- The local vascular spasm lasts from minutes to hours

- It wont stop the bleeding, but will reduce its amount of blood

Platelet:

- Platelets originate from the fragmentation of bone marrow *megakaryocytes*. The normal concentration of platelets in the blood is 150000-400000/ microliter. The platelet half-life is 8-12 days and removed mainly by the spleen

- Platelets contain:

  - **Membrane *glycoproteins*** that cause adhesion & aggregation (mainly **GPIb & GPIIb/IIIa**)
  - **Alpha-Granules** that contain: **fibrinogen & vWF**
  - **Dense granules** that contain: **Ca^{2+} , ADP, serotonin**
  - A growth factor that stimulates cellular growth that helps repair damaged vascular walls
  - Actin, myosin, and *thrombosthenin* $\longrightarrow$ platelet contraction
  - Mitochondria
  - Enzymes to synthesize prostglandins
  - Fibrin-stabilizing factor
  - Membrane phospholipids

Mechanism of the Platelet Plug: (Adhesion, Activation, Aggregation)

- When in contact with damaged vascular surface, platelets adhere to the exposed subendothelial tissue collagen through a glycoprotein called von-Willebrand factor that leaks into the traumatized tissue from the endothelium.
- vWF forms a link between the platelets glycoprotein (GPIb) and the collagen fibrils in the injured endothelium.
- When the platelet adhere to vWF, it will be activated

Mechanism of the Platelet Plug cont.....:

-When platelets get activated, its shape changed and it activates the glycoprotein IIb/IIIa, the Alpha, and the dense granules

Activated platelets also secrete thromboxane A_2

-Secretion of ADP and thromboxane A_2 ⟶ activation of nearby platelets ⟶ adherence to originally activated platelets ⟶ plug formation

(platelets to platelets aggregation by glycoprotein IIb/IIIa adherence to fibrinogen causing platelets plug)

- Original plug is loose but it will be better constructed when fibrin threads are formed and attached to it

secondary Hemostasis

(Coagulation cascade) (Ends with fibrin mesh formation)

- Coagulation cascade: is a series of amplifying enzymatic reactions that lead to the deposition of an insoluble fibrin clot.

- The clot begins to develop in 15-20 seconds in severe trauma and 1-2 minutes in minor trauma. Within 3 to 6 minutes after rupture of a vessel the entire opening end of the vessel is filled with clot, and after 20-60 minutes, because of the clot retraction further closure of the vessel

- Initiation of the clotting mechanism starts by the release of activator substances (from damaged vascular wall and platelets mainly)

- When clot is formed it can follow one of two courses:

- Invaded by fibroblasts ⟶ connective tissue all through the clot and fibrous tissue formation within 1-2 weeks
- Dissolved; where clots are extravascular and clot formation is not needed

Mechanism of Blood Coagulation:

- Substances that promote coagulation, called *procoagulants*
- Substances that inhibit coagulation are called *anticoagulants*
- Coagulation depends on the balance between the 2 groups of these substances

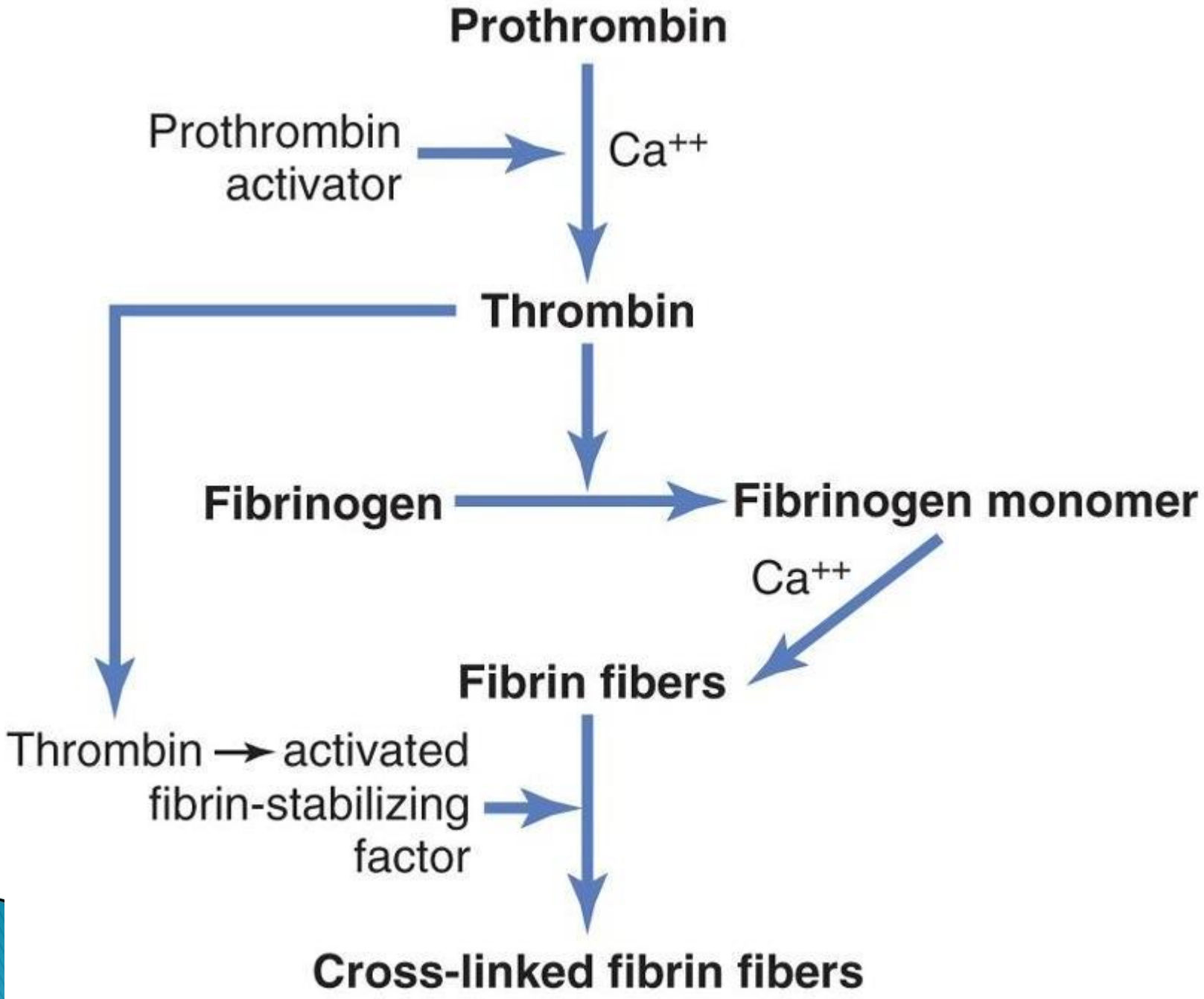
Steps of coagulation:

1- Response to rupture of the vessel ⟶ complex cascade of chemical reactions ⟶ formation of ***prothrombin activator***. ((This factor is the rate-limiting factor in the process of coagulation))

2- Conversion of prothrombin (a plasma protein, α_2-globulin) ⟶ thrombin in the presence of Ca^{2+} (prothrombin activator acts as a catalyst)

3- Thrombin (an enzyme) converts fibrinogen to fibrin fibers.

4- Thrombin activates fibrin-stabilizing factor. This factor causes covalent bonds between fibrin monomer molecules


Prothrombin
Prothrombin activator
Ca++
Thrombin
Fibrinogen
Fibrinogen monomer
Ca++
Fibrin fibers
Thrombin → activated fibrin-stabilizing factor
Cross-linked fibrin fibers

- Formation of prothrombin activator can be initiated in response to:
  - Trauma to the vascular wall and adjacent tissues
  - Trauma to the blood
  - Contact of blood with elements outside blood vessels (such as collagen fibers)

- Prothrombin activator is formed through
  - Extrinsic pathway **(trauma to vascular wall and surrounding tissues)**
  - Intrinsic pathway **(begins in blood itself)**

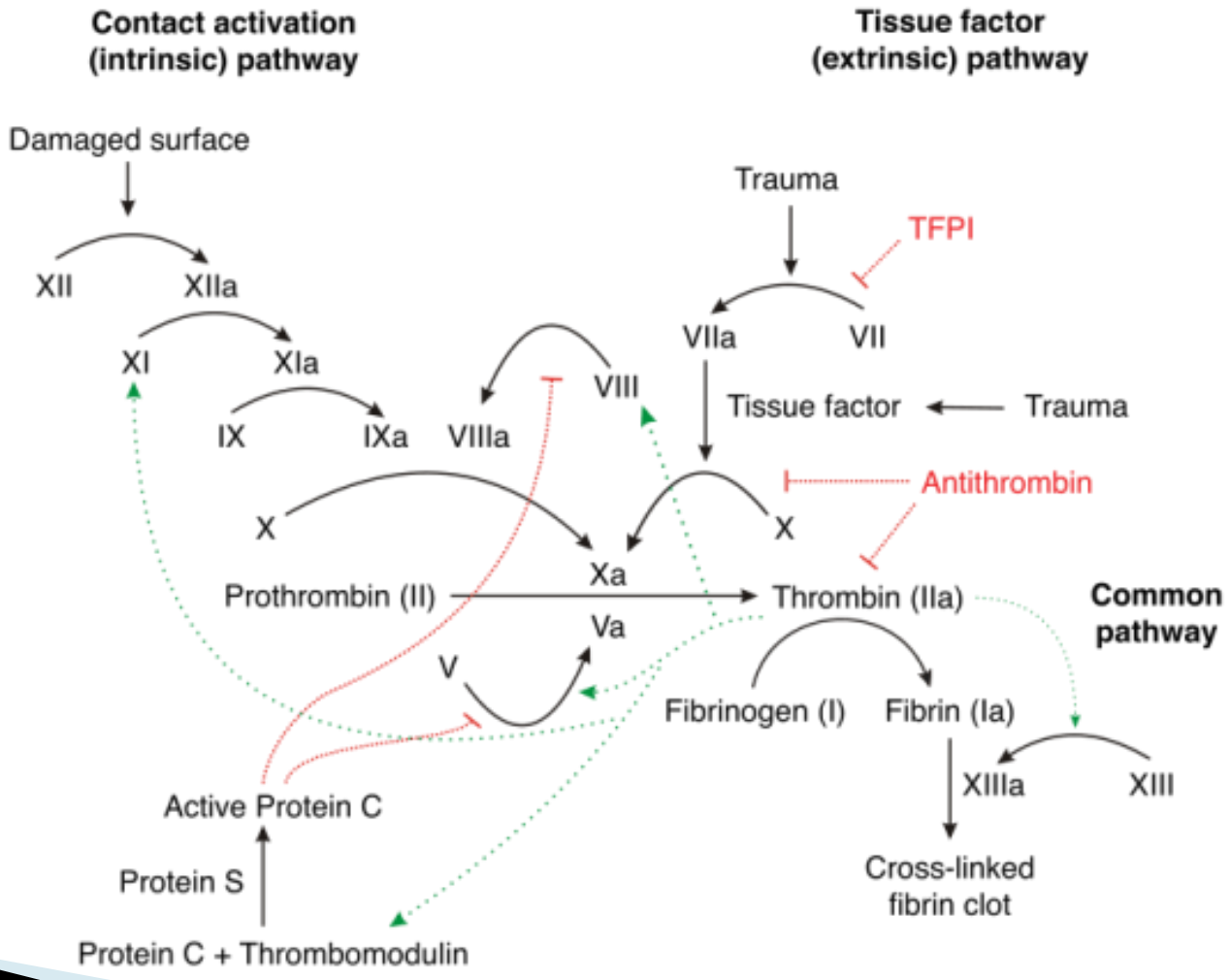
- Both extrinsic and intrinsic pathways need plasma proteins called blood-clotting factors. Most of them are inactive Proteolytic enzymes

Factors of the Coagulation Cascade

Scientific Name	Common Name	Other Names	Pathway
Factor I	Fibrinogen		Both
Factor II	Prothrombin		Both
Factor III	Tissue thromboplastin	Tissue factor	Extrinsic
Factor IV	Calcium		Both
Factor V	Proaccelerin	Labile factor Accelerator (Ac-)globulin	Both
Factor VI (Va)	Accelerin		
Factor VII	Proconvertin	Serum prothrombin conversion accelerator (SPCA) Cothromboplastin	Extrinsic
Factor VIII	Antihemophilic factor	Platelet cofactor 1 Antihemophilic globulin (AHG)	Intrinsic
Factor IX	Christmas factor	Platelet thromboplastin component (PTC) Antihemophilic factor B	Intrinsic
Factor X	Stuart factor		Both
Factor XI	Plasma thromboplastin antecedent (PTA)		Intrinsic
Factor XII	Hageman factor	Contact factor	Intrinsic
Factor XIII	Fibrin stabilizing factor (FSF)	Protransglutaminase Fibrinoligase	Both

***When a small letter "a" to the Roman numeral, this means that the factor is activated (e.g. VIIIa)

Coagulation cascade:



The extrinsic pathway

1- For the initiation of the extrinsic pathway, a factor extrinsic to blood but released from injured and damaged tissue, called tissue thromboplastin (factor III) or tissue factor, is required.

2- This factor is composed especially of *phospholipids* from the membranes of the tissue plus a *lipoprotein complex* that functions mainly as a *proteolytic enzyme*

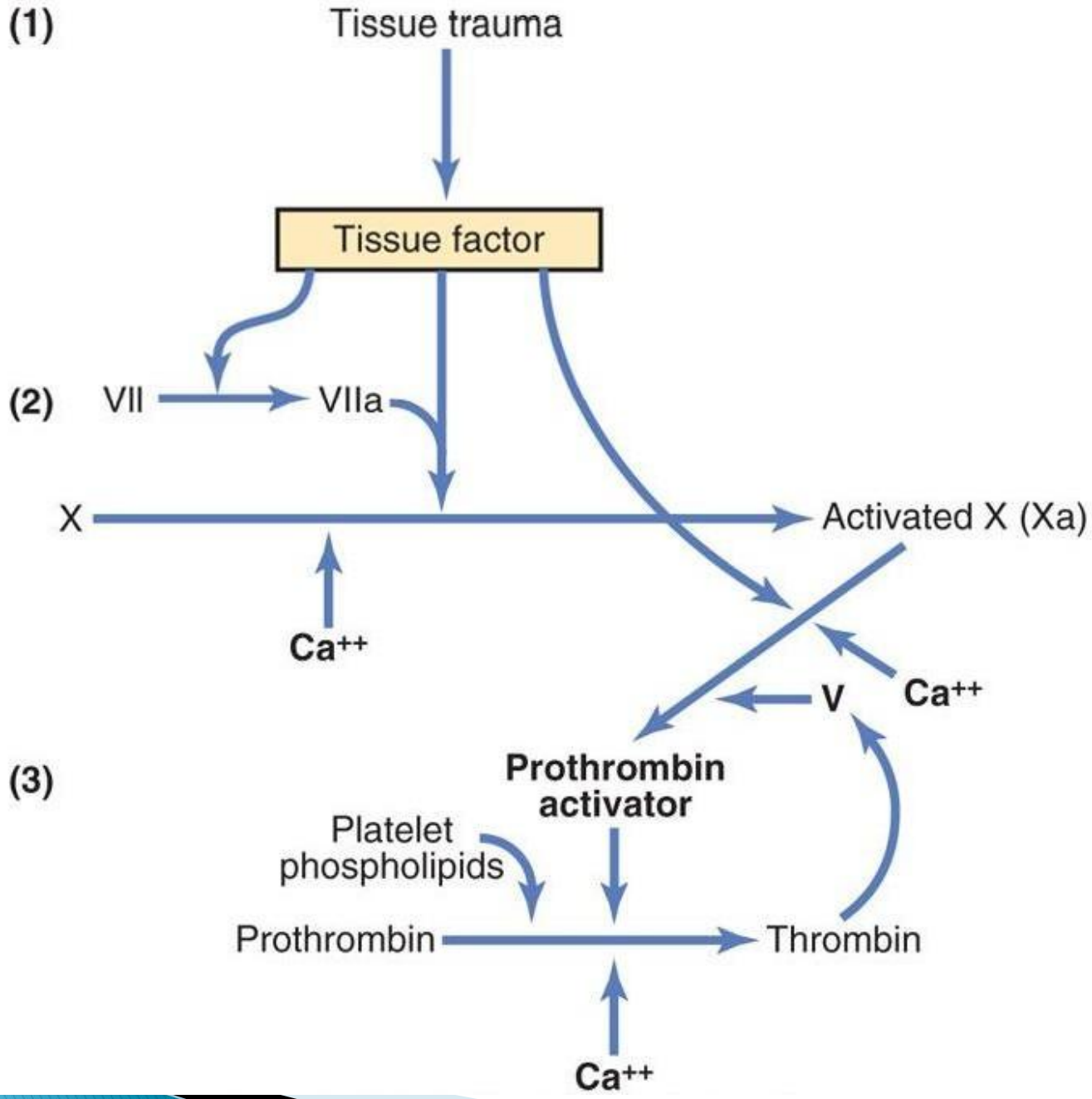
3- Thromboblastin makes a complex with factor VII and with the presence of Ca^{2+} It activates factor X to form Xa

4- Xa combines with phospholipids of thromboblastin and phospholipids released from platelets and with factor V ⟶ a complex called prothrombin activator (Ca^{2+} is needed).

Xa in the final prothrombin activator complex is the actual protease that cause the splitting of prothrombin to thrombin.

The formed thrombin cause further activation of factor V and factor X ⟶ positive feedback mechanism

Extrinsic Pathway for Initiating Clotting



The intrinsic pathway

1- The intrinsic pathway is so named because the necessary factors are contained within the blood

2- Blood trauma ⟶ activation of factor XII and release of platelet phospholipids that contain the lipoprotein called platelet factor 3.

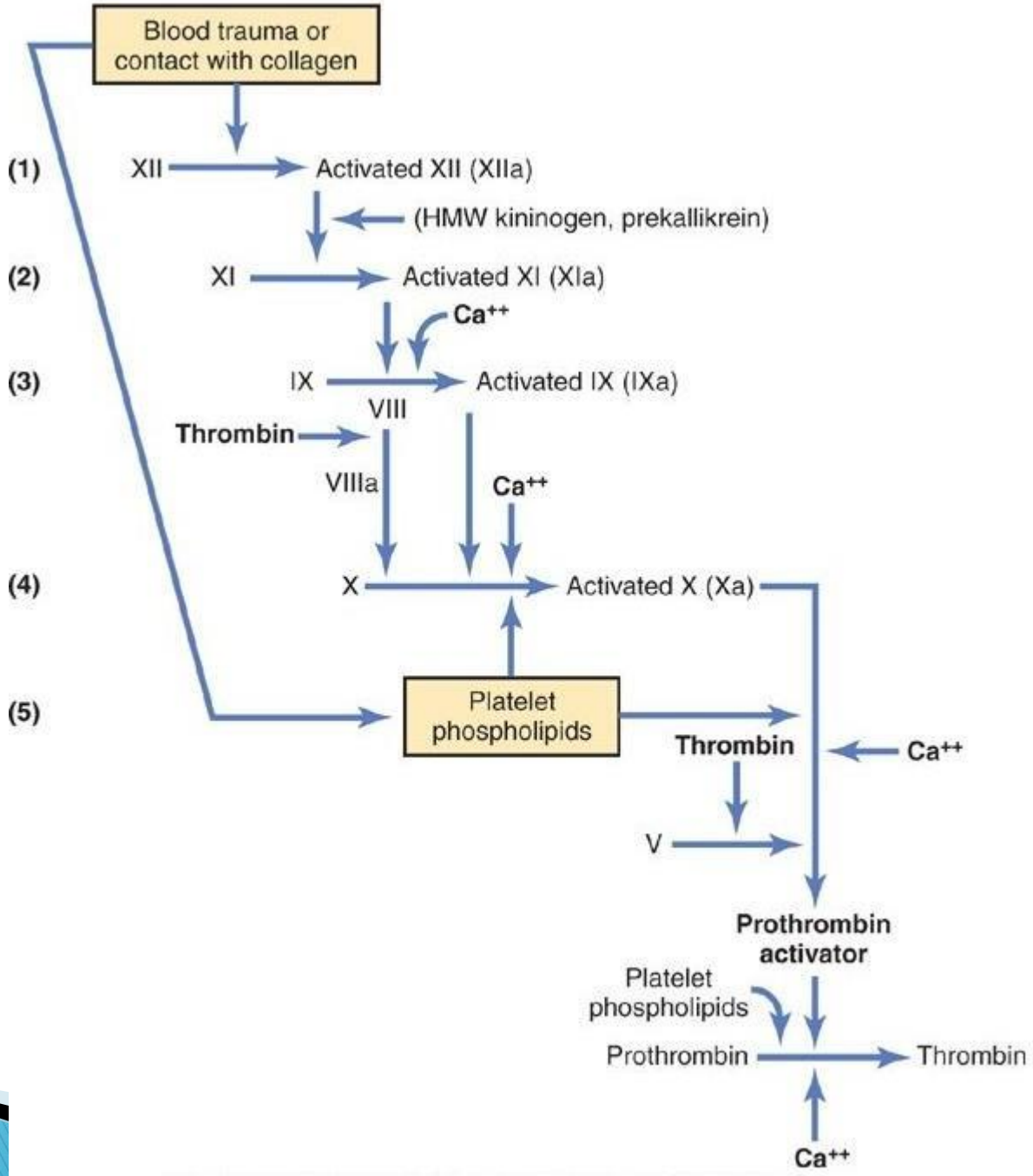
Factor XII is activated when it comes in contact with collagen or wettable surface (such as glass)

3- XIIa ⟶ activation of XI (i.e. formation of XIa). This step is accelerated by prekallikrein

4- XIa ⟶ activation of IX

5- IXa acts with VIIIa, platelet phospholipids and factor 3 to activate X (i.e. to form Xa).

6- Activation of factor X. This step is similar to the last step in the extrinsic pathway


Blood trauma or contact with collagen
(1)
XII
Activated XII (XIIa)
(HMW kininogen, prekallikrein)
(2)
XI
Activated XI (XIa)
Ca++
(3)
IX
Activated IX (IXa)
VIII
Thrombin
VIIIa
Ca++
(4)
X
Activated X (Xa)
(5)
Platelet phospholipids
Thrombin
Ca++
V
Prothrombin activator
Platelet phospholipids
Prothrombin
Thrombin
Ca++

Notes:

- Ca2+ ion is needed for both the extrinsic and intrinsic pathways and without it clotting does not occur
- The intrinsic pathway is slower in its action compared to the extrinsic. It takes 1-6 minutes to cause clotting
- Fibrinogen is synthesized by the liver.
- Vitamin K is required by the liver for normal formation of prothrombin as well as for formation of a few other clotting factors
- Clot formation is a positive feedback mechanism because of the thrombin action. The proteolytic effect of thrombin converts more prothrombin into still more thrombin

Intravascular prevention of blood clotting in the normal vascular system

- Endothelial surface factors: smoothness, glycocalyx, thrombomodulin (binds thrombin), protein C (inhibits Factors V and VIII)
- Antithrombin action of fibrin and antithrombin III
- Heparin-released by basophils and mast cells
- Plasmin-digests fibrin fibers and other clotting factors (from plasminogen-serum protein trapped in clot)

Lysis of Blood Clots The Plasmin

- Plasma contains a pro enzyme released by the liver called plasminogen (or profibrinolysin).

When activated it becomes the proteolytic enzyme plasmin (or fibrinolysin)

- Plasmin resembles trypsin and can digest fibrin fibers, fibrinogen, factor V, factor VIII, prothrombin, and factor XII.

So it can cause lysis of the clots

- When a clot is formed plasminogen is trapped in it along with other plasma proteins.
- Injured tissues start the slow release of tissue plasminogen activator (t-PA) that will convert plasminogen to active plasmin in a day or so later to the formation of the clot ⟶ blood clot removal and reopen small blood vessels

Blood Coagulation Tests

1- Bleeding time: a cut wound normally bleeds for 1-6 minutes depending on the depth of the wound and degree of hyperemia in the site of wound. It is specially prolonged by lack of platelets

2- Clotting time: Its normal value is 6-10 minutes. Its use in modern medicine is limited

3- Prothrombin time (PT):

- It is a measure of the time needed to use the whole available prothrombin when tissue factor is added to the sample of blood
- In the clinical practice this test is a measure of the extrinsic pathway
- The normal PT is 12 seconds (range 10-14 seconds). If prothrombin and/or factor VII levels are deficient the time is prolonged
- This test is used to determine the clotting tendency of blood in the measurement of warfarin dosage (double or triple the time), liver damage, and vitamin K states
- It is used in conjunction with the activated partial thromboblastin time which measure the intrinsic pathway

***INR** (the international normalized ratio): is calculated from a PT result and is used to monitor how well the blood-thinning medication (anticoagulant) is working

(INR of 1.1 > is considered normal. A range of 2.0 to 3.0 is generally an effective therapeutic range)

Blood Coagulation Tests cont....

4- Activated partial thromboplastin time (aPTT):

- It is a measure of both the intrinsic pathway (or contact activation pathway) and the common coagulation pathway
- It is used to monitor the treatment effects with heparin. It prolongs in hemophilia
- In this test phospholipid (an activator) is added to the plasma sample and the time is measured until thrombus forms. The term partial is used because tissue factor is not added
- Normal range is 25-39 seconds. Deficiency of factor VII and XIII will not be detected by PTT

BLEEDING DISORDERS

- VASCULAR DEFECTS -

BY : SUHAIB MAHAJNEH

INTRODUCTION

- Disorders of blood vessels characterised by an abnormal tendency of bleeding due to failure of haemostasis !

(supporting tissue disorders with normal laboratory tests)

- Mostly , patient complained about " ***SPONANEOUS BRUISING*** "
- Clinically , patient present with " ***MUCOCUTANEOUS BLEEDING*** "
  - Mucocutaneous bleeding → Purpura , Petechiae , Ecchymoses

- Usually patients with these diseases are diagnosed by rulling out Platelets disorders , Coagulation or Fibrinolytic disorders !

- In these disorders :
  - PLT COUNT – Normal
  - BT – High or Normal
  - PT – Normal
  - PTT – Normal
- PLT count , screening tests for coagulation factors and PLT function tests all are normal (except BT , maybe prolonged in some disorders – ex. Scurvy and marfan syndrome) !

- These disorders are divided into : Acquired and congenital disorders

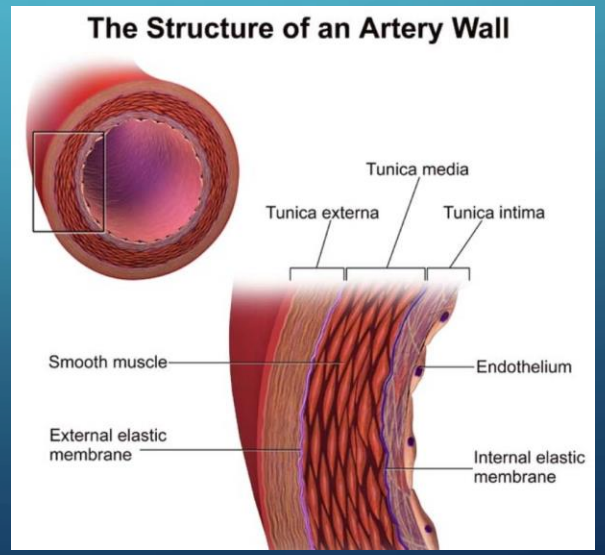
DIVIDED INTO

- **Acqired Vascular Defects :**
  - Henoch-Schoenlein syndrome
  - Scurvy
  - Senile purpura
  - Steroid purpura

- **Congenital Vascular Defects :**
  - Ehler-Danlos Syndrome
  - Rendu-weber Osler Disease
  - Marfan Syndrome

- *Anatomy of blood vessels* -

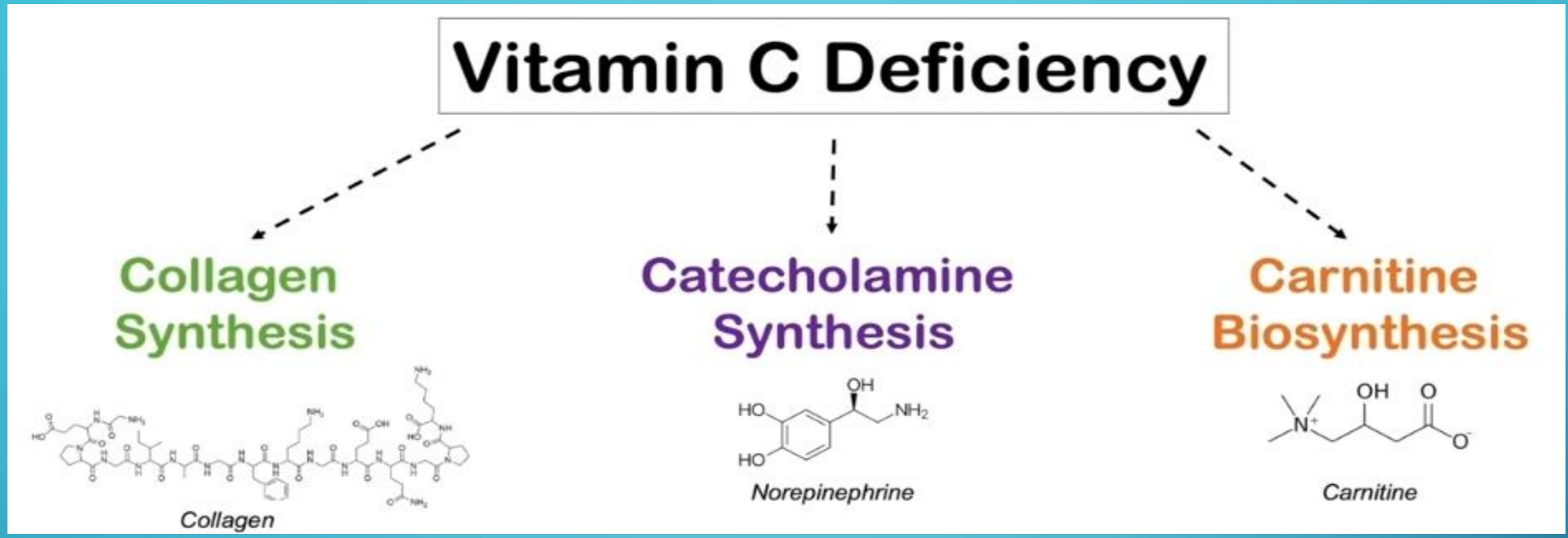
- **Tunica intima (innermost layer) – ENDOTHELIUM**
- **Tunica media (middle layer) – ELASTIN AND SMOOTH MUSCLE**
- **Tunica externa (outer layer) – INTERWOVEN COLLAGEN FIBERS**
  - **Type I and Type III Collagen are the main types in the media and adventitia !**



- ACQUIRED VASCULAR DISORDERS -

- ***Scurvy :***

- A condition of vitamin C (Ascorbic acid) deficiency .
- Occurs mostly in " Severly malnourished individuals "
- Symptoms can begin within 3 months of decreased vitamin c intake
    - Occur at vitamin C levels < 0.2 mg/dl (< 11 micromol/L)



- So , Vitamin C is absolutely essential for the synthesis of collagen !
- Nescessary for hydroxylation of proline and lysine in collagen synthesis
- Vitamin C deficiency – Collagen Hydroxilation defect – Fragile blood vessels

- Risk factors for vitamin C deficiency :
  - Alcoholism
  - Smokers
  - Type 1 diabetes
  - Individuals with Gi tract disorders (ex. IBD)
  - Patients with iron overload

- ***Clinical Features :***

- Swollen Gums
- Easy bruising
- Petechiae
- Perifollicular and subperiosteal hemorrhage
- Anemia
- Hemarthrosis
- " Corkscrew " hair

- *Diagnosis* :

- Low plasma & leukocyte vitamin C levels

- Clinical presentation

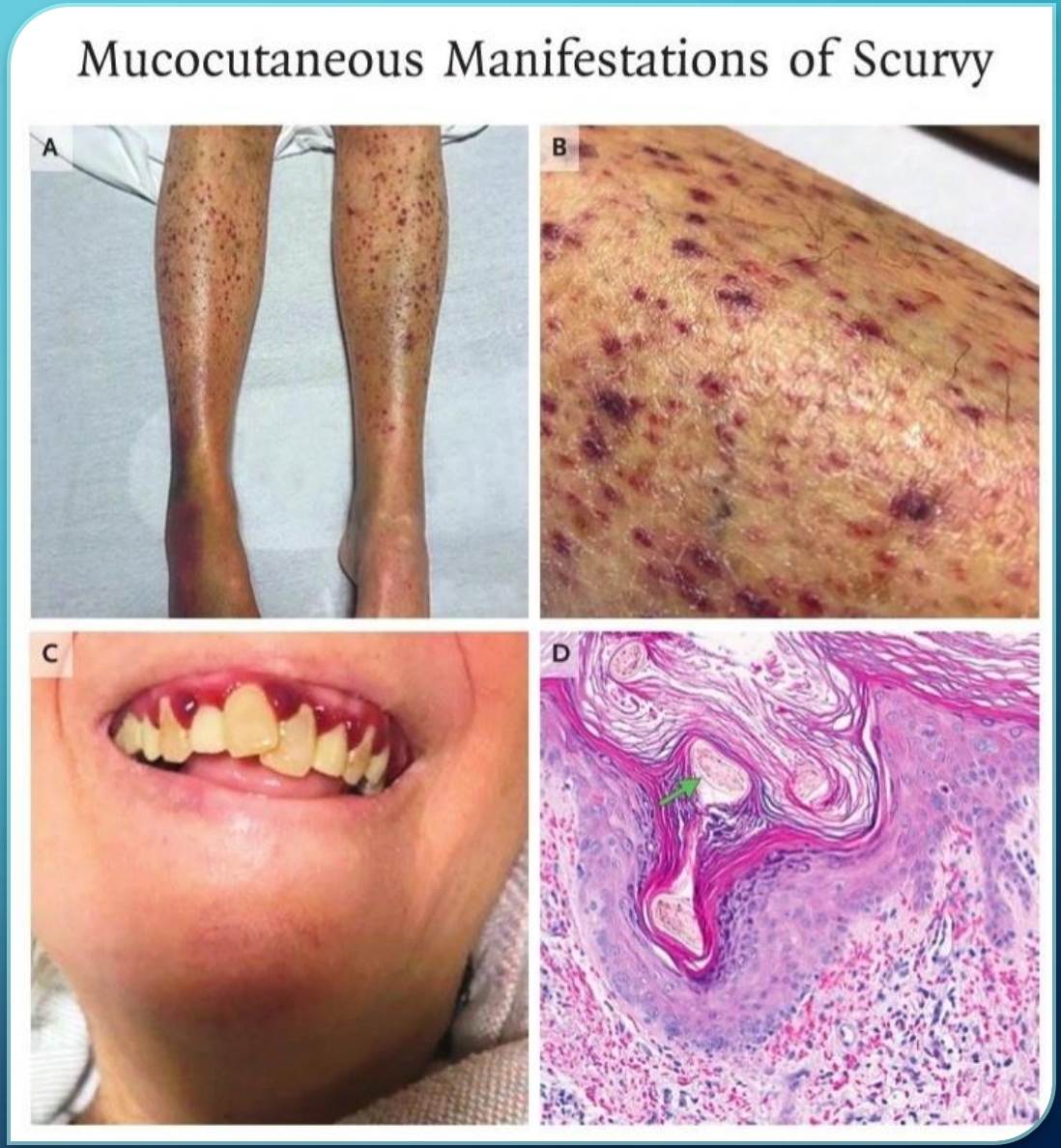
- the key to diagnosis :

“ Dietary History “

- *Management* :

- Vitamin C supplementation

- Dietary options (Fruits and vegetable)

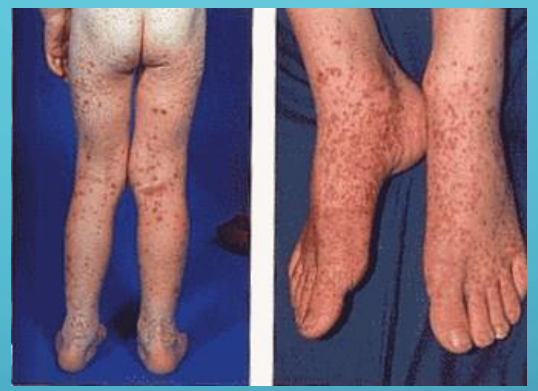


- ***Henoch-Schoenlein Purpura :***

- Benign self-limiting disorders
- It is a type III hypersensitivity reaction (Immune complex)
- Also known as " **IgA Vasculitis** "
- Characterised by immune complex deposition in small BV
- often preceded by an acute upper respiratory tract infection (usually viral or group A strep)
- usually occurs in children and young adults , has good prognosis
- The most common cause of vasculitis in children
- Male to female ration → 2:1

- ***Clinical Features :***

- Purpura over buttocks and lower legs (Palable)
- Abdominal pain and bleeding (Colicky)
- Arthritis
- Nephritis
- Subcutaneous edema
- Haematuria
- Black stool



- Classic Triad of symptoms is the most common presentation
  - Purpura
  - Colicky abdominal pain
  - arthritis

• Nephritis found in 40% of patients (onset : may occur up to 4 weeks after the onset of other symptoms) ! Prognosis is determined by severity of renal involvement .

• in adults : hypertension , abnormal renal function (proteinuria > 1.5 g/day)

- ***Investigations :***

- Tissue biopsy : demonstrates IgA depositions within and around BV
- Urinalysis : haematuria and/or proteinuria present in 20-40% of cases
- Serum IgA levels (Not diagnostic)
- BUN and creatinine levels : may be elevated from renal involvement

- ***Managment :***

- HSP is usually self-limiting ! So, Treatment for most patients supportive and is entirely symptomatic .

- Nonsteroidal anti-inflammatory drugs (NSAIDS) may help joint pain and do not worsen purpura, but NSAIDS should be used cautiously in patient with Gi disorders and renal insufficiency !

- Clinicians often use corticosteroids to treat Abdominal pain, subcutaneous edema, and nephritis but no studies have demonstrated their effectiveness

- ***Senile Purpura :***

- Known as Bateman's purpura or actinic purpura

(Actinic – because of its association with sun damage)

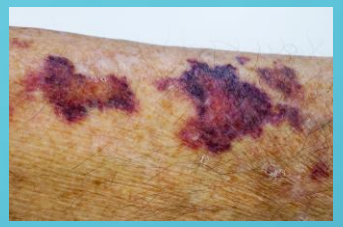
- An age-associated loss of subcutaneous fat and the collagenous support of small blood vessels , making them more prone to damage from minor trauma .

(Atrophy of the Vascular supporting Tissue)

- Occurs in elderly (Aging is the most common cause of it)

- Aging is not the only source of this kind of skin damage ! Also , UV rays weakens the connective Tissue that hold BV in their place . That's makes BV fragile

- As the body ages , the skin become thinner and more delicate !
- initial signs : Purple or Red bruises that have irregular shape
- after the bruises healed , a yellow or brown stain may appear !



- it is Characterised by discolored areas on exposed skin (arms , hands) → Usually on extensor surfaces !
- Accidently hit something → Dark flattened blotches → resolve → Age spots

- ***CLINICAL FEATURES :***

- Thin skin
- loose skin (lack elasticity)
- Purpura

- ***INVESTIGATIONS :***

- Usually diagnosed based on visual examination alone ! But some tests should be done to make sure the senile purpura not caused by something more serious.

  - CBC
  - Urinalysis (rule out blood in urine)
  - liver function tests (LFT)
  - CPR
  - Renal function tests (rule out renal Dz that causes purpura)

- ***MANAGEMENT : (*** Sunscreens , long-sleeved shirts , hats)

- CONGENITAL VASCUALR DISORDERS -

- ***Osler-Weber-Rendu Syndrome :***

- Also known as " Hereditary Hemorrhagic Telangiectasia "

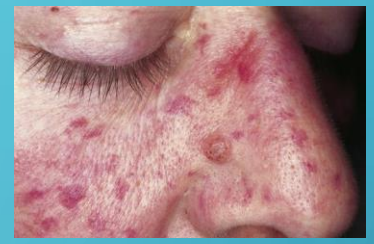
- An autosomal dominant inherited condition

→ ectasia : dilation , angio : vessels , Tele : distant / far

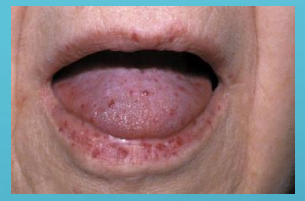
- So , distant vessels are affected ! Dilated and have thin walls

- Mechanism : mutations occurs in three genes (ENK, ALK1 or SMAD4) that encodes components of the TGF-B signalling pathway which is a potent angiogenic cytokine!

- Dilation of capillaries and small arterioles produces characteristics small Red spots that blanch on pressure in skin and mucus membrane



- Telangiectasia and small aneurysms are found on fingertips, face, tongue nasal passages, lungs and Gi tract

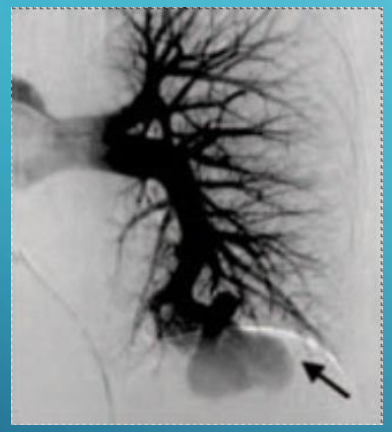


- Recurrent epistaxis and chronic Gi bleeding → Chronic iron deficiency anemia

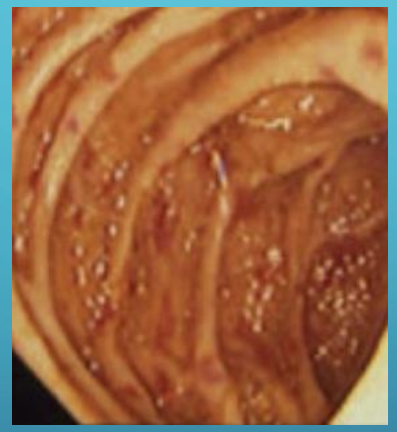
- Vascular malformations also occur in pulmonary, hepatic, cerebral, vasculature

- a significant proportion of these patients develop larger pulmonary arteriovenous malformations (PAVMs) !

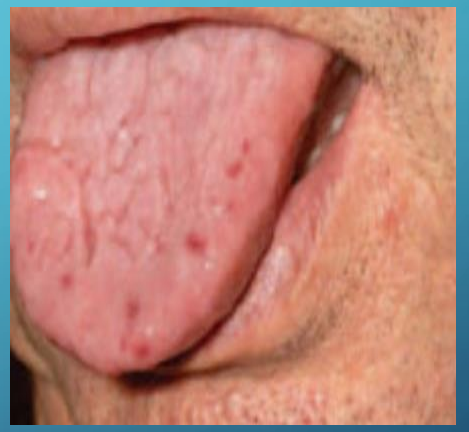
- that's causes arterial hypoxia due to right to left shunt , which allows deoxygenated systemic venous blood to bypass the lungs !! And also Paradoxical embolization complications → Stroke and brain abscess



PAVMs



Gi involvement



Tongue Involvement

- ***CLINICAL FEATURES :***

- Recurrent nosebleeds
- Iron deficiency anemia
- Tiny red spots (Tongue, fingers, face)
- Shortness of breath

- ***INVESTIGATIONS :***

- Family history and genetic testing for HHT (To confirm suspected diagnosis)
- Ultrasound (to determine if the is affected by AVMs)
- MRI (check the brain for any BV abnormalities)
- Bubble study (check any abnormal blood flow caused by lung AVMs)

- ***MANAGEMENT :***

- Drugs help reduce the bleeding associated with HHT

  - Hormone-related drugs : medications containing estrogen with high doses

  - Drugs that block BV growth → bevacizumab given IV

  - Drugs that slow the disintegration of clots : Tranexamic acid which can help stop extreme bleeding in emergencies and maybe useful if taken regularly to prevent bleeding

- ***Ehlers-Danlos Syndrome :***

- a rare autosomal dominant disorder of connective tissue

- Result from mutations in genes involved in ECM formation → loss of structural integrity within different organs

- Defect in type III procollagen (COL3A1) → in Vascular type !

- affect the structure and function of the skin, eyes, joints, BV and internal organs

- underlying defects are varied and involve abnormalities of collagen fibril synthesise and ECM molecules

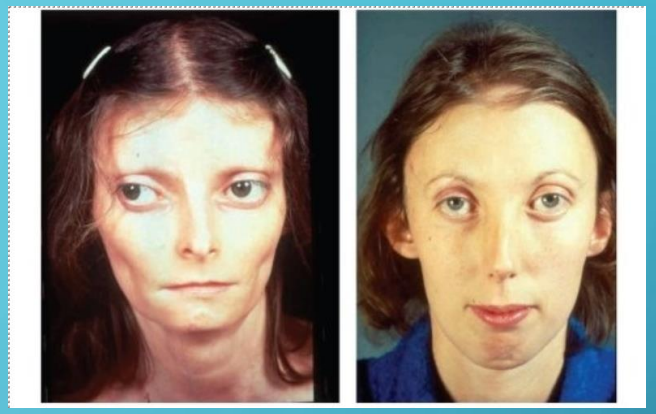
- Characterised by → Joint hypermobility , easy bruising, and lax Skin

- Maybe associated with aortic aneurysms and organ ruptures

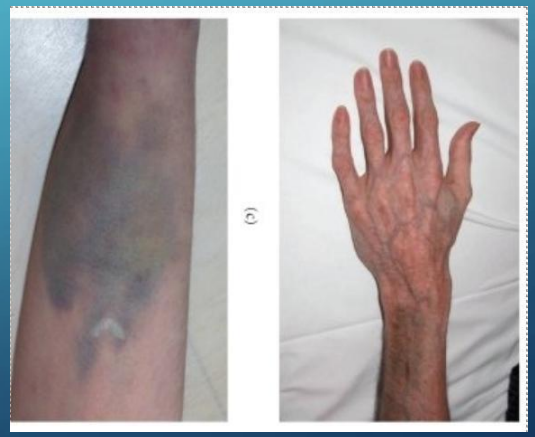
- ***CLINIAL FEATURES :***

  - Distinctive facial features :

    * Thin nose
    * Small earlobes
    * Thin upper lip
    * Prominent eyes



  - Thin, Translucent skin that bruises very easily
  - Fair-skinned people → underlying BV are very visible



- ***INVESTIGATIONS :***

- Family history for ehlers-danlos syndrome (often enough for diagnosis)

- Genetic tests on a blood sample (in Vascular type can confirm diagnosis)

    - For hyper ehlers-danlos syndrome – No genetic testing avaliable !

- presentation of clinical triad (Hyperextensibility, hypermobility, ecchymosis)

- CBC

- X-Ray spine - CXR

* Key diagnostic factors : Family history positive, joint or spine pain, and joint hypermobility and motor delay in infancy *

- ***MANAGMENT :***

- Over-the-counter pain relievers → Ibuprofen , Acetaminophen

- Blood pressure drugs → because BV are more fragile , so we need to reduce the stress on vessels by keeping BP low

- Physical therapy → to strengthen the muscles and stabilize joints to prevent dislocations of the joints !
- Surgical procedures → To repair joints damage by repeated dislocations or to repair ruptured areas in BV and organs

THANK YOU!

Platelet Disorder

× Platelets (thrombocyte) are the cells in our blood that responsible of making clots and prevent bleeding .

× They come from being a megakaryocyte cells in the bone marrow .

× Platelets growth is regulated by thrombopoietin .

× Normal counting of platelet range from 150,000 – 400,000

Lower than that consider as a thrombocytopenia and greater as a thrombocytosis .

but concern come out when symptom appears .

Thrombocytopenia

- Defined as the platelet count less than 150,000

×CAUSES :

Decrease production ; bone marrow failer , invation , injury

Increase destruction ; infection ,drug inuced,ITP, HIT, SLE, DIC , TTP

Sequestration from splenomegaly

Pregnancy

The symptom and severity vary based on the platelet count

- cutaneous bleeding ; petechiae , ecchymosis .. Minor trauma.
- Mucosal bleeding ; nose bleeding, hemoptysis ,GI GU bleeding .

- BUT WHEN PLATELET COUNT BECOME **<50,000** excessive bleeding after surgery or trauma .

THEN when **<20,000** spontaneous minor bleeding BUT less than **10,000** major spontaneous bleeding can occur, life threatening emergency !

Immune thrombocytopenia purpura

ITP; autoimmune disease ; where there are antibodies (IgG) against the glycoprotein complex that cause damage of the platelets and consequently remove them by the spleen.

So here the thrombocytopenia is due to immune **destruction** of platelets.

Acute form

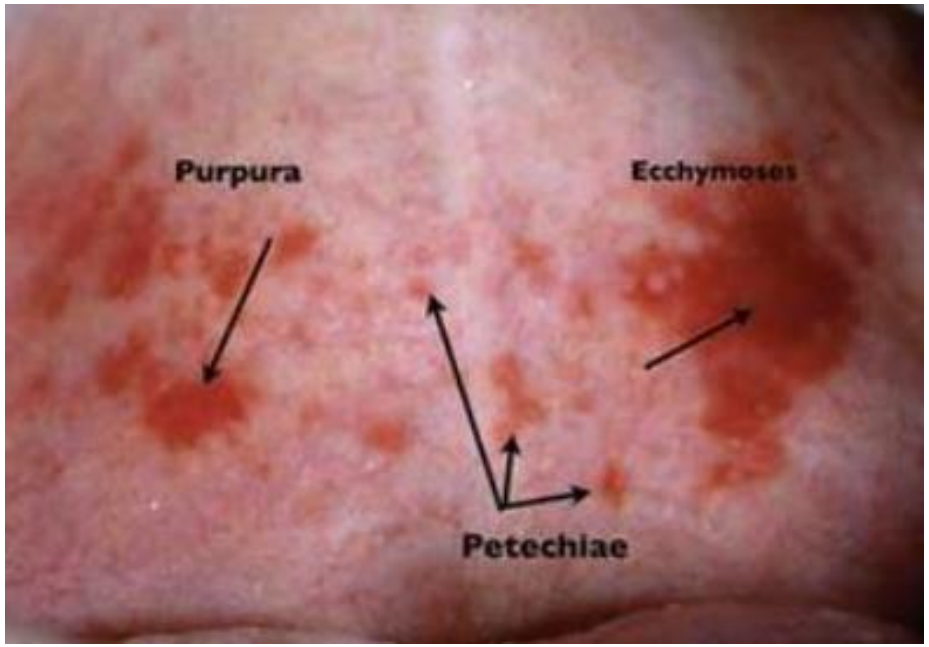
- Seen in children age group 2–6 years
- Post viral infection
- self limited – 80% spontaneously 6 month

Chronic form

- Seen in adult Common in women 20-40
- May Associate with SLE , thyroid disease , post vial infection like HIV
- Spontaneous remession is RARE

Clinical feature

- Cutaneous bleeding ; Easy bruising ,petechiae, purpura, ecchymoses
- Mucosal bleeding ; nose bleeding , hemoptysis , GI/GU bleeding
- menorrhagia
- NO SPLEENOMEGALY



Diagnosis

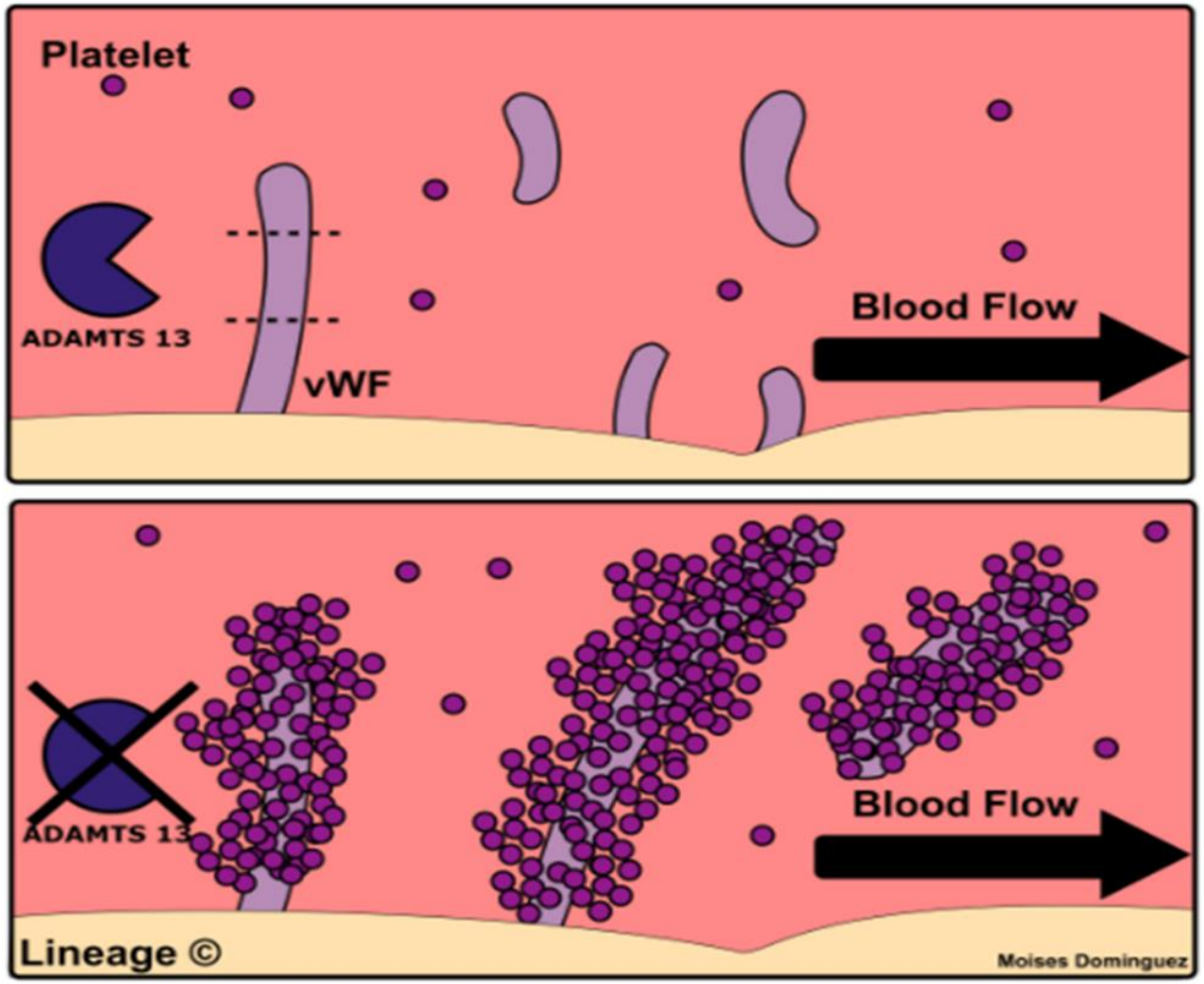
- CBC; decrease platelet count <20,000 BUT normal RBCs
- Peripheral blood smear ; decease platelet
- Bone marrow; increase megakaryocyte
- Diagnosed by exclusion not test

Treatment

- Steroid
- IVIG
- Splenectomy
- Rituximab , thrombopoietin receptor agonist
- Platelet trans. Only in sever bleeding or p.c. <30,000

Thrombotic thrombocytopenic purpura

- RARE disorder , where blood clots form in small vessels due to aggregation of the platelet .
- it can be inherited or acquired .



This microthrombi can cause :

- Thrombocytopenia due to consumption of the platelet.
- Occlusion of small vessels .
- Microangiopathic hemolytic anaemia due to the Mechanical damage of the the RBCs .

Signs and symptoms

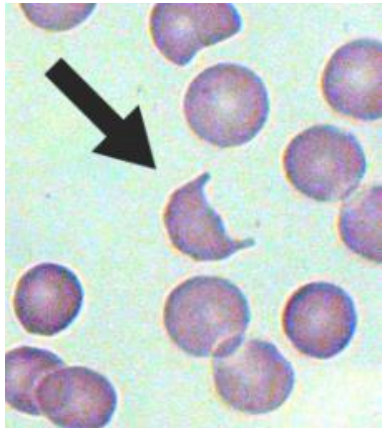
- Bruising and bleeding under your skin (petechiae , purpura)
- fever
- Signs and symptom of hemolytic anaemia ; pallor fateigue dynpea and jaundice
- Fluctuating neurological signs (speech changes- confusion-hemiplegia-syncope)
- Change in urine

Diagnosis

- CBC ; low platelet and low Hb
- Anaemia

1. High LDH
2. Low haptoglobin
3. High unconjugated bilirubin

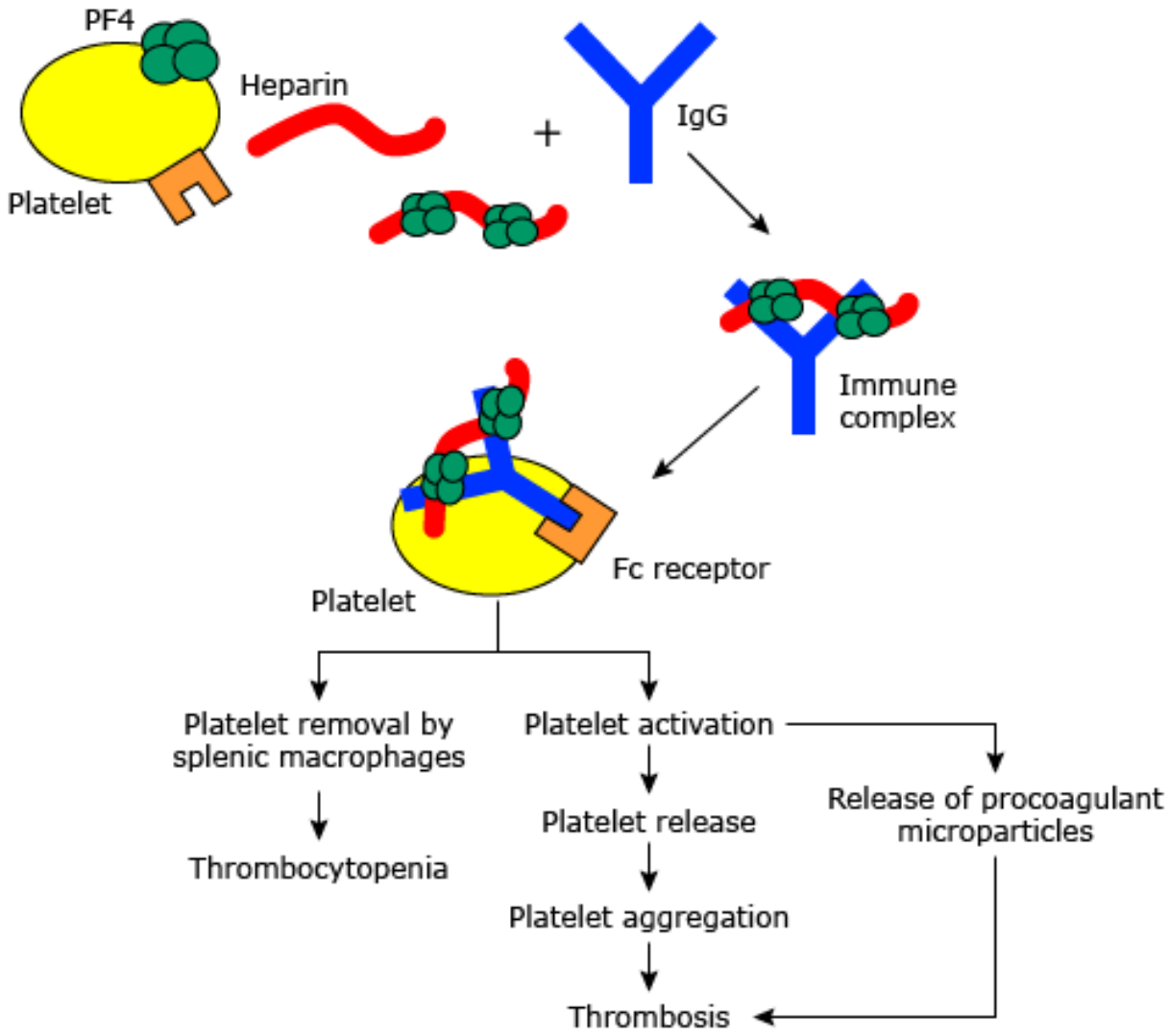
- Thrombocytopenia
- Peripheral blood smear : schistocyte



Treatment

- Plasmapheresis large volume
- Corticosteroids
- DO NOT give platelet transfusion
- its life threating emergency , Its highly responsive to therapy BUT can lead to death if untreated

Heparin induced thrombocytopenia



HIT type 1

- 1-2 days after heparin
- No risk of thrombosis
- Thrombocytopenia recover even with continue heparin use

HIT type 2

- 5-10 days after heparin
- There is risk of thrombosis
- Clinically significant

Signs and symptoms

- Arterial (MI & stroke) and venous thrombosis (DVT & PE)
- Skin necrosis (low molecular weight heparin)
- Mucosal bleeding and cutaneous bleeding

Diagnosis

- 4 Ts :

1. Timing 5-10 days after heparin
2. Thrombocytopenia decrease of platelet >50%
3. Thrombosis platelet aggregation
4. AlTernative lack of other causes of thrombocytopenia

- Decreased platelet count
- Gold standard ; serotonin releasing assay pt. Serum + donor serum + heparin
- - increase in serotonin, the diagnosis of HIT is confirmed

Treatment

- 20% mortality rate if untreated
- Stop heparin (avoid using heparin if past HIT)
- If thrombosis present non heparin for - 3 month
- If thrombosis not present nonheparin for - 4 weeks

DISSEMINATED INTRAVASCULAR COAGULATION , VON WILLEBRAND DISEASE & ACQUIRED PLATELET DISORDERS

Salem Abu Mahfouz

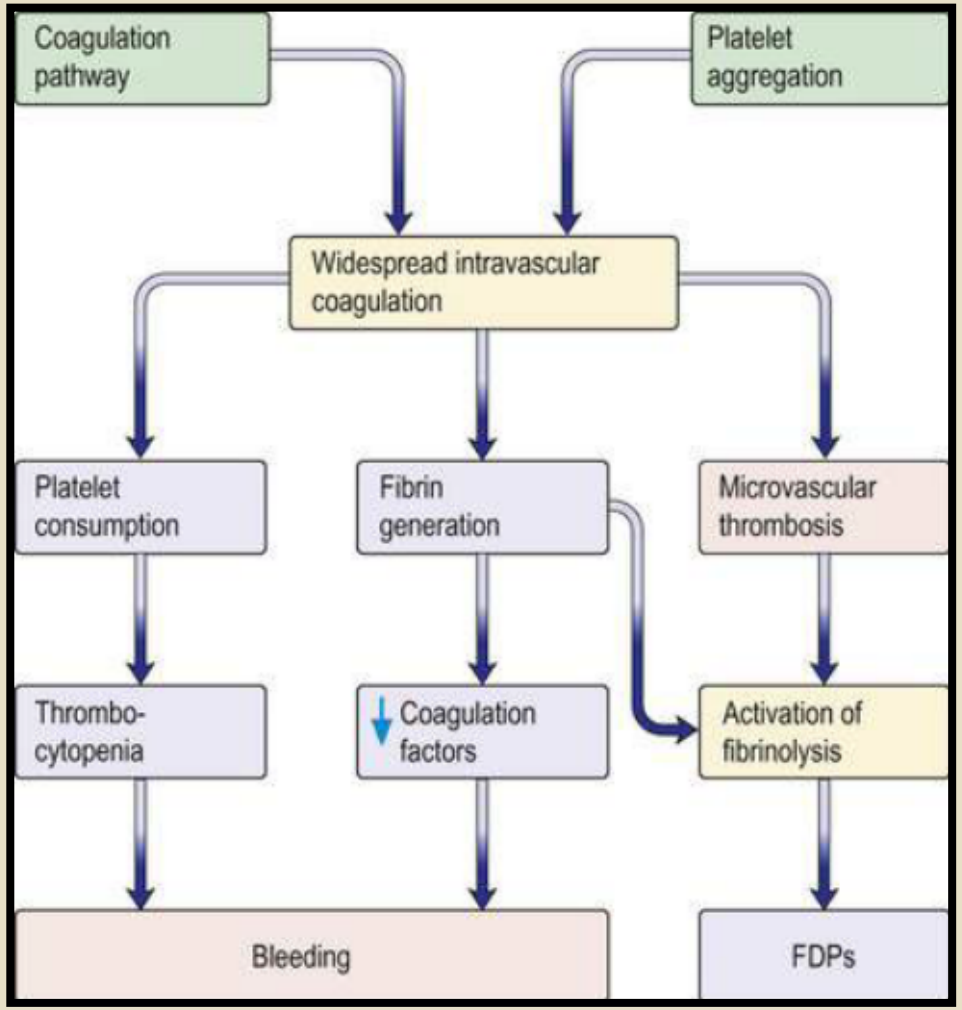
DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

Introduction

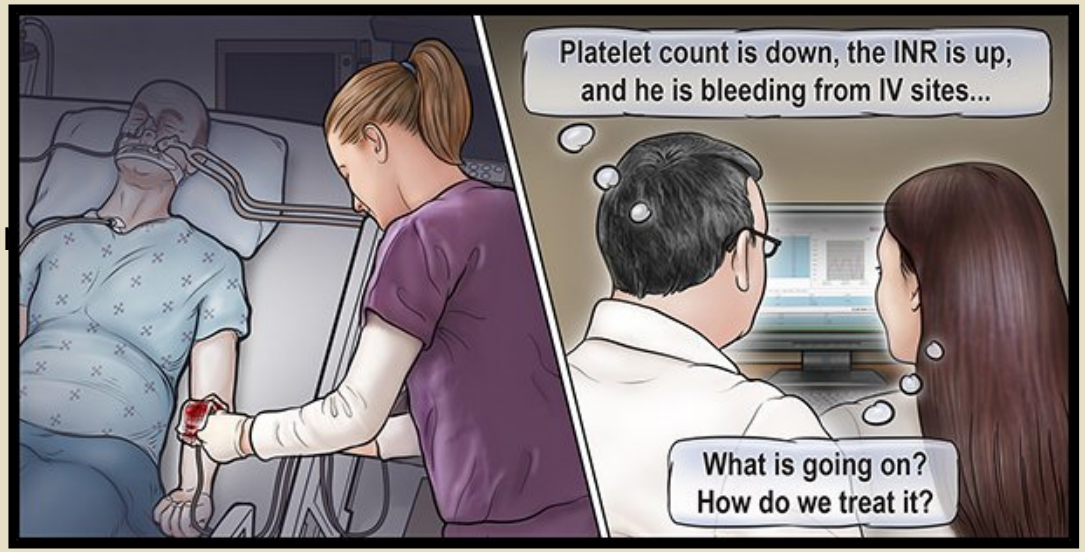
- **Arises because of systemic activation of coagulation either by release of procoagulant material, such as tissue factor, or via cytokine pathways as part of the inflammatory response.**
- **Formation of microthrombi throughout the microcirculation, leading to consumption of Platelets, Fibrin & coagulation factors**
- **Widespread thrombi cause fibrinolytic mechanisms to be activated, subsequently leading to haemorrhage (Bleeding & Thrombosis occur simultaneously)**
- **Never occurs in isolation**
- **Most commonly seen in critically ill patients, but can also occur in healthy patients**

Causes

- Snake Bites (Thrombin like glycoprotein within venom)
- Septicaemia (Especially Gram Negative microorganisms)
- Trauma, Burns, Surgery
- Obstetric Complications (Abruptio Placentae, Amniotic Fluid Embolism, Pre-eclampsia)
- Acute Pancreatitis (SIRS – Proinflammatory Cytokines.
- Malignancy (Acute Promyelocytic Leukaemia)
- Nephrotic Syndrome
- Haemolytic transfusion reactions
- Liver Disease



Clinical Features



1. **Bleeding :**
   - Range from no bleeding to profound Haemostatic Failu
   - Superficial – Ecchymosis, Petechiae, Purpura
   - GI tract, GU tract, Gingival or Oral Mucosa
   - Sites of catheters, IV lines, Drains, Incisions…
2. **Thrombosis:**
   - More common in chronic cases
   - Thrombotic events occur as a result of vessel occlusion by fibrin and platelets.
   - Any organ may be involved but the skin, brain and kidneys are most often affected.
3. **End-Organ Infarction, especially in the CNS**

Investigations

- **Bleeding Time**
- **PT**
- **PTT**
- **TT**
- **D – dimer**
- **Fibrinogen Level**
- **Platelet Count**
- **Peripheral Blood Smear**

	DIC
Platelet count	Low
Fibrinogen	Low
FDP	Elevated
D-dimer	Elevated
ATIII	Decreased
Schistocytosis	Present
Clotting times	Prolonged
Lysis times	Short

Management

1. **Treat the underlying cause**
2. **Non-Bleeders :**
   - Treatment of the underlying condition and intensive support to manage hypoxia, acidosis and organ failure
   - In critically ill, thromboprophylactic doses of Heparin are recommended
3. **Bleeders**
   - Blood Transfusion
   - Platelet Transfusion (<50,000)
   - Cryoprecipitate (Replace clotting factors & fibrinogen)
   - FFP (Replaces clotting factors)
4. **Other supportive measures (O2 & IV Fluids)**

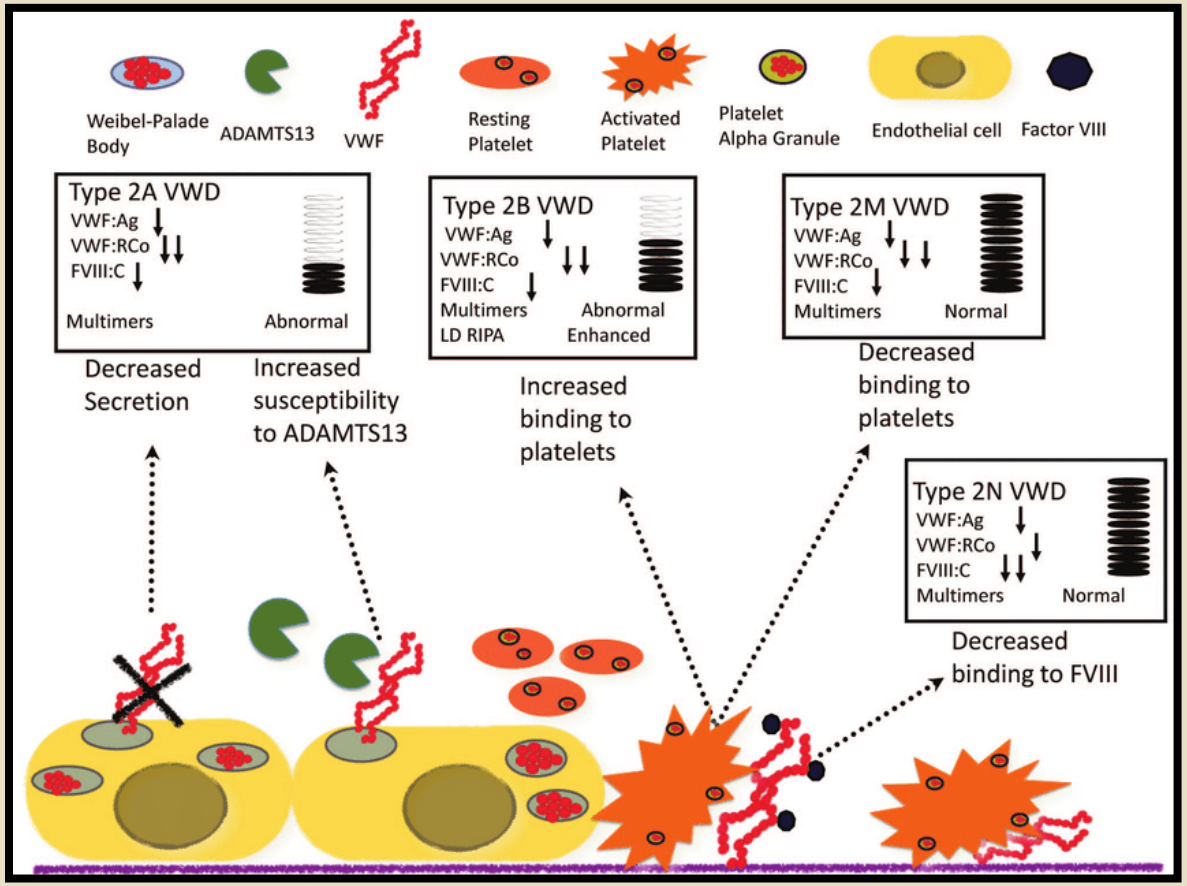
VON WILLEBRAND DISEASE (VWD)

Introduction

- **Most common bleeding disorder, affecting 1 to 3% of the population**
- **Autosomal dominant disorder, characterized by deficiency or defect of factor VIII – related antigen**
- **Von Willebrand Factor (vWF) enhances platelet aggregation and adhesion**
- **VWF gene is located on chromosome 12**
- **Defective platelet function**
- **Mutation of the vWF gene**

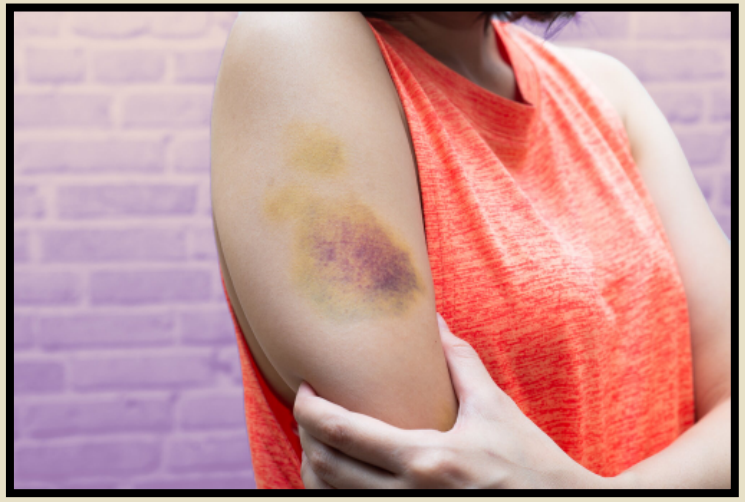
Types of VWD

- **Type 1 :**
  - Most common, mild symptoms (Eg: Nosebleeds)
  - Decreased levels of vWF
  - Usually inherited as an autosomal dominant.
- **Type 2 :**
  - Less common, mild to moderate symptoms
  - Exhibits qualitative abnormalities of vWF
  - Usually inherited as an autosomal dominant
  - Many subtypes (A, B, M, and N)
- **Type 3 :**
  - Least common, parents are often phenotypically normal
  - Absent vWF (severe disease)
  - Autosomal Recessive inheritance



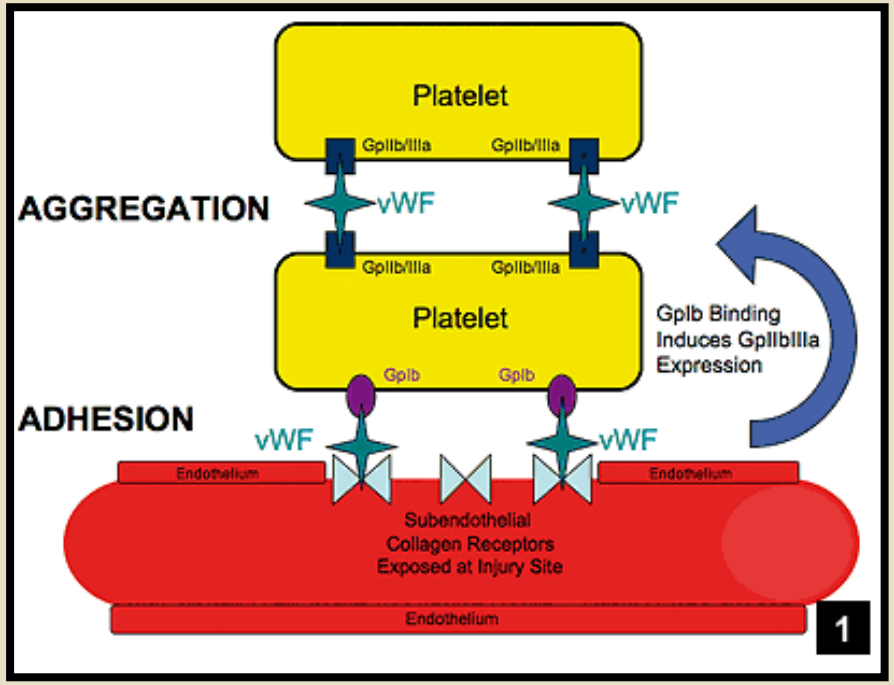
Clinical Features

- Varies from one person to another (Highly variable)
- Bleeding follows minor trauma or surgery, epistaxis and menorrhagia often occur
- Type 1 and type 2 patients usually have relatively mild clinical features
- Type 3 patients have more severe bleeding
- Cutaneous Bleeding – Easy bruising
- Gastrointestinal Bleeding

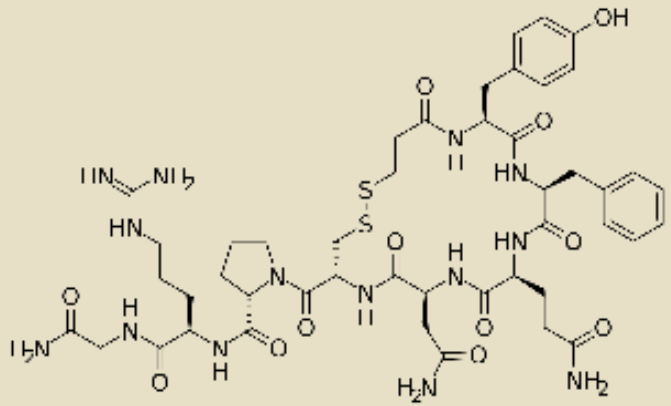


Investigations

- **Bleeding Time**
- **PT**
- **PTT**
- **Plasma vWF**
- **Factor VIII Activity**
- **Ristocetin – Induced Platelet Aggregation:**
  - When the patients serum is added to Ristocetin, and platelet aggregation occurs normally, that means that vWF is active (normal)
  - If platelet aggregation does not occur normally upon addition of Ristocetin to the patients serum, that means that vWF is defective (Abnormal)



Management

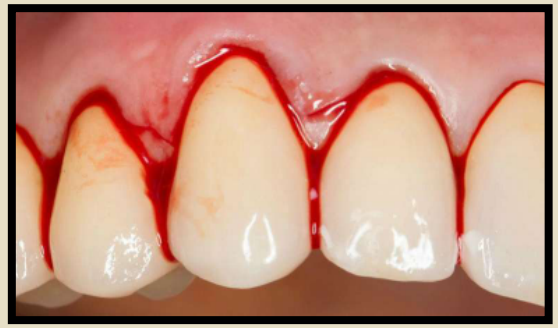


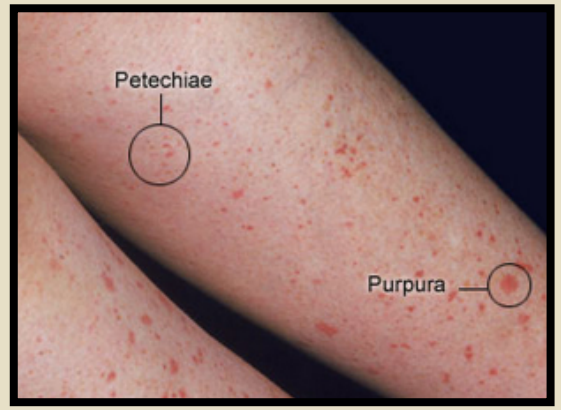
1. **Desmopressin (DDAVP) :**
   - Treatment of choice for Type 1
   - Less Effective in patients with type 2
   - Ineffective in patients with Type 3
2. **Factor VIII Concentrates :**
   - After major trauma or during surgery (All types)
   - Recommended for Type 3 vWD (Type 2 patients unresponsive to DDAVP)
3. **AVOID ASPIRIN/NSAIDS AND IM INJECTIONS :**
   - Can exacerbate bleeding tendency

ACQUIRED PLATELET DISORDERS

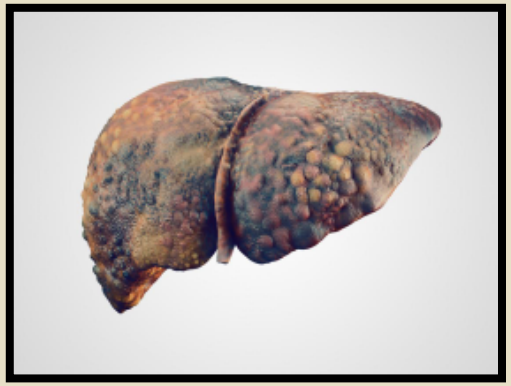
Vitamin K deficiency

- **Vitamin K is obtained through dietary sources and synthesized by intestinal flora**
- **Most commonly seen in critically ill patients**
- **Newborn babies have low levels of vitamin K, this may cause minor bleeding in the first week of life**
- **May also cause late haemorrhagic disease of newborn (2 – 26 Weeks)**
- **Causes of Vitamin K Deficiency :**
  - Broad Spectrum Antibiotics
  - Inadequate Dietary Intake
  - Oral Anticoagulant Drugs
  - Malabsorption of fat-soluble vitamins
- **Clinical Features :**
  - Petechiae
  - Purpura
  - Easy Bruising
  - Gingival Bleeding
  - Melena
  - Haematuria
- **Investigations :**
  - PT
  - PTT
- **Management :**
  - Vitamin K replacement
  - FFP (Severe bleeding)





Liver Disease



- **All clotting factors are produced by the Liver (except vWF)**
- **Liver disease must be severe for coagulopathy to develop**
- **Causes of coagulopathy in Liver Failure :**
  - Decreased Synthesis of Clotting Factors
  - Decreased Vitamin K Absorption
  - Thrombocytopenia
  - DIC
- **Clinical Features :**
  - Bleeding : (Gastrointestinal bleeding most common)
- **Investigations :**
  - PT
  - PTT
  - Platelet Count
- **Management :**
  - Cryoprecipitate of FFP if bleeding present
  - Vitamin K (If Cholestasis present)

Thank You!

Bleeding Disorders And Anticoagulants

Done by : Bahaa Nsirat

COAGULOPATHIES

It is a HEMOSTATIC disorder in which : There is Bleeding Tendency due defect in coagulation factors (hypo- coagulability)

CAUSES:

1-Inherited: Hemophilia ,von willebrand diseaseVWD(**most common**(

. 2- Acquired: liver disease, DIC, Acquired VWD.

3-Drugs: Heparin, Argatroban.

24.66 Causes of coagulopathy

Congenital

X-linked

- Haemophilia A and B

Autosomal

- Von Willebrand disease
- Factor II, V, VII, X, XI and XIII deficiencies
- Combined II, VII, IX and X deficiency
- Combined V and VIII deficiency
- Hypofibrinogenaemia
- Dysfibrinogenaemia

Acquired

Under-production

- Liver failure

Increased consumption

- Coagulation activation
  - Disseminated intravascular coagulation (DIC)
- Immune-mediated
  - Acquired haemophilia and von Willebrand syndrome
- Others
  - Acquired factor X deficiency (in amyloid)
  - Acquired von Willebrand syndrome in Wilms tumour

Drug-induced

Inhibition of function

- Heparins
- Argatroban
- Fondaparinux
- Rivaroxaban
- Apixaban
- Dabigatran

Inhibition of synthesis

- Warfarin

Haemophilia

HAeMOPHILIA

Hemophilia: rare disorder characterized by decrease in amount or function of 1 or more of the clotting factories which are responsible for secondary hemosatsis.

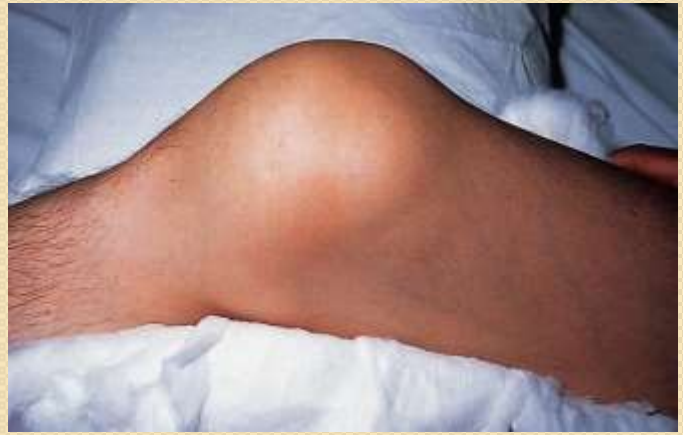
-There are two type of hemophilia : A and B

-A more common than B

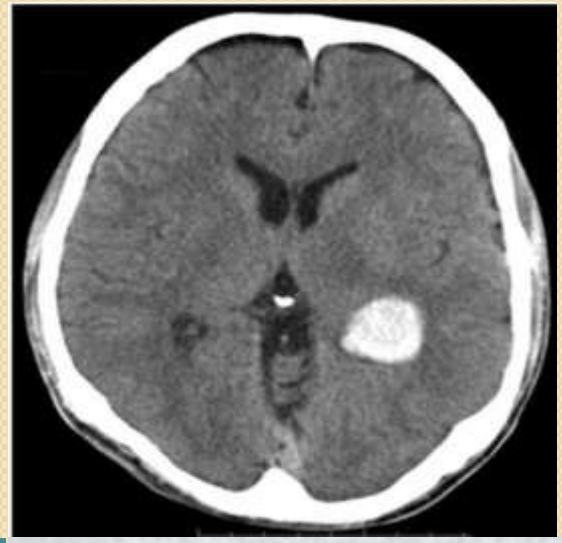
	A	B
OTHER NAMES	CLASSIC	christmas
FACOTR	VIII	IX
X-Linked recessive	Yes	Yes
DDAVP	Effective	Not effective

CLINICAL FEATURES

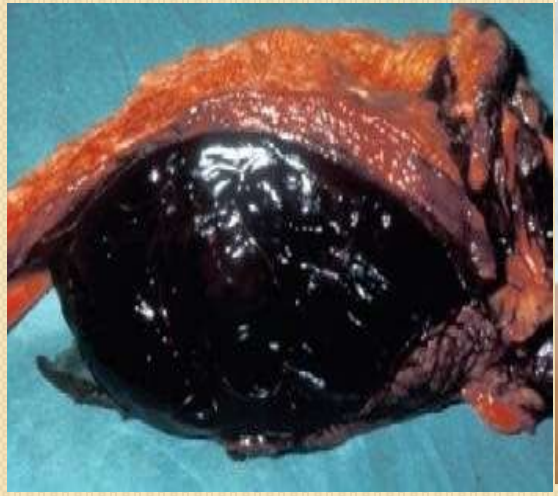
1. ***Hemarthrosis*** (bleeding into joints)—knee is the most common site, but any joint
can be involved; progressive joint destruction can occur secondary to recurrent bleeding

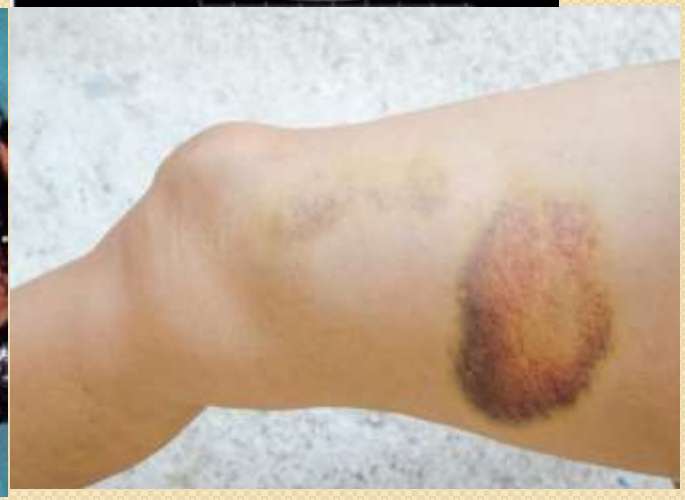


2. ***Intracranial bleeding*** — common cause of death; any head trauma is potentially life-threatening and requires urgent evaluation



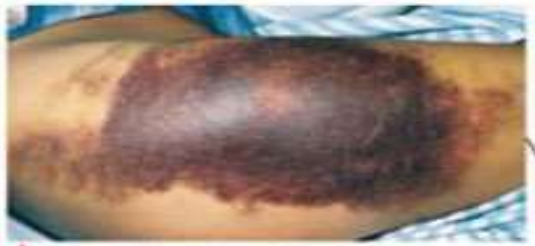
3. ***Intramuscular hematomas***





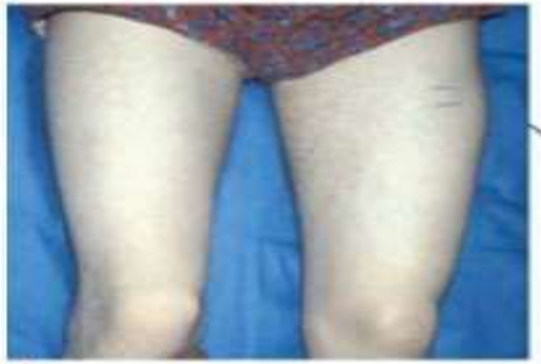
4. ***Retroperitoneal hematomas***

5. ***Hematuria or hemospermia***

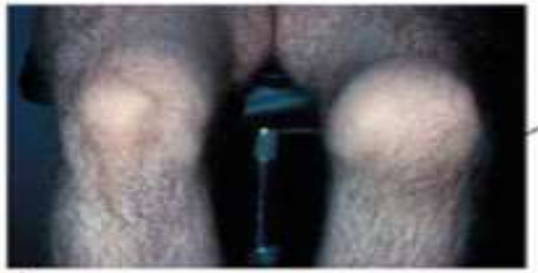


Massive bruising

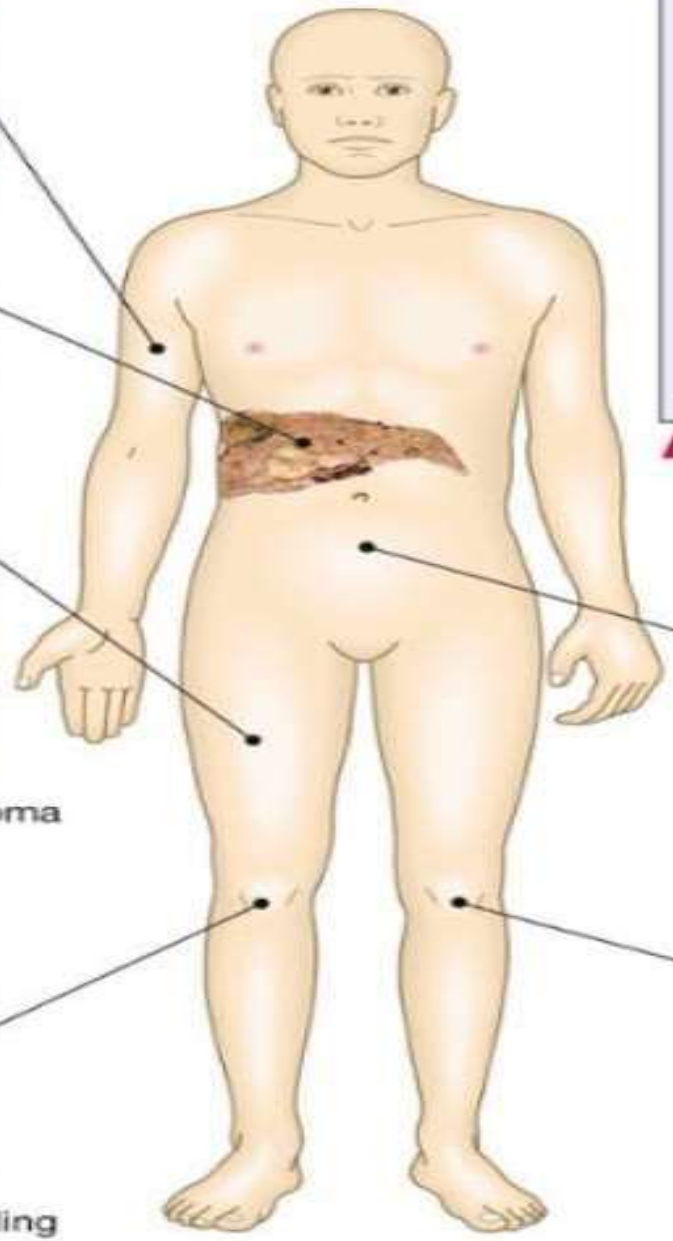
Hepatoma in cirrhotic liver secondary to HCV infection contracted from coagulation factor concentrate

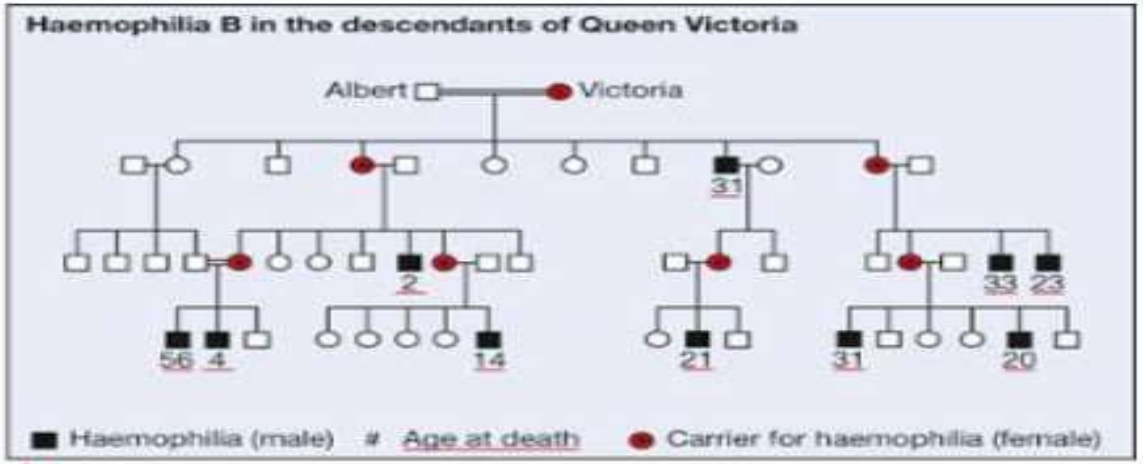


Left thigh muscle haematoma in severe haemophilia

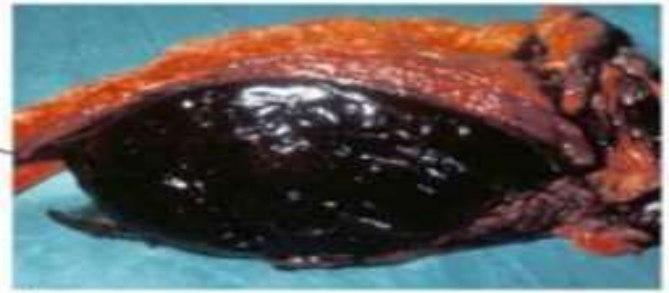


Chronic haemophilic arthropathy with joint swelling and muscle wasting on left

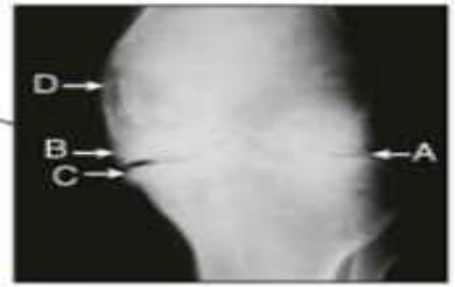




X-linked inheritance of haemophilia B



Massive retroperitoneal haemorrhage



X-ray of advanced haemophilic arthropathy

FIG. 24.32 **Clinical manifestations of haemophilia.** On the knee X-ray, repeated bleed...

Diagnosis

Laboratory findings	Haemophilia a	Haemophilia b
PT	Normal	Normal
PTT	Prolonged	Prolonged
Fibrinogen	Normal	Normal
Factor	VIII Decreased	IX Decreased

TREATMENT

Specific measures : -

-Injection Factor VIII replacement : factor VIII concentrates ,

Desmopressin (DDAVP):

-Helpful for **MILD** VIII deficiency

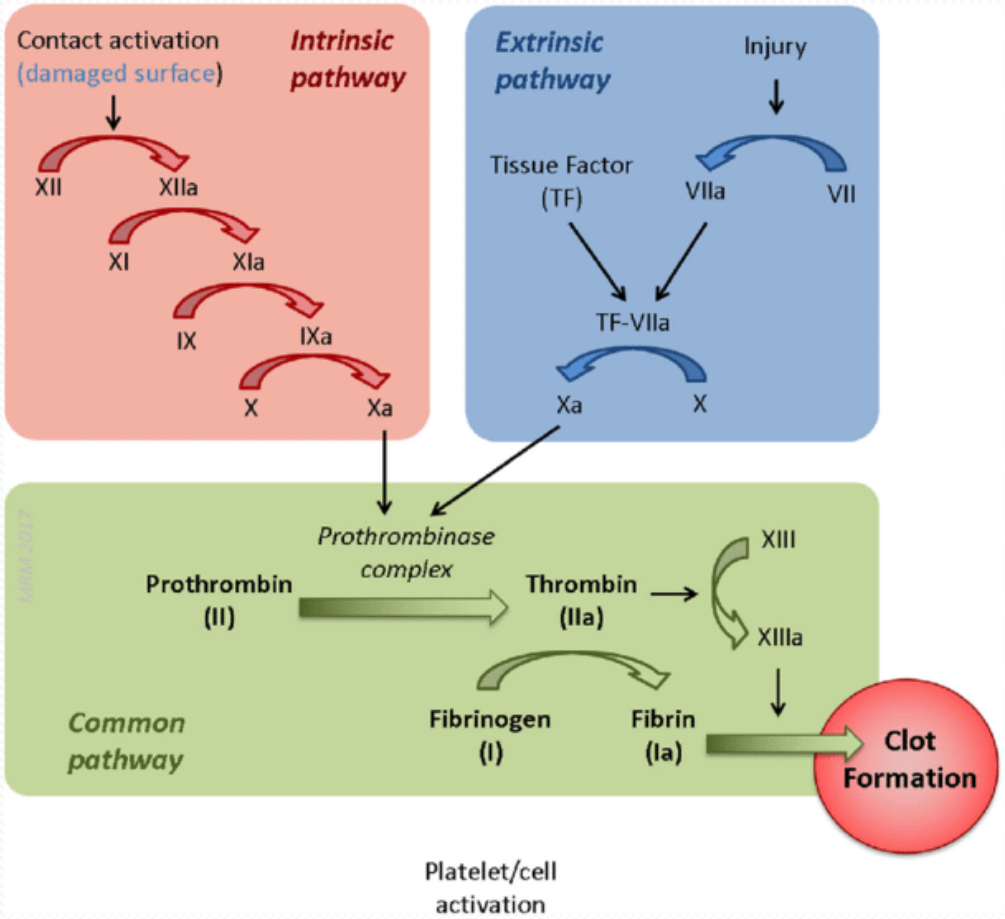
Note :

Failure to correct PTT after mixing the patient's blood with normal plasma should make you suspect the presence of factor VIII inhibitors (e.g in SLE)

!!!THANK YOU

Anticoagulant Drugs

- *Heparin*
- *Warfarin*
- *Factor Xa inhibitors*
- *Direct thrombin inhibitors*


Contact activation
(damaged surface)
Intrinsic pathway
XII
XIIa
XI
XIa
IX
IXa
X
Xa
Extrinsic pathway
Injury
Tissue Factor
(TF)
VIIa
VII
TF-VIIa
Xa
X
Prothrombinase complex
Prothrombin
(II)
Thrombin
(IIa)
XIII
XIIIa
Fibrinogen
(I)
Fibrin
(Ia)
Common pathway
Clot Formation
Platelet/cell activation

Heparin	Wrfarin
Natural sulfated polysaccharide presents in mast cells and carries –ve charge	*Synthetic coumarin compound*
Commercial preparations are derived from bovine lung or porcine intestinal extracts	
No because it precipitates by gastric HCL	*good(bioavailability is %100)*
Can not cross BBB or placenta	*Can cross BBB and placenta*
Given (IV or SC)	*Oral coagulant*

heparin

- *Activates antithrombin III in plasma.*
- *Ant thrombin 111 inhibits several factors (II, IX, X, XI, XII)*
- *Immediate and short (2-4 hrs)*

Warfarin

- *Warfarin inhibits vitamin K epoxide reductase enzyme leading to inhibition of formation of the active form of vitamin K synthesis of vitamin K dependent clotting factors (II, VII, IX, X)*
- *Delayed for 8-12hrs (time needed for depletion of clotting factors and vit K) and long (3-7d)*

heparin

- *Anticoagulant in vivo and vitro*
- *Treatment established thrombosis: heparin is given parental 5000-10,000 U to maintain blood coagulant as normal 2-3 times and prevent further extension of thrombus*
- *Prevention of thrombosis : 5000U s. c 8-12hrs*

Wrfarin

- *Anticoagulant in vivo only*
- *Warfarin is given oral 2-10 mg/day : for prevention and treatment of*
  - *DVT-*
  - *Postoperative thrombosis*
  - *Cerebral thrombosis*
  - *Coronary thrombosis treatment continued for several years*
  - *Acute arterial and pulmonary embolism anticoagulant is initiated by heparin and maintained by warfarin*
  - *AF and artificial heart valves*

heparin

- *By activated partial thrombin plastin time (APTT)*
- *It must be kept 2-3 times as the normal value*

Wrfarin

- *By prothrombin time (PT) or international normalize ratio (INR).it is the ratio of the PT in the patient to that of normal person. Tit must be kept 2-3 times as the normal value*

Adverse effects

- Bleeding is the most common and dangerous side effect (e.g. hematuria and major organ bleeding)

- :It could be treated by the following

immediate stopping f the drug-1

- ***fresh frozen plasma to provide fresh clotting-2 factors***

heparin

- *protamine sulfate (+ve-3 charge) that combines with heparin (-ve charge) to form stable complex*
- *mg of protamine can bind 1 to 100 U of heparin*

Wrfarin

- *vitan K 10mg slowly iv or-3 im to enhance synthesis of clotting factors*

heparin

- ***Hematoma*** *if given IM*
- ***Thrombocytopenia*** *: immune mediated reaction due to formation antibodies that can bind platelets . platelet count should be preformed regularly*
- ***Osteoporosis*** *and spontaneous fractures on long term therapy*
- ***Alopecia*** *and* ***dermatitis*** *rare and transient*

Wrfarin

- ***Hemorrhagic skin necrosis***
- ***Teratogenicity :****abnormal bone formation in early pregnancy (****fetal warfarin syndrome****)*
- ***CNS hemorrhage*** *in the fetus if given in late pregnancy*
- ***Sudden withdrawal*** *may lead to thrombotic catastrophes*

Unfractionated heparin and low molecular weight heparin (LMWH)

Unfractionated heparin	LMWH
Wide molecular range (from 3000-30,000 Da)	*Less than 8000 Da*
activity less specific to factor Xa	*More specific*
High banding to endothelium and plasma proteins	*Low*
Low bioavailability after s.c injection	*high*

Unfractionated heparin	LMWH
Short half life (given 3times/day)	*Long (given once a day)*
	Less common (less than%2)
Thrombocytopenia (common %10)	
High risk of bleeding	*Low*
APTT is essential	*Anti factor Xa levels and maybe unnecessary*

Unfractionated heparin and LMWH are both indirect inhibitors of factor Xa

Factor Xa inhibitors

- *:Fondaparinux*
  - *synthetic polysaccharide that have the same mechanism of LMWH (selective inhibitor of factor Xa)*
  - *It is given by s.c injection once aday (has long half time)*

- *:Rivaroxaban*
  - *Compound that has the same mechanism of LMWH*
  - *Given by the oral route*

Direct thrombi (factor II) inhibitors

:***Argatroban***

Synthetic compound that acts like direct thrombin inhibitor

Alternative to heparin to treats patients with heparin –induced thrombocytopenia

It is given iv and has immediate mechanism of action

Dabigatran: ***oral route***

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