BLEEDING AND COAGULATION

HEMOSTASIS

Definition:

Consequence of tightly regulated process that maintains blood in a fluid, clot-free state in normal vessels while introducing the rapid formation of a localized hemostatic plug at the site of vascular injury.

Mechanism:

- ✓ **Vasoconstriction**
- ✓ **Formation of platelet plug**
- ✓ **Coagulation cascade**
- ✓ **Fibrinolysis**

Vascular Spasm

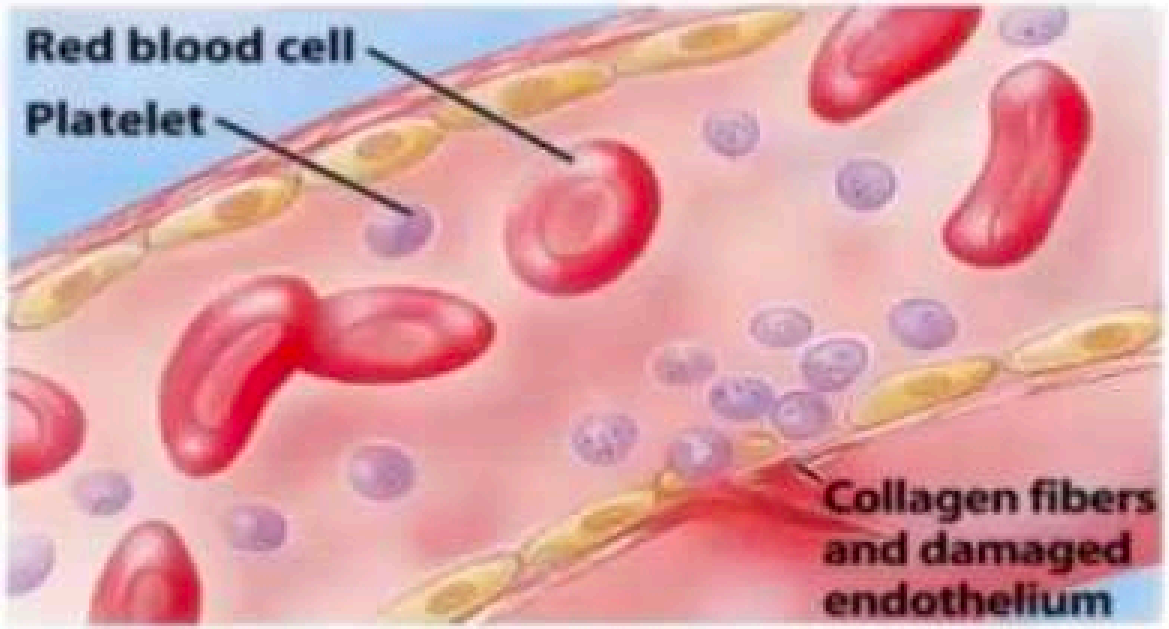
Vascular spasm results from the:

1. Local myogenic contraction of the blood vessels initiated by direct damage to the vascular wall
2. Release of Local **autacoid** factors from the traumatized tissues and blood platelets, and
3. Nervous reflexes initiated by pain nerve impulses or other sensory impulses that originate from the traumatized vessel or nearby tissues.
4. Release of a vasoconstrictor substance, **Thromboxane A_2** by the platelets which for the smaller vessels are responsible for much of the vasoconstriction

Mechanism of the Platelet Plug

- When platelets come in contact with a damaged vascular surface, especially with collagen fibers in the vascular wall, the platelets themselves immediately change their own characteristics drastically
- They begin to swell
- They assume irregular forms with numerous irradiating pseudopods protruding from their surfaces;
- Their contractile proteins contract forcefully and cause the release of granules that contain multiple active factors
- They become sticky so that they adhere to collagen in the tissues and to a protein called ***von Willebrand factor***

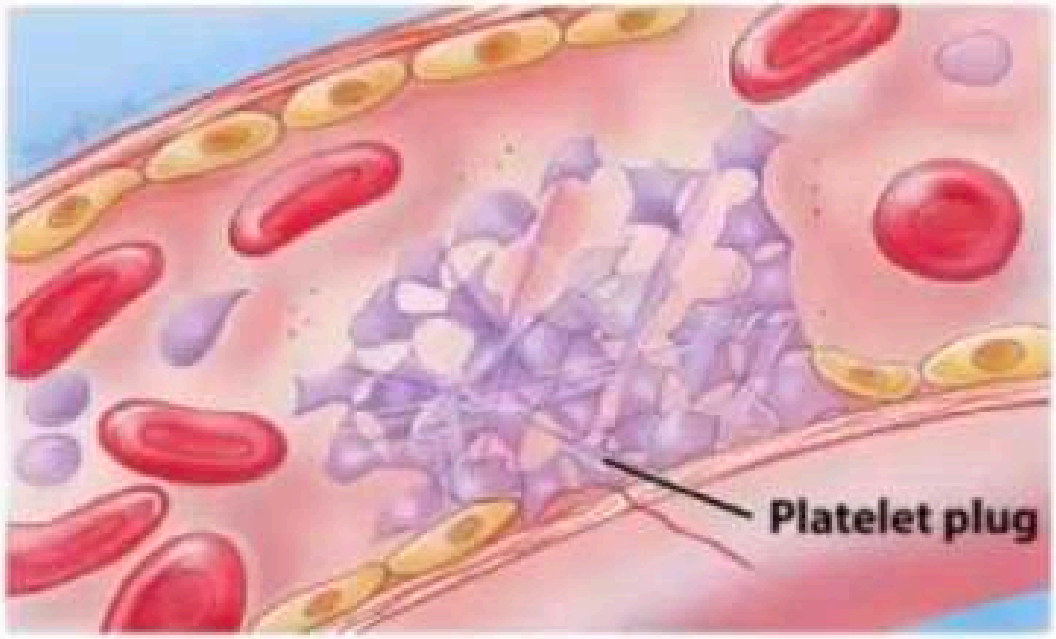
Platelet plug formation: platelet adhesion



Mechanism of the Platelet Plug Formation

- They secrete large quantities of ***ADP*** and their enzymes form ***Thromboxane A_2***
- *The ADP* and thromboxane in turn act on nearby platelets to activate them as well, and
- The stickiness of these additional platelets causes them to adhere to the original activated platelets
- Thus the damaged vascular wall activates successively increasing numbers of platelets that themselves attract more and more additional platelets, thus forming a ***platelet plug***

Platelet plug formation: platelet aggregation



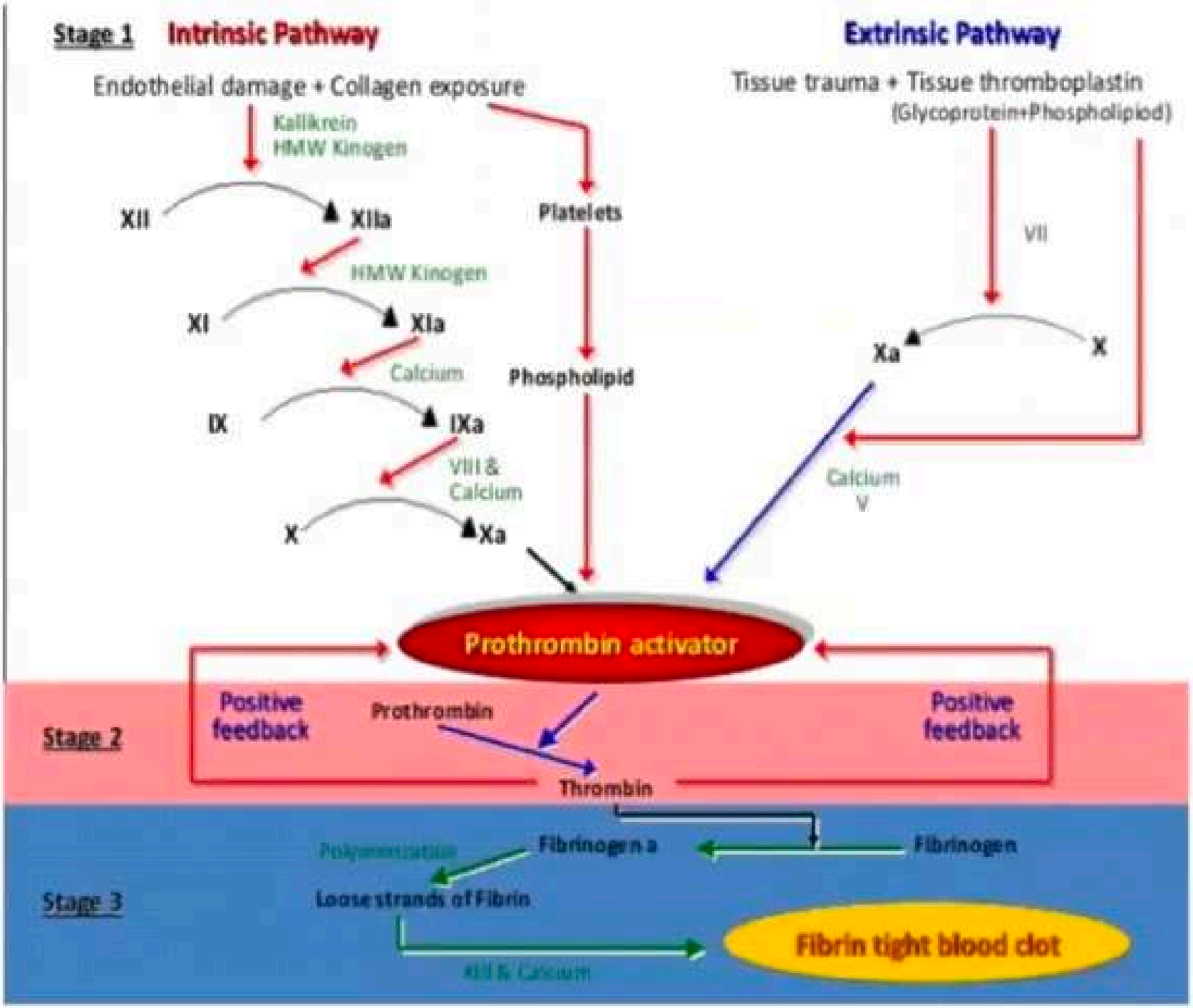
3 Platelet aggregation

COAGULATION

- Formation of blood clot

Stages of clotting

- **Phase 1:** Extrinsic and intrinsic pathways produce prothrombinase/prothrombin activator
- **Phase 2:** Prothrombinase converts prothrombin to thrombin
- **Phase 3:** Thrombin converts soluble fibrinogen into insoluble fibrin which is the thread of the clot.


Stage 1
Intrinsic Pathway
Endothelial damage + Collagen exposure
Kallikrein
HMW Kinogen
XII
XIIa
HMW Kinogen
XI
XIa
Calcium
IX
IXa
VIII &
Calcium
X
Xa
Platelets
Phospholipid
Extrinsic Pathway
Tissue trauma + Tissue thromboplastin
(Glycoprotein+Phospholipiod)
VII
Xa
X
Calcium
V
Prothrombin activator
Stage 2
Positive
feedback
Prothrombin
Positive
feedback
Thrombin
Fibrinogen a
Fibrinogen
Stage 3
Loose strands of Fibrin
Fibrin tight blood clot

A 6 years old boy was brought to the emergency department by his mother for oozing blood from his mouth following a fall about 6 hours ago. His mother related that he tended to bleed for prolonged periods from his immunization sites. He also has history of easy bruisability. His elder brother also experience these bleeding episodes.

a) What is most likely diagnosis?

b) How would you diagnose this patient?

HEMOPHILIA

Hemophilia is a genetic disorder that impairs the body's ability to make blood clots due to deficiency of blood clotting proteins (clotting factors)

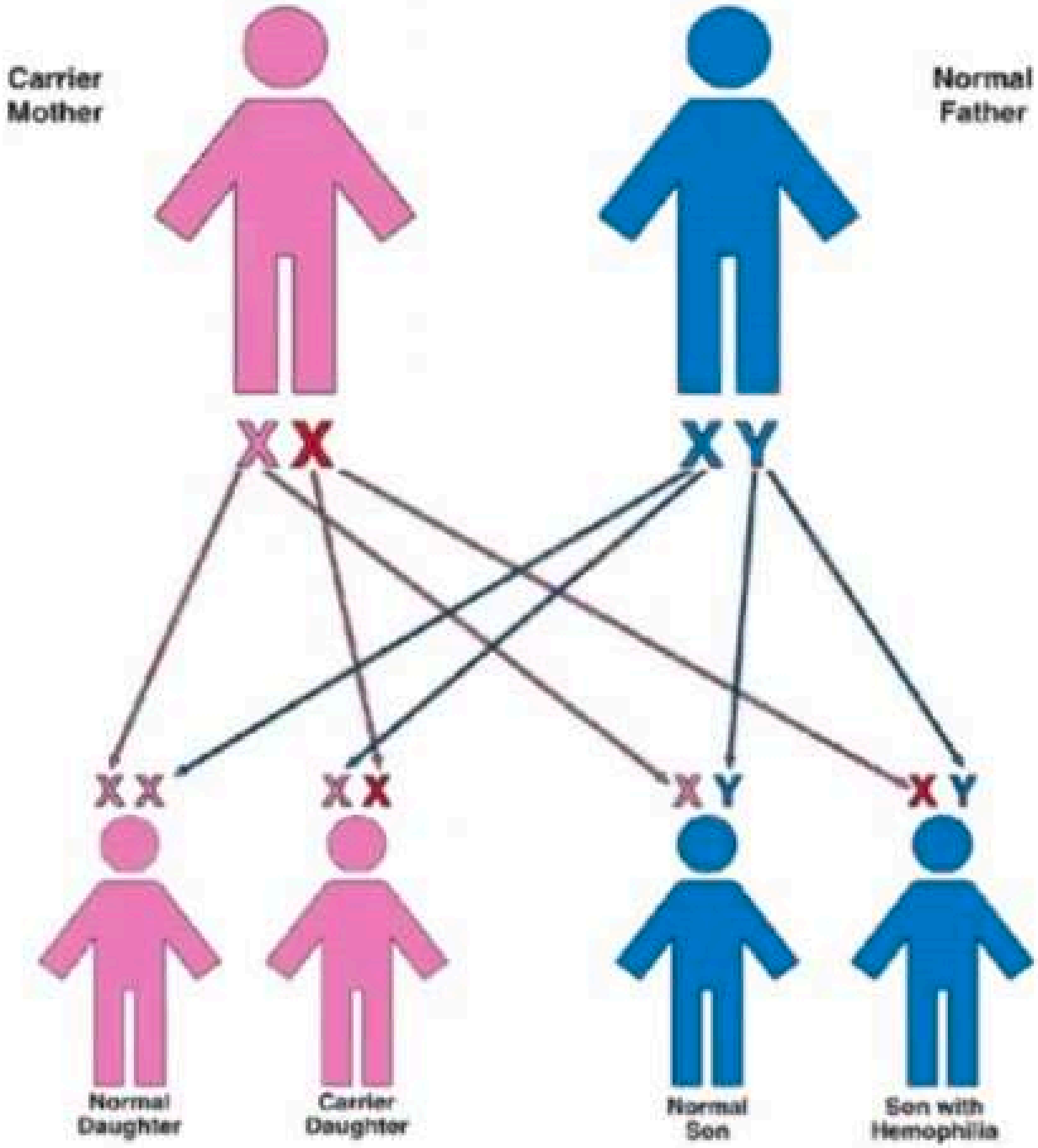
✓ Hemophilia A: X-linked disorder involving the lack of functional clotting factor VIII, it represents 90% of the hemophilic cases

✓ Hemophilia B: X-linked disorders involving lack of factor IX, more severe but less common

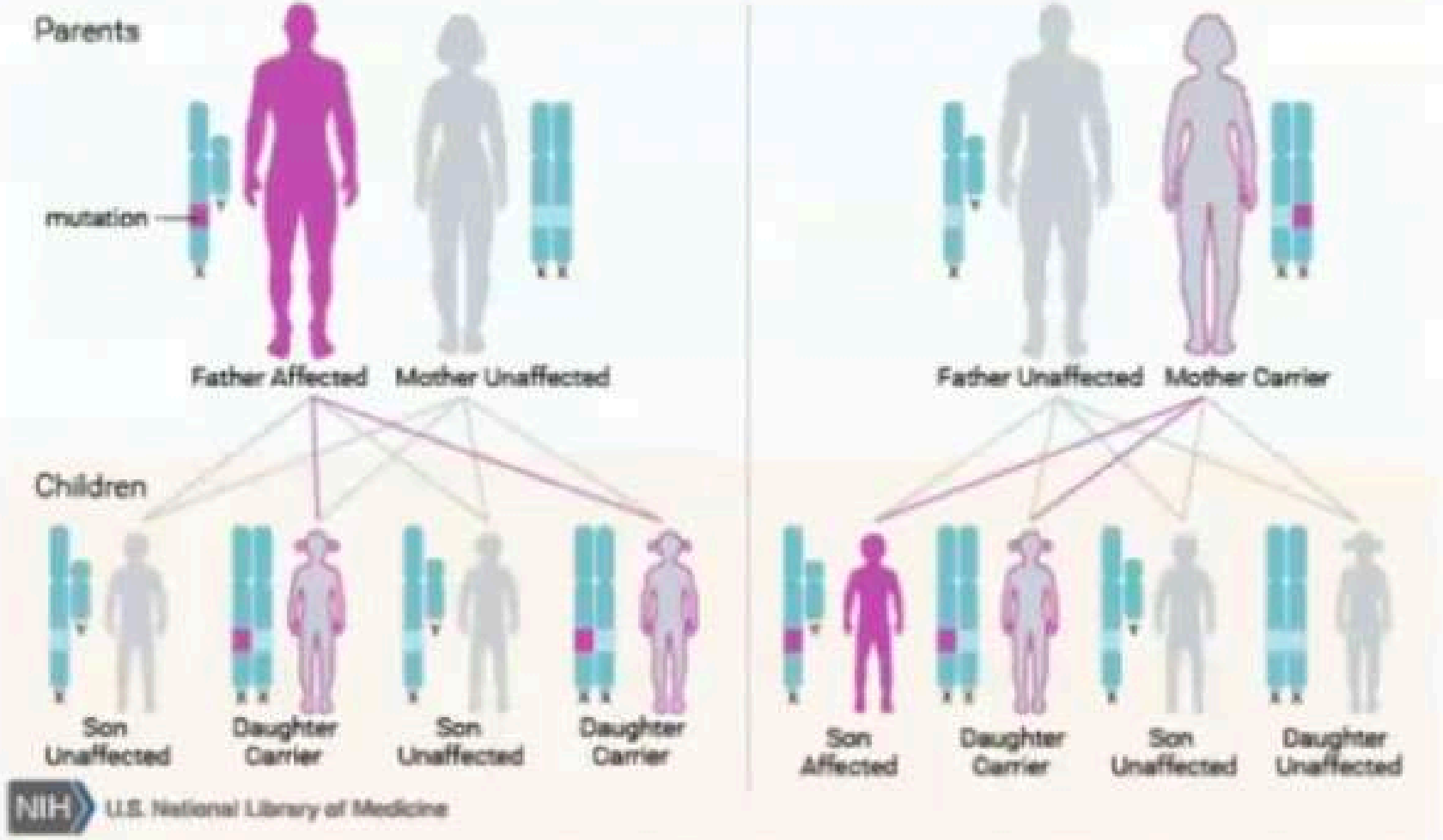
✓ Hemophilia C: Autosomal recessive disorder due to lack of factor XI

HEMOPHILIA A

- ✓ Def of Factor VIII (antihemophilic factor)
- ✓ X-linked recessive disorder
- ✓ Severity: depends upon factor level in blood
- Mild: 5-30 U/dl (%)
- Moderate: 1-5 U/dl (%)
- Severe: < 1 U/dl (%)
- Very severe: 0 %


Carrier
Mother
Normal
Father
X X
X Y
X X
X X
X Y
X Y
Normal
Daughter
Carrier
Daughter
Normal
Son
Son with
Hemophilia

X-Linked Recessive

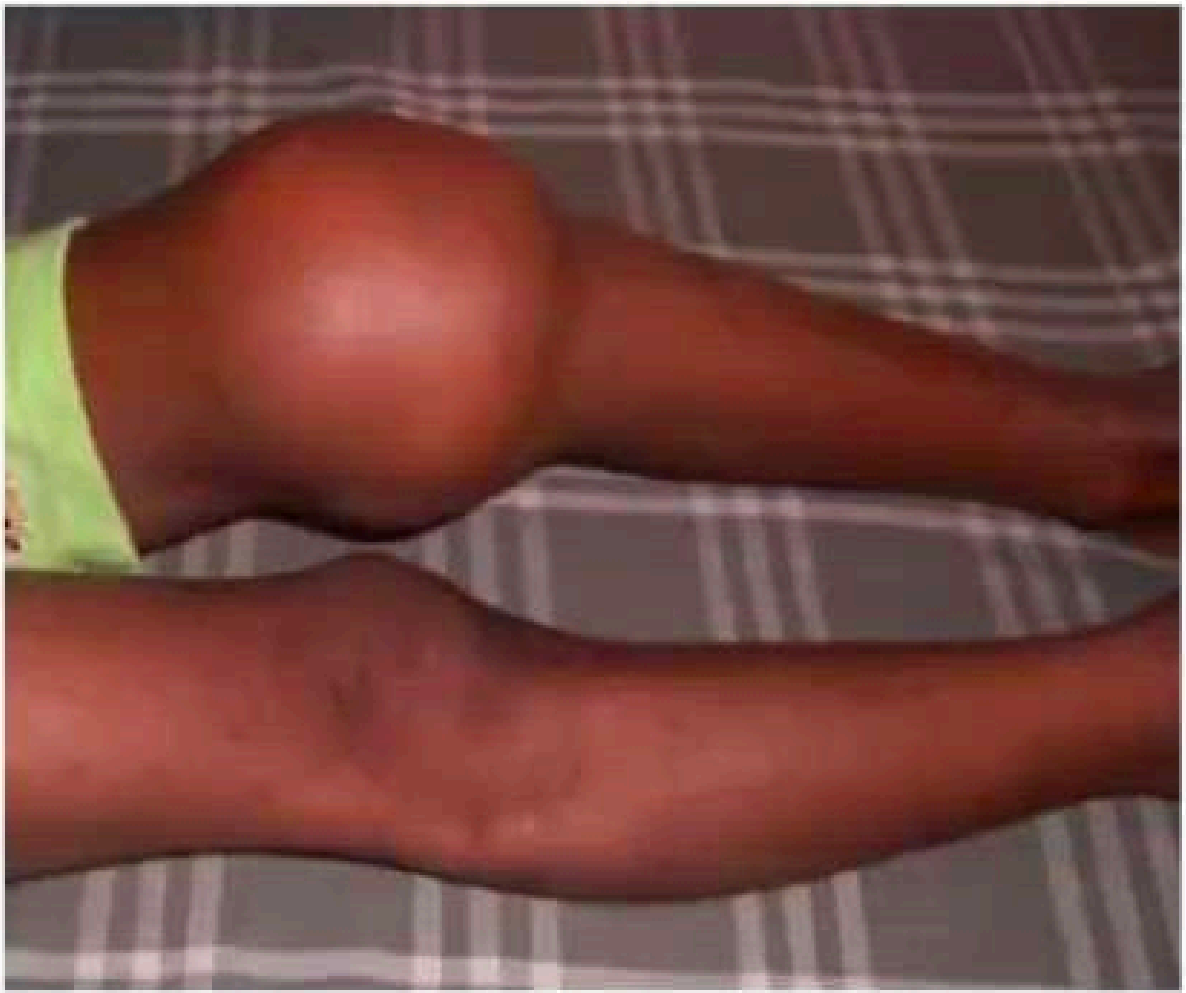


Severity of Haemophilia

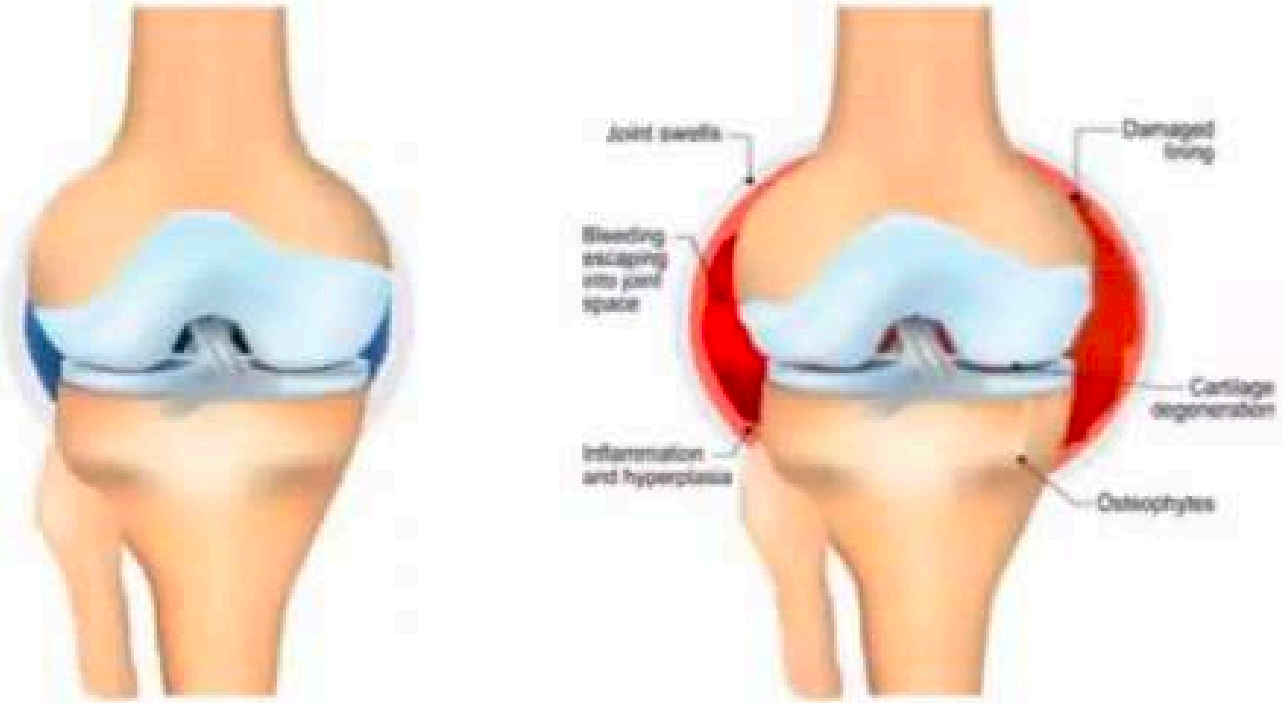
Severity	Factor level iu/dl (%)	Type of presentation
Severe	< 1	Spontaneous bleeds, Severe bleeding
Moderate	1-5	Few bleeds, Haemathrosis - traumatic
Mild	5-30	Few bleeds, Post-traumatic Post-dental surgery

CLINICAL FEATURES

- ✓ Age: after 6 months of age
- ✓ Hematomas, haemarthrosis, hematuria, GI bleeding, Spontaneous intracranial bleed
- ✓ Prolonged bleeding after tooth extraction and injury
- ✓ Haemarthrosis: bleeding into joint spaces

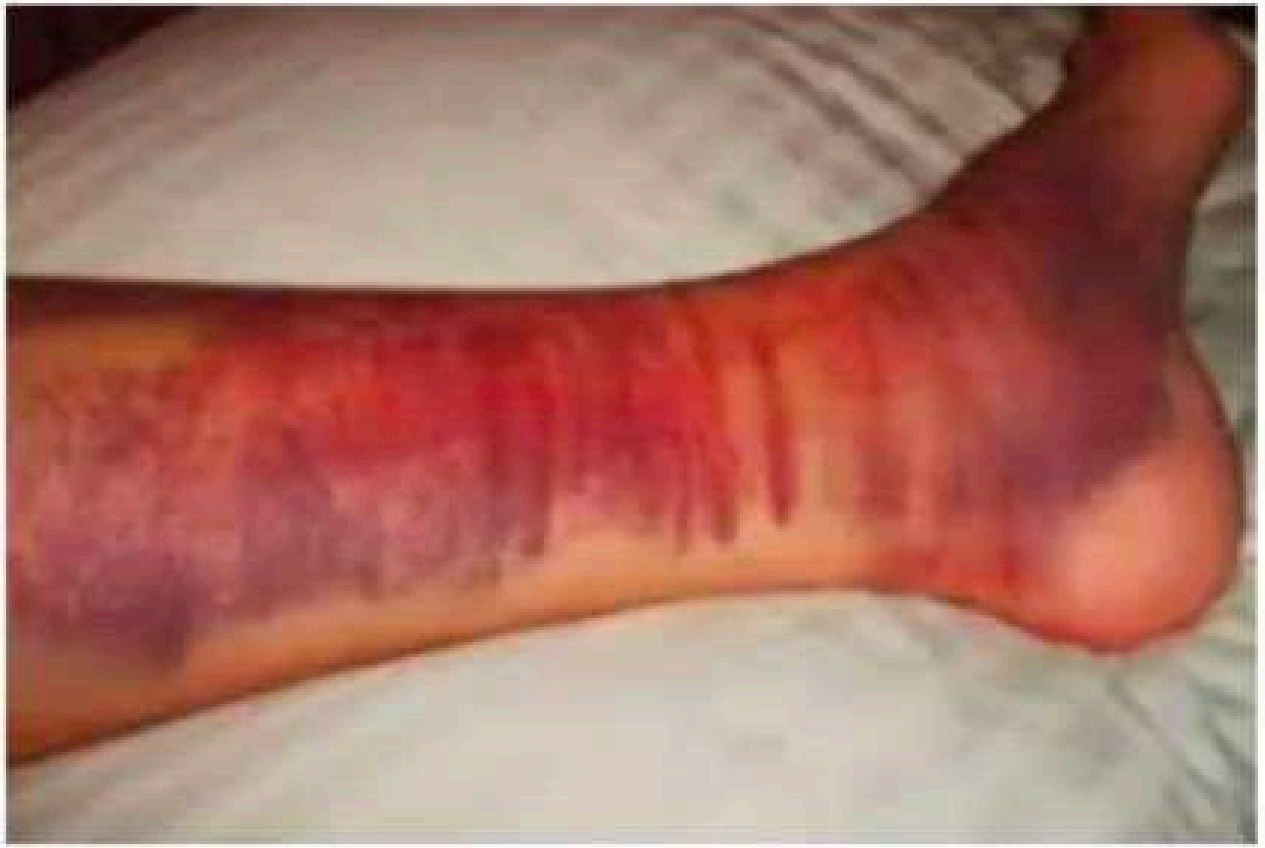


HEMOPHILIA



Healthy joint

Hemophilia



INVESTIGATIONS

- ✓ Platelet count… Normal
- ✓ Bleeding time… Normal
- ✓ PT… Normal
- ✓ APTT… Prolonged
- ✓ Clotting time… Prolonged
- ✓ Factor VIII levels

MANAGEMENT

✓ Recombinant factor VIII concentrates:

- Mainstay of treatment in severe hemophilia
- Twice or thrice weekly infusions of factor to prevent recurrent joint bleeding
- For major bleed
- Prior to high risk activities

✓ Desmopressin:

- Used in mild and moderate hemophilia
- I/V or intranasal
- Result in 2-5 fold increase in factor VIII

- ✓ **Replacement therapy:**

- **Fresh frozen plasma:** **FFPs contain all the coagulation factors.**

  1 ml of FFPs contains 1 unit of factor activity

- **Cryoprecipitate:** **prepared by slow thawing of FFPs at 4 C for 10-24 hours**

  Cryoprecipitate contain significant amount of factor VIII,

  VWF and fibrinogen

HEMOPHILIA B

- ✓ Also known as christmas disease
- ✓ X-linked recessive disorder
- ✓ Less common than hemophilia A
- ✓ Deficiency of factor IX
- ✓ Treatment… factor IX concentrates

VON WILLEBRAND DISEASE (VWD)

- ✓ Is a genetic disorder caused by a missing or defective clotting protein , Von Willebrand factor (VWF)
- ✓ VWF binds factor VIII and platelets in blood vessels which help form a platelet plug during clotting process
- ✓ Most common bleeding disorder
- ✓ Occurs equally in men and women
- ✓ Desmopressin is first line treatment

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

- ✓ Also known as autoimmune thrombocytopenic purpura
- ✓ Most common cause of acute thrombocytopenia
- ✓ Defined as isolated thrombocytopenia with normal bone marrow in the absence of other causes of thrombocytopenia
- ✓ Estimated about 1 in 20,000 children
- ✓ Acute ITP often follows an acute infection and has spontaneous resolution within 2 months
- ✓ Chronic ITP persists for > 6 months without a specific cause

PATHOPHYSIOLOGY

- ✓ ITP is a disease of increased peripheral destruction of platelets
- ✓ is mediated by autoantibodies, most often directed against the platelet membrane glycoprotein IIb/IIIa, which sensitise the platelet, resulting in premature removal from the circulation by cells of the reticulo-endothelial system
- ✓ some cases occur in isolation while others are associated with underlying immune dysregulation
- Connective tissue disorder
- Viral infections (EBV, HIV)
- B cell malignancies

CLINICAL FEATURES

- ✓ Spontaneous bleeding typically occurs only when the platelet count is below 20 × 109/L.
- ✓ Epistaxis
- ✓ Gum bleed
- ✓ Retinal haemorrhage
- ✓ Menorrhagia
- ✓ Generalized petechiae and purpura
- ✓ Non-palpable spleen... enlarged spleen should lead to search for other possible causes for thrombocytopenia

- ✓ Signs of viral infections (fever, sore throat)
- ✓ Sign and symptoms of connective tissue disorders may be apparent at presentation or emerge several years later (rash, joint pains, photosensitivity, oral ulcers, alopecia)

INVESTIGATIONS

- ✓ ITP is a diagnosis of exclusion
- ✓ CBC:
  - isolated thrombocytopenia, normal TLC and Hb
  - PLTs < 20,000/cm
  - In later stages...Hb decreased
- ✓ Peripheral blood smear:
  - Normal, apart from greatly reduced platelet count
- ✓ Bone marrow examination:
  - Increased number of megakaryocyte

- ✓ PT/APTT... normal
- ✓ Platelet associated antibodies
- ✓ Autoantibody profile (ANA, dsDNA)
- ✓ HIV serology
- ✓ Ultrasound abdomen... splenomegaly will doubt the diagnosis of ITP
- ✓ CT brain (if intracranial bleed is a concern)

TREATMENT

- ✓ Many patients with stable compensated ITP and a platelet count of more than 30 × 109/L do not require treatment to raise the platelet count, except at times of increased bleeding risk, such as surgery and biopsy
- ✓ Supportive measures:
- Reassurance
- Restrict physical activity and avoid trauma
- Avoid medications that suppress platelet production or alter their function e.g; aspirin, heparin

- ✓ Corticosteroids:
- 1st line therapy in patients with spontaneous bleeding
- Prednisolone 1mg/kd/day
- Methylprednisolone... in acute flare up of disease
- ✓ I/V Immunoglobulins:
- 0.8-1.0 g/kg/day for 1-2 days can induce rapid increase in platelet count
- Expensive
- By blocking antibody receptors on reticulo-endothelial cells

- ✓ I/V anti-D therapy:
- For Rh +ve patients
- At dose of 50-75 microgram/kg causes a rise in platelet count in 80-90% of patients
- ✓ Splenectomy:
- In chronic cases of ITP
- When symptoms are not easily controlled with corticosteroids
- In relapsed disease
- Produces complete remissions in 70% of the cases

- ✓ Thrombopoietin analogue:
- Romiplostim ... once a week
- Chronic ITP who have failed other therapies
- Need to be administered continuously to maintain platelet count > 50,000/cm
- ✓ Immunosuppressants:
- In patients who are non responsive to other drugs
- Rituximab
- Cyclosporin
- Tacrolimus

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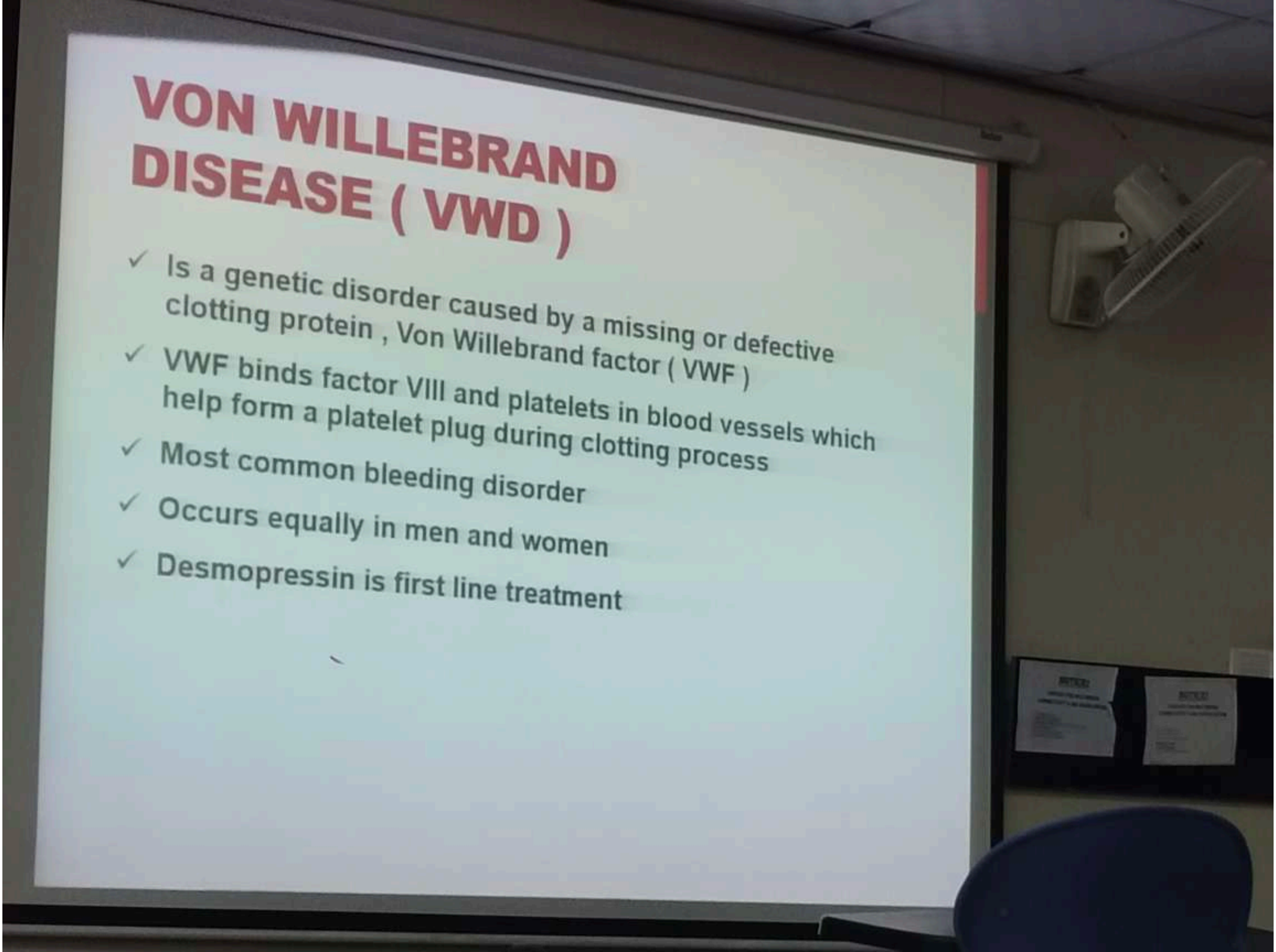
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