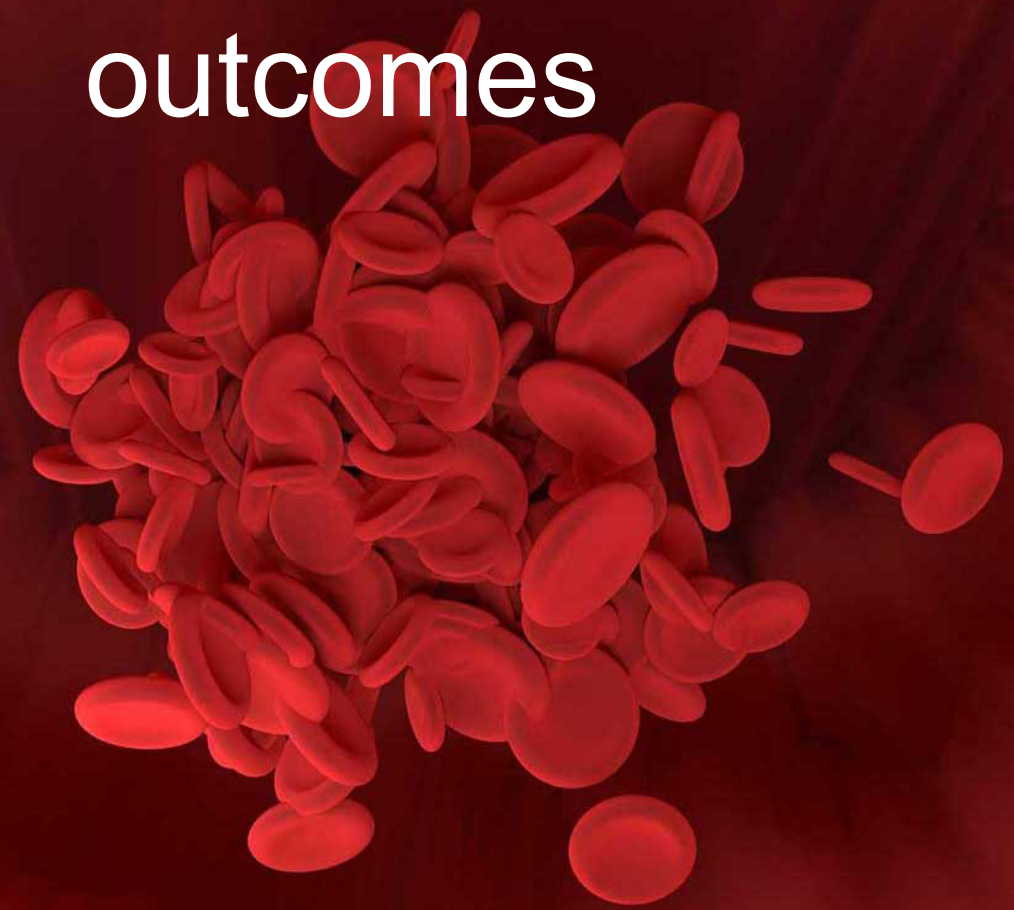
Bleeding Disorders

Presented by Dr. Nada Abdelrahman

Learning outcomes



By the end of this lecture, the students should be able to

1. **Explain the normal physiology of Blood haemostasias.**
2. **Classify bleeding disorders**
3. **Outline the aetiology of Haemophilias, their presentations and management**
4. **Outline the aetiology of VWF, its presentations and management**
5. **Outline the aetiology of ITP its presentations and management**


Blood
Haemostasis

STAGES OF HEMOSTASIS

Primary

INJURY

VESSEL WALL + PLATELET

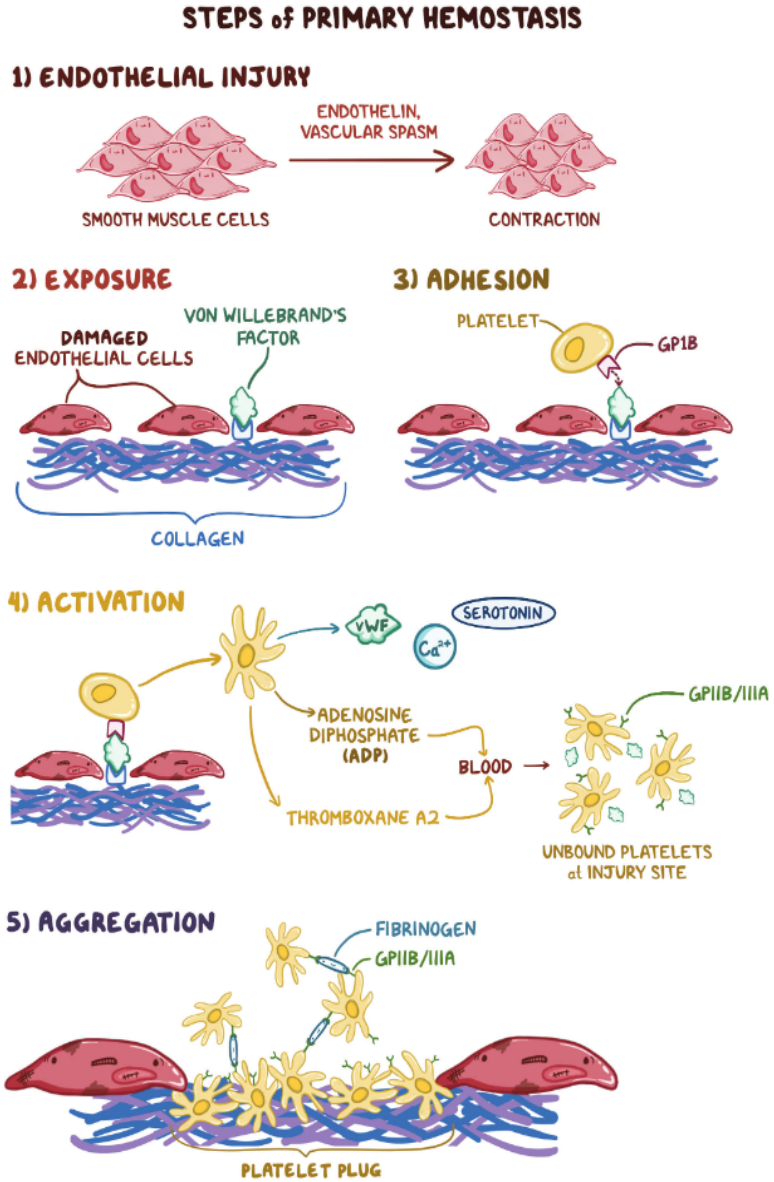
FORMATION OF P PLT PLUG

SECONDARY

ACTIVATION OF PLASMA COAGULATION FACTORS

FORMATION OF STABLE FIBRIN CLOT

DISSOLUTION OF FIBRIN CLOT BY FIBRINOLYSIS



Endothelial injury: Vasoconstriction mediated by neural reflex & endothelin released from damaged endothelial cells.

Exposure: Subendothelial collagen exposed binds to the von Willebrand factor (vWF) released from damaged endothelial cells.

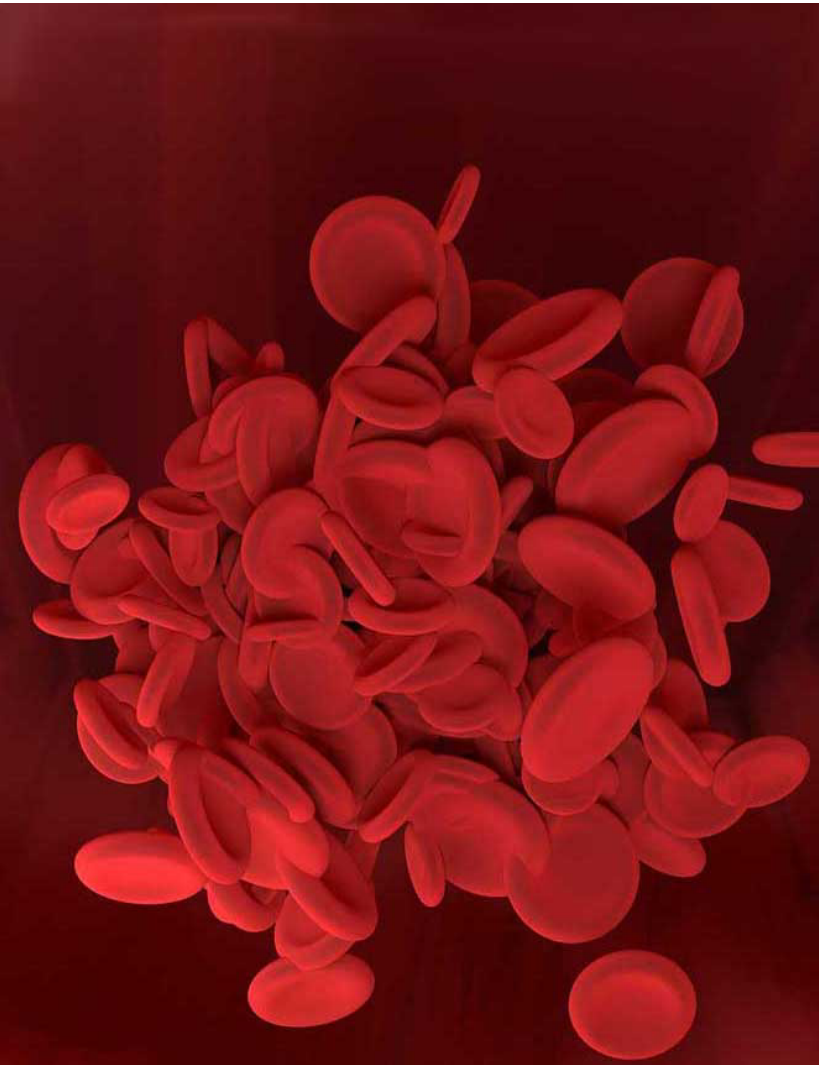
Adhesion: Then; Platelets bind to the vWF via GpIB receptors on the platelets, activating platelets.

Activation: Platelets undergo a conformational change and release calcium, ADP, and thromboxane A2. ADP binds to P2Y12 receptors on adjacent platelets & induces expression of GpIIB/IIIA receptors, mediating final step.

Aggregation: Finally, after GpIIB/IIIA expression on the platelets, fibrinogen binds these receptors and aggregate platelets together, forming a platelet plug.

HAEMOSTASIS

- Spontaneous



An investigation is done on hemostasis to determine the steps involved in preventing blood loss after injury. During the experiment, the team determines that hemostasis typically has two stages: primary and secondary hemostasis. Which of the following is true regarding primary hemostasis?

A. After an endothelial injury, vasodilation mediated by neural reflex occurs immediately

B. ADP released from activated platelets binds to P2Y12 receptors on adjacent platelets, causing increased expression of Gp2B/3A.

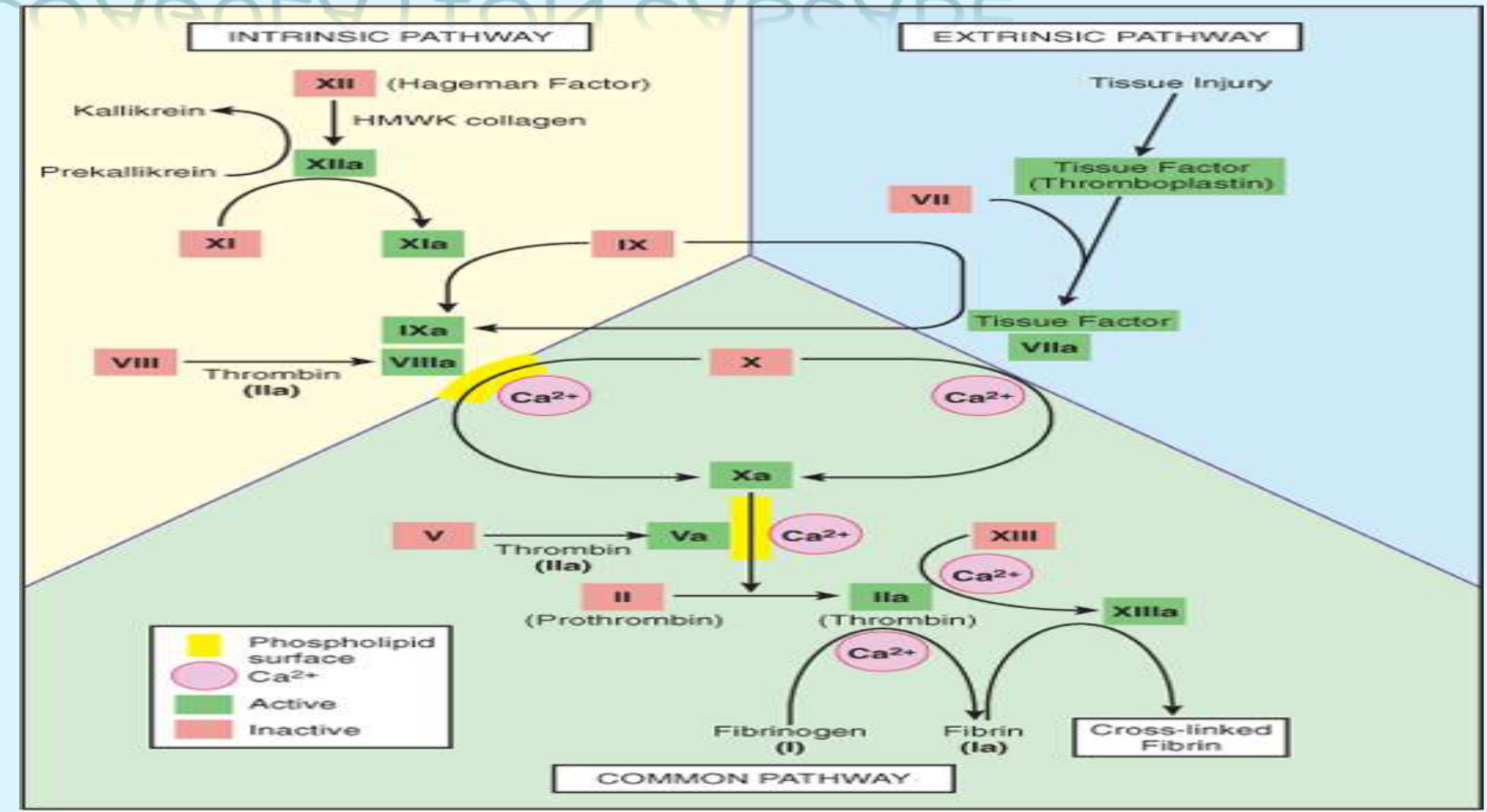
C.

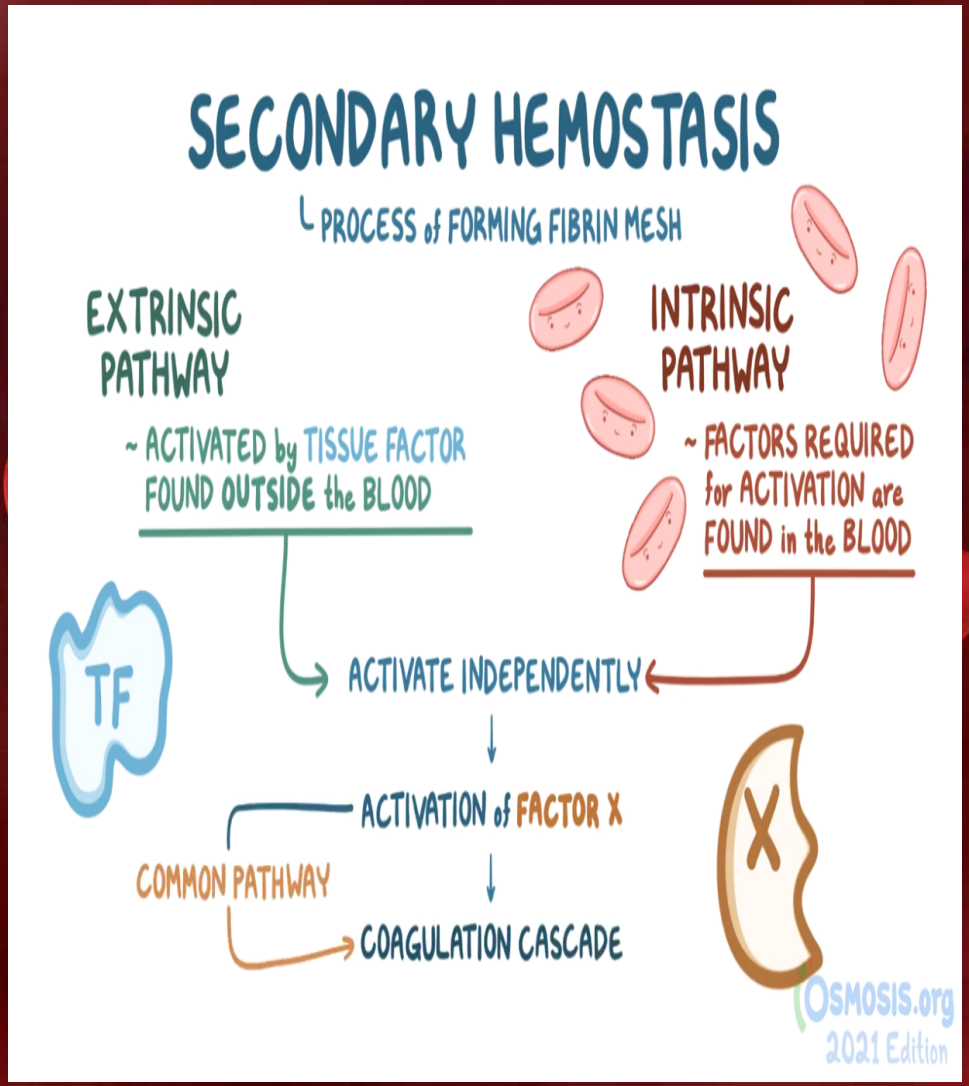
D. Calcium released from platelets binds to P2Y12 receptors on adjacent platelets, causing increased expression of Gp2b/3A.

E. Adhesion of platelets to the site of injury is mediated by binding to von Willebrand factor (vWF) via GpIIB/IIIA receptors

F. Fibrinogen mediates platelets aggregation via GpIB receptors

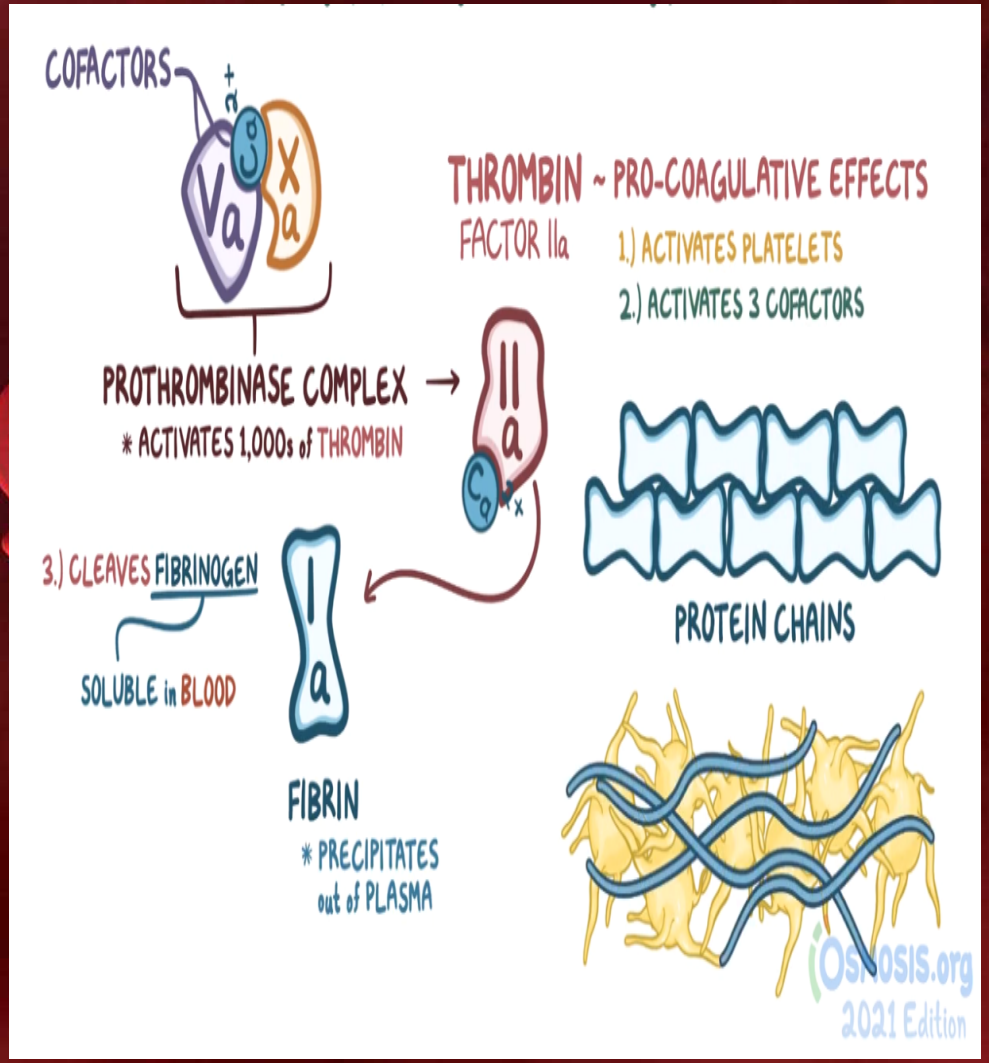
COAGULATION CASCADE





- **Intrinsic pathway** starts activation of factor **XII by subendothelial collagen or activated platelets.**
- Then (XIIa) activates factor XI, which then activates factor IX.
- Finally activated factor IX with activated factor VIII activates factor X (common pathway)

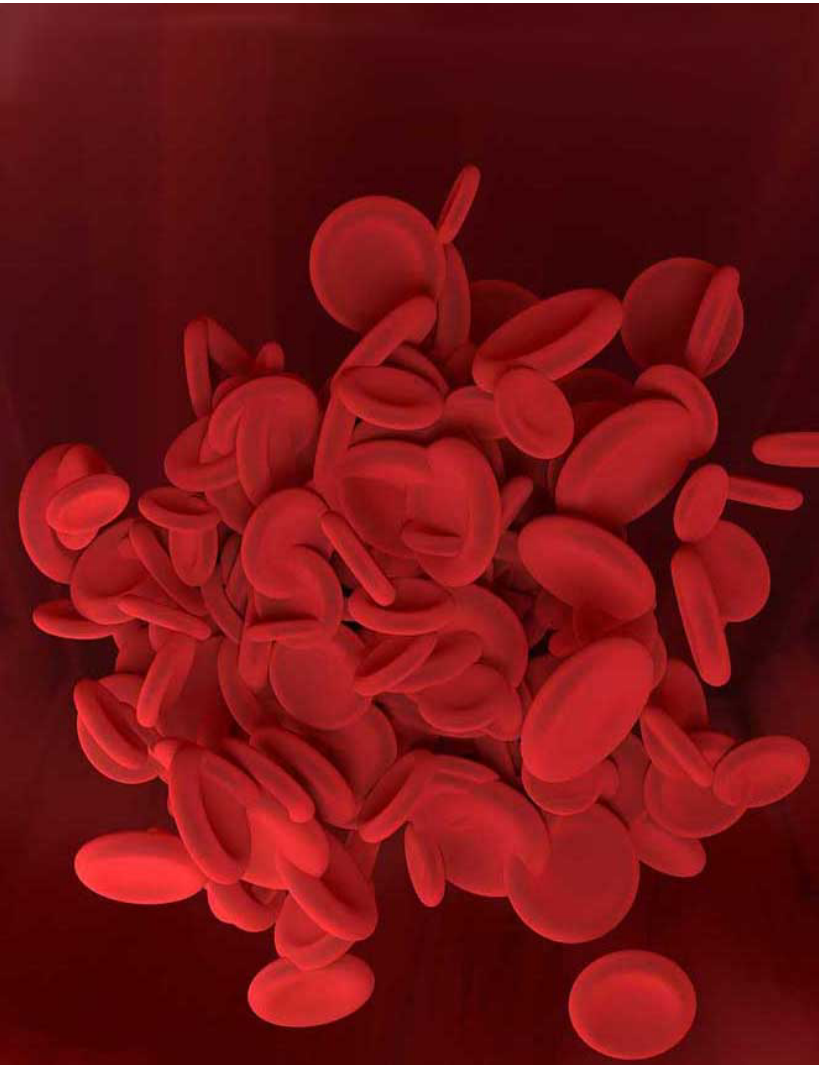
- **Extrinsic pathway**, tissue factor (factor III) activates factor VII, then activates factor X and the common pathway.



- **Secondary hemostasis** (coagulation) involves the stabilization of the platelet plug formed in primary hemostasis using a fibrin meshwork.

- Both the intrinsic and extrinsic pathways of coagulation ends by (Xa) . Factor Xa then cleaves factor V into the active form (Va), and calcium form the prothrombinase complex, which cleaves factor II (prothrombin) into the active form IIa (thrombin).

- **Thrombin 4 main functions**:
  - Activation of additional factors V, VIII, and IX; activation of platelets;
  - Conversion of fibrinogen to fibrin.
  - Fibrin is insoluble forming fibrin meshwork which stabilizes the platelet plug.
  - Activation of factor XIII stabilizing the platelet plug by forming cross-links between the fibrin molecules in the plug.



Secondary hemostasis involves the activation of clotting factors that lead to the formation of a stable fibrin mesh. This can be done using the intrinsic pathway or the extrinsic pathway. Which of the following is true regarding the intrinsic pathway and extrinsic pathway?

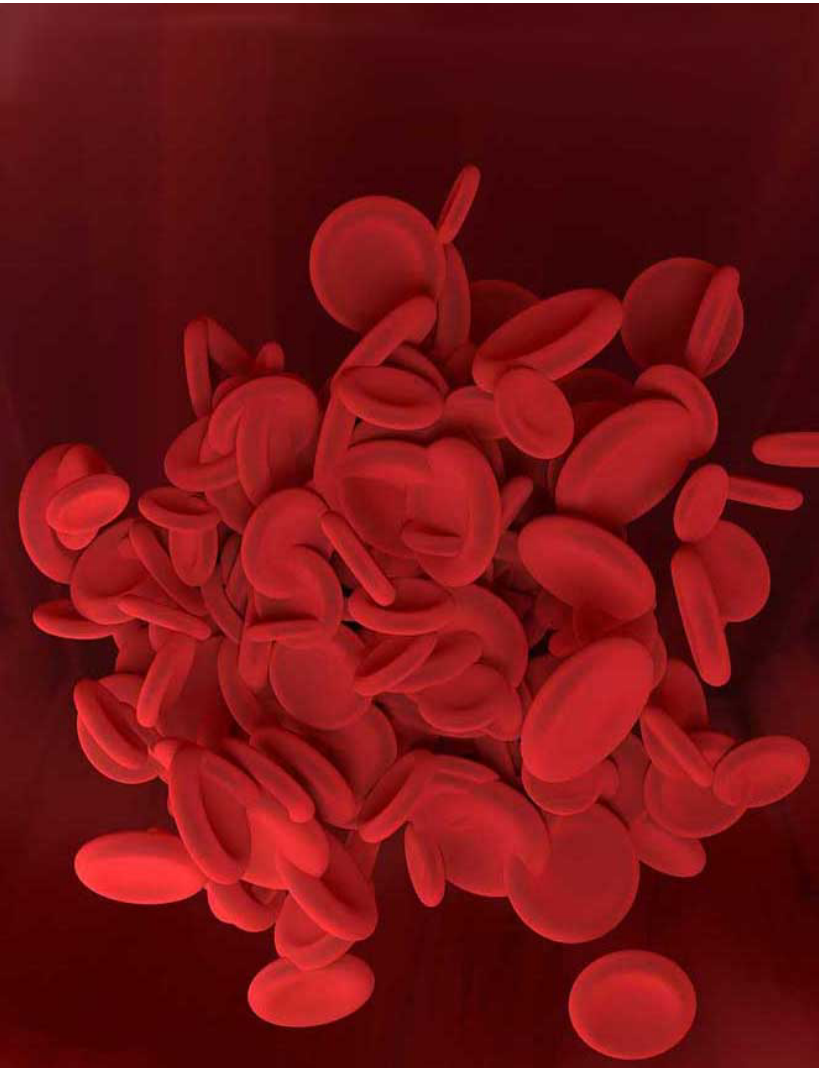
A. Tissue factor activates factor VII leading to the activation of the extrinsic pathway.

B. Tissue factor activates factor XII leading to activation of the intrinsic pathway

C. Both pathways are activated by same signals

D. Subendothelial collagen activates factor VII and leads to the activation of the intrinsic pathway.

E. The activation of the intrinsic pathway and the extrinsic pathway is dependent on each other



A lab study is simulating secondary hemostasis. In the study, both the intrinsic and extrinsic pathways of coagulation lead to the formation of the active form of factor X (Xa). Which of the following is the correct order of events to occur afterward?

A. Factor Xa cleaves fibrinogen into fibrin

B. Factor Xa alone activates factor II, which then cleaves fibrinogen into fibrin.

C. Factor Xa activates factor V, then factor Va alone activates factor II, which cleaves fibrinogen into fibrin.

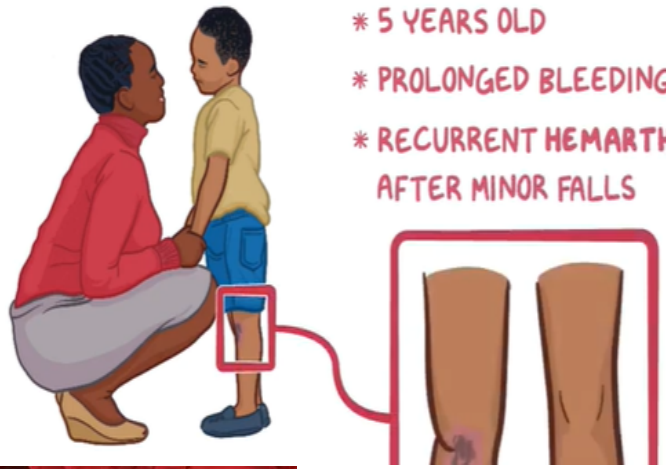
D. Factor Xa activates factor V, then factors Xa and Va activates factor II, which cleaves fibrinogen into fibrin

E. Factor Xa uses factor VIIIa as a cofactor to activate factor II, which then cleaves fibrinogen into fibrin.

So What Causes Bleeding Disorders?

Positive FH

BRADEN



* 5 YEARS OLD
* PROLONGED BLEEDING AFTER CIRCUMCISION
* RECURRENT HEMARTHROSIS AFTER MINOR FALLS

HARLOW

* 3 DAYS OLD, PRETERM
* BLEEDING SEVERELY from UMBILICUS
* DID NOT GET STANDARD CARE AFTER DELIVERY

	BRADEN	HARLOW
CBC	NORMAL PLATELET COUNT	NORMAL PLATELET COUNT
PT	NORMAL	↑↑↑
PTT	↑↑↑	↑↑↑

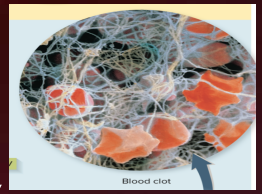
Classification

Bleeding disorders

- **Mixed platelet and coagulation disorders.**

Primary hemostasis formation of the weak platelet plug -

- **VESSEL DEFECTS**
- **PLATELET DISORDERS**



Secondary hemostasis

Strong fibrin clot activation of the coagulation pathway (intrinsic, extrinsic and common)

- **Coagulation factor: deficiency or inhibitors**

Classifications

VASCULAR DISORDERS

Acquired

- Severe infections (Meningococcal, typhoid)
- Senile purpura
- Vascular purpura
- Henoch Schonlein P
- Drugs (Sulphonamides)

Congenital

- HH Telengiectasia
- Connective tissue diseases e.g Ehlers Danlos Syn, Marfan's

QUANTITATIVE Platelet Disorders

Thrombocytopenia

- **•Increased destruction** (drugs, heparin [HIT], idiopathic, pregnancy,
- **•Diminished production** (viral infections, vitamin deficiencies, aplastic anemia, drug induced)

QUALITATIVE PL. Disorders

- Uremic platelet dysfunction,
- Drugs: aspirin, NSAIDs, clopidogrel.

DISORDERS OF COAGULATION.

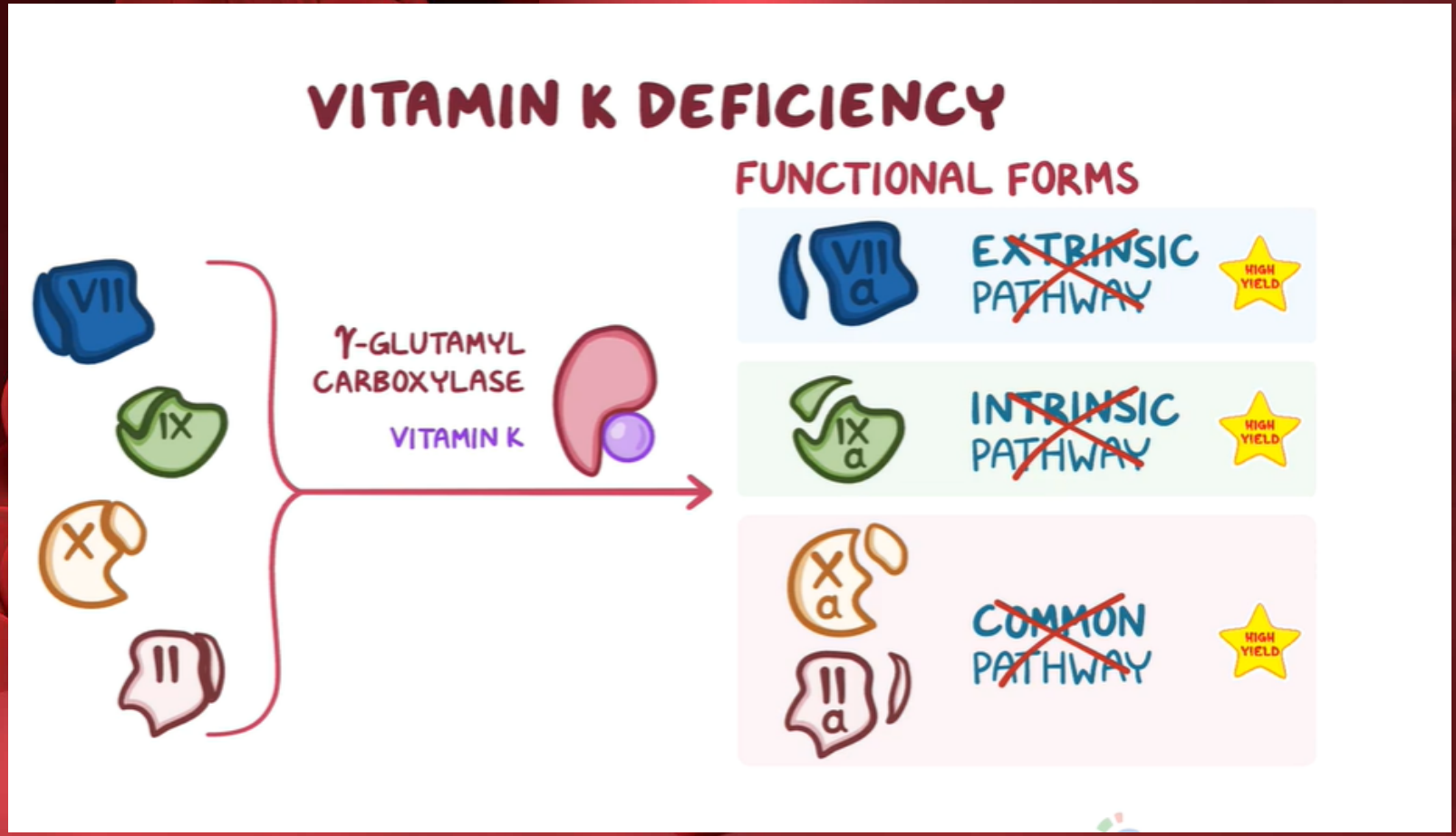
HEREDITARY

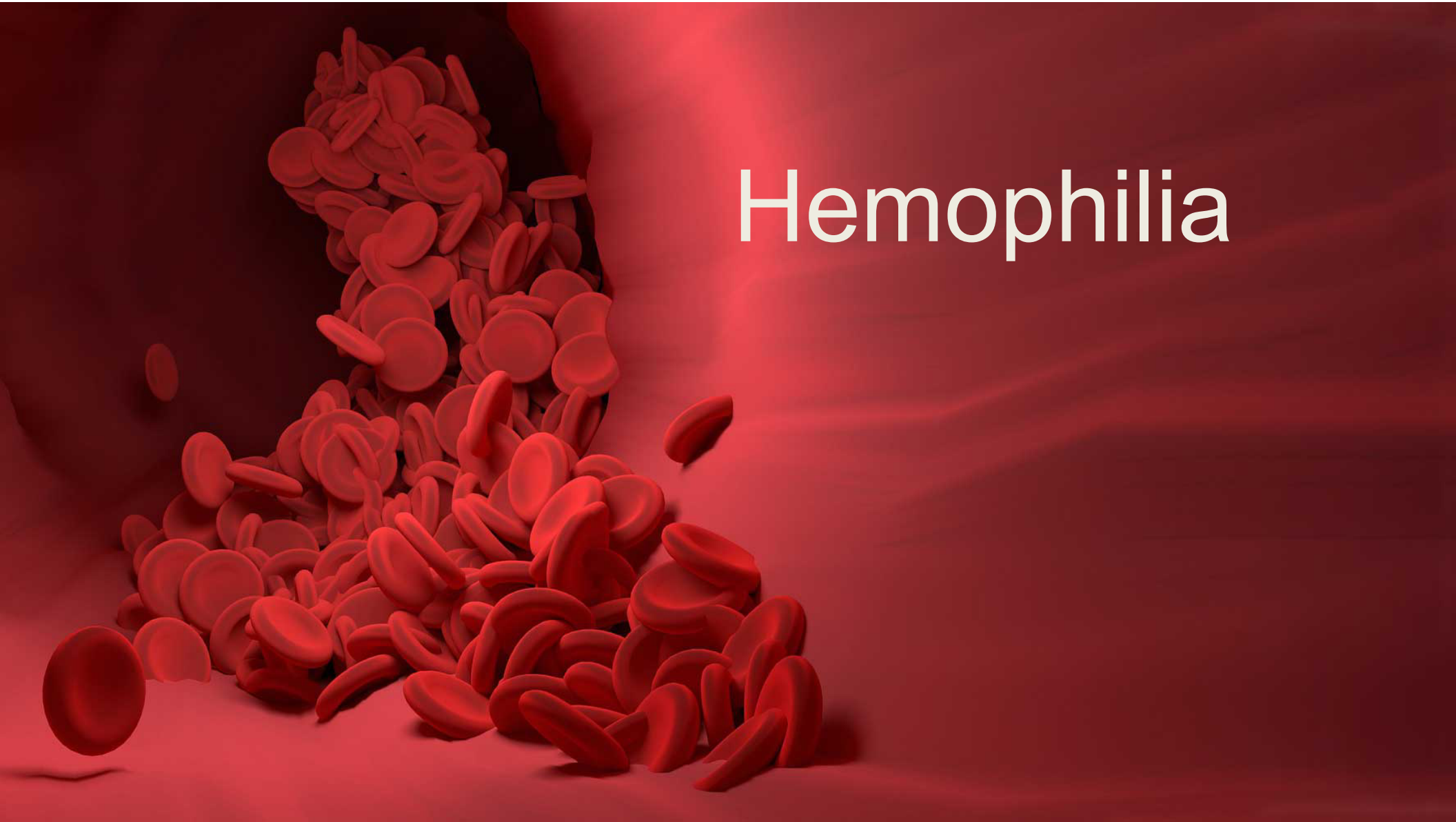
- Hemophilia A (factor VIII deficiency)
- Hemophilia B (factor IX deficiency)
- **Von Willebrand disease**,
- Disorders of fibrinogen hereditary
  - Afibrinogenaemia
  - Hypofibrinogenaemia
  - Dysfibrinogenaemia

Acquired

- Disseminated intravascular coagulation
- Liver disease
- Vit k deficiency 
- Massive transfusion of stored blood
- Acquired inhibitors of coagulation
- Heparin or oral anticoagulant therapy
- Renal disease

Vit K deficiency

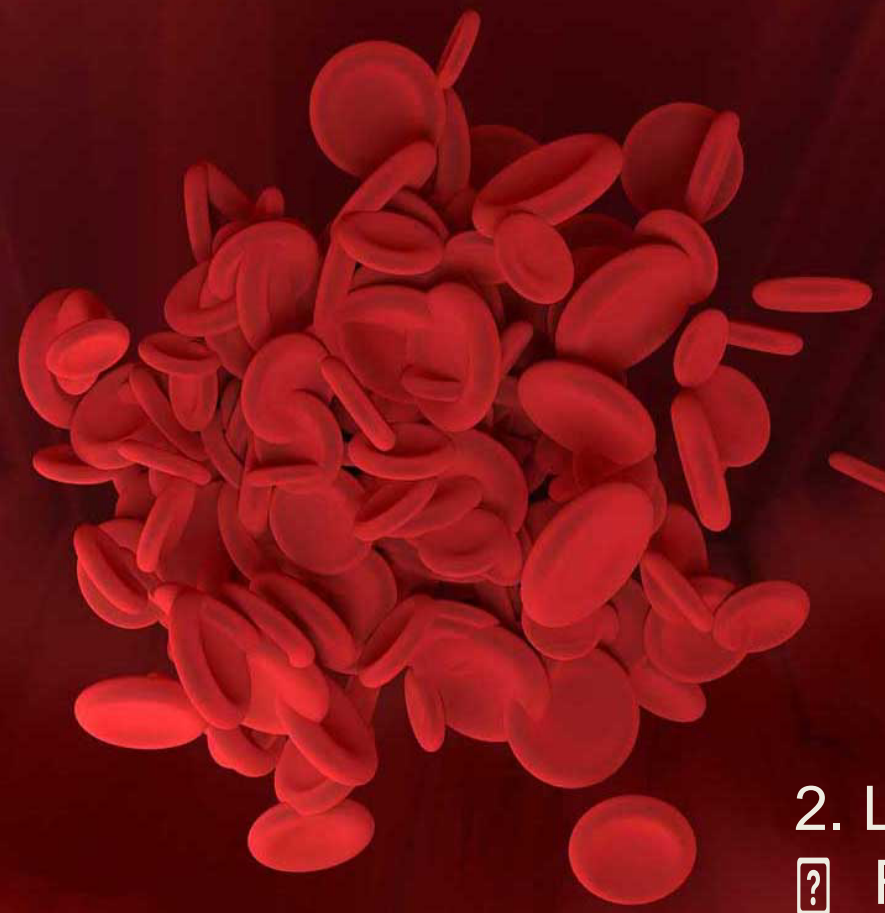



Hemophilia

Coagulation Disorders

	INHERITED DISORDERS	ACQUIRED DISORDERS
Age of presentation	Early	Later
Family history	positive	negative
Severity of bleeding	More	Less
Dominant feature	Bleeding	Underlying disorder e.g. DIC
Defect	Single factor	Multiple hemostatic defect

APPROACH TO A PATIENT OF BLEEDING Disorders



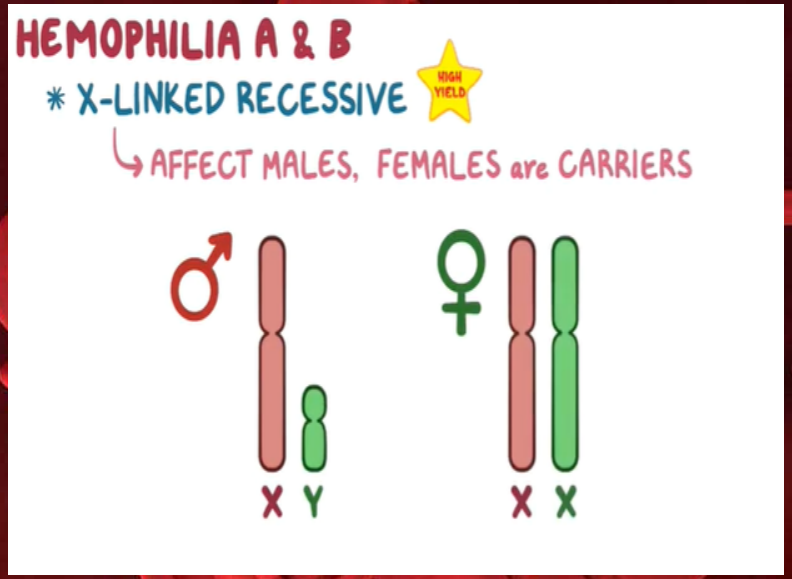
CLINICAL EVALUATION (H & E)

- HISTORY: Age of first manifestation
- FH: maternal relative with a bleeding Dis
- Bleeding spontaneous or after trauma; circumcision, or from dental procedures or cephalohematoma
- Time of manifestation after injury
- Ease with which bleeding is controlled
- Drug history.

2. Laboratory approach:

- First line screening tests.
- Second line specific tests.

Hemophilia

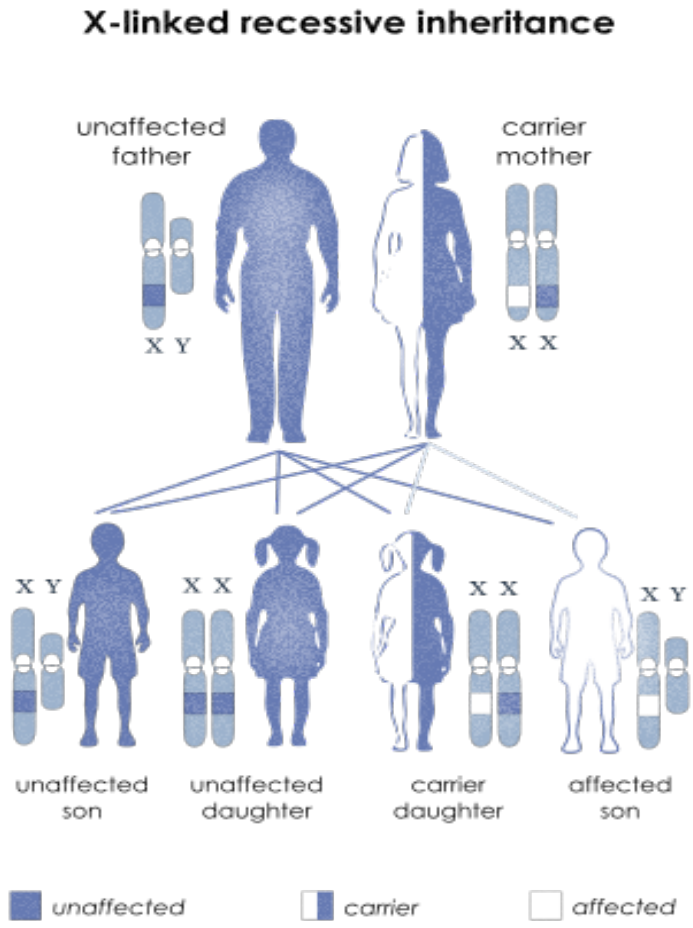


- Hemophilia A &B are an X-linked, recessive disorders caused by deficiency of functional plasma clotting factor VIII (FVIII),: inherited or acquired.
- Hemophilia C: autosomal recessive disorder, affect both males and females, leading to a deficiency in factor XI.
- Acquired hemophilia A: development of inhibitory antibodies to FVIII complicates the treatment of genetic cases.

HEMOPHILIA : B

Hemophilia B, or Christmas disease, is an inherited, X-linked, recessive disorder that results in deficiency of functional plasma coagulation factor IX.

- Hemophilia B: 20% of hemophilia cases, and about 50% have factor IX levels greater than 1%.



Coagulation Disorders

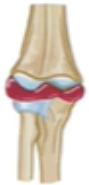
COMMON SYMPTOMS

HIGH YIELD

* "EASY BRUISING"

* ECCHYMOSES

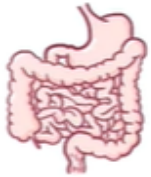
* HEMARTHROSIS



* DEEP TISSUE HEMATOMAS

* POSTERIOR EPISTAXIS

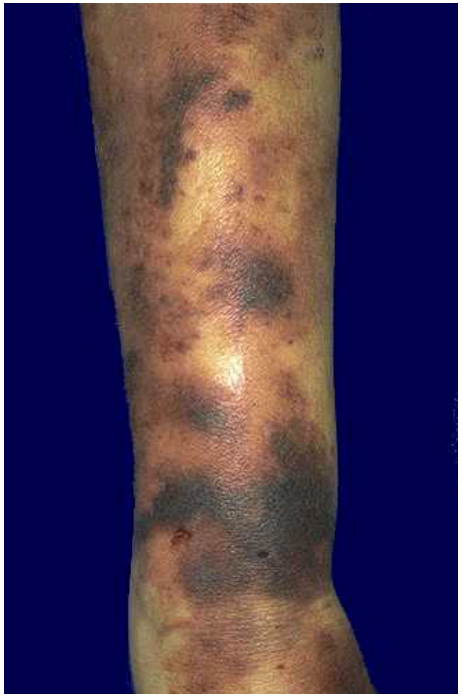
* GI BLEEDING

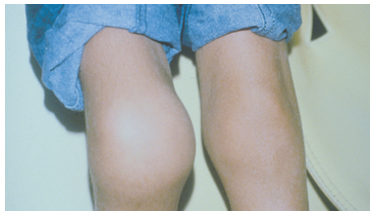


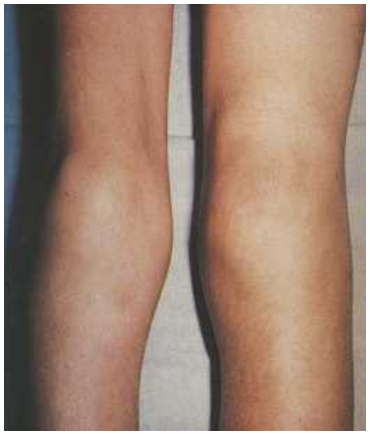
* URINARY BLEEDING

* PERSISTENT BLEEDING AFTER SURGICAL PROCEDURES

* INTRACEREBRAL HEMORRHAGE
  - ↳ STROKE/ ↑INTRACRANIAL PRESS·

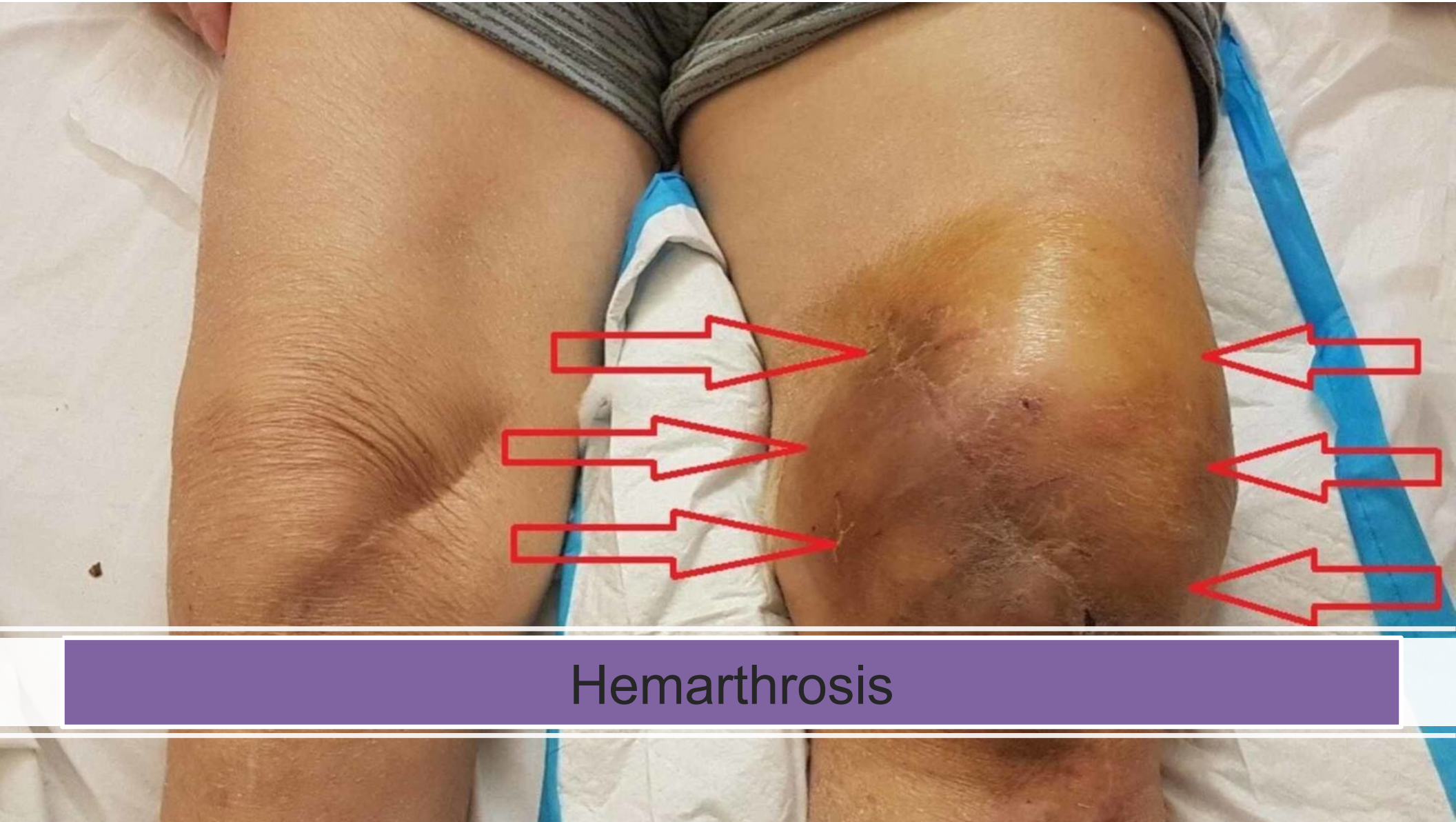






Hemarthrosis

Petechial bleeding is a common sign of platelet disorders, but NOT of coagulation disorders such as hemophilia.



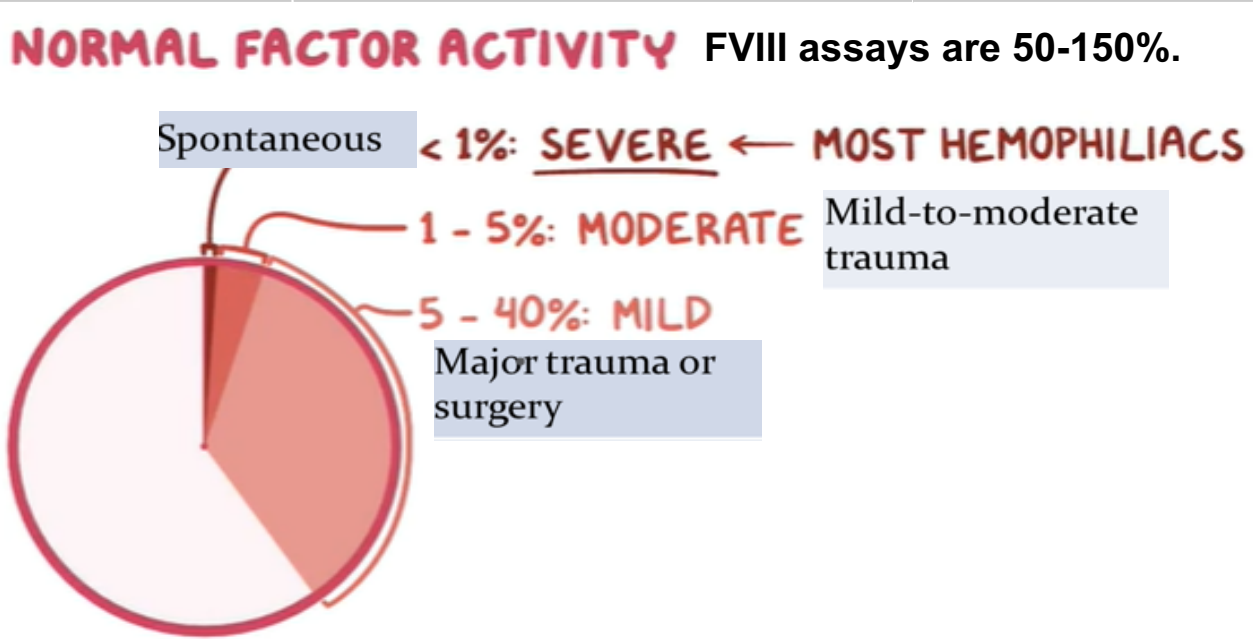
Hemarthrosis

Clinical manifestations of bleeding disorders

Bleeding symptoms	Bleeding disorder	
	Platelet defects (qualitative or quantitative)	Clotting factor deficiencies (factor VIII or factor IX)
Overview of bleeding events	**Mucocutaneous bleeding (oral, nasal, GIT, vaginal, and genitourinary sites)**	**Deep tissue bleeding (including joints and muscles)**
Excessive bleeding after minor cuts	Yes	Not usually
Epistaxis	anterior	posterior
Petechia	Common	Uncommon
Ecchymoses	small and superficial	large subcutaneous and soft tissue hematomas
Hemarthroses, muscle hematomas	Uncommon	Common severe deficiency
Bleeding with invasive procedures, including surgery	immediate, dependent upon severity of defect, ranging from mild to severe	Either with procedural bleeding or delayed bleeding

Severity, Factor Activity, and Hemorrhage

	Hemophilia A	Hemophilia B
Factor deficiency	Factor VIII	Factor IX
Inheritance	X-linked recessive	X-linked recessive
Incidence	1/10,000 males 80%	1/50,000 males



HEMOPHILIA DAIGNOSIS

Laboratory studies for hemophilia include

CBC

- Hemoglobin/hematocrit: Normal or↓
- Platelet count: Normal

Coagulation studies

- Bleeding time: Normal
- Prothrombin time: Normal
- APTT: prolonged----mixed study.

FVIII, IX, XI assays

Genetic testing screening.

Other investigations: imaging

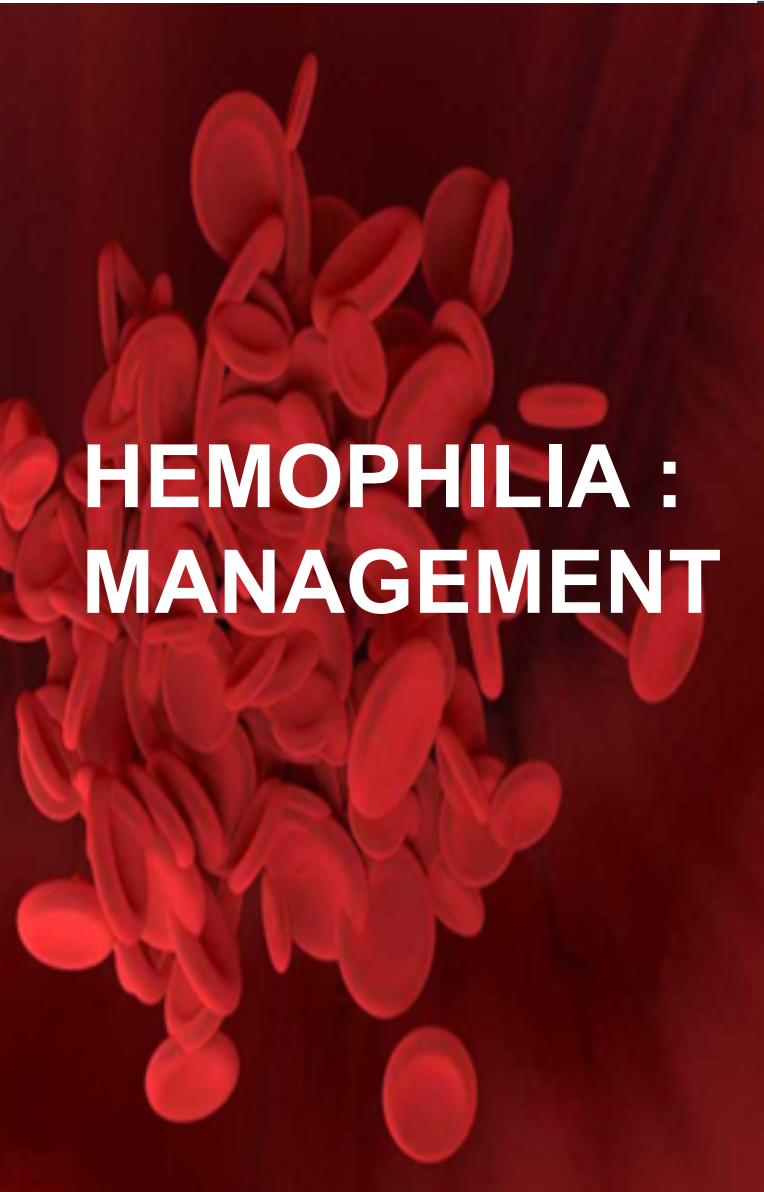
DIAGNOSTIC TESTS

HEMOPHILIA

* **PROLONGED PTT** (HIGH YIELD)
  - ↳ RULE OUT von WILLEBRAND
* **NORMAL PT & PLATELET COUNT** (HIGH YIELD)
* **MIXING STUDY**
  - ↳ PTT PROLONGATION due to TRUE FACTOR DEFICIENCY or PRESENCE of FACTOR INHIBITOR

→ **PTT**

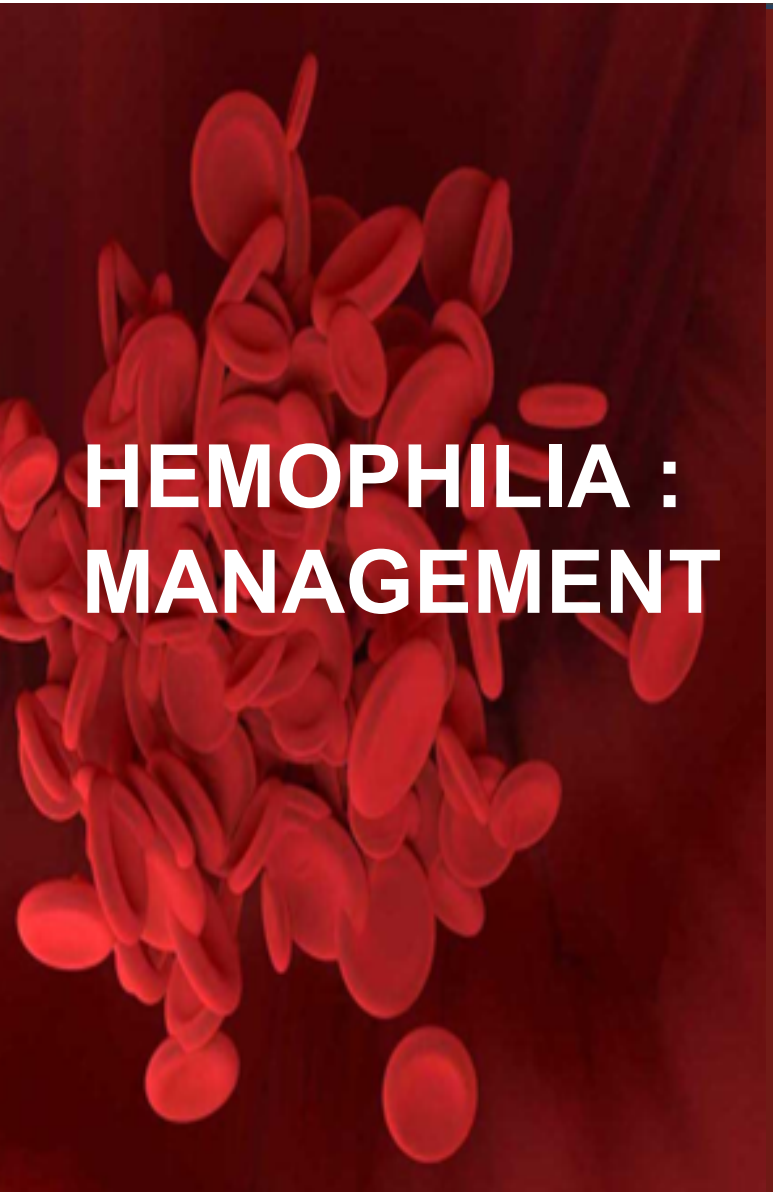
* **NORMALIZES**
  - ↳ FACTOR DEFICIENCY → HEMOPHILIA
* **DOESN'T NORMALIZE**
  - ↳ FACTOR INHIBITOR



HEMOPHILIA : MANAGEMENT

Management of hemophilia

- **Non-pharmacological**
- **Physiotherapy.**
- **Hydrotherapy.**
- **Patient education on treatment and prevention of bleeding.**
- **Avoid non-steroidal anti-inflammatory drugs (NSAIDs) and intramuscular (IM)/joint injections.**



HEMOPHILIA : MANAGEMENT

Mild hemorrhages

- Early hemarthrosis
- Epistaxis
- Gingival bleeding

FVIII level of at 30%

Major hemorrhages

- Hemarthrosis
- Muscle bleeding
- Prophylaxis after head trauma with negative findings on examination

FVIII level of at least 50%

Life-threatening bleeding

- Major trauma
- Surgery
- Advanced or recurrent hemarthrosis

FVIII level of 80-100%

Needed Number of units of FVIII: is calculated by formula:

Formula:

weight ÷ 4.4 × factor level desired = number of factor VIII units needed

HEMOPHILIA : MANAGEMENT

Desmopressin vasopressin analog, or 1-deamino-8-D-arginine vasopressin (DDAVP):

- Mild hemophilia A
- Not effective for severe hemophilia
- Peak effect is observed in 30-60 minutes
- DDAVP intranasal spray is available for outpatient use

Antifibrinolytics are used + FVIII replacement for oral mucosal hemorrhage and prophylaxis:

- Tranexamic acid

- **Emicizumab**

- humanized monoclonal bispecific antibody that reduces the risk of bleeding events
- Therapeutic use: hemophilia A
- MOA: bridges activated factor IX and factor X by binding to both factors (thereby replacing the deficient factor VIII) → activation of factor X → restored clotting cascade

Haemophilia B

Ttt: IV infusion of factor IX, longer half life than factor VIII ; transfused <frequently. Blood transfusions needed

Haemophilia C : IV infusion factor XI

HEMOPHILIA : MANAGEMENT

INHIBITORS

30% Haemophilia: Develop an antibody to the clotting factor received. These antibodies are known as inhibitors. Secondary to APS

Testing for inhibitors: Bleeding is not controlled after adequate amounts of factor concentrate are infused during a bleeding episode.

Treatment: High doses of FVIIa for bleeds or surgery. This overrides defect in FVIII or FIX deficiency.

Long-term management: eradicate inhibitors by administering high dose FVIII (or FIX) in a process called **immune tolerance**

Prognosis

- Prognosis is dependent on severity.
- Up to 60% haemophilia A have severe forms.
- Prognosis is improved with proper treatment and prevention of injuries.
- Genetic therapies are currently under development which may further improve prognosis.

- Complication of disease:
  - degenerative joint disorders (arthritis)
  - life-threatening haemorrhage.
- Complication of treatment:
  - viral infections such as hepatitis and human immunodeficiency virus (HIV) from transfusion
  - development of antibodies against the administered coagulation factors
  - opiate addiction.

- Activated partial thromboplastin time measures the _ _ _ _ **the extrinsic system** _ _ _ and the _ _ _ **the final common pathway** _ _ _ _

- Activated partial thromboplastin time measures the _**intrinsic system**_ _ _ _ _ _ _ _ and the _ _ _ _ _ _ _ _ _ _ _ _ **the final common pathway**

- A 24-year-old woman, gravida 1, para 0, at 12 weeks' gestation comes to the office for her monthly antenatal visit with her husband. She says that her father died soon after she was born due to excessive bleeding from a trauma to his head. Her father's maternal grandfather also had bleeding problems. She is concerned that her unborn child may have the same medical problem and wants to get a genetic test. She does not have any past or current medical conditions. Her husband also has no past or current medical conditions but reports a family history of hypertension. Which of the following illustrates the risk of the patient's unborn child being affected by the disorder?

A. 0% chance regardless of the sex
B. 100% chance if the fetus is a male
C. 50% chance if the fetus is a male
D. 25% chance if the fetus is a male
E. 25% chance if the fetus is a female