

## (( Primary Homeostasis & related bleeding disorders ))

- There are two stages of homeostasis:
  - Primary: formation of a weak platelet plug
  - Secondary: stabilizing the platelet plug via fibrin resulting from coagulation cascade
- Primary homeostasis:
  1. Transient vasoconstriction of the damaged vessel
  2. vWF will bind to the damaged area and act as a linker molecule to facilitate binding of platelets to it through (GpIb)
  3. ADP & thromboxane-A<sub>2</sub> will be released from platelets → leading to expression of GpIIb/GpIIIa on surface of platelets (for platelet aggregation via Fibrinogen)
- Disorders of primary homeostasis:
  - Due to abnormalities in platelets
    - Quantitative
    - Qualitative
  - Clinical features:
    - \* → Mucosal bleeding: epistaxis, hemoptysis - etc
    - Skin bleeding: petechiae, purpura, ecchymoses, easy bruising
  - Useful laboratory studies includes:
    - Platelet count: normally 150,000 - 400,000/ $\mu\text{l}$
    - Bleeding time: normally 2-7 minutes
    - Blood smear
    - Bone marrow biopsy: maybe there are no megakaryocytes 😞

\* vWF: comes from α-granules of platelets & from endothelial cells



Notice that in endothelial cells, vWF is stored in "Weibel-palade bodies"

\* ADP: is stored in dense granules in platelets

\* Thromboxane-A<sub>2</sub> is a derivative of platelet cyclooxygenase pathway

\* Notice that intracranial bleeding occurs with severe thrombocytopenia

\* Purpura > 3 mm

\* Ecchymoses > 1 cm

## I ITP (Immune Thrombocytopenic Purpura):

- Autoimmune disease with production of IgG against platelet antigens (GpIIb/IIIa)
- Splenic macrophages will eat platelets bound to antibodies
- Acute form (arising in children):
  - ↳ Thrombocytopenia weeks after viral infection or immunization → This is self-limited
- Chronic form (arising in adults):
  - ↳ In women of childbearing age
  - ↳ Can be:
    - Primary: idiopathic
    - Secondary: e.g. SLE

→ These antibodies are produced by plasma cells in the spleen



# ((Primary Homeostasis & Related Bleeding Disorders))

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## 1 ITP (continued):

### Chronic form (continued):

↳ Anti-platelet IgG can cross the placenta resulting in short-lived thrombocytopenia in offspring.

### Laboratory findings:

↳ ↓ platelet count

↳ Normal PT/PTT (coagulation cascade is normal)

↳ ↑ megakaryocytes on bone marrow biopsy

### Treatments:

↳ Corticosteroids: children respond well but adults relapse

↳ IV immunoglobulin: effect is short-lived

↳ Splenectomy: Therefore eliminating the source of antibodies and site of destruction

## 2 Microangiopathic hemolytic anemias:

↳ A platelet microthrombus is formed in small blood vessel → RBCs pass → they are sheared → resulting in schistocytes

↳ As microthrombi are formed, platelets are consumed

↳ This condition is seen in:

↳ Thrombotic Thrombocytopenic Purpura (TTP): microthrombi are formed due to deficiency in ADAMTS13 either due to a genetic defect or production of autoantibody against it

↳ Hemolytic Uremic Syndrome (HUS): platelet microthrombi are formed due to infection with E. coli O157:H7 especially in kidneys

↳ Clinical findings of TTP & HUS

↳ Skin & mucosal bleeding (↓ platelets)

↳ Microangiopathic hemolytic anemia

↳ Fever

↳ Renal insufficiency (↑ in HUS)

↳ CNS abnormalities (↑ in TTP)

↳ Laboratory findings:

↳ Thrombocytopenia & ↑ bleeding time

↳ Normal PT/PTT (coagulation is normal)

↳ Anemia with schistocytes

↳ ↑ megakaryocytes on bone marrow biopsy

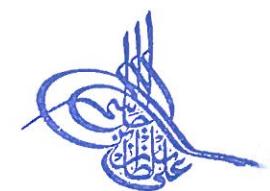
\* ADAMTS13: converting multimers of vWF into small monomers (which can be used).

\* E. coli O157:H7 is especially seen in children who get exposed to undercooked beef

\* Treatment of TTP:

↳ Plasmapheresis

↳ Corticosteroids



## (( Primary Homeostasis & Related Bleeding Disorders))

### [3] Bernard - Soulier Syndrome:

- ↳ Genetic (GpIb) deficiency thus platelet adhesion cannot occur
- ↳ Blood smear shows mild thrombocytopenia with enlarged platelets

### [4] Glanzmann thrombasthenia:

- ↳ Genetic (GpIIb/ IIIa) deficiency thus platelet aggregation is impaired

### [5] Aspirin:

- ↳ It irreversibly inactivates cyclooxygenase thus thromboxane-A<sub>2</sub> will not be formed

These are qualitative disorders of platelets

## (( Secondary Homeostasis & Related Disorders))

- End product of coagulation cascade is thrombin which will convert fibrinogen into fibrin → that will stabilize the platelet plug
- Coagulation factors are produced in their inactive state from the liver. Activation requires:
  - ↳ Exposure to an activating substance
  - ↳ Phospholipid surface → provided by platelets
  - ↳ Calcium → derived from dense granules of platelets
- Disorders of secondary homeostasis are generally due to factor abnormalities
- Clinical features:
  - ↳ Deep tissue bleeding: muscles and joints
  - ↳ R bleeding after surgical procedures
- Laboratory studies:
  - ↳ PT: measuring extrinsic and common pathways → measuring warfarin effect
  - ↳ PTT: measuring intrinsic and common pathways → measuring heparin effect

### [1] Hemophilia - A:

- ↳ Genetic deficiency of factor VIII
- ↳ X-linked recessive affecting males
- ↳ Presentation: deep tissue, joint and postsurgical bleeding
- ↳ Laboratory findings:
  - ↳ ↑ PTT, normal PT
  - ↳ ↓ Factor VIII
  - ↳ Normal platelet count & bleeding time
- ↳ Treatment: recombinant factor VIII

\* Review coagulation cascade from physiology



## ((Secondary Homeostasis & Related Disorders))

[4]

### [2] Hemophilia - B (Christmas disease):

- Genetic deficiency of Factor IX
- Clinically resembling hemophilia A

### [4] Coagulation factor inhibitor:

- Antibody against a coagulation factor leading to its impairment (anti factor VIII is common)
- How to differentiate it from hemophilia A?
  - ↳ Mixing study: taking a normal plasma & mixing it with patient's plasma:
    - PTT corrected: hemophilia A
    - PTT not corrected: antibody against factor VIII.

### [5] Von Willebrand disease:

- Autosomal dominant with ↓ levels of vWF thus resulting in problem with platelet adhesion.
- Explaining the mild mucosal and skin bleeding which can be seen (primary homeostasis is affected).
- Laboratory findings:
  - ↑ bleeding time
  - ↑ PTT (factor VIII is not stabilized), normal PT
  - \* → Abnormal ristocetin test
- Treatment: desmopressin (which will increase release of vWF from Weibel-Palade bodies of endothelial cells).

\* Ristocetin: normally causes platelets to aggregate. With lack of vWF → there will be no aggregation

### [6] Vitamin K deficiency:

- Vitamin K is important for production of following factors: II, VII, IX, X, C and S
- vitamin K is activated by epoxide reductase in the liver
- vitamin K deficiency occurs in:
  - Newborns: gut is not yet colonized by bacteria
  - Long-term antibiotic therapy: killing gut flora.
  - Malabsorption of fat-soluble vitamins (A, D, K and E)
  - Liver failure (measured by PT)



## ((Other Disorders of Homeostasis))

### 1 Heparin-induced thrombocytopenia (HIT):

↳ Heparin forming a complex with a surface molecule on platelets (heparin - PF4) → IgG will develop against this complex → resulting in destruction of these platelets by the spleen

### 2 Disseminated Intravascular Coagulation (DIC):

↳ There is pathologic activation of coagulation cascade → resulting in many microthrombi which will block blood vessels → ischemia & infarction. Notice that there will be consumption of platelets & factors → resulting in bleeding from IV sites & mucosal surfaces

→ Always secondary to other diseases:

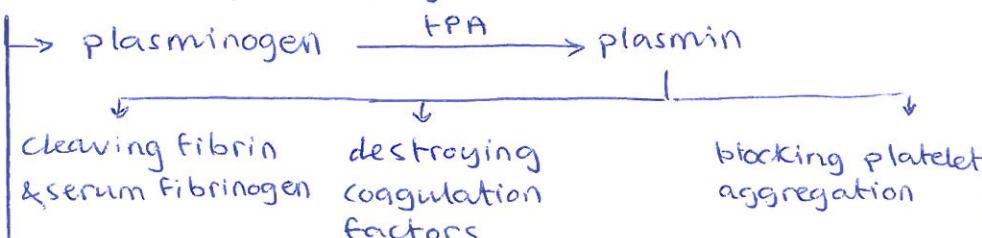
- ↳ Obstetric complication
- ↳ Sepsis: due to endotoxins
- ↳ Adenocarcinoma
- ↳ Acute promyelocytic anemia
- ↳ Rattlesnake bite

→ Laboratory findings:

- ↳ ↓ platelet count (consumed)
- ↳ ↑ PT / PTT
- ↳ ↓ fibrinogen (consumed in formation of thrombi)
- ↳ Microangiopathic hemolytic anemia
- ↳ D-dimers

→ Treatment addressing the underlying cause with transfusion of blood products

### - Disorders of Fibrinolysis:



→ In these disorders, there is overactivity of plasmin

→ Examples:

- ↳ Radical prostatectomy
- ↳ Cirrhosis of liver

→ These disorders resembling DIC in presentation

