HYPERCOAGULABLE STATES & BLEEDING DISORDERS

SUMMARY

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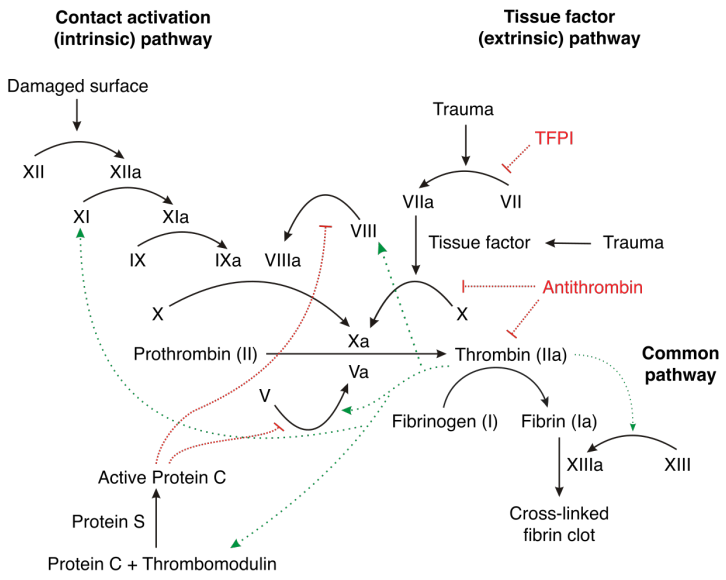
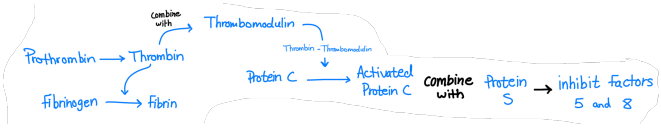
Note : you can skip the first two slides ; they're just a quick review of coagulation cascade and platelet actions

Coagulation Cascade



Coagulation Inhibitors :

1. **Antithrombin III**
   - Inhibits factors : II, VII, IX, X, XI, XII **(11/12/1972)**
   - Produced by liver
   - Deficiency → Hypercoagulable state
2. **Proteins C and S**
   - Protein C becomes activated when thrombin binds to thrombomodulin, a constitutively expressed protein on the surface of vascular endothelial cells. Activated protein C (APC) is a physiological anticoagulant through its potential to inactivate clotting factors **Va** and **VIIIa**. APC requires protein S as co-factor.



3. **Tissue factor pathway inhibitor**
   - Inactivates Xa via two mechanisms :
     - Directly binds Xa
     - Binds TF/FVIIa complex → prevents X activation

Von Willebrand Factor (VWF)

- Synthesized by endothelial cells and megakaryocytes
- **Stored in :**
  - Weibel–Palade bodies in endothelial cells
  - Present in platelets (stored in alpha granules)
  - Some found in plasma
- **Released on vascular injury :**
  - Activated platelets degranulate → release vWF
  - Endothelial cells release vWF
- **Roles :**
  - Binds platelets to damaged endothelium
  - Binds activated platelets together (aggregation)
  - Carrier protein for factor VIII

Bleeding time : Test of platelet function

Platelets Actions

1. **Adhesion**
   - Vascular damage → exposure of collagen → Subendothelial collagen binds vWF → vWF binds **GPIb** on platelets
2. **Aggregation**
   - Platelet-platelet binding (**GPIIb/IIIa** binds fibrinogen or vWF → Links platelets together
3. **Secretion: Release of granule contents**
   - Two types of platelet granules: **alpha** and **dense**
   - Released on activation by:
     - Platelet binding to collagen
     - Granule contents from other platelets

Alpha granules (most abundant)

- Fibrinogen
- VWF
- platelet factor 4 (PF4)
  - Heparin binds to PF4 (in some patients who administer heparin , antbodies maybe form against Heparin-PF4 complex → bind → platelet activation → diffuse thrombosis → ↓ platelets → **HIT** (Heparin induced thrombocytopenia)

Dense granules

- ADP
  - Inhibit platelets activation
- Calcium
- Serotonin
  - **Serotonin release assay** → Diagnostic test for HIT (HIT antibodies → excessive serotonin release)

Hypercoagulable States

- Caused by various factors :
  1. **Post operative :** Inflammation, stasis from immobility, and endothelial damage from surgery.
  2. **Trauma :** Inflammation, stasis, and endothelial damage from injuries.
  3. **Long Flights :** Prolonged immobility leads to stasis.
  4. **Malignancy :** Tumors can produce pro-coagulants, increasing clot risk.
  5. **Pregnancy :** Changes in clotting factors and fetal pressure increase DVT risk.
  6. **Oral Contraceptives** (OCPs) **:** Estrogen enhances coagulation factor production.
  7. **Elevated homocysteine :** Elevated levels caused by (Folate/B12/B6 deficiency, Homocystinuria).
  8. **Nephrotic syndrome** (loss of anti-clotting factors in urine (**ATIII**)).
  9. **Smoking**

- Hypercoagulable states increase the risk of blood clots, leading to conditions such as :
  - **Venous Thromboembolism (VTE) :**
    - Includes Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE).
  - **Arterial Thrombosis :**
    - Can result in :
      - Stroke
      - Myocardial Infarction
      - Ischemic Limb

Inherited Thrombophilia (inherited Hypercoagulable Condition) :

- Genetic tendencies to VTE
- All associated with venous clots (DVT/PE)

1] Factor V Leiden Mutation

- **Cause**: Abnormal factor V (Point mutation in factor V gene)
- It is **the most common** inherited thrombophilia presenting as **VTE** (DVT/PE).
- Pathophysiology: Abnormal factor V protein → Factor V is not inactivated by activated protein C (APC) → this leads to prolonged activity of factor V → ↑ Hypercoagulability

- **Heterozygous Factor V Leiden alone**, without a personal or strong family history of thrombosis, typically represents a mild thrombophilic condition and does not necessarily warrant prolonged or lifelong anticoagulation.

- Patients with a **first** provoked **DVT/PE** and **heterozygous Factor V Leiden mutation require anticoagulation therapy for approximately six months**. Lifelong anticoagulation is reserved for recurrent or unprovoked thrombotic events or severe thrombophilia.

2] Prothrombin Gene Mutation

The mutation leads to increase levels of prothrombin, a protein crucial for blood clothing, so ↑ prothrombin levels → ↑risk of developing VTE including DVT & PE.

3] Antithrombin III deficiency

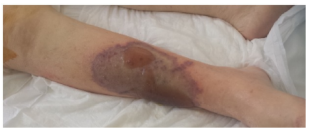
- **Inherited deficiencies** due to gene mutations
- **Acquired deficiencies:**
  - Impaired production (liver disease)
  - Protein losses (nephrotic syndrome)
  - Consumption (DIC)

- Classically presents as **heparin resistance**

  Just to explain: ATIII is crucial for inhibiting thrombin and factor Xa, and heparin enhances ATIII's activity. In ATIII deficiency, there is insufficient ATIII to interact with heparin, leading to heparin resistance and increased thromboembolism risk. Patients may require higher heparin doses for effective anticoagulation, necessitating careful monitoring.

4] Protein C or S Deficiency

- Associated Complication : **warfarin skin necrosis**
  - Initial warfarin therapy → ↓ protein C (short half life)
  - If protein C deficient → marked ↓ protein C .
  - **Result**: thrombosis of skin tissue (Large dark, purple skin lesions).



Antiphospholipid Syndrome

- Caused by antiphospholipid antibodies.
- Occur in association with **lupus** or as **primary** disease.
- There is three clinical manifestations of Antiphospholipids syndrome
  - Increased risk of venous and arterial thrombosis (Most commonly DVT , Stroke).
  - Recurrent **fetal loss**
  - Interference with Laboratory testing : ↑ **PTT**

- Antiphospholipids antibodies (Anti-cardiolipin, Anti-β2 glycoprotein, **Lupus anticoagulant**)
- Lupus anticoagulant interferes with PTT test (False elevation)
- On PTT testing, lupus anticoagulant binds phospholipid → ↑ PTT
- **Mixing study :**
  - The patient's plasma is mixed with normal plasma , the PTT is then re-measured.
  - If the PTT corrects to normal, it suggests a factor deficiency.
  - If the PTT **remains prolonged (will not corrected)**, this indicates the presence of an inhibitor, such as lupus anticoagulant.

Bleeding Disorders

- **Abnormal coagulation cascade**
  - Hemophilia, Vitamin K deficiency
- **Abnormal platelets**
  - Bernard-Soulier, Glanzmann's Thrombasthenia
  - ITP, TTP
  - Uremia
- **Mixed Disorders**
  - Von Willebrand Disease, DIC, Liver disease

- **Types of bleeding**
  - **Abnormal platelets**
    - Mucosal bleeding, skin bleeding, petechiae
  - **Abnormal coagulation factors**
    - Joint bleeding, deep tissue bleeding

Abnormal coagulation cascade

1] Hemophilia

- X- linked inheritance (A family history, particularly involving maternal uncles or male cousins).
- **Hemophilia A:** Deficiency of factor VIII (factor VIII level correlates with severity).
  - Most common cause of severe hemophilia A in Jordan is **Intron 22 inversion** .
- **Hemophilia B:** Deficiency of factor IX (factor IX level correlates with severity).
- Both Present with spontaneous or easy bruising and recurrent deep tissue bleeding, especially hemaarthrosis (joint bleeding).
- Primarily affects males

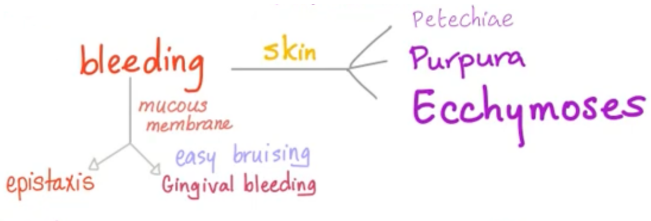
- **Labs/Tests** :
  - PTT will be prolonged
    - **REMEMBER:** Factors VIII, IX both part of intrinsic pathway
  - PT, bleeding time, platelet count all normal .
  - **Correction of PTT** on **mixing study** (distinguishing it from Platelets disorders and VWD).
  - **Factor assay** (the definitive test to distinguish hemophilia A from B).
- **Treatment** :
  - Replacement factor VIII and IX
  - Desmopressin (dDAVP)
    - Used in mild hemophilia A
  - Cryoprecipitate (Contains factor VIII)
  - Genetic counseling
  - Education

2] Vitamin K Deficiency

- Results in bleeding
- Deficiency of vitamin K-dependent factors (II, VII, IX, X) **(1972)**
- **Labs:**
  - Elevated PT/INR
  - Can see elevated PTT (less sensitive)
  - Normal bleeding time
- **Common causes:**
  - Warfarin
  - Antibiotics (deplete GI bacteria)
  - Malabsorption (Vitamin K is fat soluble)
- **Treatment** : fresh frozen plasma

Platelets Disorders

The problem in primary hemostasis
so, the bleeding → Mucocutaneous



Inherited platelets disorders

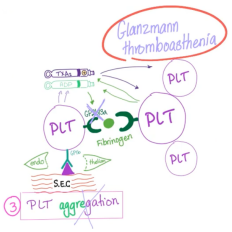
1] Bernard-Soulier syndrome (AR)

- Deficiency or Defective **GPIB** receptors
- VWF ❌ GPIB
❌ Adhesion
- Thrombocytopenia and/or Thrombesthenia

- **Lab tests:**
  - ↓ PLT counts
  - Blood smear → **Large platelets (Giant)**
  - ↑ BT
- **Symptoms**
  Epistaxis and menorrhagia
- **Treatment**
  - **Anti-fibrinolytic therapy** (tranexamic acid)
  - **PLT transfusion** in severe bleeding and befor major surgeries

2] Glanzmann's Thrombasthenia (AR)

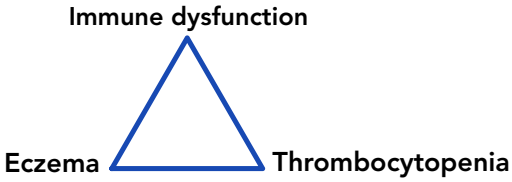
- Deficiency of **GPIIb/IIIa** → ❌ aggregation
→ Absent or impaired clot retraction



- **Lab tests :**
  - Normal platelets count (**NO** thrombocytopenia)
  - Isolated platelets (on blood smear)
  - ↑ BT
- **Symptoms**
  - Dental bleeding
  - Epistaxis
  - Menorrhagia
- **Treatment**
  - Tranexamic acid

3] Wiskott-Aldrich syndrom (X-linked)

- Immunodeficiency syndrome of **infant**
- X-linked disorder of WAS gene



Acquired platelets disorders

1] ITP (Immune Thrombocytopenic Prupura)

- Caused by **anti-GPIIb/IIIa antibodies** → over destruction of a platelets → consumption by splenic macrophage → ↓ platelets count.

- Types:

a. Idiopathic
b.secondary, due to: **S**LE, **C**LL, AP**S**, viruses: HIV, H**C**V

- Symptoms:

- Skin and the mucous membranes (Petechiae, Ecchymosis, Hemorrhagic vesicles, Gingival bleeding, and epistaxis).
- Menorrhagia
- Gastrointestinal bleeding
- Intracranial bleeding

- Diagnosis:

Diagnosis of exclusion

- Treatment:

- **Steroids**
- **IVIG** (block Fc receptors on macrophages)
- **Rituximab** (binds to CD-20 receptors on B lymphocyte → increase destruction of B lymphocytes → decrease the production of autoantibodies that target the platelets)
- **Splenectomy**
- **PLT transfusion**

Approach to the Treatment of ITP

Initial treatment	Glucocorticoids IVIG
Curative therapy	Glucocorticoids Splenectomy Rituximab
Rescue therapy	High dose glucocorticoids IVIG
Chronic therapy	Many agents **Thrombopoietin receptor agonists**

Extra Notes :

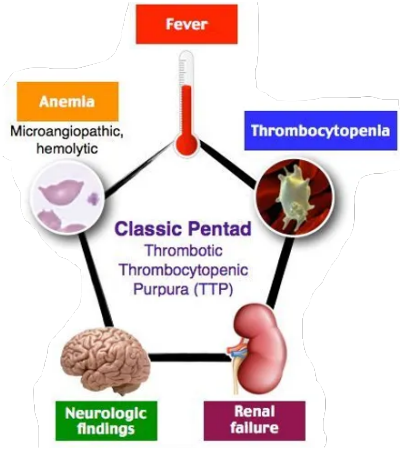
- **ITP** should have **NO** schistocytes → if you see schisocytes → TTP not ITP
- ITP should have normal RBC & WBC … PLT shows **MACRO** **thrombocytopenia** (REMEMBER: we see it also in Bernard-Soulier Syndrome).

2] TTP (Thrombotic Thrombocytopenic Prupura)

- Disorder of small vessel thrombus formation
- Consumes platelets → thrombocytopenia

- **Cause:** ↓ activity of vWF cleaving protease **ADAMTS13**
    - Acquired autoantibody to ADAMTS13 → vWF multimers in areas of high shear stress → obstruction small vessels

- **Symptoms:**
    - Fever … **Hallmark**
    - Neurological symptoms (Headache, confusion, seizures)
    - Renal failure
    - Petechiae and bleeding
    - Anemia (Microangiopathic hemolytic anemia) **(MAHA)**
        - Like any Hemolytic anemia (↑ LDH, ↓ haptoglobin)
        - Caused by shearing of RBCs as they pass through thrombi in small vessels
        - Peripheral blood smear: **schistocytes**



- **Lab tests:**
    - Hemolytic anemia
    - Thrombocytopenia
    - Schistocytes on blood smear
    - PT/PTT should be normal (Contrast with DIC 🤓)
- **Treatment**
    - Plasma exchange (plasmapheresis)
    - Glucocorticoids

3] DIC (Disseminated Intravascular Coagulation) … (mixed disorder)

- Widespread activation of clotting cascade → Diffuse thrombi (platelets/fibrin) → ischemia
- Consumption of clotting factors and platelets
- Destruction of red blood cells (due to formation of clots in small blood vessels → shearing of RBCs) → anemia (MAHA)
- Occurs secondary to another process :
    - Obstetrical emergencies (Amniotic fluid contains tissue factor)
    - **Sepsis** (the most common risk factor for DIC)
    - Leukemia (Especially APML)
- **Lab tests :**
    - ↑ PT/PTT/BT/Thrombin time/INR
    - ↓ platelets count
    - ↓ fibrinogen
    - MAHA (↓ RBC + Schistocytes on blood smear)

- **Treatment**
    - Treat underlying disorder
    - Fresh frozen plasma
    - Coagulation inhibitor concentrate (ATIII)
    - RBCs (for anemia) , platelets transfusion
    - Cryoprecipitate (for low fibrinogen)

4] Von Willebrand Disease … (mixed disorder)

- Most common inherited bleeding disorder
- Gene mutations → ↓ level (quantitative) or function (qualitative) of vWF
- Most cases AD , M=F
- **Classification :**
    - **Type 1** Partial quantitative deficiency
    - **Type 2** Qualitative deficiency
    - **Type 3** Total quantitative deficiency

- **Symptoms:**
    - Easy bruising
    - Skin bleeding
    - Prolonged bleeding from wounds/cuts and mucosal surfaces (Severe nosebleeds, **Menorrhagia**).

- **Lab tests:**
    - Normal platelet count
    - Normal PT
    - ↑ PTT (depending on severity) …. Usually no joint/deep tissue bleeding .
    - ↑ bleeding time (BT).
- **Treatment:**
    - Desmopressin (dDAVP) (for type 1)
    - Cryoprecipitate
    - vWF concentrate
    - Factor VIII concentrate (for type 2 and 3)

5] HIT (Heparin-induced thrombocytopenia)

- **5-10 days after exposure** to heparin
- **Caused by** antibodies against platelet factor 4 (PF4)-heparin complexes
- Abrupt fall in platelets (>50%)
- Arterial/vein thrombosis
- Necrotic skin lesions, Skin necrosis at site of injection
- Patients with HIT must use alternative drugs (Argatroban) , (Lepirudin, Bivalirudin → direct thrombin inhibitors).
- **Two Don'ts !!** (No **warfarin** until substantial platelet count recovery +No **platelet** transfusions)
- **Definitive diagnosis:** HIT antibody testing