**Immune Thrombocytopenic Purpura (ITP)**

Thrombocytopenia due to immune-mediated destruction of platelets, usually caused by platelet sensitization of autoantibodies

- RBCs and WBCs are not affected (normal HgB and white count), no hepatosplenomegaly or underlying genetic disorders that affect platelets
- Clinically presented as mild to moderate acute mucocutaneous bleeding and rapid drop of platelet count
- Etiology unknown
  - **Blood morphology:** Nonspecific, decreased platelets
  - **Bone marrow morphology:** Only indicated to rule out other causes of thrombocytopenia. Adequate or increased numbers of morphologically normal megakaryocytes

- **Blood work:**
  - No specific tests
  - Anti-platelet antibody testing – neither sensitive nor specific
  - Immunoassay for GP IIb/IIIa and GPIb – not specific, not routinely performed

- **Differential diagnosis:** ITP is a diagnosis of exclusion
  - Differential diagnosis includes:
    - Hypersplenism
    - Heparin induced thrombocytopenia, TTP, DIC
    - Congenital diseases: Wiskott-Aldrich syndrome, TAR syndrome
    - Myelodysplastic syndrome, acute myeloid leukemia

- **Treatment and Prognosis:** IVIG, steroid, splenectomy. Typically good prognosis

**Heparin-Induced Thrombocytopenia (HIT)**

Heparin therapy-induced thrombocytopenia is a life threatening disease caused by autoantibodies against PF4. The antibodies result in formation of immune complex of PF4 and heparin that binds to platelet Fc receptor causing platelet aggregation and thrombosis

- **Function of Heparin:** Binds and activates anti-thrombin III (AT-III)
- **Function of platelet factor 4 (PF4):** Cytokine stored in alpha-granules in platelets. Upon platelet activation, PF4 is released and binds to heparin and to luminal surface of endothelium. These functions enhance clot formation
- **Typical HIT:** Thrombocytopenia develops 5 to 10 days after receiving heparin and nadirs at 7 to 14 days.
- **Rapid HIT:** Re-exposure within 100 days to heparin may result in more rapid development of thrombocytopenia (within 24 hrs)
- **Delayed HIT:** Thrombocytopenia develops several days after cessation of heparin therapy, rare

- **Blood morphology:** Nonspecific, decreased platelets
- **Bone marrow morphology:** Normal, not indicated
- **Thrombectomy:** White clot
- **Blood work:**
4T score: Thrombocytopenia, Timing of platelet fall, Thrombosis, Other causes of thrombocytopenia

Serum PF4 antibody level: Screen test, positive if >0.4, sensitive but not specific
Serum serotonin release assay (SRA): Confirmative test

Differential diagnosis: Other types of thrombocytopenia

Treatment and Prognosis: 25%-50% mortality if untreated. Suspected patients should discontinue heparin. Treat with direct thrombin inhibitor (argatroban, bivalirudin)

Von Willebrand Disease (VWD)

Autosomal dominant (except type 2N which is recessive) disorders with quantitative or qualitative deficiency of von Willebrand factor (VWF) due to mutations in the VWF gene. Majority patients are inherited

Function of VWF: Synthesized in megakaryocytes and endothelial cells, forms large multimers before cleaved by ADAMTS13, secreted to blood and binds to Factor VIII

Type I: Quantitative deficiency of all molecular weight multimers
Type IIa: Quantitative deficiency of intermediate and high molecular weight multimers
Type IIb: Quantitative deficiency of high molecular weight multimers
Type III: Very low level of all multimers and factor VIII

Acquired type: Caused by auto-antibody to VWF in autoimmune disorders, lymphoma, myeloma, or in healthy individuals

Blood morphology: Nonspecific, decreased platelets
Bone marrow morphology: Normal, not indicated

Blood work:
- Bleeding time (obsolete), replaced by PFA-100 (screening tests)
- VWF antigen, FVIII activity, ristocetin cofactor activity
- Platelet aggregation test: Diagnose VWD and other platelet disorders
- Multimer analysis: Gel electrophoresis to diagnose subtypes of VWD

Treatment and Prognosis: Cryoprecipitate, DDAVP (desamino-D-vasopressin, induce endothelial cell release VWF from Weibel-Palade bodies). Intermediate or high purity VWF/FIIIV

Differential diagnosis: Other types of inherited platelet disorders:

Bernard-Soulier syndrome (BSS): Also known as “giant platelet syndrome”. Autosomal recessive disorder, caused by mutations in GPIba, GPIbb, or GPIX genes, mutated GPIb/IX protein complex affects binding to VWF, which affects clot formation

Glanzmann thrombasthenia (GT): Autosomal recessive disorder, defective GPIIb/IIIa protein complex on platelet surface that prevents attachment to fibrinogen, which in turn affects “bridging” between platelets and clot formation

Storage pool diseases (SPD): Autosomal dominant disorder, affects dense granules in platelets (alpha-SPD). Lack of ADP release from dense granules results in absence of secondary aggregation

Hemophilia

Hemophilia A
80-85% all hemophilia
X-linked recessive disorder affects male only. Caused by quantitative or qualitative deficiency of factor VIII resulting in inadequate formation of factor VIII/VWF complex, which in turn results in insufficient thrombin formation

>1000 different mutations identified in factor VIII gene, which spread throughout the gene
Clinical manifestation varies from mild to severe and depends on factor VIII activities. Common features include excessive bleeding after injury or surgery, subcutaneous hematoma, hematuria, deep muscle bleeding, hemarthrosis, intracranial bleeding.

**Blood morphology:** Nonspecific

**Bone marrow morphology:** Normal, not indicated

**Blood work:**
- Serum factor VIII level and activity

**Treatment and Prognosis:** Cryoprecipitate, F-VIII concentrates, recombinant F-VIII, DDAVP (desamino-D-vasopressin, induces endothelial cells to release Factor VIII and VWF from Weibel-Palade bodies)

**Hemophilia B (Christmas disease):**
X-linked recessive disorder affects male only. Caused by quantitative or qualitative deficiency of Factor IX due to mutations in F-IX gene. Clinical manifestation similar to Hemophilia A. Testing include serum F-IX level. Treatment includes recombinant F-IX, prothrombin complex concentrates, F-IX concentrates

**Differential diagnosis for hemophilia A and B:**
- **Von Willebrand disease (VWD):** F-VIII level is also decreased in VWD, can be differentiated by low VWF level and abnormal ristocetin cofactor activity
  - **Factor deficiency other than F-VIII and F-IX:** Increased bleeding tendency, can be tested by individual factor assay
  - **Factor inhibitors:** Increased bleeding tendency, can be tested by mixing study and factor inhibitor assay

**Antiphospholipid Antibody Syndrome**
A group of hypercoagulable disorders caused by autoantibodies against phospholipids on cell membrane

- **Lupus anticoagulant (LA):**
  - Autoantibodies against variable phospholipids that result in venous and/or arterial thrombosis
  - Associated with multiple conditions such as autoimmune disease, drugs, parasite infections, or healthy individuals
  - Clinical presentation is associated with thrombotic events: deep vein thrombosis, stroke, miscarriage

- **Blood morphology:** Nonspecific

- **Bone marrow morphology:** Not indicated

- **Blood work:**
  - **DRVVT (dilute Russel viper venom test):** Russel viper venom activates factor X through factor V, thus bypasses intrinsic and extrinsic pathways. Excess phospholipid is added to neutralize LA antibodies. Clotting time is compared with and without excess phospholipid
  - **Platelet neutralization procedure or hexagonal phase phospholipid test:** Since DRVVT is not 100% sensitive, a second test is needed to complement DRVVT

- **Anticardiolipin Antibody Syndrome:** Similar clinical presentation as LA. Antibodies can be detected by ELISA

- **Anti-beta2 glycoprotein antibodies:** Similar clinical presentation as LA. Antibodies can be detected by ELISA

**Differential diagnosis:**
- **Homocysteinemia:** Autosomal recessive, venous and arterial thrombosis
- **Protein C deficiency:** Autosomal dominant, venous thromboembolism
- **Protein S deficiency:** Autosomal dominant, venous and arterial thromboembolism
Activated protein C resistance (Factor V Leiden): Autosomal dominant, venous thromboembolism

Prothrombin gene mutation: Autosomal dominant, venous thromboembolism

Anti-thrombin deficiency: Autosomal dominant, venous thromboembolism, heparin resistance

**Treatment and Prognosis:** Anticoagulation therapy, steroids