Bleeding Disorders 1

- Hemostasis : blood vessel injury leads to
  - blood vessel constriction : reduced blood flow
  - platelet activation : formation of platelet plug
  - coagulation cascade (fibrin formation that strengthen the platelet plug)
- Common screening tests for coagulation
  - Platelet count and morphology
  - Bleeding time (plt count must be normal)
  - Partial Thromboplastin Time (aPTT, PTT)
  - Prothrombin Time (PT)
  - Thrombin time (TT)
- Specialized tests for coagulation
  - Factor XIIIA quantitative test
  - Clot retraction
  - Mixing studies
  - Factors assay
  - VW Factor quantitative assay
  - Platelet aggregation
- intrinsic and extrinsic pathways both activate the common pathway leading to formation of fibrin clot
- Partial thromboplastin time PTT assess the intrinsic pathway (factors 8-11)
- Prothrombin time PT assess the extrinsic pathway (factor 7)
- Thrombin time TT assess the common pathway (fibrinogen)
- Clinical Features of Bleeding Disorders
  - Platelet disorders :
    - Site of bleeding : Skin and Mucous membranes
    - Ecchymoses (bruises) : superficial
    - petechia : present
    - hemearthrosis (muscle bleeding) : absent
    - Bleeding after cuts & scratches : present
    - Bleeding after surgery or trauma : immediate
  - Coagulation factors disorders :
    - Site of bleeding : Deep in soft tissues (joints,m or muscles)
    - Ecchymoses (bruises) : hematomas (deep)
    - petechia : absent
    - hemearthrosis (muscle bleeding) : present
    - Bleeding after cuts & scratches : absent

        - Bleeding after surgery or trauma : delayed
- Coagulation factor disorders
    - Inherited
        - Hemophilia A and B
        - von Willebrands disease
    - Acquired
        - Liver disease
        - Vitamin K deficiency
        - warfarin overdose
        - DIC

Hemophilia A and B

- Hemophilia A had factor 8 deficiency and B has factor 9 deficiency
- both are x linked and hemophilia A is more common
- both have similar clinical mailestation which is bleeding specially hemearthrosis in a weight baring joint (knees) and mainly in the dominant side of the body manifested as repeated attacks with painful swelling
- Severity of bleeding is related to factor level
    - < 1% : Severe spontaneous bleeding
    - 1-5% : Moderate bleeding with mild injury
    - 5-25% : Mild bleeding with surgery or trauma
- associated with recurrent episodes of synovitis
- patients have prolonged PTT but normal PT and TT (since the issue is in the intrinsic pathway)
- platelet count is also normal with normal bleeding time
- Treatment
    - deficient factor supplement (8 or 9) : recombinant or plasma derived
        - since half life of factor 9 is longer than factor 8 we give factor 8 twice daily and 9 once daily
    - Analgesics
    - Evaluate for Synovectomy or Joint replacement
- The Factor 8 gene
    - found on Xq28
    - the most common mutation is intron 22 inversion found in hemophilia A resulting in dysfunctional factor 8
    - the second most common is missense

- Complications of therapy
  - Formation of inhibitors (antibodies)
  - Viral infections / Transmissible disease (Plasma Derived) : hepatitis B and C / HIV
- Novel therapies for patients that formed inhibitors : Emicizumab : Bispecific factor 10 and 9 directed antibody that bridges activated factor 9 and factor 10 in order to restore the function of missing activated factor 8 necessary for effective hemostasis
- Adjunctive Therapy
  - DDAVP (Stimate) can be used to increase Factor 8 levels or to aid in hemostasis in mild disease
  - Acts by releasing VWF from storage (Factor 8 is trafficked with VWF)
  - Tranexamic acid (Lysteda) can stabilize the fibrin clot

Von Willebrand Disease

- Symptoms
  - high bleeding time and everything else is normal
  - abnormal platelet aggregation
  - low VWF and low factor 8 concentration (PTT is slightly prolonged)
  - gingival bleeding and epistaxis (mucocutaneous bleeding)
  - prolonged bleeding from wounds
- this is the most common bleeding disorder
- Management
  - Cryoprecipitate
  - VWF concentrate and factor 8 concentrate
  - DDAVP
- Types
  - type 1 : partial quantitative deficiency (autosomal dominant)
  - type 2 : qualitative deficiency (reduced activity)
  - type 3 : total quantitative deficiency (autosomal recessive) most severe

Disseminated Intravascular Coagulation DIC

- Symptoms
  - petechias
  - schistocytosis
  - bleeding from puncture site
  - high reticulocyte count

    - high bilirubin
    - low platelet count (thrombocytopenia)
    - prolonged PT PTT TT
    - excess activation of fibrin leading to microvascular thrombi
    - positive D Dimer
- Common clinical conditions associated with DIC
    - Sepsis (most common)
    - Obstetrical complications (Amniotic fluid embolism and Abruptio placentae)
    - Trauma like Head injury
    - Malignancy
    - Vasculitis
    - Reaction to toxins like snake venom or drugs
    - Immunologic disorders and Transplant rejection
- DIC Mechanism
    - Intravascular deposition of fibrin
    - Depletion of platelets and coagulation factors - Bleeding
    - Thrombosis of small and midsize vessels with organ failure
- Treatment
    - Treat vigorously with IV antibiotics after blood, urine culture and septic work up
    - Hydrate and ensure adequate urine output
    - Replace missing clotting factors
    - Platelet replacement
    - fresh frozen plasma
    - Coagulation inhibitor concentrate ATIII

Bleeding Disorders 2

Glanzmann Thrombasthenia GT

- Symptoms
  - mucosal bleeding like gums, conjunctiva and epistaxis
  - skin bruises
  - heavy mensuration and GI bleeding
  - sometimes intracranial hemorrhage
  - microcytic anemia
  - normal platelet count, PT,PTT and TT
  - prolonged bleeding time
  - normal VWF
  - Clot retraction : Absent
- Fibrinogen does not bind to platelets
- Treatment
  - blood transfusion
  - tranexemic acid
  - platelet transfusion
  - recombinant factor 7 (novoseven)
- Platelet transfusions complications
  - Transfusion reactions
    - Higher incidence than in RBC transfusions
    - Bacterial contamination
  - Platelet transfusion refractoriness
    - Alloimmune destruction of platelets (HLA antigens)
    - Non immune refractoriness
    - Microangiopathic hemolytic anemia
    - Coagulopathy
    - Splenic sequestration
    - Fever and infection

Immune Thrombocytopenia ITP

- Symptoms
  - low platelet count with larger size
  - increased megakaryopoeisis
  - purpura
  - mucocutaneous bleeding specially on palate

    - no lymph node enlargement or splenomegaly
    - normal PT,PTT and TT
- more common in females
- associated with autoimmune diseases like thyroiditis and vitiligo
- Pathogenesis of ITP
    - Increased platelet destruction mediated by autoantibodies
    - Auto antibodies that react with major membrane glycoproteins
- treatment (not always indicated only when platelet count < 30K)
    - self limited in pediatrics
    - oral Prednisolone (steroids)
    - IV Igs
    - thrombopeitin agonists : Romiplostim and Eltrombopag

- Thrombocytopenias associated with shortened survival (increased destruction)
    - Immune mediated : Heparin induced and ITP and TTP
    - Non immune destruction : DIC and Sepsis, cancer or hospital associated thrombocytopenia
- Sites of bleeding in thrombocytopenia
    - Skin and mucous membranes
    - Petechiae
    - Ecchymosis
    - Hemorrhagic vesicles
    - Gingival bleeding and epistaxis
    - Menorrhagia
    - Gastrointestinal bleeding
    - Intracranial bleeding

Heparin Induced Thrombocytopenia

- Symptoms
    - drop in platelet count
    - skin inflammation and necrosis
    - slightly prolonged PTT
- the more molecular weight of heparin used the more risk of HIT
- develops within 14 days (rapid onset)
- No warfarin is given until substantial platelet count recovery

Thrombotic Thrombocytopenic Purpura

- associated with Microangiopathic Hemolytic Anemia
- Symptoms
  - low platelet count
  - fever
  - bruises and Ecchymosis
  - thrombotic events
  - polychromatic blood film with schistocytes
  - renal failure and strokes or seizures or brain edema
  - normal PT, PTT, TT and fibrinogen
  - associated with liver failure and ascites and edema
  - Bleeding from needle puncture sites
- It is an autoimmune disease against ADAM TS 13
- Treatment : Plasma exchange daily until recovery / Glucocorticoids / Rituximab
- it is a disorder of VWF Proteolysis
- A classic pentad of signs
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia
  - Neurologic dysfunction
  - Renal disease
  - Fever
- Strikes mainly young adult women