Coagulation Disorders

Basic Definitions

- Ecchymosis
  - Bruise
  - Most common complication during blood collection
  - Leakage of small amount of fluid around tissue
  - Prevented by direct pressure
- Syncope
  - Fainting
  - 2nd most common complication
- Hematoma
  - Leakage of large amount of fluid around puncture site
  - Swelling
- Petechiae
  - Small red spots
  - Pinpoint size
  - Indicate small amount of blood escape into epithelium
- Purpura
  - Purple skin discoloration
  - 1 cm or greater in diameter
  - seen with mucocutaneous bleeding
- Telangiectasia
  - Permanent dilation of small blood vessels
  - Focused red lesions in skin or mucous membrane
  - fragile
  - Telangiectasis
  - Cherry-red hemangiomas
  - Louis-Bar
- Angioma
  - tumor made up of blood vessels or lymph vessels
  - 2-6 mm
  - usually seen on trunk
- Hematuria
  - Blood in urine
- Epistaxis
  - Nose bleed

Hemorrhagic Coagulation Disorders

- Bleeding from multiple sites, recurring and spontaneous, or bleeding which requires intervention is evidence of a disorder or primary or secondary hemostasis

- Soft Tissue Hemorrhage: acquired or congenital plasma procoagulant deficiencies
    - Anatomic bleeding
    - Most are internal with few visible signs
- Hemarthroses: joint bleeds
    - Swelling and acute pain
    - Can cause permanent cartilage damage
- Mucocutaneous hemorrhage:
    - Purpura
    - Petechiae
    - Ecchymoses
    - Menorrhagia
    - Bleeding from gums
    - Epistaxis
    - Tends to be associated with:
        - thrombocytopenia
        - qualitative platelet disorders
        - vWD
        - scurvy
        - telangiectasia

Acquired Hemorrhagic Disorders

- Most are secondary to chronic disease

1. Trauma-Induced Coagulopathy
    - Accounts for most instances of fatal hemorrhage
    - Triggered by the combination of injury-related acute inflammation, hypothermia, acidosis and hypoperfusion (systemic shock)

    A. Massive Transfusion
        a. Massive hemorrhage defined as:
            i. Blood loss exceeding total blood volume within 24 hours
            ii. Loss of 50% of blood volume within a 3-hour period
            iii. Blood loss exceeding 150mL/min
            iv. Blood loss that necessitates plasma and platelet transfusion

    B. Plasma donation
        a. New term is FP-24, moving away from previous term of FFP

    C. Platelet Concentration
        a. Usually only when platelet count fall bellows 50,000/uL

    D. Concentrates

2. Liver Disease

- Produces nearly all plasma coagulation factors and regulatory proteins
- Causes of suppression
    - Hepatitis
    - Cirrhosis
    - Obstructive jaundice
    - Disorder of bilirubin metabolism
- Suppression of hepatocytes which will reduce concentrations or function of plasma coagulation factors to less than hemostatic levels (<40 units/dL)
- Affects production of vitamin K dependent factors (II, VII, IX, X, C, S, Z)
    - VII first to show decreased activity
        - ½ life = 6 hours
- *Declining factor V is specific marker of liver disease*
    - Differentiates vitamin K deficiency from liver disease (FV is not Vit. K Dependent)
- Decrease of fibrinogen < 100 mg/dL is a mark of liver failure
- Dysfibrinogenemia is seen in moderate liver disease
    - Prolonged PT and RT
- vWF, VIII, XIII can be normal or elevated
- *Thrombocytopenia occurs in 1/3 of the cases of liver disease*
- *Alcohol toxicity suppresses platelet production*

- <u>DIC in Liver Disease</u>
    - Significant complication of liver disease
    - *Decreased production of AT, protein C, or protein S and release of procoagulants*
    - Liver does not clear these procoagulants
    - Acute
        - PT, PTT, TT prolonged
        - Fibrinogen < 100 mg/dL
        - Increased FDPs
    - Chronic and compensated
        - Abnormal D-dimer
- <u>Laboratory Testing</u>
    - Factor V and VII assays
        - Differentiate vitamin K deficiency and liver disease
    - Confirmation of systemic fibrinolysis
        - Plasminogen deficiency
        - Increased D-dimer / FDPs
    - Reptilase time
        - Confirms dysfibrinogenemia (significantly prolonged)

3. Renal Failure and Hemorrhage

- Chronic renal failure associations
    - Platelet dysfunction
    - Mucocutaneous bleeding
    - Acute GI bleeding

        - Decreased PLT adhesion/aggregation
        - Decreased RBC mass and thrombocytopenia

- Hemostasis Activation Syndromes
    - Deposits fibrin into renal microvasculature which reduces glomerular filtration
        - DIC
        - HUS
        - TTP
    - Cause thrombocytopenia → bleeding
    - PT and PTT are expected to be normal
    - Bleeding time may be prolonged

- Nephrotic Syndrome
    - Increased glomerular permeability
    - Associations
        - Amyloidosis
        - Diabetic glomerulosclerosis
        - SLE
        - Glomerulonephritis
        - Renal vein thrombosis
    - LMW proteins and procoagulants found in urine
    - Coagulation factors II, VII, IX, X, XII, antithrombin and protein C been found in the urine

4. Vitamin K Deficiency

- γ-carboxylation cycle is interrupted
- Causes
    - Biliary duct obstruction
    - Fat malabsorption
    - Chronic diarrhea
    - Broad spectrum antibiotics that disrupt gut flora
- Hemorrhagic Disease of Newborn
    - Breast feeding prolongs deficiency
- Antagonists
    - Warfarin
    - Coumadin
    - Disrupt vitamin K epoxide reductase and quinone reductase reactions → release of dysfunctional *des-gamma-carboxyl prothrombin* (VII, IX, X, C, S)
        - These inactive forms are called PIVKA factors
            - *Proteins Induced by Vit. K Antagonists*
- Lab Findings
    - Prolonged PT
    - PTT can be normal or prolonged
    - Mixing study yields normal results
    - Decreased factor VII (followed by IX, X and II)

5. Acquired Anti-VIII Inhibitor and Hemophilia

- Anti-VIII is most common acquired autoantibody
    - Highest risk when > 60 years of age or women 2-5 months pregnant
- Lab findings in acquired hemophilia
    - Prolonged PTT w/likely normal PT, TT

    - Mixing study
        - Corrects on initial
        - Can be prolonged with incubation at 37 C
            - IgG isotype (time and temp dependent)
- Type I kinetics: linear in vitro neutralization over 1-2 hours
    - complete inactivation
- Type II kinetics: early rapid loss with residual activity
    - Intermediate equilibrium
- Quantified by Bethesda titer
- Treated with DDAVP or rFVIIIa

6. Acquired vWD

- Manifests w/moderate to severe mucocutaneous bleeding and no family history of bleeding
- Associations
    - Hypothyroidism
    - Lymphoproliferative or myeloproliferative disorders
    - Wilms tumor (nephroblastoma)
    - Congenital heart disease
    - HUS
    - Pesticide exposure
- Prolonged PTT is severe (↓VWF and FVIII)
- Diminished ristocetin cofactor/VWF activity/VWF antigen

<u>Congenital</u> Hemorrhagic Disorders

1. vWD
    - mucocutaneous bleeding disorder
    - caused by quantitative or qualitative abnormality of vWF
        - vWF basics
            - Main function is platelet adhesion to subendothelial collagen in high shear stress
            - Synthesized in ER and stored in weibel-palade bodies of endothelial cells and platelet α-granules
        - abnormality causes ↓ platelet adhesion impaired primary hemostasis
    - *most prevalent congenital bleeding disorder!*
    - normal plasma level 0.5 – 1 mg/dL
        - levels are normally lowest in O and highest in AB blood types
    - Domain A
        - binding site for GP Ib/V/IX and supports collagen receptor site
    - Domain C
        - provides a site that binds platelet receptor GPIIb/IIIa
    - Domain D
        - binds factor VIII

2. Hemophilia A (classic)
    - Congenital single factor deficiency marked by anatomic soft tissue bleeding
    - 85% of all hemophiliacs
    - Factor VIII deficiency
        - Factor VIII deteriorates ~5% per hour at RT in vitro

- X chromosome abnormality
- Male hemizygotes experience anatomic bleeding
    - Females are carriers
- All sons of hemophiliac men are normal if non-carrier mom
    - Daughters are carriers
- 30% arise from spontaneous germline mutations (no family history)
- Rare symptomatic females
    - True homozygosity or double heterozygosity
    - Extreme lyonization
        - Disproportional inactivation of X chromosome with normal gene
- Factor VIII inhibitor in about ~30% of sever hemophilia cases (3% in moderate cases)
- <u>Clinical manifestations</u>
    - Deep muscle and joint hemorrhage
    - Hematomas
    - Wound oozing
    - Bleeding into CNS, GI, kidneys
    - Inflammation with chronic joint bleeds
    - Cranial bleeds → neurological symptoms
- Severity is *inversely* proportional to factor VIII activity
    - <1% activity: severe
    - 1-5%: moderate
    - 5-40%: mild
        - hemorrhage follows significant trauma
- 70% cases treated before 1984 were HIV (+) or died from AIDS

- <u>Lab Findings</u>
    - Prolonged PTT
    - 90% of female carriers are detected using the ratio of factor VIII activity to vWF antigen (VWF unaffected by ↓ FVIII)
        - ratio below normal lower limit → carrier
    - If FVIII level is >30%, no inhibitor is likely
    - If FVIII level is <30%, mixing study is needed

        - Bethesda Assay (Nijmegen-Bethesda)
            - If inhibitor is suggested
            - Normal plasma providing 100 units/dL factor activity mixed at increasing dilutions (decreasing conc.) in a series of tubes with full-strength patient plasma
            - The FVIII assays are performed and the results of the dilutions are expressed as titer (BU)

3. Hemophilia B-Factor IX deficiency
    - Christmas disease
    - ~14% hemophilia
    - PTT prolonged
    - Inhibitors present in ~3%

4. Hemophilia C (Rosenthal Syndrome)
    - Factor IX Deficiency

5. Factor V deficiency
   - Prolonged bleeding
   - PT and PTT prolonged
   - DRVVT prolonged

6. Factor X deficiency
   - PT and PTT prolonged
   - DRVVT prolonged

7. Factor XIII deficiency
   - Weak clot; dissolves ~2 hours in 5 M urea
   - Normal PT, PTT, TT

Vascular Disorders

Hereditary Vascular Disorders

1. *Telangiectasis/Rendu-Weber-Osler syndrome*
   - *Thin walled blood vessels* with discontinuous endothelium
   - Inadequate smooth muscle and elastin
   - Telangiectasia on face, lips, tongue, nasal mucosa, fingers, toes, trunk
   - Lesions blanch with pressure
   - Manifests at puberty
   - *Epistaxis* is universal finding
   - Symptoms worsen with age
   - Normal bleeding time
   - Diagnosis: characteristic skin/mucous lesions

2. *Kasabach-Merritt/hemangioma thrombocytopenia*
   - Present at birth
   - Visceral or subcutaneous hemangiomas
     - May become engorged with blood
   - DIC
   - Microangiopathic hemolytic anemia

3. *Ehlers-Danlos*
   - Hyperextensible skin
   - Hypermobile joints
   - Joint laxity
   - Fragile tissues
   - Bleeding tendency
   - *Defects in collagen*
     - Structure
     - Production
     - Cross-linking
       → inadequate connective tissue
   - (+) tourniquet test and prolonged bleed time

Acquired Vascular Disorders

1. *Allergic Purpura/Henoch-Schonlein*
   - Characterized by skin rash and edema
   - Transient arthralgia
   - Nephritis
   - Abdominal pain
   - *Palpable purpura*
     - Feet
     - Elbows
     - Knees
     - Buttocks

    - Chest
- *Children* 2-7 years
    - Predominates in *boys*
- Sudden onset following *upper respiratory infection*
- Proteinuria and hematuria
- Elevated WBC and ESR
- Normal hemostasis testing

2. *Amyloidosis*
    - Deposition of abnormal quantities of amyloid in tissues
    - Clinical presentation
        - Purpura
        - Hemorrhage
        - Thrombosis

3. *Senile purpura*
    - Elderly males
    - Lack of collagen
    - Flat dark blotches

4. *Drug induced purpura*
    - Warfarin
    - Barbiturates
    - Diuretics
    - Sulfonamides
    - Iodides
    - Massive generalize petechial eruptions

Qualitative Platelet Disorders

Disorders of <u>Adhesion</u> Receptors

1. *Bernard Soulier*
    - *Giant platelets Syndrome*
    - Manifested in infancy or childhood
    - Characteristics
        - Ecchymoses
        - Epistaxis
        - Gingival bleeding
        - *Prolonged bleeding*
        - Thrombocytopenia
        - Decreased platelet survival
        - Inability to adhere to subendothelium
    - *GP Ib/IX/V is missing or dysfunctional (Autosomal recessive)*
        - Most frequently involves defect in Ib synthesis or expression
            - Contains binding sites for vWF and thrombin
        - In contrast to VWD, this abnormality cannot be corrected by the addition of normal plasma or cryoprecipitate (defect resides in the platelets)
    - No aggregation with ristocetin
        - Normal response to ADP, EPI, collagen, and arachidonic acid

2. Von Willebrand Disease
3. Acquired defects of platelet adhesion
- *Myeloproliferative and lymphoproliferative disorders*
- *Antiplatelet antibodies*
- *Cardiopulmonary bypass surgery*
- *Chronic Liver Disease*
- *Drug-induced membrane modification*

Disorders of Platelet <u>Aggregation</u>

1. *Glanzmann Thrombasthenia*
    - Heterozygotes are normal
    - Homozygotes
        - Severe bleeding problems
    - Neonatal or infancy
    - Manifestations
        - Epistaxis
        - Gingival bleeding
        - Disabling hemorrhage
        - Petechiae
        - Purpura
        - Menorrhagia
        - GI bleeding
        - Hematuria
    - *Deficiency or abnormality of GP IIb/IIIa* (no fibrinogen binding)
        - defect in platelet plug formation

- Lab findings
    - Normal platelet count and morphology
    - Markedly prolongs bleeding time
    - Lack of aggregation with all platelet activating agents
    - Ristocetin induced binding to vWF is normal

2. Hereditary afibrinogenemia

3. Acquired defects of platelet aggregation

- *acquired von Willebrand disease*
- *acquired uremia*

Disorders of Platelet <u>Secretion</u>

1. Storage Pool diseases

a. Dense Granule Deficiency

- Non-albinos
    - Normal levels of granules
    - Defect in ability to package → serotonin accumulation
- Albinism
    - Easy bruising
    - Mild bleeding
- Lack of aggregation caused by lack of ADP secretion
    - Hermansky-Pudlak
    - Chediak-Higashi
    - Wiskott Alderich
    - TAR (Thrombocytopenia with Absent Radii Syndrome)

b. *Alpha Granule Deficiency*

i. *Gray platelet syndrome*

- Mild bleeding tendency
- Prolonged bleeding time
- Moderate thrombocytopenia
- Fibrosis of marrow
- Large platelets

- ATP release in response to thrombin is reduced

2. Thromboxane Pathway Disorder

- Hereditary absence or abnormalities of components of thromboxane pathway
    - Series of phospholipases catalyze the release of arachidonic acid and other compounds from membrane phospholipids
    - Arichidonic acid is converted to intermediate prostaglandins by cyclooxygenase
    - Those intermediate prostaglandins are converted to thromboxane A_2 by thromboxane synthase
    - Thromboxane A_2 (with other compounds) mobilizes calcium from internal stores into the cytoplasm initiating events leading to secretion and aggregation of platelets
- Aspirin like defects

3. *Inherited disorders of receptors and signaling pathways*
    - Collagen Receptors defects (GP Ia/IIa or GP VI)
    - ADP Receptors defects ($P2X_1$, $P2Y_1$ and $P2Y_{12}$)
    - Epinephrine Receptor (α_2-adrenergic receptor) defects
    - Scott syndrome
        - Platelets do not transport phospholipids to outer membrane
        - Platelet plug is not stabilized due to lack of fibrin
    - Stromorken syndrome
        - Platelets always in activated state

Thrombocytopenia and Thrombocytosis (Quantitative)

Thrombocytopenia

- Platelet count < 100,000/uL (reference range 150,000 – 450,000/uL)
- Most common cause of clinically significant bleeding

- <u>Impaired/Decreased Production</u>
    - Megakaryocyte hypoplasia in BM
    - Congenital
        - Lack of adequate megakaryocytes or decreased thrombopoiesis
        - Fanconi anemia
            - pancytopenia
        - TAR syndrome
            - Rare autosomal recessive disorder
            - Neonatal thrombocytopenia (platelet count actually increases with age)
            - Hypoplasia of radial bones of forearms
            - Elevated WBC
        - Wiskott-Alderich
            - X linked
        - Bernard-Soulier
        - MYH9-Related Diseases (nonmuscle myosin heavy chain gene) –abnormal platelet size
            - May Hegglin anomaly
                - Autosomal dominant
                - Large platelets and thrombocytopenia (normal platelet activating agent responses)
                - Dohle-bodies in neutrophils
            - More rare: Sebastian syndrome, Fechtner syndrome and Epstein syndrome
        - Amegakaryocytic thrombocytopenia
            - autosomal recessive reflecting BM failure
            - Infants < 20,000 platelets at birth
            - Petichiae
            - Likely develop aplastic anemia before 1 year old
            - Reduced megakaryocyte progenitors and ↑ TPO (TPO receptor function is lost)
        - Neonatal Thrombocytopenia
            - Many types
            - Causes:
                - TORCH (**t**oxoplasmosis, **o**ther (*Treponema pallidum*, varicella-zoster virus, parvovirus B19), **r**ubella, **c**ytomegalovirus [CMV], **h**erpes)
                - Drug exposure in utero (sulfonamides)
                - Decrease or absence of megakaryocytes in neonates
    - Acquired
        - Drugs
            - Chemotherapeutic agents
            - Ethanol ingestion (months to years of excessive use)
            - Interferon therapy

- Ineffective thrombosis
    - Megaloblastic anemias
        - Thrombocytopenia caused by impaired DNA synthesis
        - Deformed megakaryocytes in BM
        - Large platelets in PB that have shortened survival time and abnormal function
- Viruses
- Bacteria
- Malignancy

- <u>Increased Platelet Destruction</u>

    - Immunologic responses
        - ITP
            - Idiopathic; no etiology
            - Acute
                - Children 2-5 years
                - Abrupt bruising, petechiae, mucosal bleeding
                - 1-3 weeks after infection (upper respiratory or GI virus)
                - self-limited
                - 3-4% considered severe with <10,000 platelets
                - binding of antibodies from previous infections to platelets
            - Chronic
                - Most prevalent in women 20-50 years
                - Mucocutaneous bleeding, menorrhagia, epistaxis, ecchymoses
                - Caused by autoantibodies attached to platelets→ shortened platelet lifespan
                - Increased platelet volume
            - Both chronic and acute will show abnormal platelet function test results
        - Drug induced
            - Quinidine/quinine/sulfonamide derivatives
                - Abrupt onset of bleeding symptoms
                - Drug combines with antibody and binds platelets by Fab regions
                - Fc regions of immunoglobulin still available to bind to Fc receptors of phagocytic cells
                - Platelet count drops rapidly and often may be <10,000/uL
            - Hapten- dependent
                - Drug combines with a carrier molecule (usually plasma protein) to then act as a complete antigen
                - Penicillin and penicillin derivatives
                - Platelet count rapidly declines and can be as low as <1,000/uL
            - Drug induced autoantibodies
                - Drugs stimulate formation of autoantibody that binds platelet in absence of drug
            - HIT (Heparin-induced thrombocytopenia)
                - Binding of therapeutic heparin to platelet factor 4 (PF4) or binding of PF4 to the platelet membrane causes conformational change in PF4
                - This creates exposed neoepitopes
                - The Fab portion of an IgG binds to the PF4 neoepitope
                - The Fc portion of the IgG binds with the platelet FcγIIa receptor, leading to platelet activation and aggregation

        - %-14 days after exposure to heparin, platelet counts rarely dip below 15,000/uL
            - Mild thrombocytopenia is more common
    - NAIT
        - Neonatal alloimmune thrombocytopenia
        - Mother lacks platelet specific antigen that fetus inherits from father
        - She makes antibodies to that fetal antigen
        - Scattered petechiae and purpuric hemorrhage soon after birth
    - Neonatal autoimmune
        - Passive transplacental transfer of antibodies from mother with ITP or systemic lupus erythematosus
    - PTP
        - Post transfusion purpura
        - Plasma from recipient contain alloantibodies to antigens on platelets of transfused product
        - Multiparous middle aged women

- Nonimmunologic Responses
    - Mechanical damage
        - platelet interaction to nonendothelial surfaces
    - Thrombocytopenia in pregnancy and preclampsia
    - Hemolytic Disease of the Newborn

    - TTP (Thrombotic Thrombocytopenic Purpura)
        - *Moschcowitz syndrome*
        - Microangiopathic hemolytic anemia
            - Thrombocytopenia
            - Neurologic abnormalities
            - Hemolysis usually sever (less than 10 mg/dL Hgb)
        - Directly related to accumulation of ultralarge von Willebrand factor (UL-VWF) multimers in the plasma
        - In normal plasma the UL-VWF multimers are rapidly cleaved into smaller VWF multimers by the VWF-cleaving protease ADAMTS13
        - Treatment: Therapeutic plasma exchange (TPE) with FFP
            - 1st: some of UL-VWF removed by apheresis
            - 2nd: plasma supplies the deficient ADAMTS13 protease
    - HUS (Hemolytic Uremic Syndrome)
        - Microangiopathic hemolytic anemia
        - more common than TTP
        - 90% of cases caused by *Shigella dysenteriae* serotypes or entrohemorrhagic *E. coli* OH serotypes (E. coli O157)
        - Toxins enter the bloodstream and attach to renal glomerular capillary endothelial cells
            - become damaged/swollen and release UL-VWF
            - can also be caused by certain drugs
        - Cardinal signs of HUS:
            - Hemolytic anemia, renal failure, and thrombocytopenia
            - Thrombocytopenia more mild in comparison to TTP

- DIC (Disseminated intravascular coagulation)
  - activation of coagulation cascade (many causes) resulting in a consumptive coagulopathy that entraps platelets in intravascular fibrin clots
  - similar to TTP including MAHA and deposition of thrombi in arterial circulation of most organs
  - DIC = red clots whereas TTP = white clots

  Acute DIC
  - Severe thrombocytopenia with decreased FV, FVIII and fibrinogen
  - D-dimer is positive

  Chronic DIC
  - clotting factors may be slightly reduced or normal and compensatory thrombocytopoiesis results in lower to normal platelet counts
  - D-dimer not usually elevated but can be slightly increased

- Purpura Fulminans
  - devastating thrombotic disorder (often acute and fatal)
  - mirror symptoms of DIC
  - can be presenting feature of acute sepsis from bacterial infection
    - inflammatory response where coagulation and complement pathways are on overdrive which leads to increased bleeding

Thrombocytosis

- Defined as abnormally high platelet count, typically >450,000/uL
- Reactive thrombocytosis used to describe elevation of platelet count secondary to inflammation
- Marked and persistent elevation in platelet count is hallmark of myeloproliferative disorders

- Reactive Thrombocytosis
    - Platelet counts between 450,000 to 800,000/uL with no change in platelet function

        - Reactive Thrombocytosis Associated with Hemorrhage or Surgery
            - Platelet count can be low for 2-6 days but rebounds to slightly elevated levels
            - Normal levels by 10-16 days after the blood loss
        - Postsplenectomy Thrombocytosis
            - Platelet count can exceed 1 million/uL
            - Spleen normally sequesters 1/3 of circulating platelets at any given time
        - Thrombocytosis Associated with Iron Deficiency Anemia
            - Believed iron plays a role in regulating thrombopoiesis
            - Platelet count as high as 2 million have been seen in IDA with return to normal when iron treatment is administered
        - Thrombocytosis Associated with Inflammation and Disease
            - Similar to elevation in C-reactive protein, fibrinogen and VWF and other acute phase reactants
            - *Kawasaki disease*
                - Disorder caused by inflammation of the walls of small and medium-sized arteries throughout the body
        - Exercise-Induced Thrombocytosis
        - Rebound Thrombocytosis

- Thrombocytosis Associated with Myeloproliferative Disorders
    - Common finding in four chronic myeloproliferative disorders including:
        - Polycythemia vera
        - Chronic myelogenous leukemia (CML)
        - Myelofibrosis with myeloid metaplasia (primary myelofibrosis)
        - Essential thrombocythemia (ET)
            - ET is a chronic myeloproliferative neoplasm
            - Most common cause of thrombocytosis when reactive thrombocytosis can be excluded
            - Platelets of 1 million/uL and proliferation of marrow megakaryocytes
            - Persistent elevation of platelet count is an absolute requirement for diagnosis
                - ET presents with hemorrhage, platelet dysfunction and thrombosis
                - Thrombosis in microvasculature or larger vasculature can occur
                - Lab Findings:
                    - Platelet size is heterogeneous and platelets may be notable clumped on smears
                    - Platelets may look agranular or hypogranular
                    - Giant or misshapen platelets is common finding
                    - Aggregation usually absent in response to EPI and ADP; Normal