NEONATAL PLATELETS AND COAGULATION

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DISCLOSURES

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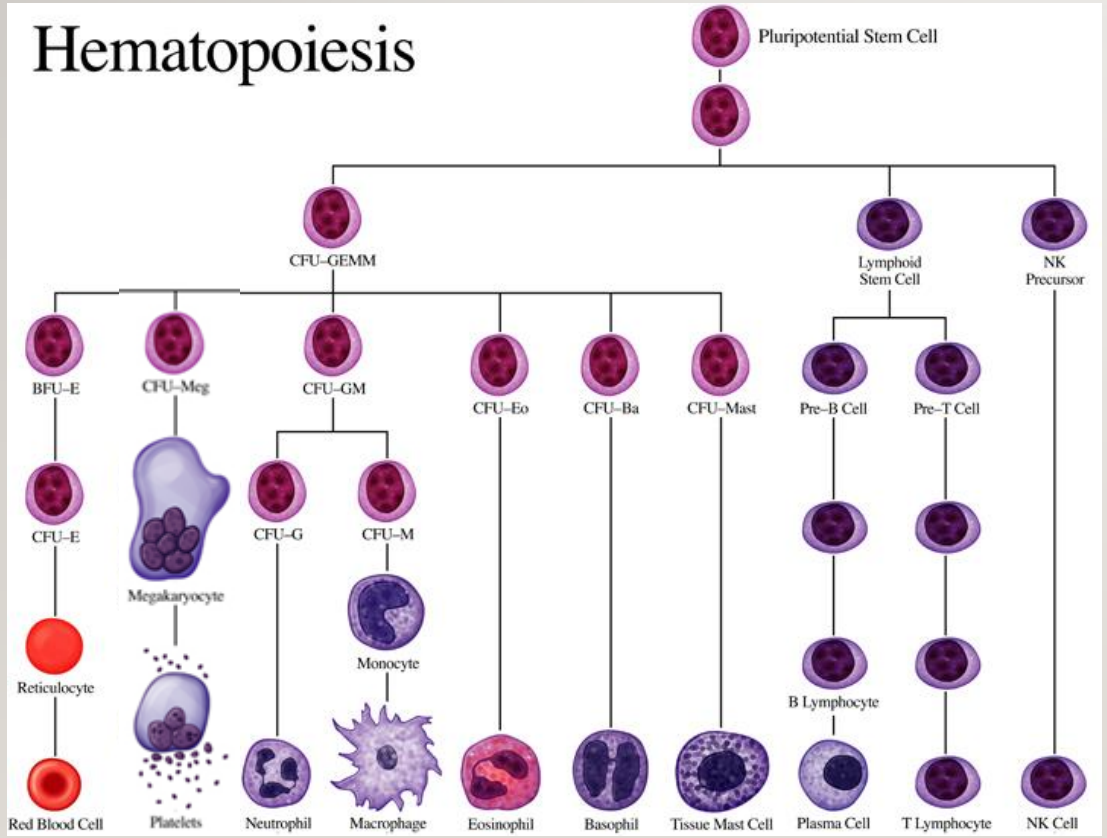
  - Takeda
  - Sanofi
  - Genentech
  - Amag
  - Sobi

GOALS AND OBJECTIVES

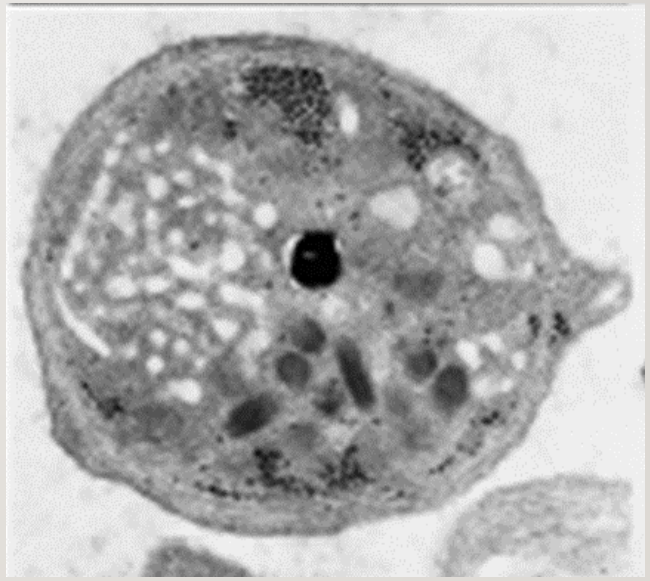
- Review normal development of platelets and the coagulation system
- Apply an approach to evaluating neonatal disorders of platelets and neonatal disorders of coagulation
- Determine the appropriate treatment for neonatal disorders of platelets and neonatal disorders of coagulation

NORMAL DEVELOPMENT OF PLATELETS



NORMAL PLATELET STRUCTURE

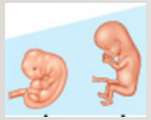
- Membrane
  - GP Ia-IIa
  - GP Ib
  - GP IIb-IIIa
- Alpha granules
  - VWF/Factor VIII
  - Fibrinogen
  - α2-antiplasmin
- Dense (δ) granules
  - ADP, ATP, serotonin, Ca, Mg



NORMAL PLATELET DEVELOPMENT

4 weeks

8-12 weeks



28-32 weeks

40 weeks

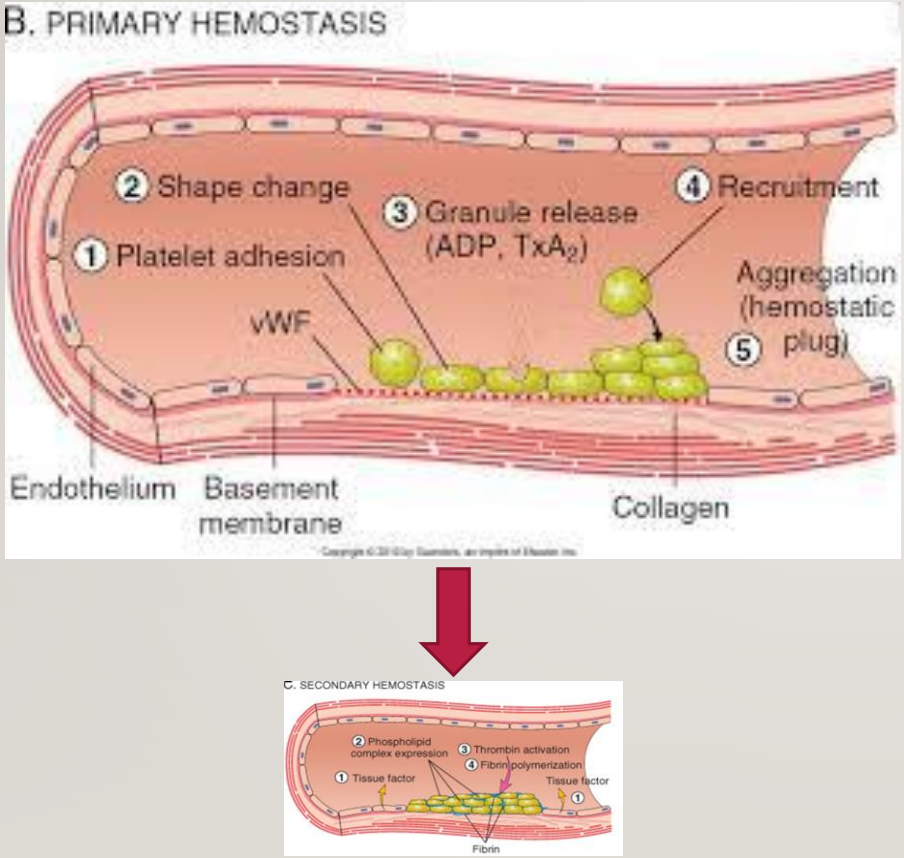
- Week 10
  - Megakaryocytes in liver and spleen.
- Week 11
  - Platelets are detectable
- Week 18
  - Normal range 150-450 X 10^9/L
- Week 30
  - Megakaryocytes in bone marrow
- Week 40
  - Rare megakaryocyte precursors found in peripheral blood
  - Diminishes rapidly in the neonatal period

Nathan and Oski's. Hematology of Infancy and Childhood.

PLATELET FUNCTION

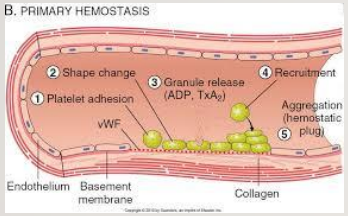
- NOT THE SAME as adults
- More function
  - Response to ristocetin
- Less Function
  - Response to ADP, epinephrine, collagen, and thrombin

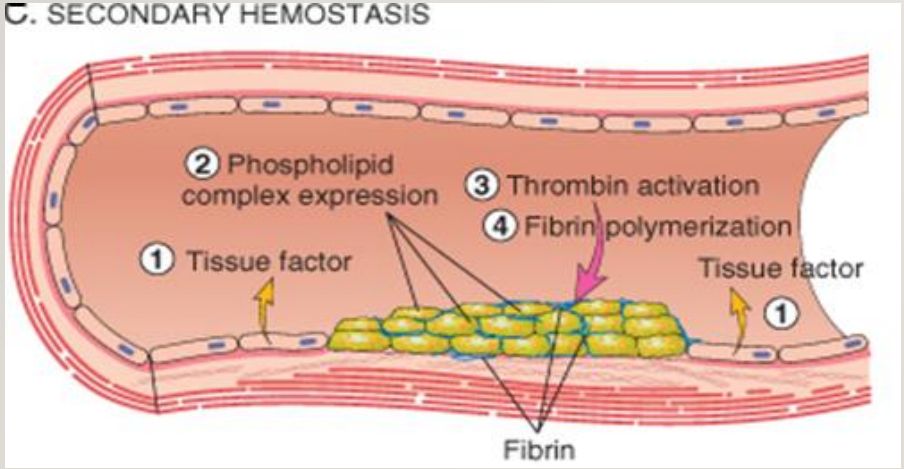
NORMAL HEMOSTASIS

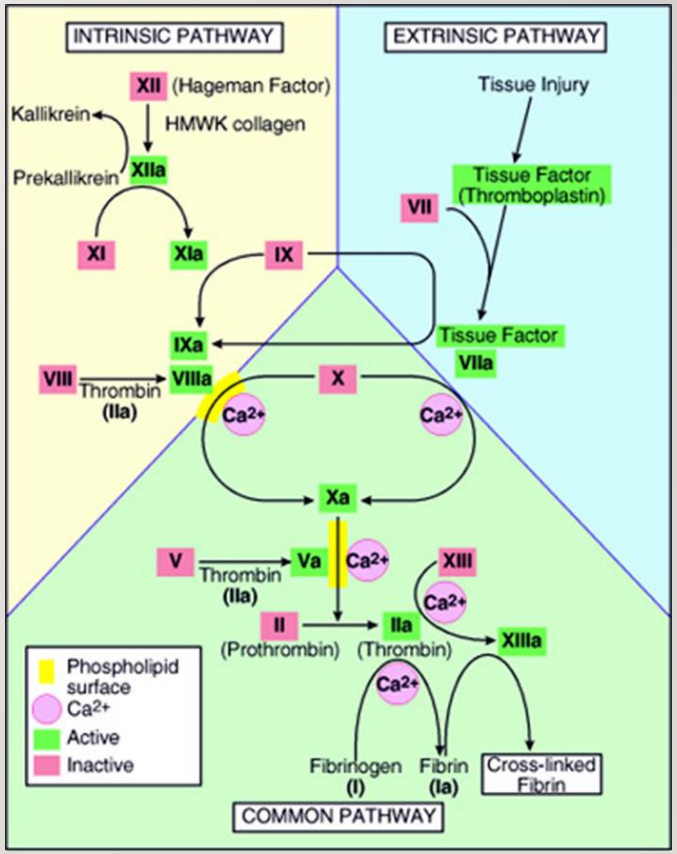


- The roles of platelets – Primary Hemostasis
  - Adhesion
  - Activation
  - Aggregation

NORMAL HEMOSTASIS COAGULATION



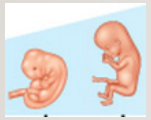




NORMAL DEVELOPMENT OF COAGULATION

4 weeks

8-12 weeks



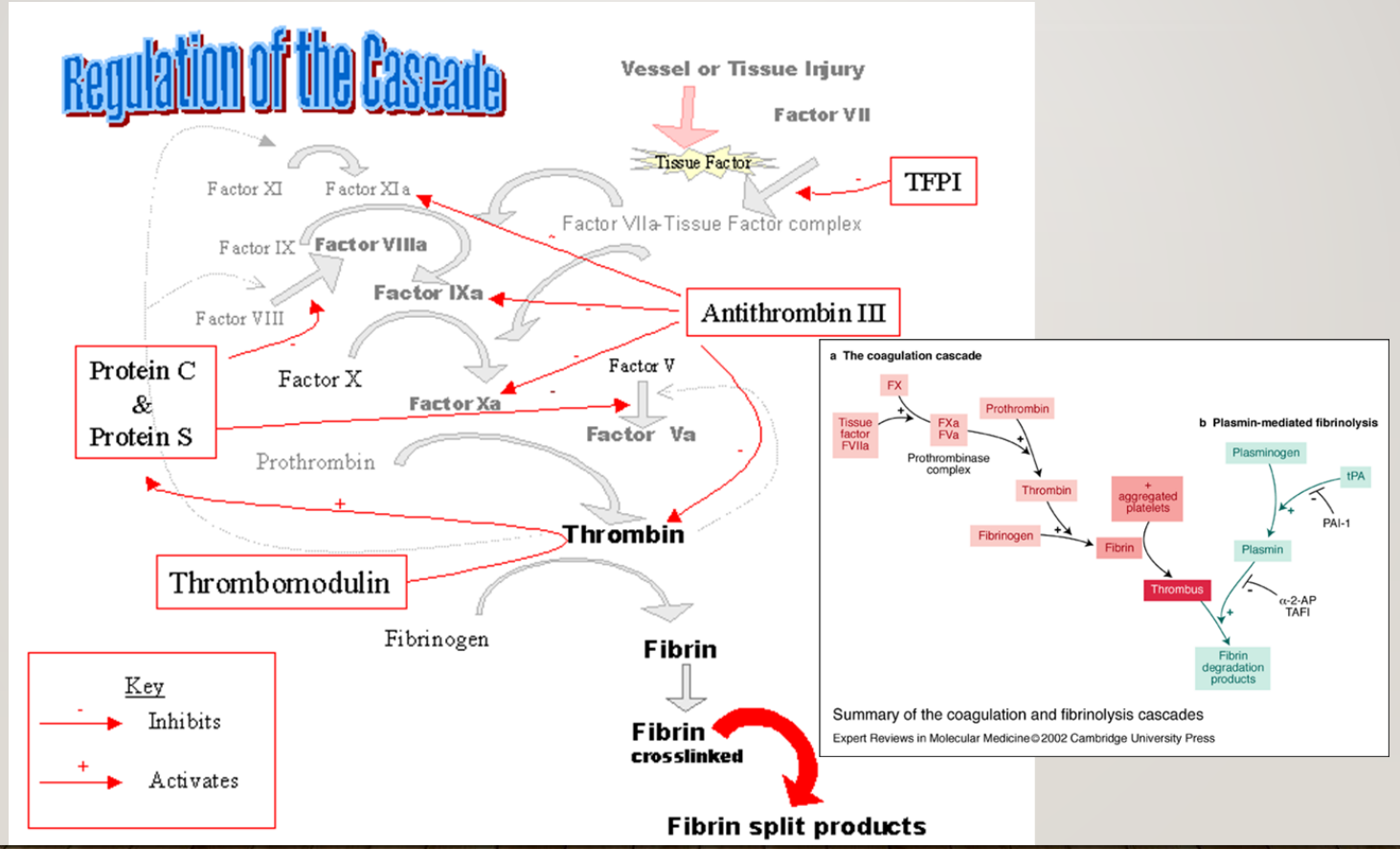
28-32 weeks

40 weeks

- 4 weeks
  - VW factor detectable in placenta and bone marrow
- 5 weeks
  - Factor I, VII, VIII, IX, X in hepatocytes
- 10 weeks
  - Detectable in circulation – 10-30%

- Factor I, V, VIII, XIII rise to adult norms by full term
- Other factors "normalize" by 6 months

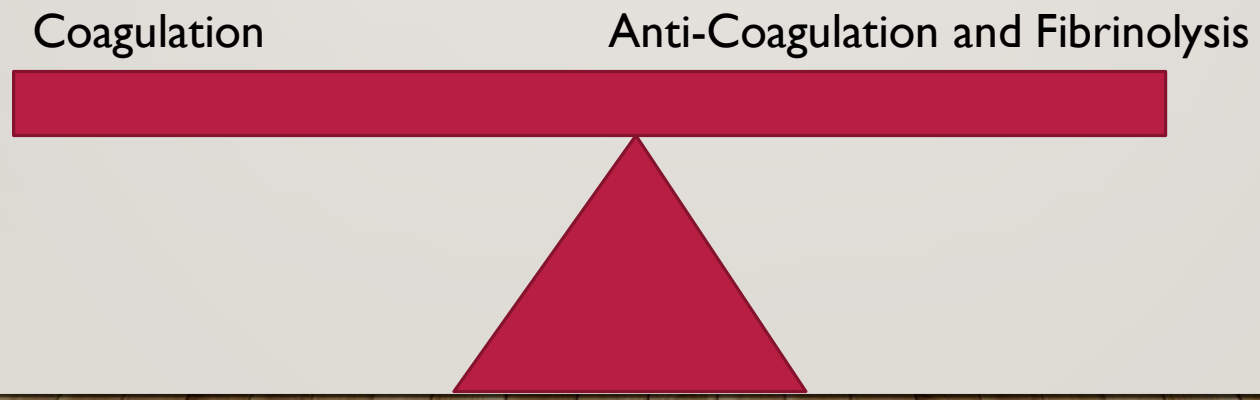
NORMAL HEMOSTASIS
ANTICOAGULATION AND THROMBOLYSIS



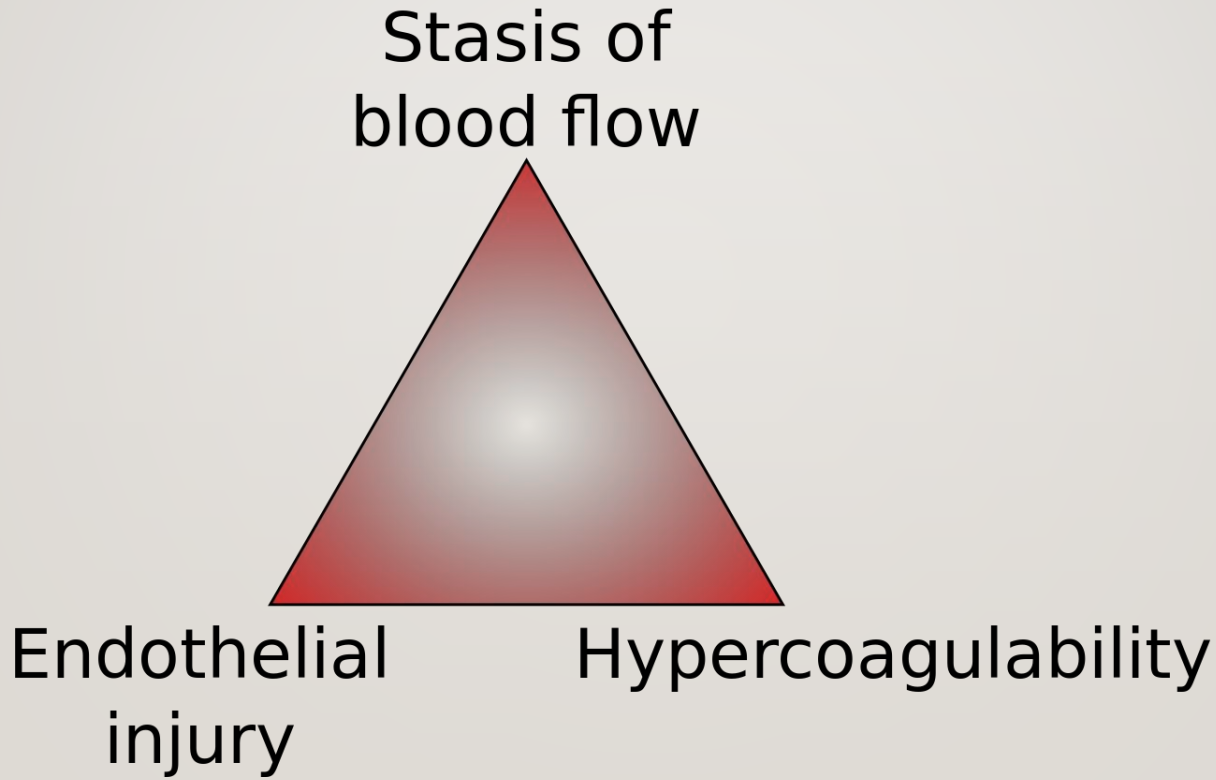
NORMAL ANTICOAGULATION AND FIBRINOLYSIS OF THE NEONATE

- Protein C (28%) is low through 6 months
- Protein S (50%) is low through 4 (free)-10 (total) months
- Antithrombin III (60%) through 3 months
- TFPI – 50%
- tPA is higher than adults
- Plasminogen – 50%
- D-dimers elevated at birth and normalize by 3 days

NORMAL HEMOSTASIS EQUILIBRIUM



NORMAL HEMOSTASIS THROMBOSIS AND VIRCHOW'S TRIAD



RECOGNIZING AND TREATING DISORDERS OF PLATELETS IN THE NEONATE

PLATELET DISORDERS

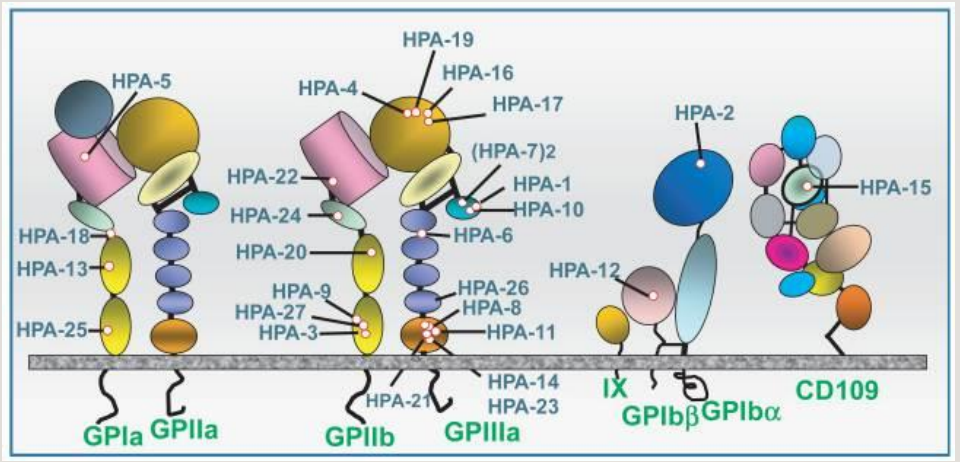
- Quantitative - Thrombocytopenia
  - Acquired
    - Immune related
    - Secondary
  - Hereditary
    - Microthrombocytopenia
    - Normothrombocytopenia
    - Macrothrombocytopenia
- Qualitative Platelet Dysfunctions

ACQUIRED THROMBOCYTOPENIA

- Mild/Mod (<150-50), Early Onset (<3 days), Well Appearing
  - Placental insufficiency (including Mat Htn, Gest Diabetes, IUGR)
  - More likely in preterm than term infants
  - Treatment: Bleeding unlikely and self resolves
- Late Onset
  - Most are caused by Sepsis and/or NEC

Chakravorty S, et al. Early Human Development, 2005.

ACQUIRED THROMBOCYTOPENIA



- Neonatal Alloimmune Thrombocytopenia
  - HPA (previously Pla) incompatibility
  - 2.5% of Caucasians are HPA1 negative
  - Treatment:
    - Platelet transfusion with HPA neg platelets <30K or actively bleeding
    - Consider IVIg or steroids

Peterson JA, et al. Br J Haematol, 2013.

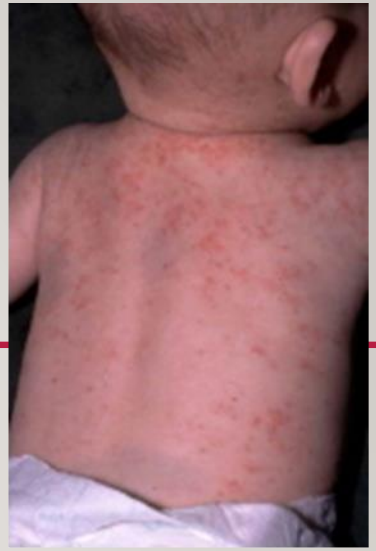
ACQUIRED THROMBOCYTOPENIA

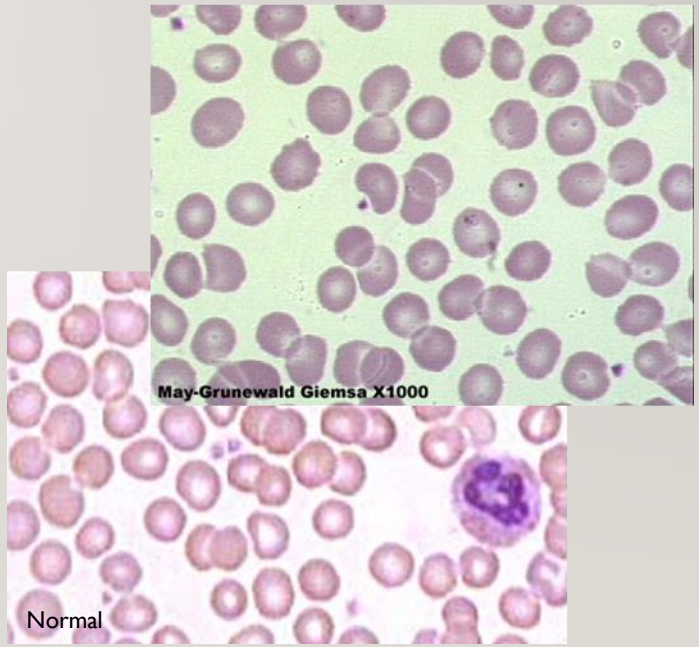
- Maternal ITP
  - Mother has ITP and these antibodies are transferred across the placenta
  - 6-10% infants have thrombocytopenia
  - ≤1% have intracranial hemorrhage
- Treatment:
  - IVIg if platelets <20K
  - Observation
  - Head ultrasound

Stavrou E and McCrae KR. Hematol Clin North Am. 2009.

WISKOTT ALDRICH SYNDROME (WAS)

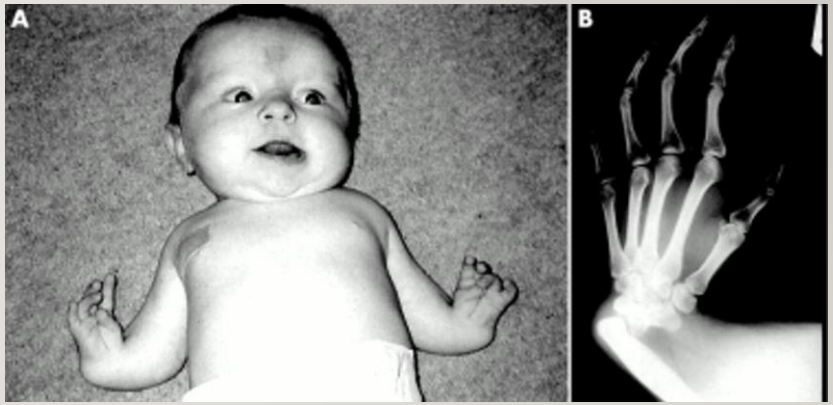
- Microthrombocytopenia
- Immunodeficiency
- Eczema
- Treatment
  - Supportive Care
  - Hematopoietic Stem Cell Transplant
- X-linked thrombocytopenia
  - Less severe mutation on WASP gene





THROMBOCYTOPENIA ABSENT RADII (TAR SYNDROME)

- Normothrombocytopenia, severe
- Autosomal Recessive
- Other anomalies may be present:
  - hip dislocation,
  - patellar dislocation
  - absent fibula
  - Milk allergy
  - GU malformations
  - Cardiac defects
- Treatment
  - Supportive care



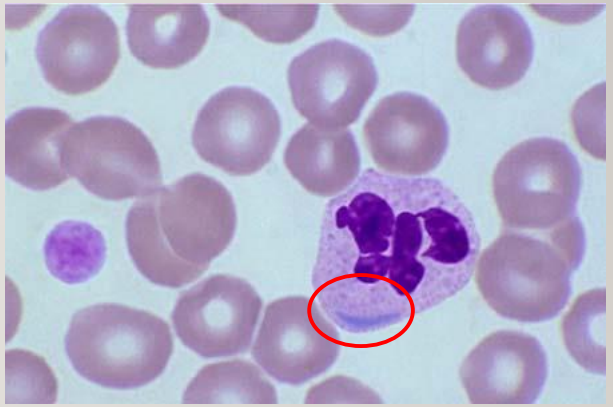
Greenhalgh KL, et al. J of Med Gen (2002)

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA (CAMT)

- Normothrombocytopenia
- Autosomal recessive mutation of c-MPL gene (TPO receptor)
- Progresses to aplastic anemia or transforms into MDS/AML
- Treatment:
  - Supportive care
  - Rapid hematopoietic stem cell transplant

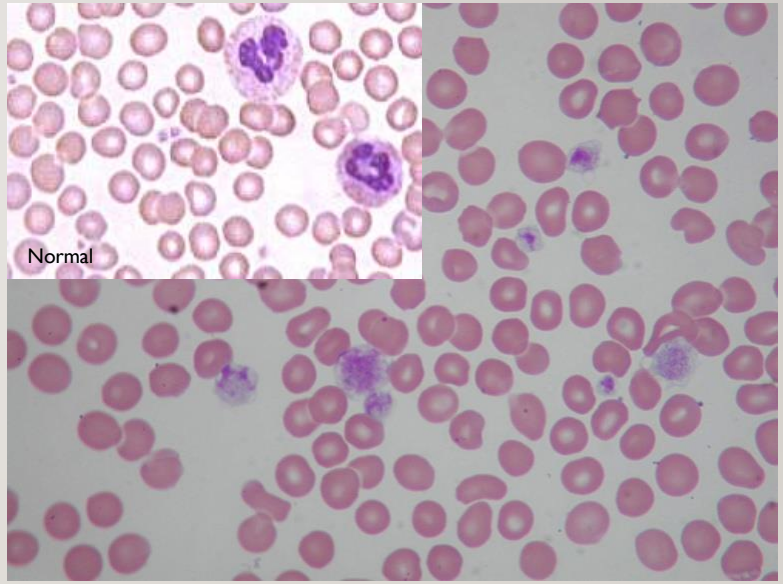
MYH9 RELATED DISORDERS (MAY-HEGGLIN)

- Macrothrombocytopenia
- Dohle Bodies
- Autosomal dominant
- Frequently misdiagnosed as chronic ITP



BERNARD SOULIER SYNDROME

- Macrothrombocytopenia
- Platelets lack GPIb function
- Platelet Glycoprotein Expression
- Responds to antifibrinolytic and DDAVP
- Frequent platelet transfusions can cause alloantibodies

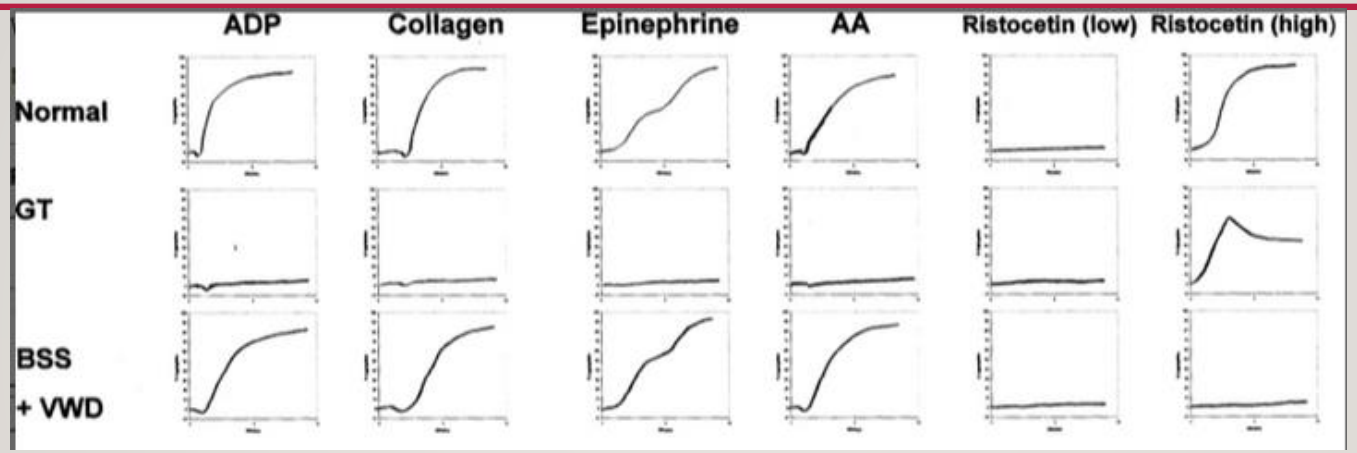


QUALITATIVE PLATELET DYSFUNCTIONS

- Unexplained bleeding with normal platelets
- Coagulation defect as well as platelet dysfunction should be suspected and investigated
  - Family history
  - Acquired factors (meds – indomethacin, heparin, aspirin)

Bolton-Maggs PHB, et al. Br J Haem. 2006.

GLANZMANN THROMBOSTHENIA

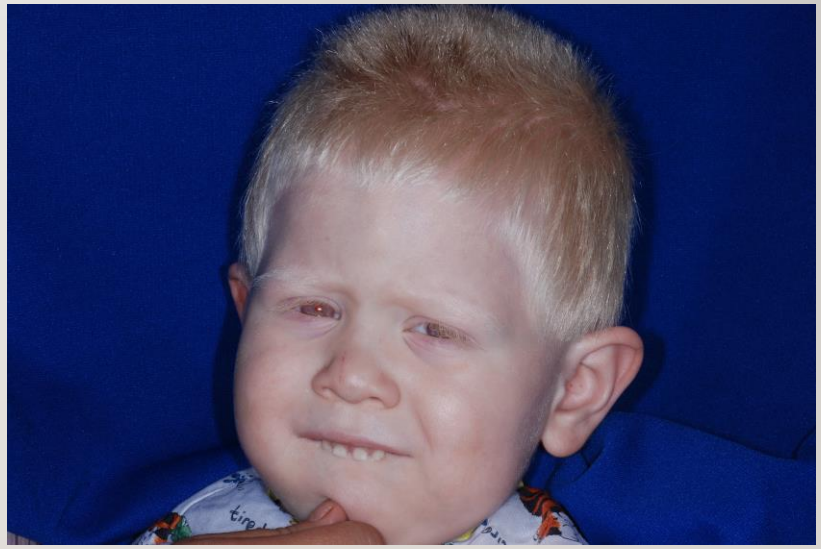


- Contrast with Bernard Soulier, platelet counts are normal
- Defect of GP IIb/IIIa
- Treatment:
  - In the neonate, bleeding may occur, but rarely is it severe
  - Bleeding responds to antifibrinolytic, DDAVP and FVIIa
  - Platelets may be used, but risk of platelet sensitization

Harrison P, et al. Br J Haem. 2011.

HERMANSKY-PUDLAK SYNDROME

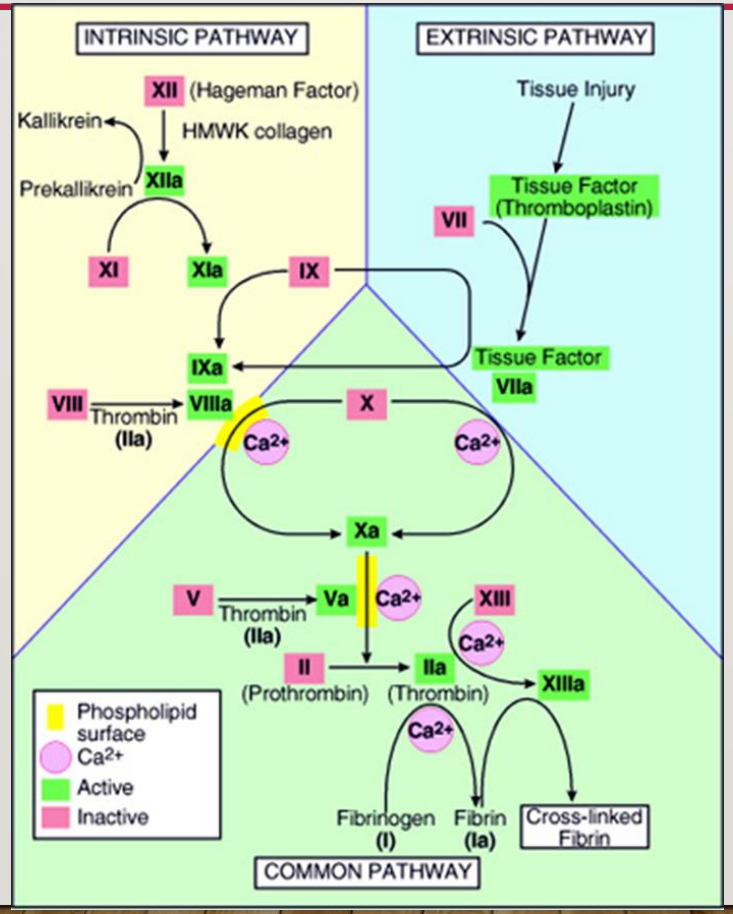
- Most common form of albinism in Puerto Rico
- Autosomal recessive
- oculocutaneous albinism
- mild/mod bleeding tendency
- Poor visual acuity/blindness
- Colitis, pulmonary fibrosis in 2nd-3rd decade
- Treatment: May respond to DDAVP, F VIIa, plasma, platelet transfusion



Asztalos ML, et al. Ped Dermatology 2017.

COAGULATION DISORDERS

HEMOPHILIA


INTRINSIC PATHWAY
EXTRINSIC PATHWAY
XII (Hageman Factor)
Kallikrein
HMWK collagen
Prekallikrein
XIIa
Tissue Injury
Tissue Factor (Thromboplastin)
VII
XI
XIa
IX
IXa
Tissue Factor
VIIa
VIII
Thrombin (IIa)
VIIIa
X
Ca2+
Ca2+
Xa
V
Thrombin (IIa)
Va
Ca2+
XIII
Ca2+
II
(Prothrombin)
IIa
(Thrombin)
XIIIa
Ca2+
Phospholipid surface
Ca2+
Active
Inactive
Fibrinogen (I)
Fibrin (Ia)
Cross-linked Fibrin
COMMON PATHWAY

HEMOPHILIA

- Maternal family history – cord blood sampling
- Signs and symptoms
- Long-term management principles
  - Severity
  - To prophy or not prophy
  - Minimize risk of inhibitors
  - The role of emicizumab

HEMOPHILIA

- Acute Management – Address the bleeding
  - Factor Replacement
    - FFP contains all coagulation factors
    - Cryo contains Factor VIII (lacks Factor IX)
      - VWF, Fibrinogen, Factor XIII
    - **Factor concentrates**
  - DDAVP (Desmopressin)
    - IV or sub-q, 0.3 mcg/kg. Repeatable after 24 hours.
    - Intranasal, not for children <2 yrs old.
  - Antifibrinolytic – mild or moderate bleeding
    - Aminocaproic acid, 50-100 mg/kg IV or PO every 6 hours
    - Tranexamic acid, 1,300 mg PO TID (>50 kg). IV requires bolus followed by continuous infusion

TREATMENT: MILD OR MODERATE BLEEDING

Type of Bleed	Hemophilia A	Hemophilia B
Epistaxis	Pressure Local Treatments (QR, packing) Antifibrinolytics, 20 U/kg Factor prn	Pressure Local Treatments (QR, packing) Antifibrinolytics 30 U/kg Factor prn
Mouth Bleeds, Teeth Extractions	20 U/kg Factor and antifibrinolytic	40 U/kg Factor and antifibrinolytic
Gross Hematuria	Bed rest 1.5X maintenance fluids 20 U/kg Factor if not controlled in 1-2 days Prednisone if HIV negative	Bed rest 1.5X maintenance fluids 30 U/kg Factor if not controlled in 1-2 days Prednisone if HIV negative

Adapted from Nathan and Oski's Hematology of Infancy and Childhood, 7th ed.

TREATMENT: MAJOR OR JOINT BLEEDS

Type of Bleed	Hemophilia A	Hemophilia B
Muscle or significant SQ hematoma	50 U/kg Factor, then 20 U/kg every other day until resolution	80 U/kg Factor then 40 U/kg every other day until resolution
Hemarthrosis	50 U/kg Factor initially, then 20 U/kg next day, then continue every other day until resolution	80 U/kg Factor initially, then 40 U/kg every other day until resolution
Iliopsoas Hemorrhage	50 U/kg Factor initially, then 25 U/kg BID until asymptomatic, then 20 U/kg every other day for 10-14 days total	80 U/kg Factor intially, then 20-40 U/kg every 12-24 hrs (to maintain levels >40%) until asymptomatic, then 30 U/kg every other day for 10-14 days total

VON WILLEBRAND DISEASE

- 3 functions:
  - Carrier protein for Factor VIII
  - Platelet adhesion in subendothelium
  - Platelet aggregation and recruitment
- Quantitative and Qualitative Defects
  - Type 1 Quantitative, relative deficiency
  - Type 2 Qualitative, varies because multiple functions
  - Type 3 Quantitative, absolute deficiency and severe

VON WILLEBRAND DISEASE

- Treatment
  - Factor Replacement
    - FFP contains all coagulation factors
    - Cryo contains Factor VIII, VWF, Fibrinogen, Factor XIII
    - Factor concentrates
  - DDAVP (Desmopressin), contraindicated in type 2b
    - IV or sub-q, 0.3 mcg/kg. Repeatable after 24 hours.
    - Intranasal, not for children <2 yrs old.
  - Antifibrinolytic – mild or moderate bleeding
    - Aminocaproic acid, 50-100 mg/kg IV or PO every 6 hours
    - Tranexamic acid, 1,300 mg PO TID (>50 kg). IV requires bolus followed by continuous infusion

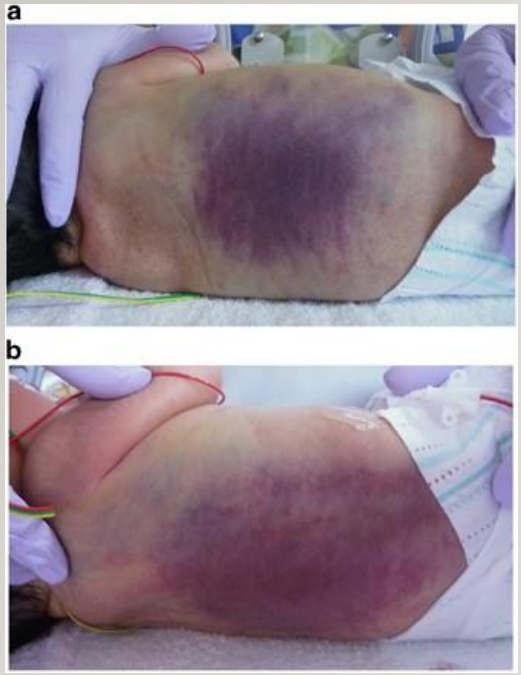
HYPOFIBRINOGENEMIA

- Autosomal inheritance
- Low fibrinogen levels = hypofibrinogenemia (heterozygotes)
- Absent fibrinogen levels = afibrinogenemia (homozygotes)
- Thrombin Time (TT) are characteristically prolonged, but in severe hypofibrinogenemia and afibrinogenemia, PT and aPTT may be prolonged as well
  - Reptilase time is similar to TT but unaffected by heparin
- Treated with cryoprecipitate, FFP, or Riastap ®, or Fibryga®

FACTOR XIII DEFICIENCY

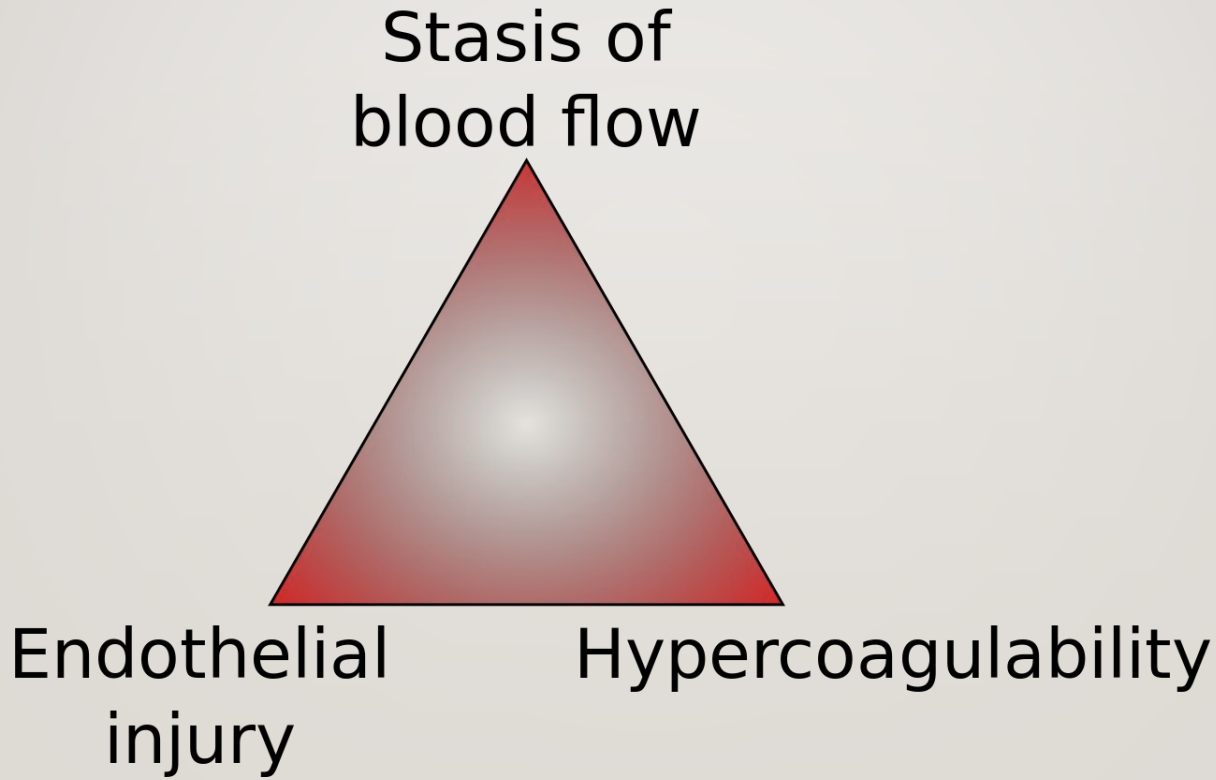
- Crosslinks fibrin clot to stabilize the clot at end of coagulation
- Autosomal recessive
- Presentations:
  - Delayed bleeding, intracranial hemorrhages, delayed separation of umbilical stump, delayed wound healing, recurrent pregnancy loss
- PT, aPTT, TT, Fibrinogen all normal
- 5M urea solubility test used for screening or quantitative Elisa testing
- FFP, cryoprecipitate, plama concentrate (Corifact ®), recombinant (Tretten®) are available

VITAMIN K DEFICIENCY BLEEDING OF THE NEWBORN (HEMORRHAGIC DISEASE OF THE NEWBORN)



- Hemorrhaging in an otherwise healthy infant
- Relatively greater deficiency of II, VII, IX, X compared to Prot C, Prot S
- Prophylaxis –
  - Vit K 0.5-1 mg IM or 2-4 mg PO
  - Takes 12-24 hours for correction
- Without prophylactic Vit K, 0.25-1.7% incidence
- Emergencies (ICH) should be treated with FFP or PCC (FEIBA or K-centra)

NEONATAL THROMBOSIS



DIAGNOSTIC APPROACH TO NEONATAL THROMBUS

- Symptomatic or Asymptomatic
- Provoked clots vs. Unprovoked clots
  - Sepsis
  - Lines
  - Injuries
- Imaging
- Laboratory evaluations – PT/INR, aPTT, CBC, CMP, D-dimers

VTE
ACUTE MANAGEMENT

- Unfractionated Heparin
  - Continuous infusion
    - Consider initial bolus of 80 units/kg (20-100)
    - Initial drip rate of 18 units/kg/hr (20-33)
    - Goal is to maintain aPTT approximately 2X normal or Xa level of 0.3-0.7
    - Reverse with protamine
  - Frequent monitoring with CBC (pre and daily), aPTT, Xa, and/or heparin levels
- Appropriate in unstable patients when rapid stoppage of the anticoagulant effect may be important, i.e. cardiac surgery patients

VTE
ACUTE MANAGEMENT

- LMW Heparin
  - Enoxaparin(Lovenox), 1.5 mg/kg SQ BID for neonates
  - Fondaparinux (Arixtra), 0.1 mg/kg once daily dosing
  - Dalteparin (Fragmin)
- Monitor with Factor Xa assay 4-6 hours after dosing to keep at 0.5-1
- Used for both acute and chronic management

VTE
ACUTE MANAGEMENT

- Symptomatic and provoked VTE
  - Delayed removal of lines
  - Anticoagulation for 6-12 weeks
- Unprovoked VTE
  - Anticoagulation for 12 weeks-6 months

VTE
LONG-TERM MANAGEMENT

- To test or not to test
- Strategizing the need for an anticoagulation plan

QUESTIONS?