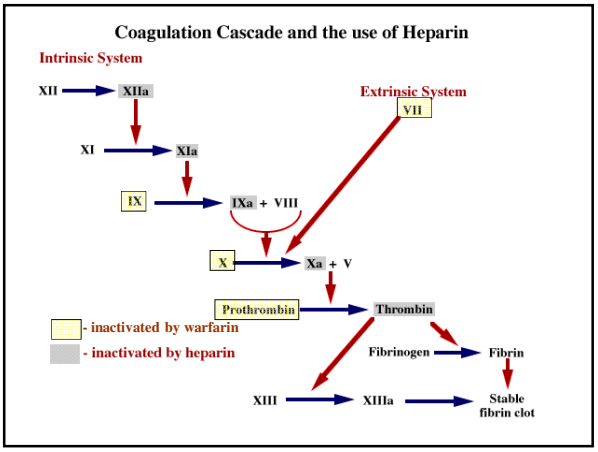
Bleeding and Clotting

Hemostasis

- Normal Hemostasis - Arrest of Bleeding
  - Platelets
  - Clotting/Coagulation Factors
  - Blood Vessels /Vasculature
- Control of Hemostatic Mechanisms
  - Properties of Normal Vascular Endothelium Prevent Clotting
    - Smooth Texture of Endothelial Lining
    - Negative Charge of Endothelial Wall Protein
  - Damage of Vascular Endothelium Destroys
  - Once Activated, Coagulation is controlled by anticoagulant substances, some are components in the Coagulation Cascade

Hemostasis

- Sequence of events
  - Vasoconstriction/Vasospasm
  - Platelet Plug
  - Activation of the Clotting Cascade
    - Intrinsic Pathway - Subendothelial exposure
    - Extrinsic Pathway - Tissue Thromboplastin
  - Final Common Pathway - final pathway of intrinsic/extrinsic pathway resulting in activation of Fibrinogen to form Fibrin
    - Controlled by antithrombin
  - Blood Clot Formation
  - Fibrinolysis (clot retraction and dissolution)
  - NOTE: If Blood Vessel Injury is Minor, Platelet Plugs may be sufficient to result in Hemostasis (without the clotting cascade)



Platelet Function

- Collagen-containing subendothelial tissue is exposed
- Platelets are attracted to the vessel injury site (15-20 seconds)
- Platelets begin to fill endothelial gaps
- Platelets Degranulate

Platelet Degranulation Products

- Serotonin and Histamine
  - Immediate Vasoconstriction
  - Promotes platelet degranulation
- **Thromboxane A2 (TXA2)****
  - Vasoconstriction
  - Promotes platelet degranulation
- **Adenosine Diphosphate (ADP)****
  - Stimulates Platelet Aggregation by causing their plasma membranes to be ruffly and sticky
  - Promotes nearby Platelets to degranulate
- Platelet Factor 3 - Stimulates Coagulation Cascades
- Platelet Factor 4 - Heparin Neutralizing Factor

Platelet Functions

- Adhesion (to collagen)
  - VonWillebrand Factor (a plasma protein)
  - ADP from platelets
- Platelet Activation
  - Changes in platelet shape and the formation of pseudopods
  - Activation of the Arachidonic Pathway
- Platelet Aggregation
  - Induced by the release of TXA2
  - Stabilizes the platelet plug
  - Activation of Clotting Cascade
  - Prostcyclin I2 (PGI2) from endothelial cells
    - Promotes Inflammation and Vasodilation
    - Inhibits additional Platelet Degranulation
  - Calcium Dependent

Platelet Function

- Clot retraction and Clot Dissolution
  - Contractile Elements of platelets join edges of injured vessel
- Clot Dissolution - regulated by thrombin plasminogen activators

Clotting Cascade

- Series of Enzymatic Reactions among the Clotting Factors (zymogens)
- Results in Fibrin - a meshwork of protein strands that stabilizes the platelet plug (binds to GP IIb/IIIa receptor on platelet)
- Intrinsic, Extrinsic, and Final Common Pathways – Plasma Proteins

Retraction and Lysis of Blood Clots

- Platelet Contraction and stabilization of the Fibrin threads
- Fibrinolytic System
  - Mediated by Plasmin - a proteolytic enzyme activated during coagulation or inflammation
  - Plasmin Splits Fibrin and Fibrinogen into Fibrin degredation Products (FDPs), which dissolve the clot

Coagulation Monitoring

- Platelet Count
- Partial Thromboplastin Time (PTT/APTT)
  - Measures activity of the Intrinsic and Final Common Pathways
  - Normal = ~30 seconds
- Prothrombin Time (PT)
  - Measures activity of the Extrinsic and Final Common Pathways
  - Normal = ~12 seconds
- International Normalized Ratio (INR)
  - Standardizes evaluation of extrinisic pathway
  - Normal = 1
- Others

Coagulopathies

Bleeding Disorders

- General Manifestations
  - Ecchymosis - Red and Purple/Black and Blue, skin discoloration caused by extravasation of blood into the subcutaneous tissue
    - Purpura - greater than 0.5 cm diameter
    - Petechiae - less than 0.5 cm diameter
  - Hemorrhage
    - Epistaxis = Nose Bleed
    - Hemoptysis = Cough up Blood
    - Hematemesis = Vomit Bright Red Blood
    - Coffee Ground Emesis = Vomit Digested Old Blood
    - Hematechezia = Bright Red Bloody Stools
    - Melena = Black Tarry Stools (digested blood)

Disorders of Platelets

- Quantitative
  - Too few platelets
- Qualitative
  - Platelets not formed correctly

Thrombocytopenia - Quantitative

- Platelet counts < 100,000/mm3
  - Magnitude
    - (i) <50,000/mm3 = Bleeding Potential
    - (ii) <20,000/mm3 = High risk for spontaneous bleeding
  - Causes
    - (i) Defective Platelet Production
    - (ii) Disordered Platelet Distribution
    - (iii) Accelerated Platelet Destruction

Thrombocytosis - Quantitative

- Platelet counts >400,000/mm3
- Primary Hemmorhagic Thrombocytosis
  - Disorder where Megakaryocytes in Bone Marrow Overproduce
- Secondary Thrombocytosis
  - Associated with splenectomy, cancer or arthritis

Qualitative Platelet Disorders

- Inherited
- Acquired - associated with drugs (aspirin) or other disorders (uremia)

Coagulation Disorders

- Caused by defects or deficiencies in one or more clotting factors
  - Vitamin K Deficiency
  - DIC
  - Liver disease
  - Thromboembolic Disease
  - Hemophilia

Vitamin K Deficiency

- Necessary for the production of Prothrombin, Factors II, VII, IX, & X
- Fat Soluble Vitamin
  - Green Leafy Vegetables
  - Resident Intestinal Bacteria
- Causes
  - Insufficient Dietary Intake
  - Absence of Bile Salts necessary for Vit K absorption
  - Intestinal Malabsorption Syndromes
  - Oral Antibiotics that Kill Resident Intestinal Bacteria
  - Neonates - Immature Liver and lack of normal intestinal flora

DIC

- Acquired coagulopathy in which clotting and hemmorhage occur within the vascular system; Caused by various clinical conditions that activate clotting mechanisms (infection, hemmorhage, shock)
  - Endothelial Damage
  - Release of Tissue Thromboplastin
  - Activation of Factor X
  - Pregnancey (pre-clampsia)
  - Septic Shock
- Widespread Clotting Occurs
  - Vascular Occlusion
  - Organ/tissue ischemia/infarction/necrosis
- Consumption of Platelets and Coagulation Factors results
  - Platelets and clotting factors are now deficient
  - Normal Fibrinolysis Occurs in all preestablished clots

DIC

- Manifestations
  - Bleeding
  - Platelet Count <100,000/mm3
  - Fibrinogen <300 mg/dl
  - Fibrin split product >40 mg/dl
  - INR increased
  - PTT >40 seconds
  - D-Dimer
    - Early indicator of DIC in Preeclampsia

DIC

- Treatment
  - Supportive care
    - ABC Management
    - Cardiopulmonary support
  - Treat underlying disorder
    - Example: Delivery in pregnancy related DIC
    - Example: Antibiotics in sepsis
  - Transfuse Blood Products as needed
    - Packed Red Blood Cells
    - Platelet transfusion for platelets <20,000 to 40,000
    - Fresh frozen plasma (preferred over cryoprecipitate)
    - Coagulation Factors
    - Fibrinogen
  - Heparin (controversial)

Thromboembolic Disease

- Thrombus - A stationary clot adhering to the vessel wall
- Embolus - A floating clot within the Blood
- Virchow's Triad - Factors favoring Clot Formation
  - Loss of integrity of vessel wall (atherosclerosis)
  - Abnormalities of blood flow (sluggish or turbulent blood flow)
  - Alterations in the blood constituents (thrombocytosis)

Thromboembolic Diseases

- MI
- CVA
- DVT
- PE
- AAA
- AF
- Hypercoagulable disorders

Thromboembolic Disease

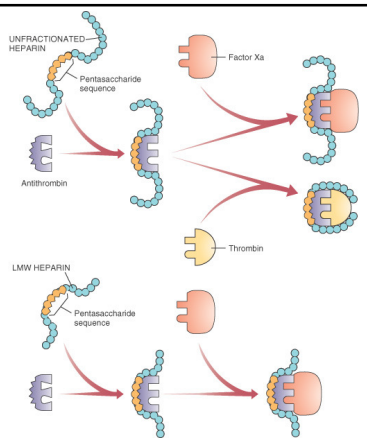
- Primary Therapy is Pharmacologic Anticoagulation
  - Anticoagulants – best against venous thrombi
  - Antiplatelet – best against
  - Thrombolytics – dissolve existing thrombi
- Prevention
  - Treat underlying disease
  - Maintain circulation: movement/exercise

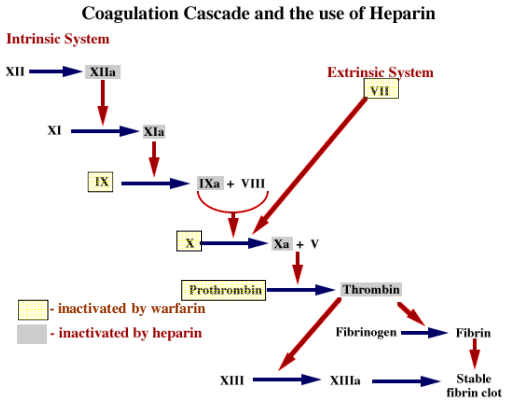
Anticoagulants

- Inhibit clotting factors
  - Intrinsic Pathway
    - Heparins
  - Extrinsic Pathway
    - Warfarin

Heparin

- Collection of substances that occur naturally in the body
- Available as
  - Unfractionated
  - Low molecular weight heparins (LMWH)
- Action
  - Enhances action of antithrombin
    - Unfractionated: inactivation of thrombin and factor Xa
    - LMW: inactivation of Factor Xa only





Unfractionated Heparin

- Pharmcokinetics
  - Absorption
    - PO: none
    - IV and SC only
    - Cannot cross BBB, placenta or milk ducts
  - Availability
    - Binds to plasma proteins, monos, endothelial cells
    - Available Levels vary wildly inter- and intra-patient
    - Requires careful monitoring.

Unfractionated Heparin

- Metabolism and Excretion
  - Hepatic metabolism and renal excretion
  - Half-life 1.5 hours
- Time Course of Effects
  - IV therapy starts with a bolus, then drip
  - Therapeutic action within seconds
  - If D/C'd effects fade rapidly

Unfractionated Heparin

- Uses
  - Pregnancy
  - PE
  - DVT
  - Evolving stroke
  - Open heart surgery
  - Dialysis
  - DIC
  - Acute MI (adjunct)

Unfractionated Heparin

- Adverse Effects
  - Bleeding
  - Heparin Induced Thrombocytopenia
    - Low Platelets
    - Increased Clotting
  - Hypersensitivity
  - Neurologic Injury with surgery
- Warnings: patients with high risk of bleed
- Contraindications:
  - Thrombocytopenia, uncontrolled bleeding, surgery of eye, brain, spinal cord, lumbar puncture, regional (spinal) anesthesia

Unfractionated Heparin

- Interactions
  - Antiplatelet drugs
  - Protamine Sulfate: Inactivates Heparin
- Lab monitoring
  - PTT (normal ~40 sec) therapeutic range 60-80
  - Monitor 4-6 hours until stable

Dosing

- Units NOT milligrams
- Different concentrations
  - Range from 1,000 – 40,000 unit/ml
  - An easy way to kill someone
- IV:
  - Intermittent: not common
  - Continuous: must be on a pump
- Subcutaneous
  - Apply pressure to site of injection for 2 minutes
  - High dose: not common
  - Low dose: usually 5000 units BID; PTT monitoring usually not necessary

Low Molecular Weight Heparins

- As effective as unfractionated Heparin
- Do not bind to monos and proteins
- Longer half-life
- No need to monitor PTT
- Subcutaneous only administration
- Adverse events
  - Bleeding
  - Thrombocytopenia – incidence 10x lower
  - Neurologic injury

LMW Heparins

- Enoxaparin (Lovenox)
- Dalteparin (Fragmin)
- Tinzaprin (Innohep)

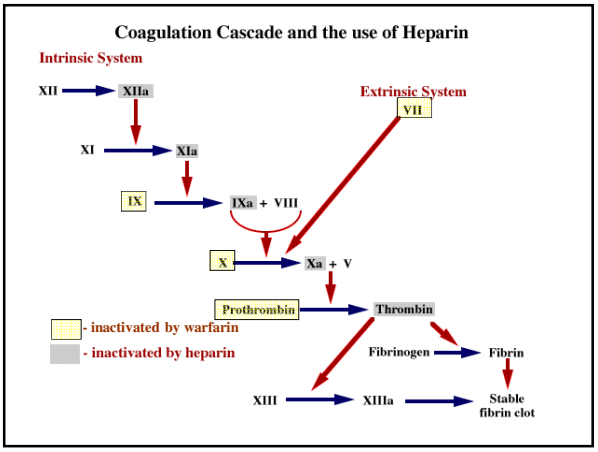
- Weighted dosing: based on weight of the patient. Ensure patient's weight is up to date.

Other Parenteral Anticoagulants

- Heparin-like
  - Fondaparinux
  - Danaparoid
- Direct Thrombin Inhibitors
  - Bivalirudin
  - Lepirudin
  - Argatroban

Oral Anticoagulants

- Warfarin (Coumadin)
  - Rat poison
- Anisindione – rare in the U.S.



Warfarin

- Suppresses extrinsic pathway
- Antagonizes vitamin K, inhibiting synthesis of Factors 7, 9, 10, and prothrombin)
- Absorbs easily in stomach
- 99% of warfarin in blood is bound to protein
- Readily crosses placenta and milk ducts
- Hepatic metabolism and renal excretion

Warfarin

- Inhibits factor synthesis quickly
- But has no effect on existing factor
- Takes 2 to 5 days before therapeutic effect is seen
  - Need to cover the interim with a parenteral anticoagulant
  - The "Comedy of Errors"
- Interacts with everything including the kitchen sink

Warfarin

- Indications
  - Prevent DVT and PE
  - Prevention of thrombus in mechanical heart valves
  - Prevention of thrombus is AF
- Off label
  - Reduce TIAs
  - Reduce Recurrent MI (non emergent)

Monitoring

- PT and INR
  - Therapeutic INRs range from 2 – 4.5
- Monitor
  - Daily for first 5 days of therapy
  - Twice a week for the next two weeks
  - Once a week for the next 2 months
  - Every 2-4 weeks after that
  - Any time a drug that interacts is added or removed
- Heparin can interfere with PT times

Adverse Events

- Bleeding
  - Wear Medic Alert bracelet
  - Inform dentists and surgeons of warfarin use **before** arriving
- Fetal Hemorrhage, and Teratogenesis
- Breast milk

Drug Interactions

- More than any other drug
- Patients absolutely must avoid all drugs not prescribed by their nurse practitioner including OTCs including
  - Aspirin, Ibuprofen
  - Acetaminophen
  - Monistat
- Vitamin K_1 reverses action

Antiplatelet Drugs

- Better for arterial thrombi
- Groups
  - Aspirin
  - ADP receptor antagonists
  - GP IIb/IIIa antagonists

Aspirin

- Irreversibly inhibits Platelet COX-1
  - Small amounts only
  - Larger amounts decrease prostacyclin and push toward COX-2
- 5 year bleeding risk
  - GI: 2-4/1000 patients treated
  - Hemorrhagic stroke 0-2/1000 patients treated
  - Buffered or enteric coated does not reduce risk
- Use low dose 81mg/day for prophylaxis
- Use medium dose 162-325mg/day for acute MI

ADP Antagonists

- Irreversibly inhibit platelet ADP receptors
  - Inhibit aggregation
- Agents:
  - Ticlopidine (Ticlid) – Stroke prophylaxis
  - Clopidogrel (Plavix) – MI and Stroke
- Adverse effects
  - Bleeding
  - Netropenia/Agranulocytosis
  - Thrombotic Thrombocytopenic Purpura

GP IIb/IIIa Antagonists

- Revolutionized treatment of acute MI
- Three agents
  - All given IV
  - Usually in combination with ASA and heparin
  - Acute coronary syndrome
    - Unstable angina and non-Q wave MI
    - Percutaneous Coronary Interventions

GP IIb/IIIa Antagonists

- Abciximab (ReoPro)
- Eptifibatide (Integrillin)
- Tirofiban (Aggrastat)

- Adverse events
  - Bleeding
  - Especially from PCI or IV site

Other Antiplatelet Drugs

- Dipyramidole – heart valve surgery
- Dypyramidole with ASA (Aggrenox) –TIA
- Cilostazol – also a vasodilator; use for intermittent claudication

Thrombolytics

- Anticoagulants prevent new thrombi and prevent enlargement of existing
  - Do not actually break down existing clots
- Thrombolytics
  - Break down existing clots
  - Also called fibrinolytics or "clot busters"
  - Extreme risk of bleeding
  - Only used for life threatening illnesses

Thrombolytics

- Streptokinase
- Tenecteplase (tPA)