Pulmonary Embolism & Deep Vein Thrombosis

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Definitions
- **DVT** - blood clot in venous circulation composed of erythrocytes, leukocytes, fibrin
  - Primarily in the proximal large veins of lower extremities/thighs, calf veins (primarily), or knee veins or in venous segments exposed to direct trauma
  - 20% of calf vein thrombi extend into proximal venous system
- **PE** - thrombus from the venous system that lodges in the pulmonary vasculature
  - Majority from proximal leg veins
  - Less commonly from deep pelvic or renal veins, IVC, the right heart or axillary veins

Epidemiology
- Annual incidence 48 per 100,000 for DVT and 69 per 100,000 for PE (with or without DVT)
- 600,000 patients in US have venous thromboembolism annually; up to 200,000 die from PE
- More common in men than women
- Increases with age

Virchow’s Triad
- **Stasis**
  - Decreased or abnormal blood flow
  - Pooling of blood in venous sinuses or valve cusps
  - Concentration of activated clotting factors
- **Vascular Wall Injury/Endothelial Damage**
  - Mechanical trauma or chemical trauma
  - Inflammatory response (phlebitis)
  - Increased ADP -> platelet adhesion and release of collagen -> activation and aggregation of platelets -> increased coagulation and formation of intraluminal thrombus
- **Hypercoagulability**
  - Imbalance between clotting and fibrinolytic systems
  - Inherited conditions- APC resistance, ATIII, Protein C or S deficiencies, anti-phospholipid antibody syndrome, Lupus anticoagulant
  - Acquired: Estrogen therapy, certain malignancies
Risk Factors

- Prolonged immobility
- Trauma (lower limb)
- Surgery (ortho)
- AMI
- Estrogen, BCPs
- Pregnancy, postpartum
- Coagulation Disorders
- Advanced Age
- Previous DVT
- Comorbidities-CHF, Stroke
- Smoking
- Obesity
- Prosthetic Heart Valves
- Malignancies

Clinical Presentation

- **DVT**
  - Unilateral pain/tenderness, discoloration/cyanosis
  - Swelling, edema, palpable cord, warmth
  - Homan's sign
  - 75% with clinically suspected DVT do not have clot
- **PE**
  - Dyspnea*, tachypnea*, pleuritic chest pain*
  - Tachycardia, hemoptysis, cough
  - Apprehension, fever
  - Pleural effusions, widened P(A-a)O2 gradient
  - Massive- hypoxemia, right ventricular failure

Differential Diagnosis

- **DVT**
  - Muscle strain/trauma
  - Arterial insufficiency, varicose veins
  - Postphlebitic syndrome
  - Lymphedema
- **PE**
  - Pneumonia, bronchitis, CHF, atelectasis
  - Pneumothorax, pulmonary edema, pericarditis, AMI
Diagnosis: DVT
- Ultrasonography-Doppler, Real-time B-Mode, Duplex
  - Extremely sensitive for proximal vein thrombosis, less so for calf or non-occlusive thrombosis
  - Serial testing over 10-14 days if non-diagnostic lung scan for PE and adequate cardiopulmonary reserve
- Impedance Plethysmography
  - Measures obstruction in venous outflow after deflation of a pneumatic thigh cuff
  - Sensitive and specific for proximal not calf or non-occlusive DVT; false + if disorders in flow
  - Inferior to doppler
- Venography
  - Gold standard - most sensitive and specific
  - Invasive, S, risk of hypersensitivity reactions and nephrotoxicity due to radiocontrast dye
- D-Dimer
  - Degradation product of fibrin from clot dissolution
  - If a sensitive assay is used - elevated levels are highly sensitive but low specificity for DVT/PE (most useful for negative predictive value)
  - May be beneficial in combination with noninvasive testing

Diagnosis: PE
- Clinical Suspicion
- Ventilation/Perfusion (V/Q) Scan
  - Main screening test
  - Estimates probability of PE based upon patterns of inhaled and injected radioactive dyes
  - High probability - reliable confirmation
  - Intermediate or low probability - further testing may be necessary
  - Normal V/Q - excludes PE
- Pulmonary Angiography
  - Invasive, risks
  - Reserved for patients with poor cardiorespiratory reserve
  - Confirmatory test
- Spiral Computed Tomography (CT)
  - Increased vascular contrast and visualization of filling defects
  - Sensitivity 96-100%, specificity 96%
  - Availability in hospital settings may be limited

Treatment Goals: Venous Thrombosis
- Prevent development of PE
- Reduce mortality and morbidity of PE
  - 80% of deaths from PE within 2 hours of symptoms
- Reduce morbidity from DVT
  - Significant recurrence in < 5% proximal DVT during 5-7 days of heparin and in 2% during 3 months of warfarin
- Achieve above with minimal ADRs and costs (direct and indirect)

Postphlebitic Syndrome
- Incidence 22.8% after 2 yrs, 28% after 5 yrs, and 29.1% after 8 yrs
- Venous valve destruction by clots causes venous hypertension and direction of blood from deep venous system into superficial system → edema and impaired viability of tissue → venous ulceration
- Symptoms of calf pain, pigmentation and induration of ankle and lower leg areas, and ulceration
Post Thrombotic Syndrome

Treatment: Unfractionated Heparin (UH)

- **Mechanism of Action**
  - Binds and catalyzes ATIII accelerating the neutralization of IX, X, XI, XII, plasmin, kallikrein, and thrombin
  - Prevents the further growth of the thrombus

- **Dose**
  - LD 75-100 (80) U/kg then 15-25 (18) U/kg/hr IV infusion adjusted to goal aPTT 1.5-2.5 times control (institution specific range must correspond to specific UH conc)
  - Alternative- Adjusted-dose SQ (17,500 U SQ BID) to aPTT 1.5 times control

- **Duration**
  - 5-10 days or warfarin therapeutic (INR > 2) X 2 days

- **ADRs**
  - Hemorrhage (5% clinically significant)
  - Thrombocytopenia (HIT I/HAT and HIT II)
    - HAT- incidence 25%, mild, transient, nonimmune, decr in 1-4 days, platelets > 100,000/mm³, return to nl despite heparin, nonthrombogenic
    - HIT II- Incid 1-3%, immunoglobulin mediated, platelets decrease > 50% to < 150/mm³ (nadir 59) in 5-14 days, 30-75% thrombosis, must DC heparin
  - Osteoporosis (doses > 20,000 U/day for > 6 months)

- **Reversal**
  - Mild- DC UH and recheck aPTT in 4-6 hr
  - Severe
    - Protamine 1 mg IV neutralizes 100 U UH
    - Fresh Frozen Plasma, Whole Blood


Treatment: Unfractionated Heparin (UH)

- Weight Based Dosing Nomograms versus ad hoc approach*
- **Goal**
  - Controversy whether therapeutic PTT in 24 hrs is predictor of recurrence

- **Monitor**
  - aPTT 6 hr after bolus or change in infusion rate and then QD once stable
  - Platelets, Hgb, bleeding

*Treatment: Low Molecular Weight Heparins

- **Mechanism of Action**
  - Greater factor Xa to IIa (thrombin) ratio than UH
  - Longer t 1/2
  - Lower protein binding

- **Clinical Experience**
  - At least as effective as UH for DVT treatment
  - Convenience, lack of frequent aPTT monitoring
  - May need anti-Xa levels to optimize dosing, prevent bleeding
  - May be effective in submassive PE treatment but limited data and needs confirmation in larger trials
Treatment: Low Molecular Weight Heparins

- **Dosing (for treatment)**
  - Enoxaparin (Lovenox®) 1 mg/kg SQ BID (Outpatient DVT) or 1.5 mg/kg SQ QD (Inpatient DVT with or without PE)
  - Dalteparin (Fragmin®) 100 U/Kg SQ BID or 200 U/Kg SQ QD
    - Not FDA approved
  - Tinzaparin (Innohep®) 175 U/kg QD

- **Duration**
  - At least 5 days or warfarin therapeutic for 2 days

- **ADRs**
  - Hemorrhage, thrombocytopenia

Not interchangeable or equivalent

PTT not useful for monitoring as LMWH minimally inhibit thrombin

Anti-Xa levels not correlated with clinical outcomes but may be useful in select pts*

- Obese (?), small weight (?), pregnancy, renal failure
- Assay not universally available and variability among manufacturers and methods
- Peak (2-4 hrs after dose); 0.4-1.1 U/mL for treatment or 0.1-0.2 U/mL for prophylaxis


Outpatient DVT Treatment with LMWH: Exclusions

- Thrombocytopenia, HIT II (High cross reactivity in-vitro)
- Renal or hepatic failure
- PE with hemodynamic instability or multiple DVTs
- Pregnancy
- Catheter related DVT
- Obesity (> 30% over IBW)
- Severe HTN
- Active bleeding, hypercoagulable state, malignancy

Treatment: Fondaparinux (Arixtra®)

- **Mechanism of action**
  - Pentasaccharide, selectively binds to antithrombin III and inactivates Xa, interrupting the coag cascade and inhibiting thrombin formation without inactivating thrombin (factor II).
  - Given SQ, peak in 2 hrs, t1/2 13-17 hrs
  - Cautions- bleeding (major bleeds dose-related)
  - Adjust dosage in renal failure (50% dose-related)
    - Monitor anti-factor Xa activity
  - No cross-reactivity with heparin-PF4 antibodies nor elicits HIT II antibodies
    - Good alternative in acute HIT II

FDA Approval

- Prophylaxis of DVT in hip and knee surgery
  - Dosage 2.5 mg SQ QD
  - Cost approx $31-35/day

Unapproved Uses

- Treatment of DVT and ACS (phase III trials)
  - Dosage ? 7.5 mg SQ qd: trials 5 (< 50 kg), 7.5 (50-100 kg), 10 (>100 kg) mg SQ qd

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Mechanism of Action

- Anticoagulant and antithrombotic
- Inhibition of the reduction of Vit K leading to partially active or inactive clotting factors II, VII, IX, X and also limits the carboxylation of proteins C and S
- Due to t 1/2s of clotting factors (VII shortest with 4-6 hrs and II longest with 42-72 hrs), may not have full antithrombotic effects for 2-7 days post initiation
- S-warfarin three times more potent vs R-warfarin
Treatment: Warfarin

- **Dosing**
  - 2-10 mg PO daily (lower in elderly or very small patients, higher if ATIII or protein C/S deficiencies, or Lupus anticoagulant)
  - Generally 5 mg daily PO
  - No rationale for loading
  - Initiated within 24 hrs of heparin ideally and overlap for 4-5 days or until INR therapeutic
  - Adjust by 5-20% daily

- **Duration**
  - Calf vein thrombosis → 6 weeks to 3 months
  - Proximal vein thrombosis/1st event → 3-6 months
  - PE or idiopathic etiology of DVT and 1st event → Therapeutic dilemma—at least 3-6 months vs indefinite
  - Recurrent thrombus → 12 months to lifelong
  - 1st event with unresolved cancer, protein C resistance, antiphospholipid antibody syndrome, deficiency of antithrombin/protein C or S → 12 months to lifelong, or as long as risk factor is present

- **Monitoring**
  - INR 2.0-3.0 goal
  - 3.0-4.5 if recurrent, mechanical valves, or antiphospholipid syndrome

- **ADRs**
  - Hemorrhage, skin necrosis, purple-toe syndrome, fetal malformation

- **Reversal**
  - Minor- Hold warfarin
  - Serious- Vitamin K PO, SQ, or IV 1-10 mg, FFP

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Treatment: Thrombolysis

- **Thrombolytics** are indicated for pts with acute massive PE who are hemodynamically unstable and not prone to severe bleeding.

- **Thrombolytics** provide more rapid improvement of abnormal hemodynamic status, clot resolution and reperfusion in PE vs heparin alone but no difference in short term mortality, increased bleeding incidence, and $$$. They may potentially decrease long-term complications.

- **Goals of lytics in DVT** are to reduce incidence of post-phlebitic syndrome.

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Thrombolytics in PE & DVT

<table>
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<tr>
<th>Lytic</th>
<th>LD</th>
<th>MD</th>
<th>Duration (PE)</th>
<th>Duration (DVT)</th>
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<tr>
<td>SK</td>
<td>250,000 IU</td>
<td>100,000 IU/hr</td>
<td>24 hr</td>
<td>48-72 hr</td>
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<tr>
<td>UK</td>
<td>4,400 IU/Kg</td>
<td>4,400 IU/kg/hr</td>
<td>12 hr</td>
<td>48-72 hr</td>
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<tr>
<td>t-PA</td>
<td>NA</td>
<td>100 mg over 2 hr</td>
<td>2 hr</td>
<td>Not approved</td>
</tr>
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- **Administration**
  - Stop heparin infusion and begin thrombotic when aPTT is < 1.5 times control
  - Initiate heparin (no load) post lytic when aPTT is back to 1.5-2 times control and then transition to warfarin

- **Monitoring**
  - Coagulation tests not necessary

- **Catheter-directed instillation of lytic into DVT clot**
  - Less bleeding
Treatment: Surgical Procedures

- IVC Filters (Greenfield, Birds’ Nest filters)
  - For pts with contraindication to or complication of anticoagulation or with recurrent thromboembolism despite adequate anticoagulation
- Pulmonary Embolectomy
  - For massive PE with hemodynamic instability and lytic failure or contraindication
- Venous Thrombectomy (clot removal)
  - If severe limb ischemia
  - May prevent postphlebitic syndrome

Prophylaxis

- Necessity of use dependent upon
  - Type of surgery (general, hip/knee, neurosurgery)
  - Medical conditions (multi trauma, spinal cord injury, ischemic stroke, AMI, degree of immobility)
  - Number of risk factors
- Graduated compression stockings (Teds hose)
- Intermittent Pneumatic Compression (Pneumoboots, Plexipulse)

Prophylaxis

- Unfractionated Heparin
  - 5000 u SQ BID or TID
  - 7500 u SQ BID
- Low Molecular Weight Heparin
  - Enoxaparin 30 mg SQ BID (Hip/knee replacements) or 40 mg SQ QD (Hip, Gyne, Abdominal surgery, general medicine)
  - Dalteparin 2500-5000 IU SQ QD (Hip or abdominal surgery)
  - Ardeparin (Normiflo®) 50 anti-Xa U/Kg SQ q 12 hr (Knee)

Prophylaxis

- Fondaparinux 2.5 mg SQ QD
- Warfarin (INR 2.0-3.0)