Pulmonary Embolism & Deep Vein Thrombosis

Suzanne J. Tschida, Pharm.D, BCPS
Clinical Pharmacy Manager/Critical Care Specialist
Regions Hospital
Clinical Assistant Professor
University of Minnesota

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

Pathophysiology: Virchow’s Triad

- **Venous 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

Pathophysiology: 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
- Advanced age
- Trauma (lower limb)
- Previous DVT
- Surgery (ortho)
- Comorbidities - CHF, Stroke
- AMI
- Smoking
- Estrogen, BCPs
- Obesity
- Pregnancy, postpartum
- Prosthetic Heart Valves
- Coagulation Disorders
- 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

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

Diagnosis: DVT

- Venography
  - Gold standard - most sensitive and specific
  - Invasive, $, 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

- 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

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

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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: Unfractionated Heparin (UH)

- 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, deec 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)

Treatment: Unfractionated Heparin (UH)

- 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: 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

**Clinical Experience**

- **Dosing (for treatment*)**
  - Enoxapirin (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


Treatment: Fondaparinux (Arixtra®)

- **Mechanism of action**
  - Selective pentasaccharide, directly accelerates antithrombin-mediated Xa inactivation in a dose-dependent manner without inhibiting thrombin.
  - Given SQ, peak in 2 hrs, t1/2 13-17 hrs
  - Cautions- bleeding (major bleeds dose-related)
  - Adjust dosage in renal failure (50% renal elim)
    - Monitor anti-factor Xa activity
  - No cross-reactivity with heparin -PF4 antibodies nor elicits HIT II antibodies
  - Good alternative in acute HIT II

**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®)**

- **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, 7.5, 10, 12 mg SQ qd)
Treatment: Warfarin

- **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

- **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 → At least 6 months
  - 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

- **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

Thrombolytics in PE & DVT

- **Thrombolytics**
  - SK 250,000 IU 100,000 IU/hr 24 hr 48-72 hr
  - UK 4,400 IU/Kg 4,400 IU/kg/hr 12 hr 48-72 hr
  - t-PA NA 100 mg over 2 hr 2 hr Not approved
Thrombolytics in PE & DVT

- Administration
  - Stop heparin infusion and begin thrombolytic 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

Prophylaxis

- Necessity of use dependent upon
  - Type of surgery (general, hip/knee, neurosurgery)
  - Medical conditions (mult 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

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

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

- Unfractionated Heparin
  - 5000 u SQ BID or TID
  - 7500 u SQ BID
- Low Molecular Weight Heparin
  - Enoxapirin 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)
- Fondaparinux 2.5 mg SQ QD
- Warfarin (INR 2.0 - 3.0)