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Pathophysiology

- Typically thrombus arises in deep leg venous system. It lodges into the pulmonary circulation.
- 10-30% embolize to become pulmonary embolism (PE).
- Acute PE vs. Chronic PE and Large vs. Small
  - When clot lodges --> acute increase in pulmonary arterial and RV pressures, decrease in cardiac output.
  - Increased V/Q mismatch --> hypoxemia.
- 300,000 people die in US from acute PE each year.

Risk Factors of VTE

- DVT risk factors (Virchow’s triad)
  - 1. Hypercoagulability
    - Hereditary:
      - (Protein C/S def, Factor V Leiden, Prothrombin gene mutation, Dysfibrinogenemia, Antithrombin III deficiency)
    - Acquired:
      - Malignancy (+ chemo)
      - OCP, HRT
      - Pregnancy
      - Hematologic (Polycythemia vera, APLA)
  - 2. Endothelial Damage
    - Trauma
    - Smoking
    - Surgery
    - Vascular manipulation
  - 3. Stasis
    - Surgery
    - Long flight/plane ride (Increases risk by 18% for each 2-hour increment)
    - Obesity
    - Age (>60yo doubles risk each decade)
    - Hospitalization / Acute illness
- Another way to think about it: THROMBOSIS
  - T - Trauma, Travel
  - H - Hypercoagulable, hormone replacement
  - R - Recreational Drugs (IV use)
  - O (old age >60)
  - M - Malignancy
  - B - Birth Control Pill
  - O - Obesity, Obstetrics
  - S - Surgery/Smoking
  - I - Immobilization
  - S - Sickness (CHF/MI, nephrotic syndrome, IBD, vasculitis, etc...)

Pulmonary Embolism (PE)

Symptoms

- Patients with PE have few symptoms, and many non-specific and non-sensitive.
- General Symptoms:
  - Tachypnea (90%)
  - Chest or pleuritic pain (85%)
  - Dyspnea (84%)
  - Anxiety, crackles, cough.
  - Likelihood of PE is lower if does not have dyspnea or tachycardia.

Pre-Test Probability

- Signs an symptoms are non-sensitive and non-specific
- Several diagnostic Risk Scores have been developed to decrease need for imaging.
Here are some prediction scoring systems:

### Well’s Criteria for PE

- Clinically suspected DVT (3 Points)
- Alternative dx is less likely (3 Points)
- Tachycardia > 100 (1.5 points)
- Immobilization/Surgery in past 4 weeks (1.5 points)
- Hx of prev DVT or PE (1.5 points)
- Hemoptyisis (1.0 points)
- Malignancy (tx within 6 mo, palliative) (1.0 points)

### Traditional Interpretation

- **Score >6.0** – High (probability 59%)
- **Score 2.0-6.0** – Moderate (29%)
- **Score <2.0** – Low (15%) (consider D-dimer)

### "Modified Scoring"

- **Score >4** – PE likely, consider dx imaging
- **Score <= 4** – PE unlikely, consider D-dimer

### Revised Geneva Scoring System

<table>
<thead>
<tr>
<th>Risk Factors:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65y</td>
<td>(1 point)</td>
</tr>
<tr>
<td>Prev DVT or PE</td>
<td>(3 points)</td>
</tr>
<tr>
<td>Surgery under GA or fracture of LL in 1mo</td>
<td>(2 points)</td>
</tr>
<tr>
<td>Active Cancer (if active or cured in &lt;1yr)</td>
<td>(2 points)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral Lower Limb Pain</td>
<td>(3 points)</td>
</tr>
<tr>
<td>Hemoptyisis</td>
<td>(2 points)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Heart Rate 75–94/min</td>
<td>(3 points)</td>
</tr>
<tr>
<td>Heart Rate ≥ 95/min</td>
<td>(5 points)</td>
</tr>
<tr>
<td>Pain on LL deep venous palpation and unilateral edema</td>
<td>(4 points)</td>
</tr>
</tbody>
</table>

### Pretest Probability of PE:

- 0 - 3 points = LOW
- 4 - 10 points = INTERMEDIATE
- ≥11 points = HIGH

• PERC rule: (Pulmonary Embolism Rule Out Criteria)
  • Used mostly used by ER physicians (for VERY LOW pre-test probability)
    - 1. Age <50
2. HR <100
3. O2 sat >94% on RA
4. No Hx of DVT/PE
5. No recent surgery
6. No hemoptysis
7. No estrogen replacement
8. No clinical signs of DVT

If all are negative: <2% chance of PE
Can use only if DO NOT suspect PE

• Use of D-Dimer in patients with suspected PE/DVT will save 30% of pts from further investigations.
  ◦ D-Dimer not recommended for moderate to high risk of PE or in hospitalized patients.
  ◦ Use only if LOW pre-test probability (if high risk of PE, D-dimer does not change pretest as much)

Initial Investigations / D-Dimer
• ECG, CXR to rule out other causes (Pneumonia, ACS)
  ◦ ECG in PE:
    ▪ Most common: sinus tachycardia.
    ▪ R-sided heart strain: (most aren't large enough to cause R-heart strain)
      ▪ S1Q3T3 (only seen in minority of patients)
      ▪ R-axis deviation and RBBB
      ▪ Large R-atrium.
    ◦ CXR: Hampton's Hump (wedge shape density in the periphery due to infarction) or Westermark sign (darker area of reduced perfusion)

  • D-Dimer:
    ◦ Use of D-Dimer in patients with suspected PE/DVT will save 30% of pts from further investigations.
D-Dimer not recommended for moderate to high risk of PE or in hospitalized patients.

Use only if LOW pre-test probability (if high risk of PE, D-dimer does not change pretest as much)

- **Negative Predictive Value = 94%**
  - D-Dimer is NOT useful when POSITIVE (poor specificity), only useful if negative.
  - In pregnant patients D-dimer levels increase, but still useful in first trimester as at least 50% will normally have a negative D-dimer, which safely excludes TE.
    - In 2nd trimester 75% will be positive, and in 3rd trimester nearly all are positive. If positive may need a low-dose perfusion scan or V/Q scan, consult radiology.

**Definitive PE Studies**

- **CT angio (Sn + Sp > 90%)**
  - Primary method of diagnosis of PE due to high Sn and Sp.
  - **Advantages:**
    - May provide other diagnostic clues.
    - Preferred if baseline CXR abnormal (VQ scan difficult to interpret)
  - **Disadvantages:**
    - High radiation exposure
    - More challenging in obese people (hard to time contrast to pulmonary vasculature). May need an open scanner.
- **V/Q scan (Sn 50–98%, Sp 20–60%)**
  - VQ scan is an option if CT angiography not available or contraindicated.
  - **Advantages:**
    - Low radiation dose.
    - No contrast dye.
    - Useful with normal cardiopulmonary status at baseline.
    - Preferred for chronic PEs with multiple lobar perfusion defects w/o anatomic matching ventilation abnormalities.
    - Normal results practically exclude PE in setting of high pretest probability.
  - **Disadvantages:**
    - Unreliable if structural lung disease (COPD, etc.) or if holding breath is difficult.
    - VQ interpretation dependent on pre-test likelihood.
- **Gold Standard:** Conventional pulmonary angiography with digital subtraction
  - Invasive: only reserved for patients if uncertainty remains after CT angiography.
  - OR if direct measurement of hemodynamics is needed.

**DVT Studies in PE**

- If unable to get chest imaging to exclude PE, it may be worthwhile to perform a compression ultrasound of legs.
  - 90% of clots start in legs.
  - If positive leg venous ultrasound --> will treat for DVT and presumed PE (treatment similar)
- If no DVT is found: may need chest imaging.
- **If PE is found on chest imaging --> Leg USS is not indicated (will not change management)**

**Other Investigations**

- Echocardiography
  - For select patients with suspected or confirmed PE who are too unstable for CTA or VQ scanning.
  - **Findings:**
    - Elevated PA systolic pressure.
    - RV dilation / hypokinesis
    - Paradoxical septal motion
    - Diminished LV size.
    - **McConnel Sign**

**Treatment:**

- Tx almost the same for DVT and PE. No evidence that PE needs different LMWH or warfarin therapy.
  - Tx reduces PE mortality from 30% to 2-8%
For PE: Decide if hemodynamically stable or not.
Can use cardiac markers of strain to help distinguish if significant or not (Trop, BNP, echo), but not used for used in criteria for "unstable".

Stable

- Achieve anticoagulation within 24hrs to prevent progression and recurrence of clot.
  - Allow time for natural lysis of existing clot (days to weeks).
  - Acutely use: UFH, LMWH, and rarely Fondaparinux (pentasaccharide)
    - New oral medications (rivaroxaban, dabigatran etc..) possible but less experience.
  - If anticoagulation (active internal bleed, hemorrhagic stroke, coagulopathy, remote GI bleed, brain mets). Must weigh risks--benefits.
  - Can start warfarin right away, but do not bolus (initially hypercoagulable), and continue LMWH/UFH for 4-5 days until reach target INR levels and >2 days of stable INR. (2 days overlap) to ensure reliable anticoagulation.

- Big controversy whether thrombolytics should be used for stable patients but RV strain on CT or Echo.
  - Dilation, decreased RV systolic function.
  - Can look at biomarkers (troponin, BNP levels)
  - Area of active research, no definitive answer.

Unstable

- These are patients that have high mortality rate, and may require thrombolysis.
- They are hemodynamically unstable patients have high risk of death:
  - NO TIME to wait for natural clot resorption --> Thrombolytic therapy, followed by anticoagulation.
  - Other options:
    - Catheter embolectomy or surgical embolectomy.
- Defined as refractory hypotension
  - Very high pulmonary vascular resistance and high pulmonary pressure. Drop in cardiac output.
  - May need mechanical ventilation.
  - Give VOLUME --> fluid rescueitation to improve preload to RV.
    - However too much fluid can overload the RV (can cause ischemia of RV).
- Contraindications for thrombolytic therapy:
  - History of intracranial bleeding
  - CVA within the past 3mo (ischemic CVA within the past 3 hours)
  - Closed head or facial trauma within the past 3 mo
  - Suspected aortic dissection
  - Active internal bleeding
  - Uncontrolled hypertension (sBP > 180, dBP > 100)

Risks of thrombolysis:
- 2.1% risk of ICH
- 1.6% risk of fatal non-ICH hemorrhage.
Long-Term Management

- In acute PE, pts are at a substantial risk of recurrence (esp in first 1 month)
- Continue anticoagulation for at least 3 months.
- **Standard therapy:**
  - Warfarin (INR 2-3)
  - NEW: Rivaroxaban
- **How long to continue?**
  - 3 months of anticoagulation for everyone, after that:
    - Can stop if known predisposing factor that is resolved.
    - Continue as long as predisposing factor present (surgery, immobility)
    - Consider indefinitely if:
      - predisposing factor continuous (cancer).
      - History of proximal DVT
      - Idiopathic (aka "unprovoked") VTE
  - Some perform D-Dimer 2 weeks before stopping anticoagulation and also check 2-weeks after stopping.
    - If positive, then four-fold risk of recurrent PE than normal D-Dimer.
    - Helps risk-stratify, if D-Dimer positive --> consider continuing.
- **NOTE:** For patients requiring long-term oral anticoagulants, role of NOACs is uncertain.

IVC Filters

- **Indications:**
  - If not candidate for acute or chronic anticoagulation.
  - Clotting despite anticoagulation
  - High risk of recurrent emboli
  - Low cardiopulmonary reserve (such as pulmonary HTN) - even if on anticoagulation.
- Placed into IVC below renal veins.
- Prevent any DVTs that embolize.
- **Disadvantages:**
  - Higher risk of lower-limb DVT with filter in-situ.
  - Filter can migrate (even into RV)
  - Filter can endothelialize if not removed after few months (will be impossible to safely remove)
  - Clot can form on filter, above filter, or around the filter. (Can cause chronic pain)
  - Can get venous collateralization around the filter, and emboli can bypass.
- Preferable to continue anticoagulation after filter installed.
- MOST (80-90%) are never removed and forgotten. DO NOT forget to remove if not needed.

VTE Prophylaxis


- **Risk Factors:**
  - NYHA class III/IV HF
  - Acute respiratory failure
  - Active cancer
  - Stroke with paresis
  - History of VTE
  - Acute infectious illness
  - Age >60 years
  - Thrombophilia
  - Acute rheumatic disease
  - Inflammatory bowel disease
  - Immobility
- Divide patients into LOW and HIGH risk.
- All acutely ill hospitalized medical patients at increased risk of thrombosis need thromboprophylaxis with:
  - Low Molecular Weight Heparin (LMWH)
  - Low Dose Unfractionated Heparin (LD UFH) BID or TID
  - Fondaparinux

<table>
<thead>
<tr>
<th>VTE Risk Factors</th>
<th>Prophylaxis Options</th>
<th>Contraindications to VTE proph</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NYHA class III/IV HF</td>
<td>Unfractionated Heparin, 5000u SC q8-12h</td>
<td>- Active or high risk of bleed</td>
</tr>
<tr>
<td>• Acute respiratory failure</td>
<td>Enoxaparin, 40mg SC q24h</td>
<td>- Coagulopathy (abnormal PTT or PT not due to lupus anticoagulant)</td>
</tr>
<tr>
<td>• Active cancer</td>
<td>Dalteparin 5000u SC q24h</td>
<td></td>
</tr>
<tr>
<td>• Stroke with paresis</td>
<td>Fondaparinux, 2.5 SC q24h</td>
<td>- Thrombocytopenia (&lt;50,000/uL)</td>
</tr>
<tr>
<td>• History of VTE</td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>• Acute infectious illness</td>
<td>Intermittent pneumatic compression</td>
<td></td>
</tr>
<tr>
<td>• Age &gt;60 years</td>
<td>(if pharmacologic contraindicated)</td>
<td></td>
</tr>
<tr>
<td>• Thrombophilia</td>
<td></td>
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In pts with stroke, active cancer, surgery --> LMWH is superior to UFH.

**Superficial Thrombophlebitis**

- Superficial vein thrombosis.
- Same as DVT: Use therapeutic dose of LMWH / Heparin.
  - In the past superficial vein thrombophlebitis used with ibuprophene and compression stalkings.
  - However, recent studies has similar risk factors as DVT. It can progress to cause true DVT and PE.
- Vein ligation used for symptomatic recurrent thrombophlebitis.

**CTEPH**

- Chronic Thromboembolic Pulmonary Hypertension
- Lifelong anticoagulation with warfarin
- No trials comparing shorter anticoagulation, or anticoag vs. surgery.
- Assess all patients for surgery
  - Pulmonary Thromboendarterectomy Assessment
    - Surgical Accessibility (main, lobar, segmental)
    - Hemodynamic/ventilatory impairment
    - Comorbidities/Risks of Surgery
    - Patient preference
• DOACs = Dabigatran, Rivaroxaban, Apixaban, Edoxaban
• Choice of Anticoagulation Agent:
  • No Malignancy
    ▪ 1st line: DOAC
    ▪ 2nd line: VKA
    ▪ 3rd line: LMWH
  • Malignancy
    ▪ 1st line: LMWH (CLOT Trial = LMWH vs. Warfarin in malignancy)
    ▪ 2nd line: Warfarin
• Anticoagulate?
  • Distal Leg DVT:
    ▪ RF for Progression OR Significant Symptoms?
      ▪ YES --> Treat x3mo (Same agents)
      ▪ NO --> Serial imaging of deep veins x2w
  • Subsegmental PE (and no proximal leg DVT)
    ▪ Low Risk of Recurrent VTE --> Surveillance
    ▪ High Risk of Recurrent VTE --> Anticoagulate
  • Indications for Thrombolysis of PE
    ▪ sBP < 90mmHg (despite resuscitation) + Low Risk of Bleeding
    ▪ Cardiopulmonary Deterioration despite anticoagulation (if not yet hypotensive) + Low Bleeding Risk
      ▪ Includes: Symptoms, vitals, tissue perfusion, gas exchange, cardiac biomarkers
  • CTEPH (chronic thromboembolic pulmonary hypertension)
    ▪ Consider pulmonary thromboendarterectomy (consult experienced team)
  • Upper Extremity DVT (Axillary or more proximal veins)
    ▪ Anticoagulate!
    ▪ Thrombolysis can be considered in select pts (see guideline), but must still anticoagulate
  • Recurrent VTE
    ▪ Switch to LMWH for at least 1mo AND Re-evaluate (evaluate compliance + malignancy)
    ▪ If have recurrent VTE on LMWH (compliant) --> increase dose of LMWH (1/4 to 1/3)
• Duration of Therapy
- **NOTES:**
  - Catheter directed thrombolysis NOT RECOMMENDED (peripheral vein systemic therapy preferred)
  - Catheter thrombus removal if:
    - High bleeding risk
    - Failed systemic thrombolysis
    - Shock that is likely to cause death before systemic thrombolysis can take effect (hrs)
  - Edoxaban and Dabigatran need initial IV anticoagulation (rivaroxaban and apixaban do not)
  - Do not use compressions stockings to prevent post-thrombotic syndrome.

**Indications for Thrombophilia Testing**

[Indications for thrombophilia workup](#)