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Case Conference

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Discussion

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Pulmonary embolism

Risk Factors for Venous Thromboembolism.

- Age >40 yr
- History of venous thromboembolism
- Surgery requiring >30 min of anesthesia
- Prolonged immobilization
- Cerebrovascular accident
- Congestive heart failure
- Cancer
- Fracture of pelvis, femur, or tibia
- Obesity
- Pregnancy or recent delivery
- Estrogen therapy
- Inflammatory bowel disease
- Genetic or acquired thrombophilia
- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency
- Prothrombin G20210A mutation
- Factor V Leiden
- Anticardiolipin antibody syndrome
- Lupus anticoagulant

Signs and Symptoms of PE

- • Dyspnea 73%
- • Pleuritc Pain 66%
- • Cough 43%
- • Leg Swelling 33%
- • Leg Pain 30%
- • Hemoptysis 15%
- • Palpitations 12%
- • Wheezing 10%
- • Angina-Like pain 5%
  - *The signs and symptoms serve only to raise the suspicion ofpulmonary embolus*

Diagnosis of Pulmonary Embolism

- **Clinical picture.**
- **Look for risk or predisposing factors for DVT**
- **Look for ventilation-perfusion mismatch**
- **Testing for PE.**
  - **chest radiograph**
  - **ECG**
  - **Ventilation-perfusion scanning (V/Q scanning).**
  - **Angiography**
  - **Spiral CT**

Canadian (Wells) prediction score

- Variable and score
  - DVT symptoms and signs — 3.0
  - PE as likely as or more likely than alternative diagnosis — 3.0†
  - Heart rate >100 beats/min — 1.5
  - Immobilization or surgery in previous 4 wk — 1.5
  - Previous DVT or PE — 1.5
  - Hemoptysis — 1.0
  - Cancer — 1.0
- Total score‡
  - <2.0 — low pretest probability
  - 2.0 to 6.0 — moderate pretest probability
  - >6.0 — high pretest probability
- Dichotomized Wells score§
  - ≤4 — PE unlikely
  - >4 — PE likely

Original Geneva Score

- Age:
  - 60 – 79 years (1 point)
  - 80+ years (2 points)
- Previous DVT or PE (2 points)
- Recent surgery within 4 weeks (3 points)
- Heart rate >100 beats per minute (1 point)
- PaCO2 (partial pressure of CO2 in arterial blood):
  - <35mmHg (2 points)
  - 35 - 39mmHg (1 point)
- PaO2 (partial pressure of O2 in arterial blood):
  - <49mmHg (4 points)
  - 49 - 59mmHg (3 points)
  - 60 - 71mmHg (2 points)
  - 72 - 82mmHg (1 point)
- Chest X-ray findings:
  - Band atelectasis (1 point)
  - Elevation of hemidiaphragm (1 point)
- The score obtained relates to the probability of the patient having had a pulmonary embolism (the lower the score, the lower the probability):
  - <5 points indicates a low probability of PE
  - 5 - 8 points indicates a moderate probability of PE
  - >8 points indicates a high probability of PE

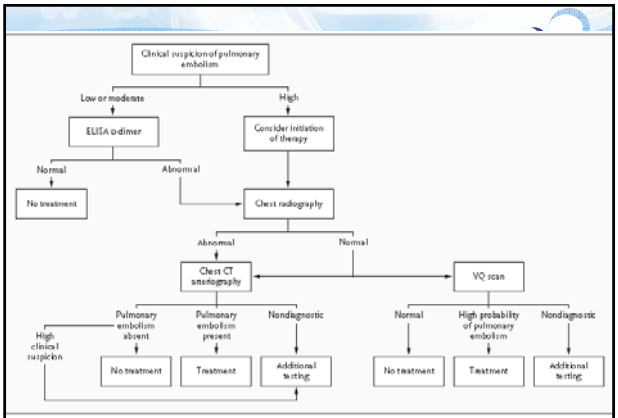
Revised Geneva Score

- Age 65 years or over (1 point)
- Previous DVT or PE (3 points)
- Surgery or fracture within 1 month (2 points)
- Active malignant condition (2 points)
- Unilateral lower limb pain (3 points)
- Haemoptysis (2 points)
- Heart rate:
  - 75 to 94 beats per minute (3 points)
  - 95 or more beats per minute (5 points)
- Pain on deep palpation of lower limb and unilateral oedema (4 points)
- The score obtained relates to probability of PE:
  - 0 - 3 points indicates low probability (8%)
  - 4 – 10 points indicates intermediate probability (28%)
  - 11 points or more indicates high probability (74%)

Pulmonary Embolism Rule-out Criteria

- Pulmonary Embolism Rule-out Criteria(PERC rule)
  - assess patients in whom pulmonary embolism is suspected,
    - but unlikely. Unlike the Wells Score and Geneva score(low risk category)
  - age < 50 years,
  - pulse < 100 beats min,
  - SaO2 ≥ 95%, no hemoptysis,
  - no estrogen use,
  - no surgery/trauma requiring hospitalization within 4 weeks,
  - no prior venous thromboembolism (VTE),
  - no unilateral leg swelling],
- The PERC rule has a sensitivity of 97.4% and specificity of 21.9% with a false negative rate of 1.0%

1.(2008). "Prospective multicenter evaluation of the pulmonary embolism rule-out criteria". *Journal of Thrombosis and Haemostasis* **6** (5): 772–780.
2. J Thromb Haemost. 2004 Aug;2(8):1247-55. **Clinical criteria to prevent unnecessary diagnostic tes emergency department patients with suspected pulmonary embolism.**



N Engl J Med 2008;358:1037-52.

Treatment of acute pulmonary embolism

- **HEPARIN THERAPY**
  - -- Unfractionated heparin
  - -- Low molecular weight heparin
- **ORAL ANTICOAGULANT THERAPY**
  - -- Warfarin
- **THROMBOLYTIC THERAPY**
  - -- Urokinase
  - -- Streptokinase
  - -- Alteplase

HEPARIN

- Simultaneous initiation of heparin (either unfractionated or low-molecular weight) and oral warfarin

--The standard anticoagulant regimen for venous thromboembolism in all medically stable patients.

HEPARIN

- Monitor the response, using either the activated partial thromboplastin time (aPTT) or heparin levels, and to titrate the dose to the individual patient.
- Critical therapeutic level of heparin, as measured by the aPTT, is 1.5 times the mean of the control value or the upper limit of the normal aPTT range, with a target range (aPTT ratio) of 1.5 to 2.5

HEPARIN

- Experimental studies and clinical trials have established that the efficacy of heparin therapy depends upon achieving a critical therapeutic level of heparin within the first 24 hours of treatment, usually via a continuous heparin infusion
- Heparin infusion of 1000 IU/hr and who had an aPTT ratio of <1.5 times control for three days or more threefold increase in the risk of recurrent venous thromboembolism

Low molecular weight heparin

- Greater bioavailability when given by subcutaneous injection
- The duration of the anticoagulant effect is greater (once or twice daily)
- The anticoagulant response is highly correlated with body weight, permitting administration of a fixed dose
  -- Laboratory monitoring is not necessary except in pregnancy, morbid obesity and renal failure
- Less likely to induce thrombocytopenia

- At present, the alteplase regimen in which 100 mg is administered intravenously over two hours is the most rapidly administered protocol that is currently approved for use in the United States

TABLE 56-5 Regimens Approved by the Food and Drug Administration for the Acute Treatment of Pulmonary Embolism

Drug	Dosage
Unfractionated heparin	80 units/kg bolus IV, then 18 units/kg per h to maintain partial thromboplastin time, INR = 2.5-3.0
Fractionated heparin	
Enoxaparin	1 mg/kg SC BID
Fibrinolytic therapy	
Streptokinase	250,000 units IV over 30 min followed by 100,000 units/h for 24 h
Urokinase	4400 units/kg IV over 10 min followed by 4000 units/kg per h for 12 h
Alteplase	15-mg IV bolus followed by 0.5-mg/kg infusion of 0.5 mg/kg over 30 min, then 0.75 mg/kg over 60 min (maximum dose 100 mg); discontinue heparin during infusion

Abbreviation: INR = international normalized ratio.

TABLE 56-6 Factors That Can Help Prognose the Short-Term Outcome of Normotensive Patients with Pulmonary Embolism

Good Outcome Likely	Adverse Outcome More Likely
No syncope or seizure at presentation	Syncope or seizure with respiratory distress at presentation
Age <50 y	Age >70 y
Absence of COPD, CHF, or prior PE	Presence of COPD, CHF, or prior PE
<50% pulmonary vascular occlusion	>50% pulmonary vascular occlusion; floating thrombus in the RV or right atrium observed on echocardiography or CT angiography
Normal ECG	ECG with T-wave inversion in V_1–V_4 and a new incomplete right bundle branch block
Heart rate/systolic blood pressure <0.8	Heart rate/systolic blood pressure >1.0
Pulse oximetry reading >94% breathing room air	Pulse oximetry reading <94% breathing room air
Troponin I concentration <0.4 μg/L	Troponin I concentration >1.0 μg/L
Normal RV function and size	RV dilation or hypokinesis, or an estimated RV systolic pressure >40 mm Hg

Lancet 353:1386, 1999

Thrombolytic theapy Indications

Patients with massive PE associated with hemodynamic compromise are reasonable candidates for intravenous thrombolytic therapy.

Potential Indications for Thrombolytic Therapy in Venous Thromboembolism

- Presence of hypotension related to PE†
- Presence of severe hypoxemia
- Substantial perfusion defect
- Right ventricular dysfunction associated with PE
- Extensive deep vein thrombosis

† This indication is widely accepted; the other potential indications require careful review of relative contraindications to thrombolytic therapy.

Buller, HR, Agnelli, G, Hull, RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:401S.

Contraindications

- These should be particularly scrutinized if lytic therapy is considered

Contraindications to Thrombolytic Therapy in Pulmonary Embolism

Absolute
Hemorrhagic stroke
Active intracranial neoplasm
Recent (< 2 months) intracranial surgery or trauma
Active or recent internal bleeding in prior 6 months

Relative
Bleeding diathesis
Uncontrolled severe hypertension (systolic BP >200 mmHg or diastolic BP >110 mmHg)
Cardiopulmonary resuscitation
Nonhemorrhagic stroke within prior 2 months
Surgery within the previous 10 days
Thrombocytopenia (<100,000 platelets per mm3)

Therapeutic regimens of Acute PE

Approved Thrombolytic Regimens for Acute Pulmonary Embolism

Tissue-type plasminogen activator: 100 mg IV over 2 hr

Streptokinase: 250,000 U IV (loading dose over 30 min); then 100,000 U/hr for 24 hr†

Urokinase: 2000 U/lb IV (loading dose over 10 min); then 2000 U/lb per hr for 12-24 hr

† This regimen, infused over 24 to 72 hr, has also been approved for use in patients with extensive DVT

General guidelines for administration

Guidelines for Thrombolytic Therapy in Venous Thromboembolism

- Clear documentation of PE (or DVT)†
- Potential contraindications carefully reviewed
- Delivery by peripheral intravenous infusion
- Initiate or continue other supportive therapy
- Discontinue heparin during thrombolytic infusion

†High-probability ventilation-perfusion scan or positive pulmonary arteriogram

Buller, HR, Agnelli, G, Hull, RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:401S.

THROMBOLYSIS FOR PE

Alteplase versus heparin

- A randomized controlled trial of alteplase plus heparin versus placebo plus heparin was conducted in 256 patients.
  -- Therapy with alteplase was associated with a decreased need for escalation of therapy (10 versus 25 percent)
  -- In-hospital mortality did not differ significantly between groups.

- conjunction with heparin, alteplase can improve the clinical course of stable patients who have acute submassive pulmonary embolism
  - can prevent clinical deterioration requiring the escalation of treatment during the hospital stay

Konstantinides, S, Geibel, A, Heusel, G, et al.
Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism.
N Engl J Med 2002; 347:1143

Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism

- Once-daily, subcutaneous administration of fondaparinux without monitoring
  - as effective
  - as safe as adjusted-dose,
- intravenous administration of unfractionated heparin
  - in the initial treatment of hemodynamically stable patients with pulmonaryembolism.

Table 3. Clinical Outcomes during the Study Period.

Population	Fondaparinux	Unfractionated Heparin
All patients randomly assigned to a study group		
No. of patients	1103	1110
Recurrent venous thromboembolism — no. (%)		
Initial treatment	14 (1.3)	39 (3.7)
Entire study	42 (3.8)	56 (5.0)
Type of recurrence — no.		
Fatal pulmonary embolism	16	15
Nonfatal pulmonary embolism	14	24
Deep-vein thrombosis only	12	17
Patients as treated		
No. of patients	1092	1092
Major bleeding — no. (%)		
Initial treatment	14 (1.3)	32 (3.1)
Entire study	22 (2.0)	26 (2.4)
Clinically relevant nonmajor bleeding only — no. (%)		
Initial treatment	35 (3.2)	57 (5.2)
Entire study	62 (5.7)	92 (8.4)
Death — no. (%)		
Initial treatment	9 (0.8)	12 (1.1)
Entire study	57 (5.2)	48 (4.4)

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Thanks for your attention