Disclosure

I am the Co-editor in Chief of the Adult Internal Medicine and Primary Care Section of UpToDate and receive royalties for this work.

An Overview of the Diagnosis and Treatment of Pulmonary Embolism

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A 27 year old woman with dyspnea

Chief Complaint: Dyspnea
History of Present Illness: 15 year history of asthma. Infrequent use of inhalers most of life. Periodic exacerbations with wheezing on auscultation.
Past History: Obesity; on oral contraceptives and albuterol inhalers
Family and Social History: not significant

Her dyspnea worsened

- 1/14/06: She developed a cough, wheezing and worsening dyspnea; Exam revealed bilateral wheezing; She was treated with beta agonists and inhaled steroids
- 1/24/06: She called complaining of worsening dyspnea and a low grade fever. Her exam revealed a mildly dyspneic woman with BP 122/80 mm Hg. pulse of 104; O2 saturation of 93%. She was treated with antibiotics and prednisone.

She has a syncopal event

- 1/25/06: She had been lying in bed most of the past 3 days because of her respiratory problems. She got up from a couch and fell to the ground.
- An ambulance was called and she was taken to the emergency room. She was acutely dyspneic with a respiratory rate of 30 breaths per minute. Her O2 saturation was 87%; pulse 120 beats per minute, temperature 37.5 degrees Celsius and BP 155/90 mm Hg
- An EKG demonstrated sinus tachycardia. While awaiting further diagnostic studies she suffered a cardiac arrest but could not be resuscitated.

An autopsy was performed

What do you think it revealed?
1) Overwhelming pneumonia
2) Massive pulmonary embolism
3) Severe changes of asthma
4) Acute myocardial infarction
Massive Pulmonary Embolism

- Acute pulmonary embolism (PE) is a common and often fatal disease.
- Mortality can be reduced by prompt diagnosis and therapy.
- Unfortunately, as we saw in this patient the clinical presentation of PE is variable and nonspecific.
- Accurate diagnosis therefore can be difficult.

Questions addressed in today’s presentation

- What is age specific prevalence and mortality?
- What are risk factors and clinical signs and symptoms?
- What are the diagnostic strategies and how to apply decision rules?
- What are common pitfalls in management?
- What are the therapeutic strategies?
- How long to treat? (how to use the d-dimer)

Prevalence and Prognosis

- In U.S. estimated at a minimum 500,000 cases a year.
- 200,000 deaths a year.
- Prognosis:
  - 30% untreated
  - 2-3% treated

Risk Factors

- Malignancy
- Immobilization
- Surgery within last 3 months (hip and knee replacement surgery; complicated foot and ankle surgery, trauma)
- Stroke
- Preexisting respiratory disease
- Prior h/o VTE
- Chronic heart disease
- Thrombophilia
- In women
  - Obesity
  - Hypertension
  - Heavy cigarette use
  - OCP’s/HRT

Age-specific pulmonary embolism mortality in the US, by race and gender,
A 66 year old woman

- She comes in with vague complaints of dyspnea. She is otherwise healthy and only on levothyroxine for hypothyroidism. Your history reveals major new stressors in her life but no h/o hemoptysis or chest pain. And, by the way she just returned from London. The exam is unremarkable except for a pulse of 104/min. Her EKG and chest x-ray are completely normal. Your differential diagnosis includes anxiety (most likely), too high a thyroid replacement dose and a PE (the one you are most worried about although in your mind, least likely).

A 66 year old woman

- It is 4:45 PM. The radiologists are on their way home. You recommend and ultimately urge her to go to the ED but she insists that she will not do that as she has a “vital” dinner engagement. She agrees to get a d-dimer after you mention that a low d-dimer will rule out a PE. She gives you her cell phone number and you give her your beeper number.

A 66 year old woman

- The d-dimer comes back at 7 PM slightly high at 598. You curse yourself for agreeing to this strategy and try her cell phone.
- Of course it doesn’t work but after 30 or 40 calls you reach her at 11 PM. (she mentions that she enjoyed her dinner)
- She finally agrees to go to the ED.
- She spends the next 8 hours there and the CT angio finally comes back as negative.
- She calls you the next day extremely upset at the way you handled her case. (sigh!!!!!!)

Truisms about PE’s

- It has been said that pulmonary embolism is the most overdiagnosed and most underdiagnosed of diseases.
- You will spend more sleepless nights and more time agonizing over this disease than almost any other.

A 70 year old man with dyspnea

- A 70 year old man with hypertension and heart failure presents to your office with a 3 day history of worsening dyspnea. He did not complain of chest pain and you review your records and note that a recent cardiac echo documented an EF of 45%. His exam was notable only for a pulse of 100 per minute, a respiratory rate of 20 and an O₂ saturation of 93%. His EKG shows only a sinus tachycardia at a rate of 104/minute and a chest X ray showed mild cardiomegaly that was unchanged.

Based on the history, physical exam, EKG and CXR what plan would you consider the safest and most appropriate plan in caring for this gentleman?

1) Obtain d-dimer, CT angio or VQ to r/o a PE
2) Obtain a cardiac echo to r/o pericardial tamponade
3) Get a BNP and cardiac echo to r/o CHF
Modified Wells criteria

- Clinical symptoms of DVT (leg swelling, pain with palpation) - 3.0
- Other diagnosis less likely than pulmonary embolism - 3.0
- Heart rate >100 - 1.5
- Immobilization (3 days) or surgery in the previous four weeks - 1.5
- Previous DVT/PE - 1.5
- Hemoptysis - 1.0
- Malignancy - 1.0


Modified Wells Criteria

- Probability Score
  - Traditional clinical probability assessment
    - High >6.0
    - Moderate 2.0 to 6.0
    - Low <2.0
  - Simplified clinical probability assessment
    - PE likely >4.0
    - PE unlikely <4.0


- The author’s objective was to develop a simple score based on clinical variables alone
- They used variables that did not require a judgment of pre-test probability as the Wells score requires or an ABG as the initial Geneva score required

Modified Wells’ Criteria for PE

<table>
<thead>
<tr>
<th>Probability Score</th>
<th>Score</th>
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<tbody>
<tr>
<td>High</td>
<td>6.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.0</td>
</tr>
<tr>
<td>Low</td>
<td>1.0</td>
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</tbody>
</table>


- They used data from a multicenter prospective study in Europe on PE
- Using these data they derived a score
- Then they externally validated the score in an independent cohort
The Revised Geneva Rule

**Variable** | **Points**
--- | ---
Age ≥ 60 | 1
Peak O2 sat | 1
D-dimer | 2
Diabetes mellitus | 1
Symptoms | 1
Respiratory Illness | 1
Hemorrhage | 2
Clinical signs | 1
History | 1
Past | 1
Pain in calf or thigh or leg | 1
Clinical Probability | 1
Low | ≤ 0.20
Intermediate | 0.21-0.62
High | ≥ 0.63

**Figure.** Prevalence of pulmonary embolism (PE) according to the revised Geneva score in the derivation and validation sets. Patients with scores ≤ 12 were pooled because of small numbers. 

**Bottom Line**
- Think about the diagnosis
- It is far safer to overtest than to miss it
- Use Decision Rules. They have been tested and they work. For now the Well’s rule is the gold standard but the Geneva Rule if confirmed has the hope of providing objective as opposed to subjective data on which to base your decisions.
- You still have to use clinical judgment- remember it is a diagnosis you can’t afford to miss!

**Options for diagnosis once you decide to rule in or out a PE**

**Primary Strategies**
- CT angio based strategy
- D-dimer strategy combined with CT angio
- VQ scan based strategy

**Adjunctive Data**
- ABG’s
- CXR’s
- EKG’s (S1Q3T3)
- Labs: BNP, troponins
- Echocardiograms
- Impedance plethysmography

**Spiral / Multislice CT Results**
- Degradation product of cross linked fibrin
- Detectable above 500 ng/ml in nearly all cases of VTE Common in many other conditions
- i.e. it is sensitive but not specific (94% negative predictive value)

**D-Dimer**
*Image from Wikipedia*
Diagnostic strategy used in patients with suspected pulmonary embolism: CT scan


VQ Scan

Pros and Cons of each strategy

- VQ is safer; used for years but not readily available in ED’s; requires good clinical judgment re prior probability and reading skills of the radiologists
- CT angio’s are readily available but require dye and also considerable expertise. It often picks up other diagnoses (be cautious about that as it is not a full CT scan); it is an advancing technology though and is getting better and better

Pulmonary Angiogram

MRI MR Angiogram

- Very good to visualize the blood flow.
- Almost similar to angiogram
How well do we do?

Appropriateness of Diagnostic Management and Outcomes of Suspected Pulmonary Embolism.

• Prospective study of 1,529 patients with suspected PE in 117 centers in Europe
• Patients were followed for 3 months to confirm diagnosis
• Measurements:
  – Appropriateness of management using international guidelines
  – Incidence of PE during the follow up

Examples of Inappropriate Evaluation

- No CT, V/Q or ultrasound
- Normal ultrasound, no CT or V/Q
- Normal CT in patients with intermediate or high probability
- Low probability V/Q in patients with intermediate or high probability

<table>
<thead>
<tr>
<th>Diagnostic Work-up</th>
<th>Patients Receiving Appropriate Management (n = 416)</th>
<th>Patients Receiving Inappropriate Management (n = 506)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thromboembolic event, n (%)</td>
<td>5 (1.2)</td>
<td>59 (11.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nontotal thromboembolic event, n</td>
<td>2</td>
<td>10</td>
<td>0.04</td>
</tr>
<tr>
<td>Unexplained sudden death, n</td>
<td>3</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Patients who received anticoagulation for reasons other than thromboembolism were excluded from follow-up analysis.

Anticoagulation

Modified after Valentine and Hall; Anticoagulation in Acute Pulmonary Embolism. UpToDate

- It reduces mortality; it is the principle treatment in nearly all patients.
- It reduces mortality by preventing recurrent PE’s
- Initiate early with heparin (either unfractionated or LMWH)
- Warfarin can be started at the same time as heparin
- Best to overlap heparin and warfarin for at least 5 days and only stop heparin once INR is 2-3 for 2 consecutive days

Risks with warfarin

Valentine and Hall; Anticoagulation in Acute Pulmonary Embolism. UpToDate

- Advanced age (>75 years)
- Concurrent aspirin therapy
- Previous bleeding
- Hypertension
- Cerebrovascular disease
- Advanced heart disease
- Renal insufficiency
- Cancer
Special Considerations

- PE a/w cancer or pregnancy requires heparin
- Patients with massive clots should be on heparin longer until stable
- Anticoagulation clinics save lives and are cost effective; reimbursement not great

Patients with Cancer

- All hospitalized cancer patients should be considered for prophylaxis against VTE, in the absence of bleeding or other contraindications
- Prophylaxis is not recommended for ambulatory patients unless they are under treatment for multiple myeloma with thalidomide or lenalidomide
- Patients undergoing major surgery should be considered for prophylaxis, as well as those undergoing minor surgical procedures lasting longer than 30 minutes. (Prophylaxis should continue for roughly a week, and in high-risk patients after major surgery, it should continue for up to 4 weeks.)
- Low-molecular-weight heparin is the preferred agent for treating VTE.
- Journal of Clinical Oncology article (Free PDF)

Duration of therapy

- 3 months for first PE if temporary risk factor (e.g. lower extremity fracture)
- At least 6-12 months for idiopathic PE. Consider indefinite or d-dimer strategy to guide decision
- At least 6-12 months in those with irreversible factors (e.g. Factor V Leiden mutation) and possibly indefinite; at least 12 months for antiphospholipid syndrome
- Indefinite Rx for 2 or more PE’s

D-Dimer testing to determine the duration of anticoagulation therapy


<table>
<thead>
<tr>
<th>Table 1: Main outcomes (primary vs. treat-zapping)</th>
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<tr>
<td>Outcome</td>
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<tr>
<td>Normal o-Dimer level (n=110)</td>
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<tr>
<td>Abnormal o-Dimer level without Anticoagulation (n=129)</td>
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<tr>
<td>Abnormal o-Dimer level with Anticoagulation (n=20)</td>
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<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>No. of patients (%)</td>
</tr>
<tr>
<td>34 (31.0)</td>
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<tr>
<td>35 (12.7)</td>
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<tr>
<td>75 (7.0)</td>
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<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>No. of events (%)</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>10</td>
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<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Deep vein thrombus (n=10)</td>
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<tr>
<td>Deep vein thrombus (n=10)</td>
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<tr>
<td>DVT and pulmonary embolism (n=10)</td>
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D-Dimer Study Design

- Patients enrolled after DVT/PE and Rx’d at least 3 months with warfarin
- D-dimer performed one month after D/C of warfarin
- Those with normal D-dimer were observed off warfarin
- Those with elevated D-dimer were randomly assigned to resume warfarin or to remain off of it
- Endpoint was recurrence of thromboembolism; average follow up 1.4 years

D-Dimer: results
Thrombolysis of a massive pulmonary embolism

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

* Only generally agreed upon criteria

Contraindications to thrombolytic therapy in pulmonary embolism

- Absolute
  - History of 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)
  - Nonhemorrhagic stroke within prior 2 months
  - Surgery within the previous 10 days
  - Thrombocytopenia (<100,000 platelets per mm3)

Indications for Inferior Vena Cava Filter

- Absolute contraindication to anticoagulation (eg, active bleeding).
- Recurrent PE during adequate anticoagulant therapy.
- Complication of anticoagulation (eg, severe bleeding).
- Major trauma

Summary

- PE is common, often fatal, difficult to diagnose
- New decision rules help
- CT and VQ scans are best studied diagnostic tests
- There are pitfalls; be cautious
- Anticoagulation is effective AND hazardous
- D-Dimer helps determine length of therapy
- Consider thrombolysis or if contraindicated extraction embolectomy for shock
- Consider IVC filters when anticoagulation fails or is contraindicated

References

- Effectiveness of Managing Suspected Pulmonary Embolism Using an Algorithm Combining Clinical Probability, D-Dimer Testing, and Computed Tomography. Writing Group for the Christopher Study Investigators. JAMA 2006;295:172
- Valentine and Hall. Anticoagulation in Acute Pulmonary Embolism. UpToDate Inc