PE in the ED: Managing the Spectrum from Thromboneurosis to Sub-massive Emboli

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Disclosures

- Thrombosis Canada
- PI – PRIHS – Imaging in Suspected PE
- Bayer – speaking fees to CAEP
- CanVector investigator
- PEGED study investigator
- Member of GRADE working group
What is thromboneurosis?

• Concerns about VTE that are not always grounded in science
• CT/PE rates rise when there’s a bad outcome
• Equivocal CT/PE studies often result in treatment
• Understandable concerns in patients with Sx and Hx of VTE
Objectives

• Develop an evidence-informed diagnostic strategy for the spectrum of possible and likely PE patients

• Become knowledgeable on the most appropriate indications for thrombolytic therapy in PE

• Revisit management and disposition decision-making for PE patients at low risk for decompensation
Take Home Messages

• Wells and PERC and d-Dimer are valuable tools in diagnostic evaluation
• Lytics still not ready for wide use in submassive PE
• Risk stratify your confirmed PEs
• Outpatient options are viable
• Adjust d-Dimer for age of patient
Case Scenario

- 42 year old female
- ED for mild pleuritic C/P and SOB
- 3 mos. post partum and breast-feeding
- Recent URI with cough ++
- VS normal / chest wall tender
- No evidence of DVT
- CXR and EKG normal
Backdrop for PE Dx

- Missed PE is real – it will happen to you
- PE is a masquerader
- Mostly a failure to consider than failed Dx tools
- Over-imaging is a real danger (CWC / ACEP)
- Perception – reality mismatch on over-imaging
Pulse of the room

• Are 20% or more of CT / PE studies in your shop performed without evidence-based indications?
2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)
### Table 1  Classes of recommendations

<table>
<thead>
<tr>
<th>Classes of recommendations</th>
<th>Definition</th>
<th>Suggested wording to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td>
<td>Is recommended/is indicated</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td>
<td>Should be considered</td>
</tr>
<tr>
<td><strong>Class IIa</strong></td>
<td>Weight of evidence/opinion is in favour of usefulness/efficacy.</td>
<td></td>
</tr>
<tr>
<td><strong>Class IIb</strong></td>
<td>Usefulness/efficacy is less well established by evidence/opinion.</td>
<td>May be considered</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given treatment is not useful/effective in cases most.</td>
<td>Is not recommended</td>
</tr>
</tbody>
</table>

### Table 2  Levels of evidence

<table>
<thead>
<tr>
<th>Level of evidence A</th>
<th>Data derived from multiple randomized clinical trials or meta-analyses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies.</td>
</tr>
<tr>
<td>Level of evidence C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</td>
</tr>
</tbody>
</table>
Table 3  Clinical characteristics of patients with suspected PE in the emergency department (adapted from Pollack et al. (2011)).

<table>
<thead>
<tr>
<th>Feature</th>
<th>PE confirmed (n = 1880)</th>
<th>PE not confirmed (n = 528)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>50%</td>
<td>51%</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>39%</td>
<td>28%</td>
</tr>
<tr>
<td>Cough</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>Substernal chest pain</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>Fever</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Syncope</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Unilateral leg pain</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Signs of DVT (unilateral extremity swelling)</td>
<td>24%</td>
<td>18%</td>
</tr>
</tbody>
</table>
Suspected PE without shock or hypotension

Assess clinical probability of PE
Clinical judgment or prediction rule²

Low/intermediate clinical probability or PE unlikely

D-dimer

negative

no PE

No treatment³

positive

CT angiography

PE confirmed³

Treatment³

High clinical probability or PE likely

CT angiography

no PE

No treatment³ or investigate further⁴

Treatment³

CT = computed tomographic; PE = pulmonary embolism.

²Two alternative classification schemes may be used for clinical probability assessment, i.e. a three-level scheme (clinical probability defined as low, intermediate, or high) or a two-level scheme (PE unlikely or PE likely). When using a moderately sensitive assay, D-dimer measurement should be restricted to patients with low clinical probability or a PE-unlikely classification, while highly sensitive assays may also be used in patients with intermediate clinical probability of PE. Note that plasma D-dimer measurement is of limited use in suspected PE occurring in hospitalized patients.

³Treatment refers to anticoagulation treatment for PE.

⁴CT angiogram is considered to be diagnostic of PE if it shows PE at the segmental or more proximal level.

⁵In case of a negative CT angiogram in patients with high clinical probability, further investigation may be considered before withholding PE-specific treatment.
My thoughts

- Probably pleuritis or MSK
- Could she have a pulmonary embolism?
- I think she is low pre-test probability
- Can we exclude VTE without a d-Dimer?
- PERC rule?
The Issues

• Pulmonary embolism is a life-threatening diagnosis that can present with varied and non-specific symptoms and can be challenging to diagnose

• The advent of CT Pulmonary Angiography (CTPA) has dramatically improved access to, ease, and speed of high-quality imaging to rule-out PE

• Many patients and physicians are more trusting of definitive testing despite its inherent risks and costs
The Issues

- The majority of CTPA ordered are normal (~80-85% in Canada and 90-95% in the US)
- There is wide variation in use of CTPA by physicians
- CT use continues to grow rapidly (up to 10% per year), leading to:
  - Increased radiation exposure and cancer risk
  - Increased cost
  - Increased length of stay
  - Incidental findings of unclear significance
The Solution

• Evidence-based Diagnostic Algorithm
  – Pulmonary Embolism Rule-Out Criteria (PERC) Rule
  – Wells Score
  – Appropriate use of D-dimer and CTPA
## PERC Rule for Pulmonary Embolism

Shows the PERC criteria, which can rule out PE if all criteria are present and pre-test probability is ≤ 15%.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 50?</td>
<td></td>
</tr>
<tr>
<td>HR &lt; 100?</td>
<td></td>
</tr>
<tr>
<td>O₂ Sat on Room Air &gt; 94%?</td>
<td></td>
</tr>
<tr>
<td>No Prior History of DVT/PE?</td>
<td></td>
</tr>
<tr>
<td>No Recent Trauma or Surgery?</td>
<td></td>
</tr>
<tr>
<td>No Hemoptysis?</td>
<td></td>
</tr>
<tr>
<td>No Exogenous Estrogen?</td>
<td></td>
</tr>
<tr>
<td>No Clinical Signs Suggesting DVT?</td>
<td></td>
</tr>
</tbody>
</table>

**Patient has none of these**

**Score**

**Click!** _points_
The PERC Rule

Diagnostic Accuracy of Pulmonary Embolism Rule-Out Criteria: A Systematic Review and Meta-analysis

Balwinder Singh, MBBS, Ajay K. Parsaik, MBBS, Dipti Agarwal, MBBS, Alok Surana, MBBS, Soniya S. Mascarenhas, RN, Subhash Chandra, MBBS

- Meta-analysis of 12 studies in 6 countries with 13,885 patients
  - Sensitivity: 0.97 (0.96-0.98)
  - Specificity: 0.23 (0.22-0.24)
  - LR-: 0.18 (0.13-0.23)
  - NPV: 99.68%

Bottom Line: Numbers Matter

- **PERC Rule**
  - Miss Rate: **0.32%** or about **1 in 300**
  - False positive rate: **77%**
    - But there is still a chance to rule out with D-dimer
  - Can rule out approximately **20%** of patients

- **D-dimer** (PE Unlikely, Wells < 4, but estimates vary by assay)
  - Miss Rate: Up to ~**1 in 100**
  - False positive rate: ~**55%**
Bottom Line: Numbers Matter

- **CTPA**
  - Neither perfectly sensitive nor perfectly specific
  - Miss rate: ~1% (Christopher Study, JAMA 2006)
  - False Positive Rate: **Up to 10%**
    - Radiographic false positives (mixing artifacts, etc)
    - Diagnosing non-clinically significant PE (Sheh SH, AJR 2012)

- **Lifetime cancer risk** (Smith-Bindman, ArchIM 2009):
  - 20yo female – **1 in 330**
  - 60yo male – **1 in 1770**
Barriers to Evidence-Based Practice

- Difficulty remembering and applying the evidence
- Lack of certainty in patient outcomes
- Perceived imposition on physician autonomy
- Medico-legal concerns
- Disruption to clinical workflow (ease of use)
- Expectation from admitting services or other colleagues
- Patient expectations
### Well's Score

<table>
<thead>
<tr>
<th>Wells &lt; 2</th>
<th>Wells 2 - 3.5</th>
<th>Wells &gt;= 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERC (-)</td>
<td>PERC (+)</td>
<td>PERC (+)</td>
</tr>
<tr>
<td>D-Dimer (-)</td>
<td>D-Dimer (+)</td>
<td>D-Dimer (+)</td>
</tr>
<tr>
<td>CTPA (-)</td>
<td>CTPA (+)</td>
<td>CTPA (+)</td>
</tr>
<tr>
<td>PE Unlikely</td>
<td>D-Dimer</td>
<td>PE Unlikely</td>
</tr>
<tr>
<td>D-dimer (-)</td>
<td>D-dimer (+)</td>
<td>CTPA (-)</td>
</tr>
</tbody>
</table>

### Clinical Signs and Symptoms of DVT
- Leg swelling and pain with palpitation of the deep veins

### Pulmonary Embolism More Likely than Alternative Diagnosis

### Heart Rate > 100 Beats/Minute

### Immobilization or Surgery in Previous 4 Weeks

### Previous Deep Vein Thrombosis/Pulmonary Embolism

### Hemoptysis

### Malignancy (Treatment Ongoing or within Previous 6 Months or Palliative)

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http://136.159.190.176/pe/?
Search and use CLINICAL GUIDES at Point of Care

Download the Thrombosis Canada Web App Now!
Clinical suspicion of PE

Shock / hypotension?

Yes

Diagnostic algorithm as in Figure 3

No

Diagnostic algorithm as in Figure 4

PE confirmed

Assess clinical risk (PESI or sPESI)

PESI class III–IV or sPESI ≥ 1

Intermediate risk

Consider further risk stratification

RV function (echo or CT)\(^a\)

Laboratory testing\(^b\)

Both positive

High risk

A/C; monitoring; consider rescue reperfusion\(^d\)

Intermediate–high risk

A/C; hospitalization\(^e\)

Intermediate–low risk

Low risk\(^c\)

A/C; consider early discharge and home treatment, if feasible\(^f\)
Systematic review and meta-analysis for thrombolysis treatment in patients with acute submassive pulmonary embolism

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolytic therapy</th>
<th>Heparin or placebo</th>
<th>Risk ratio (M-H, fixed, 95% CI)</th>
<th>Risk ratio (M-H, fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total Weight</td>
</tr>
<tr>
<td><strong>Yi &amp; H</strong></td>
<td>0</td>
<td>28</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td><strong>Goldhaber 1993</strong></td>
<td>0</td>
<td>46</td>
<td>2</td>
<td>55</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td><strong>Yi &amp; H</strong></td>
<td>0.24 (0.01, 4.84)</td>
<td>0.07 (0.00, 1.25)</td>
<td>0.36 (0.02, 8.40)</td>
<td></td>
</tr>
<tr>
<td><strong>Goldhaber 1993</strong></td>
<td>0.24 (0.01, 4.84)</td>
<td>0.07 (0.00, 1.25)</td>
<td>0.36 (0.02, 8.40)</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**: 0.24 (0.01, 4.84)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original version\textsuperscript{214}</th>
<th>Simplified version\textsuperscript{218}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age in years</td>
<td>1 point (if age &gt;80 years)</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10 points</td>
<td>–</td>
</tr>
<tr>
<td>Cancer</td>
<td>+30 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+10 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>+10 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Pulse rate $\geq$110 b.p.m.</td>
<td>+20 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Systolic blood pressure $&lt;100$ mm Hg</td>
<td>+30 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Respiratory rate $&gt;30$ breaths per minute</td>
<td>+20 points</td>
<td>–</td>
</tr>
<tr>
<td>Temperature $&lt;36$ $^\circ$C</td>
<td>+20 points</td>
<td>–</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60 points</td>
<td>–</td>
</tr>
<tr>
<td>Arterial oxyhaemoglobin saturation $&lt;90%$</td>
<td>+20 points</td>
<td>1 point</td>
</tr>
</tbody>
</table>

**Risk strata\textsuperscript{a}**

- **Class I**: $\leq$65 points
  - very low 30-day mortality risk (0–1.6%)
  - low mortality risk (1.7–3.5%)

- **Class II**: 66–85 points
  - moderate mortality risk (3.2–7.1%)

- **Class III**: 86–105 points
  - high mortality risk (4.0–11.4%)

- **Class IV**: 106–125 points
  - very high mortality risk (10.0–24.5%)

- **Class V**: $>125$ points
  - 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

\textsuperscript{a} 0 points = 30-day mortality risk 1.0% (95% CI 0.0%–2.1%)
### Pulmonary Embolism Severity Index (PESI)

Predicts 30-day outcome of patients with pulmonary embolism using 11 clinical criteria.

<table>
<thead>
<tr>
<th>Age (years) (+1 per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Patient (+10)</td>
</tr>
<tr>
<td>History of Cancer (+30)</td>
</tr>
<tr>
<td>History of heart failure (+10)</td>
</tr>
<tr>
<td>History of chronic lung disease (+10)</td>
</tr>
<tr>
<td>Heart Rate ≥ 110 (+20)</td>
</tr>
<tr>
<td>Systolic Blood Pressure &lt; 100 mmHg (+30)</td>
</tr>
<tr>
<td>Respiratory Rate ≥ 30/min (+20)</td>
</tr>
<tr>
<td>Temperature &lt; 36° C (96.8° F) (+20)</td>
</tr>
<tr>
<td>Altered Mental Status (disorientation, lethargy, stupor, or coma) (+60)</td>
</tr>
</tbody>
</table>
Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected thromboembolism

What is already known on this topic

A negative D-dimer test can rule out venous thromboembolism in patients with a non-high clinical probability.
Since D-dimer levels increase with age, the proportion of false positive D-dimer test results for venous thromboembolism using conventional cut-off values (500 µg/L) increases in older patients and the specificity decreases.
Age adjusted D-dimer cut-off values (age × 10 µg/L) have therefore been introduced.

What this study adds

This systematic review and meta-analysis established a poor specificity (around 15%) of D-dimer testing with the conventional cut-off value in the eldest patients (>80 years).
The application of the age adjusted cut-off value increased the specificity of the D-dimer test to 35% in the eldest patients, while hardly affecting the sensitivity.
Use of age adjusted D-dimer cut-off values would result in imaging examinations being correctly avoided in 30-54% of older patients with a non-high clinical probability of venous thromboembolism.
Take Home Messages

• Missed PE is usually a failure to consider
• Once in a work-up mode – beware of over-testing – Choosing Wisely
• Wells / PERC = 1-2 punch to better utilize’n
• Sub-massive PE not ready for lytics
• Use PESI or sPESI to risk stratify for admission
Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Suspected Pulmonary Embolism

From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Suspected Pulmonary Embolism:

Francis M. Fesmire, MD (Subcommittee Chair; Committee Co-Chair)
Michael D. Brown, MD, MSc
James A. Espinosa, MD
Richard D. Shih, MD
Scott M. Silvers, MD
Stephen J. Wolf, MD
Wyatt W. Decker, MD (Committee Co-Chair)
Guidance

• **ACEP: Level B recommendations / Class II and III Evidence**

• In patients with a low pretest probability for suspected PE, consider using the PERC to exclude the diagnosis based on historical and physical examination data alone.
## Recommendations for pulmonary embolism in pregnancy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Classa</th>
<th>Levelb</th>
<th>Refc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicion of PE in pregnancy warrants formal diagnostic assessment with validated methods.</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>D-dimer measurement may be performed in order to avoid unnecessary irradiation, as a negative result has a similar clinical significance as in non-pregnant patients.</td>
<td>IIb</td>
<td>C</td>
<td>418, 419</td>
</tr>
<tr>
<td>Venous compression ultrasonography may be considered in order to avoid unnecessary irradiation, as a diagnosis of proximal DVT confirms PE.</td>
<td>IIb</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Perfusion scintigraphy may be considered to rule out suspected PE in pregnant women with normal chest X-ray.</td>
<td>IIb</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>CT angiography should be considered if the chest X-ray is abnormal or if lung scintigraphy is not readily available.</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>A weight-adjusted dose of LMWH is the recommended therapy during pregnancy in patients without shock or hypotension.</td>
<td>I</td>
<td>B</td>
<td>432, 433</td>
</tr>
</tbody>
</table>