Deep Venous Thrombosis
Pulmonary Embolism, D-dimer and Point-of-Care

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Director of Scientific Affairs
Alere
Objectives

• Review of Pathophysiology of DVT and PE
• Diagnosis
  • History & Physical examination
  • Imaging
  • Lab work
• D-dimer Tests
  • Latex
  • Immunometric
  • Specificity
  • Point of Care
Venous Thromboembolism

- A blood clot, or thrombosis, develops abnormally in the blood vessel; usually the extremities.
- A deep vein thrombosis (DVT) forms primarily in the deep calf or thigh veins behind a valve.
  - May cause swelling if it persists
  - Most are relatively minor and go unnoticed
  - Pain occurs once extended along the vein and enters into thigh vein
- If DVT is not treated immediately, the blood clot may reach the lungs and cause a potentially fatal pulmonary embolism
- 90% of blood clots resulting in a PE stem from a DVT
Venous Thromboembolism (VTE)

- 3rd most common cardiovascular disease
- Encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE)

Ileo-femoral DVT
Pulmonary Embolism (PE)

- Clots that travel through the venous system to reach and block a pulmonary vessel.
- If a clot reaches the pulmonary arteries, blood circulation is disturbed and subsequently gas exchange is partly hindered.
Partial List of Risk Factors

- Age >40 yr
- History of VTE
- Surgery/Trauma
- Prolonged immobilization
- Congestive heart failure
- Fracture of pelvis, femur or tibia

- Cancer
- Obesity
- Pregnancy or recent delivery
- Oral contraceptives/Estrogen therapy
- Inflammatory bowel disease
- Burns
- Genetic or acquired thrombophilia
Clinical Symptoms of PE and/or DVT

- Shortness of breath 73%
- Chest Pain 66%
- Leg Pain or Swelling 33% (due to DVT)
- Cough 43%, sometimes with blood 15%
- Tachycardia
- Dizziness
- Syncope
- Tachypnea
- Crackles
- Jugular venous distention
- Fever
- EKG changes

#1 method for diagnosis:

**Autopsy**

"Unfortunately, we won't know what's wrong with you until we do an autopsy."
Issues in Diagnosing Patients with SOB

- Differential diagnoses
  - PE
  - Myocardial Infarction
  - Congestive Heart Failure
  - Pneumonia
  - COPD
  - Cardiac Tamponade

- Diagnostic testing
  - Cardiac markers
  - D-dimer
  - CBC, chemistry, lipid panel
  - EKG
  - CXR
  - VQ scan/CT scan
  - Cultures
  - Echocardiogram
  - Stress test
  - Left/Right Heart Catheterization
  - Pulmonary Function Test
Other Causes of D-dimer Elevation

- DIC
- AMI
- Atherosclerosis
- Trauma
- Hepatic disease
- Sepsis
- Surgery

- Infection
- Pregnancy
- Inflammation
- Age
- Cancer
- Thrombolytic therapy

- Hence a positive test does not prove the existence of DVT/PE
Current practice in PE diagnosis?

General disadvantages:
1. Instrument and skilled staff have to be available
2. Potential of renal damage as a result of imaging dye administration
So What’s The Problem?

• The clinical presentation of both DVT and PE may be misinterpreted, subtle or asymptomatic

• Radiologic studies are expensive, subjective and often non-diagnostic, potentially harmful to the patient and not always readily available

• Need a simple, fast, inexpensive test that is highly sensitive and preferably specific
Challenges Associated With D-dimer

- Not specific to a disease, detects breakdown of clot
  - May encounter false positives for PE/DVT
  - Value is in ability to reduce further evaluation of patients with a negative D-dimer

- No standard for D-dimer; results vary, correlation is difficult
  - Latex agglutination subjective and has 80% sensitivity, vs. sandwich immunoassays (ELISA and FIA) assays with nearly 100% sensitivity

How is D-dimer Being Used?

D-dimer often used inappropriately

• No pretest probability assessment
• Blanket test of all chest pain patients
  • Overuse diminishes the value of the test
    • Lowers specificity / increases FP rate, decreases clinician/lab confidence in test!
  • Shortens life of the scanner
    • With D-dimer screening, the positive rate of CT scans for PE is 11%* - 15%**
    • Without D-dimer screening, the positive rate is 5%** - 8%*
• Irradiates patients
  • The radiation from one chest CT ≥ 40 chest x-rays
• D-dimer TATs insufficient to make rapid clinical decisions for imaging
  • Ordering D-dimer, but sending concurrently for imaging, if available

* Kline, et al, Annals of Emergency Medicine, Nov 2004
** Night Radiologist et al. Sharp Hospital. Unpublished
Appropriate Use of D-dimer

American College of Emergency Physicians Clinical Policy Statement

- In most cases, low probability patients are candidates
- Screen patients with a Pre-test Probability Score (Wells, Hamilton, Charlotte, Geneva, etc)
- Use in out-patient population
  - Hospitalized, pregnant, post surgical patients will likely be elevated due to other clinical conditions/risk factors
- When used appropriately, D-dimer assists in reducing the number of patients requiring CT scans
- Physician education will be VERY useful
  - Use on low probability patients that would otherwise be sent for imaging/scanning as part of a PE or DVT workup

ACEP Clinical Policy

- In patients with low pre-test probability the following can be used to exclude PE:
  - Negative quantitative D-dimer
  - Negative whole blood qualitative D-dimer AND Wells’ score < 2

<table>
<thead>
<tr>
<th>Low Probability</th>
<th>&lt;2.0</th>
<th>(3.6% Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>2.0 – 6.0</td>
<td>(20.5% Risk)</td>
</tr>
<tr>
<td>High Probability</td>
<td>&gt;6.0</td>
<td>(66.7% Risk)</td>
</tr>
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</table>

**Clinical Characteristics**

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
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<tbody>
<tr>
<td>Clinical signs and symptoms of DVT</td>
<td>3</td>
</tr>
<tr>
<td>PE likely or more likely than alternative diagnosis</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate greater than 100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization (bedrest ≥ 30 days) or surgery in the previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy (Receiving treatment, treated in the last 6 months, or palliative care)</td>
<td>1.0</td>
</tr>
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Strategy For Diagnosis of PE

Outpatient or ED

Clinical Assessment and Risk Profile

Inpatient or high risk

Lower Risk
- D-dimer ELISA
  - Normal: Stop
  - Elevated

Higher Risk
- Imaging
  - Renal insufficiency or contrast allergy Lung Scan
  - Kidney function OK no allergy Chest CT

Note: Major role for D-dimer is the low risk ED or outpatient

Note: High risk or inpatient: little role for D-dimer: But remember DIC
Implementation of a Rapid Whole Blood D-Dimer Test in the Emergency Department

Lewandrowski et al., Am J Clin Pathol 2009;132:326-331
Rapid Whole Blood Test in the ED

• Study Objectives – To Assess:
  • ED length of stay pre- and post-implementation of POC D-dimer;
  • Admission and discharge rates pre- and post-implementation of POC D-dimer; and
  • Utilization of imaging test rates pre- and post-implementation of POC D-dimer.

Methods and Materials

- 252 patients pre-implementation and 211 patients post-implementation were evaluated for:
  - test results, turnaround times, and test volumes
  - ED LOS
  - patient chart reviews

Results

• Following implementation of the rapid D-dimer test the total test turnaround time (from blood draw to availability of the test result) decreased from approximately 2 hours (central laboratory, depending on the shift and time of day) to 25 minutes, representing an approximately 79% decrease.

Results

• The volume of D-dimer tests requested by the ED increased from a mean of 127 per month before implementation of the rapid D-dimer test to a mean of 154 tests per month (a 21.3% increase; \( P = 0.037 \)), reflecting increased utilization.

• Some of this increase can be explained by an approximately 6% increase in ED visits during the study period (daily average of 221 before to 235 after implementation).

### Results

**Rates of Hospital Admission, Discharge, and Admit to Observe for Patients Before and After Implementation of the Rapid Whole Blood D-Dimer Test in the Emergency Department**

<table>
<thead>
<tr>
<th></th>
<th>Before Implementation</th>
<th>After Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted (%)</td>
<td>36.5</td>
<td>22.7</td>
</tr>
<tr>
<td>Discharged (%)</td>
<td>42.9</td>
<td>50.2</td>
</tr>
<tr>
<td>Admit to observe (%)</td>
<td>20.6</td>
<td>27.0</td>
</tr>
</tbody>
</table>

- The difference pre- and post-implementation was significant ($P = 0.005$), indicating that the availability of the rapid test may have influenced patient disposition decisions.

Results

Rates of Follow-up Radiologic Testing* Before and After Implementation of the Rapid Whole Blood D-Dimer Test in the Emergency Department

<table>
<thead>
<tr>
<th>Radiologic Study</th>
<th>Before Implementation</th>
<th>After Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%)</td>
<td>60.3</td>
<td>61.1</td>
</tr>
<tr>
<td>Yes (%)</td>
<td>39.7</td>
<td>38.9</td>
</tr>
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</table>

* Venous ultrasound, lung scan, or computed tomography.

- There was no statistical difference in imaging rates, i.e., implementation of POC D-dimer did not increase imaging.
Key Points

• The POC test performed as well as the Lab test while producing
  • A significantly shorter ED LOS
  • Fewer admissions
  • No change in the rate of imaging
• These changes should result in decreased costs.

Diagnostic Accuracy and User-Friendliness of 5 Point-of-Care D-Dimer Tests for the exclusion of Deep Vein Thrombosis

DVT Rule Out Study

- Study Objectives – To Assess:
  - Accuracy of five POC D-dimer tests in the assessment of deep vein thrombosis (DVT);
  - Nursing opinion on the ease of use of the tests.

Methods

• Protocol
  • 577 patients suspected of having a DVT were evaluated using:
    • Vidas (bioMerieux)
    • Pathfast (Mitsubishi)
    • Triage (Alere)
    • Cardiac (Roche)
    • Clearview Simplify (Alere)

• Ease of Use
  • Twenty nurses completed questionnaires dealing the ease of use of the five test methods.
Results

• Accuracy:
  • Differences in the calculated sensitivities and specificities and negative predictive values were largely a result of differences in the cutoffs used.
  • There were no significant differences in the area under the curves (AUC) for the ROC analyses.
Results

• Ease of use:
  • “On the basis of user-friendliness the Cardiac and Triage devices may be preferred for use in an emergency department setting or small primary care clinics. In addition, these tests produce a D-dimer test result within 15 min and can provide measurements of other (cardiovascular) biomarkers …”
  • “The Clearview Simplify test is also user-friendly for primary care, because it is easily portable, requires no analyzer, can be performed on capillary whole blood, and requires no calibration.”
  • The drawback to the Clearview Simplify is that the interpretation of test results was rated more difficult because of the subjective nature of the reading.

D-dimer tests - Choices and Challenges

- Latex Agglutination
  - Qualitative or semi-quantitative
  - Relatively insensitive
- Whole Blood Agglutination
  - More sensitive than latex
  - Somewhat subjective
- Turbidimetric
  - Much less subjective
- ELISA/Immunoassay
  - High analytical sensitivity
  - Historically laborious

- Standardization challenges
  - No recognized standard
  - Purified D-dimer from plasmin digested clots (ng/mL)
  - D-dimer from totally lysed fibrin clots (Fibrin Equivalent Units, FEU)

- Patient variables
Tests of Fibrinolysis

- Fibrinogen
- Platelet count
- Fibrin degradation products
  - FpA
  - FpB
  - Fragment D
  - Fragment E
  - D-dimer ("cross-linked" fibrin degradation product)

- Only D-dimer is useful for DVT and PE
How Were D-Dimers Measured?

- Latex Agglutination:
  - Big clumps that are visible to the naked eye

- Turbidimetric assays:
  - Big clumps that scatter light – the less light detected, the more analyte is present
Turbidimetric Assays

• Shine a light on one side and measure the light coming through on the other side
ELISA / EIA

- **Enzyme-Linked Immunosorbent Assay**
  - Synonymous with Enzyme Immunoassay (EIA)
  - 1st ELISAs were run in microtiter plates (aka ELISA plates)

- **Member of a class of immunoassays (Immunometric or “Sandwich”)**
  - All involve capturing the analyte
  - All involve measuring captured analyte using a form of signal generator
    - EIA uses an enzyme-labeled antibody to convert an “invisible” molecule into a “visible” molecule
    - FIA (Fluorescence immunoassays, or IFA, immunofluorometric assay) are similar to EIA except that they use a fluorescent-labeled antibody as the signal
    - ELFA-Enzyme linked fluorescent immunoassay
  - FIA can be just as sensitive as EIA (e.g., TnI or BNP)
“Sandwich” Immunoassay

• Typically used for analytes with multiple epitopes (Cardiac Markers, D-dimer, Microbiology).
Assays Compared

• Shown below is a POC immunometric (sandwich) assay versus an immunometric Lab assay (left panel) and the POC assay versus a turbidimetric Lab assay (right panel).

**Figure 1: Methods Comparison**

**POC versus Immunometric**

- Triage = 1.08(Vidas) - 147
- $r = 0.9450$
- $n = 197$

**POC versus Turbidimetric**

- Triage = 1.27(Stago) - 95.3
- $r = 0.8791$
- $n = 124$
Value of D-dimer Antibody Specificity

- False positives reduce the value of D-dimer and increase clinician and lab frustration.
- Tests with high affinity antibodies for D-dimer reduce false positives.

- The 3B6 monoclonal antibody offers high specificity due to its affinity to the cross-linking epitope (recognition site) of D-dimer.
Review of 78 DVT/PE Studies

- 78 prospective clinical studies investigated the use of D-dimer for the exclusion of acute VTE and PE
- The specificity the 3B6-based whole blood assay was identified as clinically and statistically superior to the rapid ELISA and automated latex immunoassay methods for acute DVT and PE.

Fibrin Assay Comparison Trial (FACT)

• Study Findings:
  • The main reason for differences between D-dimer assays is due to differences in antibody specificity
  • Assays displaying cross-reactivity with non-cross linked fibrinogen and fibrin derivatives will show falsely high
    • Diagnostica Stago assays (MAbs 8D2, 2.1.16) showed greater than 30% cross-reactivity
  • Assays using 3B6 antibodies were identified as the most specific for D-dimer. 3B6 assays had the least false positives.

Plasmin-derived FDPs may be detected in addition to D-dimer, resulting in an erroneously elevated result.
Distinguish from other FDPs

- False positives reduce the value of D-dimer and increase clinician and lab frustration
- Tests with high affinity antibodies for D-dimer reduce false positives
- The 3B6 monoclonal antibody offers high specificity due to its affinity to the cross-linking epitope of D-dimer
Is D-dimer useful for DIC?

Diagnostic algorithm for the diagnosis of overt disseminated intravascular coagulation.

• Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

• If yes, proceed. If no, do not use this algorithm;

1. Order global coagulation tests (platelet count, PT, fibrinogen, soluble fibrin monomers, or fibrin degradation products).
Is D-dimer useful for DIC?

2. Score global coagulation test results:
   - Platelet count
     - $(>100 \times 10^9/L = 0, <100 \times 10^9/L = 1, <50 \times 10^9/L = 2)$
   - Elevated fibrin-related marker (e.g. soluble fibrin monomers/fibrin degradation products - **D-dimer**)
     - Historical abnormal D-dimers can be split into tertiles
       - no increase scores a 0; mild increase (1\textsuperscript{st} tertile) scores a 1; moderate increase (2\textsuperscript{nd} tertile) scores a 2; strong increase (3\textsuperscript{rd} tertile) scores a 3.
   - Prolonged prothrombin time
     - $(<3 \text{ s} = 0, >3 \text{ but } <6 \text{ s} = 1, >6 \text{ s} = 2)$
   - Fibrinogen level
     - $(>1.0 \text{ g/l} = 0, <1.0 \text{ g/l} = 1)$
Is D-dimer useful for DIC?

3. Calculate score.

- If $\geq 5$: compatible with overt DIC; repeat scoring daily.
- If $< 5$: suggestive (not affirmative) for non-overt DIC; repeat next day.
D-dimer, conclusions

• Most appropriate for ED patients as hospitalized will usually have elevated levels

• When used appropriately, D-dimer is a useful tool for ruling out venous thromboembolism and reducing costs and adverse outcomes that result from unnecessary imaging studies.

• D-dimer can be used on in-patients to help assess disseminated intravascular coagulation (DIC).
Questions???