EDUCATIONAL COMMENTARY – D-DIMER UPDATE

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Learning Outcomes
Upon completion of this exercise, the participant should be able to:

- describe the limitations of the D-dimer test when the result is positive.
- define clinical decision rules and describe how they are used when evaluating venous thrombotic events.

After the D-dimer antigen was first identified in the 1970s, it was proposed for a number of roles in clinical practice. Many of the proposed roles were evaluated and rejected, and new roles for patient monitoring and patient management have emerged for the D-dimer antigen.

In a perfect world, finding the D-dimer antigen in plasma would mean that the patient has a significant clot (or thrombus) and that the clot is being dissolved by plasmin, resulting in a positive D-dimer test result. But the list of pathologic states resulting in positive findings is long. In addition, the D-dimer test result is reported to be elevated in many normal conditions. The D-dimer test result is most useful when found to be negative and is considered in light of the clinical presentation and the likelihood of abnormal clotting. If the application is narrowed to a negative finding and that negative result is used in context with clinical rules, the D-dimer test has a significant role in today’s health care delivery system.

**D-Dimer and the Fibrin Strand**
Fibrin strands are generated when thrombin converts fibrinogen molecules to fibrin monomers. This involves removal of fibrinopeptides from fibrinogen. The fibrin monomers polymerize to form insoluble fibers that interlace the platelet plug. These polymers are then cross-linked by factor XIII. The chemical bonds that first hold the polymer together are weak, but the bonds formed by factor XIIIa are strong covalent bonds.
When plasmin dissolves a clot, the fibrin strand is cut between the D and E regions on the fibrin. Plasmin does not cut the covalent bonds made by factor XIIIa, so the end result is fragments of polymer (called “oligomers”), which contain cross-linked D antigens. These oligomers are detected by the D-dimer antibody. The oligomers vary in size, which presents some problems in the quantitation of D-dimer because the antigen is present on a diverse spectrum of fragments. It does not detect a single molecule, but detects the D-dimer identity on large and small pieces of fibrin.
Figure 2 illustrates the digestion of fibrin by plasmin and the resulting fragments containing D-dimer identity.

**Figure 2.**
Model of crosslinked fibrin digestion by plasmin. The resulting fragments containing D-dimer vary in shape and molecular weight. These fragments circulate as oligomers (few repeating units) as opposed to the fibrin polymer (many repeating units).

**Measurement Techniques**

The measurement techniques developed earlier used latex beads coated with anti-D-dimer antibody. When the antigen was present in sufficient quantity, the beads agglutinated forming a visible reaction. It was not quantitative but could be used as a semiquantitative test by testing various dilutions. The next generation of tests looked at the rate of bead agglutination and correlated that rate with the quantity of antigen present. Studies showed that test sensitivity depended on the size of fragments.

Present-day measurement techniques provide sensitive quantitative analysis. These include enzyme-linked immunoabsorbent assays (ELISA), fluorescence endpoint assays, immunofiltration assays, turbidimetric assays,
and whole blood rapid assays. Rapid assays, such as the immunofiltration and whole blood methods, offer the advantage of a shortened turnaround time, thus facilitating clinical decision making. No one perfect assay is available. Each test system requires tradeoffs of speed, practicality, sensitivity, and specificity. The wide variety of measurement platforms requires each laboratory to determine a cutoff value above which the D-dimer is considered positive for clinical decisions. This cutoff value must be clearly communicated to the clinician.

The quantitative D-dimer level provides evidence about the presence or absence of a thrombus in the patient’s circulation. If the D-dimer result is below the cutoff value, the patient is unlikely to have a thrombus. Conversely, a high level means a higher likelihood of a thrombus. The tricky part is that for most patients, a thrombus is a normal response to injury. But for other patients the thrombus is pathologic, often life threatening, and is commonly called “thrombosis” or a “thromboembolism.”

What Is Venous Thromboembolism?
A clot that blocks a vein is a venous thromboembolism (VTE). The term is most commonly used to describe a deep vein thrombosis (DVT) or a pulmonary embolism (PE). The DVT is a clot in a vein that is deep in the body, and DVTs are most commonly found in major leg veins (such as the femoral or popliteal) and in major pelvic veins. Clots may also occur in major arm veins, but these are rare. PE is blockage of the main artery to the lung and is most commonly due to the thrombus from a deep vein traveling through the circulation to the lung.

The gold standard for diagnosis of DVT is venography, a technique that takes radiographs of veins after a special dye is injected near the site via a catheter inserted in the groin. This is an expensive and invasive procedure. Other techniques use ultrasound, but these are also expensive and inefficient when compared to a blood test. The D-dimer test has been proposed as an efficient and inexpensive way to rule out VTE and has been found to be effective when used with appropriate clinical prediction rules.

What Are Clinical Prediction Rules?
Clinical prediction rules are scoring criteria on the likelihood of VTE used to reach the correct diagnosis while minimizing the need for expensive sonograms. Several validated clinical prediction rules are used for VTE but all work by evaluating patient history and clinical presentation. One common rule set, called the “Wells method,” includes:
- Questions on history of cancer treatment
- Recent surgery that required general anesthesia
- Lower extremity weakness, paralysis, or immobilization
- Tenderness and swelling of the leg and calf
- Previously documented DVT
- Likelihood of other diagnoses

In every method, each answer is scored numerically. The scores are totaled, and the likelihood of VTE is determined as either likely or unlikely.
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The specific rules for DVT and PE are different but follow a similar strategy. If the DVT is likely and the patient has a high pre-test probability, the rule points to venography to make the diagnosis. If DVT probability is determined to be low to moderate, the D-dimer test is performed. If the D-dimer test result is low (negative), the diagnosis of VTE is excluded, but if the D-dimer is elevated (positive), the rule is to proceed with the venography for diagnosis.

Used this way, D-dimer test is reported to have a high negative-predictive value for VTE, i.e., a high number of patients with negative test results are correctly diagnosed. Use of the predictive rules and the D-dimer test speeds the diagnosis and saves healthcare dollars. Figure 3 shows a simplified version of the algorithm for DVT.

### Figure 3
Simplified version of the algorithm for deep vein thrombosis. VTE indicates venous thromboembolism.

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**Monitoring and Tailoring Anticoagulant Treatment Following VTE**

Periodically measuring the D-dimer level on outpatients undergoing anticoagulant therapy following VTE helps to tailor the therapy and predict recurrence according to two recent studies. Patients are usually anticoagulated with oral anticoagulants for some period after hospitalization for VTE, but the optimum length of this period is unknown. In the first study, the patients were treated for three months, and then the D-dimer level was tested one month later by a simple qualitative method. Patients who were positive for D-dimer had a significantly higher risk of recurrence, and this finding suggests that D-dimer testing could determine how long a patient should be treated.

In the second study, patients were tested every two months for a year after cessation of anticoagulant therapy, and similar results were found. Studies like these suggest a possible solid application for the original simple latex agglutination test.
Testing for Disseminated Intravascular Coagulation
The D-dimer is frequently listed as a “fibrin-related marker” to score patients for the likelihood of disseminated intravascular coagulation (DIC). But as in other clinical applications, the usefulness of the D-dimer result is limited by the sensitivity and lack of specificity of positive findings.

Suggested Reading


Glossary
Cross-link: a chemical bond between different chains of atoms in a polymer or other complex molecule

Dimer: a molecule or molecular complex consisting of two identical molecules linked together

Epitope: the part of an antigen molecule to which an antibody attaches itself; also called the “antigenic determinant”

Oligomer: a polymer whose molecules consist of relatively few repeating units

Plasmin: an enzyme derived from plasminogen that destroys blood clots

Polymer: a substance with a molecular structure consisting chiefly or entirely of a large number of similar units bonded together

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