

EDUCATIONAL COMMENTARY – D-DIMER

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Learning Outcomes

Upon completion of this exercise, the participant will be able to:

- Discuss the use of D-dimer assays in the diagnosis of venous thromboembolism (VTE).
- State the desirable properties to consider when choosing a D-dimer assay.

Over 2 million people in the United States are diagnosed with venous thromboembolism (VTE) annually, and it is a contributing factor in an estimated 60,000-200,000 deaths. VTE consists of 2 serious disorders--deep vein thrombosis (DVT) and pulmonary embolism (PE)--that are difficult to diagnose because patients typically present with vague symptoms, such as pain and swelling for DVT or breathing difficulty for PE. In DVT, clots form in the body's deep veins, primarily in the legs, and block blood flow causing pain, swelling, and tissue damage. If a piece of the clot breaks off, it can be carried to the lungs where it can cause blockage as a PE.

Diagnosis of VTE is difficult and may involve the use of invasive and time-consuming imaging procedures, such as venography, compression ultrasound (CUS), pulmonary angiography, spiral computed tomography, and lung scan. Venography and pulmonary angiography are considered the "gold standards" in the diagnosis of DVT and PE respectively. Both of these procedures include injection of contrast dye followed by imaging of the blood vessels. They are time-consuming, expensive, and have associated risks. Since approximately 75% of patients presenting to the emergency department with suspected VTE do not actually have the condition, many institutions have developed diagnostic algorithms designed to rapidly and economically rule out VTE without increasing patient risk. The first step in most cases of suspected VTE is performance of a pretest probability (PTP) assessment, such as the one developed by Wells. Using a set of risk factors and symptoms, a PTP score can be determined and the patient's risk defined as either low, moderate, or high. In most algorithms the followup testing is determined by the risk category. For example, patients with low risk typically undergo a non-invasive test as followup, whereas high-risk patients undergo definitive invasive procedures, such as venography or pulmonary angiography. One of the non-invasive test options now available is the D-dimer assay. A negative (typically a value below a cutoff of 500 ng/mL) D-dimer result for patients in the low-risk or possibly moderate-risk category is considered significant justification for ruling out VTE. The D-dimer assay also offers some value in the investigation of high-risk patients.

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What does the D-dimer assay measure? Following injury to a blood vessel a series of steps known as the coagulation cascade initiates clot formation. During this process fibrin threads are cross-linked by thrombin to form a structure that entraps platelets to form the clot (thrombus). After healing occurs plasmin breaks the clot into fibrin degradation products. One of the fibrin degradation products is D-dimer, which is actually a mixture of various-sized pieces of cross-linked fibrin. Fibrin degradation products (FDP) result from the degradation of both fibrinogen and fibrin, whereas D-dimer is a specific degradation product of fibrin. Normally D-dimer is undetectable in blood and its presence indicates that the fibrinolytic system has been activated. D-dimer assays have replaced FDP assays in many situations.

The specimen for D-dimer testing is plasma collected in a citrate (blue-top) tube. Instructions typically state to separate the plasma from the cells and freeze if the sample is not going to be tested soon (hours) after collection. There is a lack of standardization between D-dimer assays due in part to the fact that D-dimer is a complex variety of cross-linked fibrin derivatives and not a single molecule. Results are expressed in units of pg/mL, mg/L, ng/mL, or ng FEU/mL. FEU, or fibrinogen equivalent units, is a term used by some commercial manufacturers. Use of FEU assumes that 1 lysed native fibrinogen molecule gives rise to 2 D-dimer units. Although results from different methods may not correlate exactly, clinical interpretations relative to a cutoff do seem to correlate. Several studies using different assays and a D-dimer cutoff of 500 ng FEU/mL have demonstrated negative predictive values of 98% -100% for low-risk out-patient populations. Thus, the D-dimer assay is an excellent tool to rule-out VTE when used in this specific population. In the moderate-risk to high-risk and other selected populations, such as hospitalized, elderly, or pregnant patients, the specificity of the test is much lower. In fact, elevated D-dimer levels may occur in any of the following circumstances: hospitalization, old age, pregnancy, surgery, trauma, peripheral arteriopathy, disseminated intravascular coagulation (DIC), coronary disease, thrombolytic treatment, cancer, liver disease, infection, inflammation, and hematoma.

The D-dimer assay may also be used to diagnose or monitor effectiveness of treatment for disseminated intravascular coagulation (DIC), another condition characterized by inappropriate blood clot formation. DIC is an acute condition that may occur in a variety of conditions, including surgery, septic shock, liver disease, and the postpartum period. In DIC numerous minute blood clots form and patients are susceptible to excessive bleeding due to depletion of clotting factors.

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All of the D-dimer assays currently available incorporate antibody recognition of and binding to the D-dimer molecules. The types of immunoassays available for D-dimer measurement include: enzyme-linked immunosorbent (ELISA), whole blood agglutination, turbidimetric, immunofiltration, latex-enhanced photometric, immunochromatographic, and manual latex agglutination methodologies. Not all of these assays have the sensitivity and/or FDA approval to be used to exclude the diagnosis of DVT or PE when used with a pretest probability assessment. Historically, ELISA-based D-dimer assays have been considered the gold standard methodology, but recent studies have demonstrated that selected latex turbidimetric assays produce results equivalent to ELISAs. To date, the assays approved by the FDA for the exclusion of DVT or PE include ELISA and latex turbidimetric methodologies. When choosing D-dimer assays, laboratorians must be aware of the intended uses and limitations of the assays. Particular attention should be paid to the intended use statement in the manufacturer's package insert for each assay. The intended use statement "for the exclusion of DVT and as an aid in the diagnosis of PE" is used for those assays that have been approved by the FDA for this use based on clinical studies demonstrating the safety and efficacy of this particular assay. D-dimer assays that have not been approved for this use will have either one of the following intended use statements: "for the in vitro quantitative determination of fibrin degradation products including the D-dimer fragment, which is useful for DIC applications" or "as an aid in the diagnosis of DVT and PE."

In summary, D-dimer assays when used in conjunction with pretest probability testing provide clinicians a useful non-invasive tool for ruling out deep vein thrombosis and pulmonary embolism in low risk patients. Clinicians and laboratorians should be aware of limitations of D-dimer testing such as use in the wrong patient population and using an assay for something other than its FDA-approved intended use.

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