Focus on Diagnosis: A Primer on D-dimer
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A Primer on D-dimer

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Introduction
The D-dimer antigen is a degradation byproduct of the fibrinolytic process (Figure) and is commonly used as a biomarker in various clinical settings such as the evaluation of venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC). Much more literature on and collective experience with use of the D-dimer assay exists for adult than pediatric patients. However, thrombotic complications are becoming increasingly recognized in infants and children, and reports on this assay’s utility in a variety of other pediatric applications are increasing. This review examines the biochemical basis of D-dimer formation, issues raised by the varied testing methods used to measure D-dimer, and the scenarios in which this assay may provide information useful for medical management.

D-dimer Formation
D-dimer formation begins with cleavage of fibrinogen molecules by activated thrombin into fibrin monomers, which then polymerize. Thrombin activates fibrin-bound factor XIII to form factor XIIIa that, in turn, catalyzes formation of covalent bonds between D-domains of the polymerized fibrin. Finally, during fibrinolysis, plasminogen is activated to plasmin, which cleaves the fibrin polymers at specific locations and releases fibrin degradation products that vary in molecular weight and size but include moieties containing the exposed D-dimer antigen. Thus, D-dimer concentrations are increased under any conditions of increased fibrin formation, as with hemostasis, thrombosis, and tissue repair.

Laboratory Considerations
A wide variety of testing methods has evolved over the years for detection of the D-dimer antigen, but the lack of standardization among these methods has been an ongoing source of concern. Although all modern commercially available assays use monoclonal antibodies specific for the D domain on factor XIIIa-cross-linked fibrin, they are not identical in the precise epitope (antigenic determinant) that they identify. The assays also differ in format, calibration methods, instrumentation, sensitivity, and specificity. Ideally, only assays that have been validated in clinical studies of relevant test populations and for which specific cutoff values have been reliably determined should be used. Unfortunately, this requirement is especially problematic in pediatrics due to the paucity of such validation testing and the reliance on reference ranges provided by studies in adults when there are significant age-related differences in D-dimer values.

A recent study reported a six- to eightfold higher D-dimer reference range for newborns compared with adults. Although this difference largely resolves during infancy, subtle differences persist into late childhood. Such findings are consistent with the concept of “developmental hemostasis” coined by Andrew and associates (1) to describe the physiologic, age-related variation in concentrations of many coagulation proteins. However, developmental hemostasis places a significant burden on laboratories striving to provide optimal care to pediatric patients because age-related reference ranges

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for the specific reagent/analyzer combination used in a given laboratory must be determined for many coagulation tests, including the D-dimer assay. Otherwise, use of reference ranges based on studies of adults or different analyzer systems may lead to inaccurate interpretation of test results in pediatric patients.

**Clinical Uses of D-dimer Antigen Assay**

The D-dimer assay is commonly used in adult patients for assessment of possible VTE. In selected adult patient populations, a normal D-dimer result is as sensitive for the exclusion of VTE as a negative imaging study. Specificity is much lower, however, because a positive D-dimer finding is not sufficient to diagnose VTE or dictate therapy; it only directs the clinician toward more diagnostically specific imaging studies. Limited retrospective studies in children tend to support the assay’s high sensitivity in this setting but suggest that its specificity for VTE may be even lower than in adults (specificity no higher than 57% among the limited number of pediatric patients studied).

Other uses of the D-dimer assay in adults include stratifying risk for recurrent VTE, especially in identifying patients who would benefit from longer duration of anticoagulation therapy. Again, limited studies in children suggest that a markedly elevated D-dimer value is a marker for negative outcomes of VTE, including clot persistence, clot recurrence, and the long-term complication known as the postthrombotic syndrome (characterized by limb asymmetry, skin changes, and chronic pain in the most severe cases).

A recent small study suggests a role for D-dimer in assessing the prognosis and cause of pediatric arterial ischemic stroke. (2) Strokes of cardioembolic subtype were associated with significantly higher D-dimer values than noncardioembolic subtypes (eg, arterioopathies), consistent with the concept that a hypercoagulable state is more relevant to the former type of stroke. If confirmed in larger studies, the ability to distinguish between pediatric stroke subtypes could aid decision-making about the use of antithrombotic therapy as well as guide diagnostic approaches for new-onset childhood stroke.

D-dimer is commonly used to assess for the presence of DIC, which may accompany extreme states such as sepsis, trauma, malignancy, and obstetric emergencies. DIC is characterized by continuous intravascular thrombin and fibrin formation that may lead to clinical bleeding caused by depletion of coagulation factors. However, the diagnosis of DIC is not based solely on the D-dimer result, but on a combination of laboratory values, including platelet count, fibrinogen value, and prothrombin time, in addition to the detection of markers of fibrin formation (such as D-dimer).

The test also has been used to guide decisions about the adequacy of anticoagulation therapy in patients who have rare thrombotic disorders such as severe protein C deficiency because a markedly elevated or rising D-dimer value can be a sign of developing VTE or DIC in such patients.

Inflammation and coagulation pathways are intimately linked, leading to D-dimer elevation during inflammatory disease states. An application of this association is the use of D-dimer to monitor outcomes in patients who have systemic juvenile id-

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**Figure.** Sequential process of fibrinogen cleavage, fibrin polymerization, cross-linking, and fibrinolysis that leads to degradation products containing the D-dimer antigen. This diagram is simplified by depicting only a single fibrin strand and degradation products of uniform composition. Adapted from Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. Blood. 2009;113:2878–2887.
idiopathic arthritis (JIA). Elevated D-dimer values seen in JIA are believed to result from cytokine-induced endothelial activation and are associated with disease activity and poor response to therapy. Persistently elevated D-dimer values, despite therapy with immune modulators, predict a poor outcome for these patients. D-dimer testing, thus, holds promise as a predictive tool to help target more intensive treatment for high-risk JIA patients early in the disease course.

Elevated D-dimer has also been reported in the setting of other systemic vascular diseases such as Kawasaki disease, Henoch-Schönlein purpura, and hemolytic-uremic syndrome. In such cases, D-dimer values tend to correlate with disease stage, and it has been suggested that D-dimer measurement might serve as a prognostic tool for these conditions or to help differentiate among other diagnostic considerations.

Of special relevance to the general pediatrician, elevated D-dimer concentrations also have been associated with poorer outcomes in pediatric patients who develop community-acquired pneumonia (CAP). Patients who have CAP and elevated D-dimer concentrations may be at higher risk for developing parapneumonic effusion or empyema. Patients who experience these complications may exhibit increased coagulation activity and fibrin deposition in the pleural space, leading to increased fibrinolysis and D-dimer formation. D-dimer values showed an increasing trend among groups of patients who had CAP, pneumonia with effusion, and empyema, respectively, and were higher than in healthy children. However, further prospective studies are required.

Future Considerations

D-dimer is a widely available test, and an increasing number of applications for its use within adult medicine are evolving. Although additional validation studies and studies of age-related changes in D-dimer values still need to be performed to allow for reliable and interpretable results for pediatricians, D-dimer measurement holds promise for monitoring of pediatric diseases. Prospective studies are required to examine the dynamics of D-dimer plasma concentrations, such as time to normalization, so clinicians can interpret when an abnormal result is suggestive of significant new or ongoing disease rather than expected recovery from an elevated concentration after surgery or a resolving infection.

Additional studies of the utility of D-dimer measurement in specific clinical situations are required. Candidate disorders for such study include inflammatory diseases such as other vasculitides and inflammatory bowel disease. Given the link between inflammation and obesity, D-dimer could also prove useful in assessing vascular risk in obese children, as suggested by a recent study.

3) However, at present, rigorous studies of D-dimer applications in pediatric medicine are limited. Thus, caution should be exercised in interpreting D-dimer results in the clinical care of pediatric patients because reference ranges, cut-off values, and interpretation of clinical research studies in adults cannot be reliably extended to children. The D-dimer assay will have only limited utility in general pediatrics until the necessary prospective clinical validation studies in children are performed.

References


Suggested Reading
