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Current Developments in the Management of Hematologic Disorders

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The Role of D-dimer Testing in Clinical Hematology and Oncology



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H&O What is D dimer?

CG D dimer is a specific antigen derived from the degradation of factor XIIIa cross-linked fibrin. Monoclonal antibodies specific for D-dimer antigen were developed to provide clinicians with a laboratory test that could distinguish between products derived from fibrinogen degradation and those derived from fibrin degradation. The D-dimer antigen measured in clinical samples is derived from the degradation of fibrin formed by the combined action of thrombin, factor XIIIa, and plasmin.¹

H&O How is D dimer measured?

CG Each manufacturer of D-dimer tests uses a specific monoclonal antibody and unique detection technology to quantify D dimer in clinical samples. These tests can be grouped according to their sensitivity at detecting D-dimer-related antigen.¹

The first D-dimer assay to receive approval from the US Food and Drug Administration (FDA) was based on the agglutination of latex beads coated with monoclonal antibody. Quantitative and automated point-of-care assays were subsequently developed as potential tools to exclude venous thromboembolism (VTE), monitor disseminated intravascular coagulation (DIC), detect excess fibrinolysis, and monitor anticoagulation therapy.¹

Several assays and instruments are suited for either central laboratory or point-of-care testing. Central laboratory assays are more sensitive than point-of-care assays. Central laboratory assays use either enzyme-linked immunosorbent assay (ELISA) technology or immunoturbidimetric assays, both of which are classified as highly

sensitive assays. In contrast, assays used in point-of-care settings are read by visually inspecting the development of color on a slide and are designated as moderately sensitive.

Clinicians must establish whether to use a highly sensitive or moderately sensitive assay to detect D dimer in their clinical practice and rule out deep vein thrombosis (DVT) or pulmonary embolism (PE).

H&O What makes the D-dimer assay so difficult to interpret in a hematology/oncology practice?

CG Fibrin plays a role both in the repair of normal tissue and in repair after pathologic injury. Significant intravascular and extravascular fibrin formation in patients with

The D-dimer test is best used diagnostically to exclude VTE rather than to confirm it.

cancer lowers the specificity of D dimer for thrombosis.² Hematology/oncology specialists treat elderly patients, who typically have comorbidities that increase D-dimer levels. D-dimer fragments can circulate for hours until cleared by the mononuclear phagocyte system in the liver and spleen, and many of these patients have liver disease or splenia. D-dimer levels indicate the balance between

the rate and magnitude of intravascular and extravascular fibrin formation, as well as the clearance of D dimer.

The use of D-dimer levels to rule out VTE in a hematology/oncology practice is problematic because so many patients have elevated levels for other reasons. However, in a patient who presents with a painful swollen extremity, chest pain, syncope, or shortness of breath after cancer therapy or treatment for VTE, the D-dimer assay may be useful for excluding DVT. In practices focused on the management of hypercoagulable states, the outpatient quantitative D-dimer test can exclude VTE, especially after anticoagulant therapy has been stopped.

H&O How useful is testing, given its poor specificity in the diagnosis of DVT and PE?

CG D dimers are detectable at levels above 500 ng/mL in virtually all patients with VTE. Because of its good sensitivity and poor specificity, the D-dimer test is best used diagnostically to exclude VTE rather than to confirm it.³

An even more accurate way to rule out VTE is to add a clinical pretest probability score to D-dimer testing. A low clinical pretest probability score plus a low D-dimer value can rule out the need for further testing (with ultrasound) because DVT will develop in only 0.4 % of such patients.⁴ These data apply to outpatients who present without any history of active malignancy.

An elevated D-dimer level suggests persistent activation of clotting or inflammatory pathways, and extremely elevated levels may be a predictor of post-thrombotic syndrome.⁵ Furthermore, an increase in the D-dimer level measured after oral anticoagulant therapy has been stopped may be predictive of recurrent VTE in patients who have had a unprovoked blood clot.⁶

More recent studies suggest that the rate of recurrent VTE—whether provoked or not—is too high, even in the patients who test negative for D dimer.⁷ As a result, some practitioners have stopped monitoring D dimer and consider using low-dose rivaroxaban (Xarelto, Janssen) to prevent recurrent thrombosis. Future studies are needed to identify those most likely to benefit from long-term therapy without bleeding complications.⁸

The risk for recurrence is high in patients with cancer and VTE, and anticoagulant therapy is not stopped. After 3 months of anticoagulant therapy for VTE provoked by surgical resection of a tumor, however, D-dimer levels are measured to assist in determining the duration of anticoagulation. Unless D-dimer levels have dropped to age-adjusted levels and the thrombus is completely lysed, anticoagulant therapy is often continued for another 3 months depending on the patient's weight and other factors affecting risk.

Practice patterns may change in response to clinical

trial data showing that the rate of recurrence is high even in those who have a negative D-dimer test result after a provoked blood clot,⁷ and as researchers discover newer agents that can prevent recurrence with a lower rate of bleeding.⁸

Patients with cancer are at high risk for VTE. Because of the poor specificity of the clinical scores and the D-dimer test, initial D-dimer testing is of limited usefulness, and these patients must undergo ultrasonography and imaging studies.

Hospitalized hematology/oncology patients generally have other disease processes that elevate D-dimer levels, making a negative D-dimer test result unlikely. Therefore, the usefulness of D-dimer testing for the inpatient evaluation of VTE is limited. D-dimer levels also are age-dependent, and because levels increase with age, it is less common for individuals older than 60 years to have a negative D-dimer test result unless age-adjusted values are used.⁹ Many of the assays used in clinical practice have not established the age-adjusted D-dimer cutoff value and clinicians should not use them unless validated by clinical studies.

H&O When should hematology/oncology practitioners measure the D-dimer level?

CG There are 4 distinct settings in which D-dimer testing can be considered in hematology/oncology practice: (1) to rule out DVT; (2) to rule out PE; (3) to detect the presence and extent of DIC; and (4) to determine whether a hyperfibrinolytic disorder is causing a thrombohemorrhagic state.

In the population of adult patients who have a low or unlikely pretest probability score for DVT, a negative D-dimer test result has a negative predictive value of 99%. Assay results should always be paired with a clinical pretest probability score for outpatients presenting with signs or symptoms of VTE.

Most hematology/oncology practitioners care for individuals with comorbidities that are associated with elevated D-dimer levels (Table). This reduces the percentage of patients in whom the combination of a low pretest clinical probability score and a negative D-dimer test result is clinically useful. Nonetheless, there are some clinical settings in which the combination may be useful. One example is the patient who presents to the emergency department with symptoms consistent with VTE and who is in remission following cancer chemotherapy.

In a pregnant patient with a low pretest probability score, a negative D-dimer test result is useful to exclude VTE, especially in the first trimester. Furthermore, D-dimer testing may help to define the cause of thrombocytopenia in pregnancy.¹⁰ Severe thrombocytopenia and elevated D-dimer levels may lead to the diagnosis of systemic lupus

Table. Comorbidities That Elevate D-dimer Levels

- Abnormal fibrinolysis, use of thrombolytic agents
- Acute limb ischemia
- Acute renal failure
- Atrial fibrillation
- Cardiovascular disease, congestive heart failure
- Chronic renal failure and underlying cardiovascular disease
- Disseminated intravascular coagulation
- Intracardiac thrombus
- Myocardial infarction
- Nephrotic syndrome (eg, renal vein thrombosis)
- Normal pregnancy
- Preeclampsia and eclampsia
- Severe infection/sepsis/inflammation
- Severe liver disease (decreased clearance)
- Stroke
- Surgery/trauma (eg, tissue ischemia, necrosis)
- Systemic inflammatory response syndrome
- Vaso-occlusive episodes of sickle cell disease
- Venous malformations

erythematosus (SLE) or other vasculitides provoked by pregnancy.

D-dimer levels can be used to monitor the response to anticoagulant therapy. A decline in the D-dimer level provides assurance that the dose of anticoagulant being used is suppressing blood coagulation. Those patients without D-dimer suppression on anticoagulants typically have SLE, obesity, or an infection, any of which may trigger extravascular fibrin formation or overwhelm the ability of the anticoagulant to suppress fibrin formation.

Interestingly, patients with an unexplained increase in their D-dimer level and a negative Doppler study were found to be at an increased risk for malignancy. This finding suggests that close follow-up is indicated in this cohort of patients.¹¹

A work-up for VTE based on an elevated D-dimer level is not indicated because many patients have chronic inflammatory conditions, including obesity, that cause low-grade intravascular and extravascular fibrin formation.

In the evaluation of DIC, several laboratory and clinical observations can be required to learn if there is a persistent stimulus for the intravascular activation of blood coagulation. D-dimer levels increase as the process

continues. The D-dimer level is used as part of the DIC Score of the International Society on Thrombosis and Haemostasis (ISTH).¹²

H&O Does D-dimer testing have any other uses in the management of hematology/oncology patients?

CG Unless the practitioner has experience with the interpretation of D-dimer assays and has a specific reason for monitoring the level of this fibrin-specific degradation product, the test should not be used.

The previous practice of monitoring changes in D-dimer levels in response to the discontinuation of anti-coagulant therapy after an unprovoked VTE in women has been called into question,⁷ and many experts use either aspirin or rivaroxaban to reduce the risk for recurrence long term, depending on the patient's risk for bleeding and comorbidities.⁸

D-dimer levels can be increased when only a small percentage of fibrin is lysed by plasmin. Any increase in the D-dimer level within 1 month after the discontinuation of anticoagulant therapy has been shown to be a useful marker to predict recurrence of DVT.

If a patient is on anticoagulant therapy for a provoked VTE and presents with a painful, swollen leg after the therapy has been stopped, a negative D-dimer test allows the physician to look for explanations other than DVT for poor venous drainage, such as May-Thurner syndrome. Clinical decisions based on a single measurement are risky, and the successful management of clinically complex cases may require additional testing.

H&O What role does D-dimer testing play in monitoring disease activity?

CG One could view the D-dimer test as a sensitive assay for any disease process that causes intravascular or extravascular injury through infection, inflammation, cancer, or trauma. The D-dimer test has been used in clinical research to help define stage of cancer, response to therapy, and progression of disease, but it has not been used in routine clinical practice. A high D-dimer level may be a risk factor for the development of thromboembolism in response to chemotherapy and is a part of some risk scores used in clinical research.¹³ In patients with SLE, a high D-dimer level indicates a high risk for thrombosis.¹⁴

H&O In what diseases treated by hematology/oncology specialists has D dimer been studied?

CG Investigators have reported changes in D-dimer levels depending on stage and response to treatment in

patients with acute myelogenous leukemia or cancers of the breast, lung, prostate, colon, pancreas, or stomach. An increase in D-dimer levels has been reported in hemolytic disorders, including sickle cell disease. The utility of D-dimer levels outside clinical studies has not been established. In some clinical settings, a low D-dimer level can be of negative predictive value in monitoring for the development of aortic dissection.¹⁵ Low D-dimer levels are of high negative predictive value for excluding cerebral venous thrombosis in patients with isolated headache.¹⁶

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Suggested Readings

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