Saint Luke's Regional Laboratories
Clinical Laboratory Letter

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Evaluation of Rapid Quantitative D-dimer Assay in Diagnosis of DIC

The International Society of Thrombosis and Hemostasis (ISTH) recently proposed a scoring system for the diagnosis of disseminated intravascular coagulation (DIC) based on the presence of a predisposing clinical condition (eg sepsis, trauma), and assigning a score based on four laboratory parameters including decreased platelet count, elevated fibrin-related marker such as D-dimer, elevated protime (PT), and decreased fibrinogen.

Algorithm for Diagnosis of Overt DIC

1. Patient must have an underlying disorder known to be associated with DIC
2. Score coagulation test results as follows:
   - platelet count
     - >100 = 0
     - <100 but >50 = 1
     - <50 = 2
   - elevated D-dimer
     - no increase = 0
     - moderate increase = 2
     - strong increase = 3
   - prolonged PT
     - <3 sec = 0
     - >3 sec but <6 sec = 1
     - >6 sec = 2
   - fibrinogen
     - >100 mg/dL = 0
     - <100 mg/dL = 1
3. If score ≥5: compatible with overt DIC; repeat scoring daily
   If score <5: may be compatible with non-overt (compensated) DIC, repeat testing in 1-2 days.

Quantitative, rapid D-dimer assays have been widely utilized for several years, primarily for their high sensitivity in ruling out acute venous thromboembolism. D-dimer is a key component in the laboratory diagnosis of DIC, however little has been known about the performance of the newer D-dimer assays in the context of DIC diagnosis.

A recent study evaluated the analytical performance of a quantitative D-dimer assay in hospitalized patients with suspected DIC (Am J Clin Pathol 2004; 122:178-184). D-dimer results were retrospectively analyzed in 241 hospitalized patients (134 women and 107 men aged 19-91 years) in whom D-dimer was ordered over a 12 month period. Medical records were reviewed for clinical and laboratory evidence consistent with DIC. The prevalence of DIC in this group was 22.4% (54/241 patients). The majority of those with DIC had sepsis or cancer. Patients with clinical DIC had a median D-dimer value of 21.7ug/mL (reference range 0-0.5ug/mL), while the median value in those without DIC was 2.7ug/mL. Using ROC curve analysis, a D-dimer cutoff of 8.2ug/mL optimized the sensitivity and specificity of the D-dimer assay for the diagnosis of DIC (sensitivity was 98%, specificity 86%, negative predictive value 99%, and positive predictive value 66%). The optimal D-dimer cutoff value (8.2ug/mL) was validated in a cohort of 286 additional patients. The high negative predictive value for D-dimer at this cutoff confirms the value of this assay in ruling out DIC. ROC curve analysis also showed that D-dimer had the best discriminatory value in the diagnosis of DIC of the four laboratory tests included in the ISTH scoring system. In the ISTH scoring system, a score of 3 (strong increase) should be assigned to a D-dimer value greater than 8.2 ug/mL. We would arbitrarily suggest that a score of 2 (moderate increase) be assigned to a D-dimer value greater than 4.0 ug/mL, but less than 8.2 ug/mL.

The authors confirmed the relatively low specificity of D-dimer by demonstrating that D-dimer was elevated (>0.5 ug/dL) in 70% of 59 hospitalized patients without venous thromboembolism, cancer or DIC, and 90% of 27 patients with cancer and no evidence of venous thromboembolism or DIC. Use of the ISTH algorithm resulted in a higher specificity and positive predictive value for the diagnosis of DIC than use of the D-dimer result alone.

In conclusion, a sensitive, rapid, quantitative D-dimer assay provides excellent sensitivity and negative predictive value for the diagnosis of DIC, optimized at a cutoff of 8.2ug/mL. Specificity and

positive predictive value is improved by using the ISTH algorithm for DIC diagnosis. The rapid quantitative D-dimer assay is available at Saint Luke's Regional Laboratories 7 days a week. A 5mL blue-top tube is required.

False Positive Urine Drug Screens

Urine drug screens are frequently ordered on patients who exhibit symptoms of intoxication, experience trauma or have a history of drug ingestion. Most hospital laboratories use immunoassays to detect drugs because they are relatively simple to perform, have high sensitivity for drugs of abuse and provide rapid turnaround time. The laboratories in the Saint Luke's Health System use the Triage Drugs of Abuse Panel which incorporates 7 discrete monoclonal antibodies for the detection and identification of amphetamine, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine and tetrahydrocannibinol (THC). This assay is designed to detect urine drug levels above a predetermined cutoff concentration. The major problem with all rapid immunoassays is their less than perfect specificity for each drug class. Prescription and over the counter medications, as well as herbal supplements, may cause false positive results. In our experience, false positive reactions for THC occur most commonly because several prescription medications including Clozaril, Propulsid, Protonix, Paxil, Tegretol and Zocor cross-react with the anti-THC monoclonal antibody. Over the counter remedies can produce false positive results in the phencyclidine and benzodiazepine assays. Herbal supplements containing ephedra may produce a positive amphetamine reaction, while ingestion of poppy seeds may produce a positive opiate reaction.

Physicians need to be aware of the limitations of urine drug screens. If a falsely positive drug screen is suspected, a confirmatory drug screen should be ordered. As a reminder, Saint Luke's Regional Laboratories has recently revised the comment attached to urine drug screens. The new comment states, "This drug screen provides presumptive results for medical purposes only. False positive results may occur. Physicians should order confirmatory testing on this sample if the results are considered clinically significant".

Potassium Reference Range Change

The plasma potassium reference range has been changed from 3.6 – 5.0 mEq/L to 3.5 – 5.1 mEq/L.

Second Tier Follow-up Testing for Congenital Adrenal Hyperplasia

Newborn screening includes testing for congenital adrenal hyperplasia (CAH), which is an autosomal recessive disorder that affects approximately 1 in 10,000 newborns and results in deficient secretion of cortisol. Decreased cortisol synthesis leads to elevated ACTH levels, which produces adrenal hyperplasia. Five different enzyme deficiencies can cause CAH, but deficiency of 21-alpha-hydroxylase accounts for more than 90% of cases. Impaired 21-hydroxylase activity causes deficient production of cortisol and aldosterone. Depending on the extent of the enzyme deficiency, CAH may present as either a salt losing (75% of cases) or a non-salt losing disorder during the newborn period. Both types of CAH are associated with genital abnormalities because 21-hydroxylase deficiency prevents precursor hormones, such as 17-hydroxyprogesterone (17-OHP), from entering the cortisol metabolic pathway. These precursors accumulate and spill over into the androgen metabolic pathway, forming androstenedione and testosterone.

CAH screening is performed by measuring levels of 17-OHP in dried blood spots. Levels of <50 ng/mL are considered normal for a normal weight infant of 2250 grams or greater. A significant problem with CAH screening programs, is that 17-OHP levels are elevated in very low birth weight (<1500 grams) and extremely low birth weight (< 1000 grams) infants, resulting in many falsely positive results. Second Tier CAH testing is recommended for all newborns with abnormal 17-OHP screening results.

Second tier testing by tandem mass spectrometry simultaneously measures 17-OHP, androstenedione and cortisol. Patients with CAH have elevated androstenedione and low or absent cortisol. Findings of elevated 17-0HP values (>10.2 ng/mL) and a high 17-OHP + androstenedione/cortisol ratio (>2.5) support the initial abnormal screening result. The Saint Luke's Hospital Reference Laboratory can be contacted at (816)932-2424 for further information or to obtain Mayo Medical Laboratories' blood spot collection cards.