Saint Luke's Regional Laboratories
Clinical Laboratory Letter

May 2005

HbA1c is a CV Risk Factor

HbA1c is a marker for average blood glucose concentrations over the preceding three months. The level of HbA1c is strongly linked to the risk of developing eye, kidney and nerve disease in people with type 1 and type 2 diabetes mellitus. Randomized trials have clearly demonstrated that decreasing the HbA1c level reduces these risks.

Two recent studies in the Annals of Internal Medicine have also validated that HbA1c is a progressive risk factor for CV disease in individuals with and without diabetes (Ann Intern Med 2004; 141:413-20 & 421-31). Every 1% absolute increase in HbA1c above the nonglycemic level of 5% predicts a 20% relative increase in the incidence of CV events even after adjustment for systolic blood pressure, cholesterol level, body mass index, waist to hip ratio, smoking and previous myocardial infarction or stroke. A similar relationship exists for total mortality.

These studies confirm that HbA1c should be added to the list of other clearly established indicators of CV risk such as blood pressure and cholesterol. Saint Luke's Regional Laboratory (SLRL) has included HbA1c in its Cardiovascular Risk Panel since August 2001. This panel includes fibrinogen, high sensitivity CRP, homocysteine, lipoprotein (a) and hemoglobin A1c. The risks included in this panel have been adjusted for lab values reported at SLRL and should not be applied to results obtained from other laboratories.

Caution Regarding Lyme Serology

The Centers for Disease Control (CDC) recently issued a cautionary statement (MMWR 54;125) regarding testing for Lyme disease. Several assays are available through commercial laboratories that do not have adequately established accuracy or clinical utility. These assays include urine antigen tests, immunofluorescent staining for cell-wall deficient forms of Borrelia burgdorferi, lymphocyte transformation tests and PCR on inappropriate specimens such as urine. Western immunoblot testing is also potentially problematic in that criteria for interpretation are often not consistent between laboratories.

The recommended test protocol for the diagnosis of Lyme disease is an initial screening assay by enzyme immunoassay (EIA) or immunofluorescent assay (IFA). Specimens testing positive by either method should be evaluated further by a standardized Western blot immunoassay. Specimens negative on initial screening do not need further testing, however, if a patient with suspected early Lyme disease has negative serology the screening test should be repeated in 4-6 weeks.

Saint Luke's Regional Laboratories performs Lyme antibody screening by EIA which detects class-specific IgM or IgG to Borrelia burgdorferi. IgM levels usually peak 3-6 weeks after infection. IgG antibodies begin to be detectable several weeks after infection. The IgG response may continue to develop over the course of several months and generally persists for years. All specimens testing positive or equivocal for Lyme antibody are automatically forwarded to Mayo Medical Laboratories for Western blot.

Prolongation of the Activated Partial Thromboplastin Time

The activated partial thromboplastin time (APTT) is a global plasma coagulation test affected by abnormalities in the intrinsic and common portions of the classic coagulation pathway. The concept of separate intrinsic and extrinsic pathways of coagulation is useful for understanding and diagnosing blood coagulation abnormalities in vitro, however it should be appreciated that in vivo there are interactions between the two pathways outside of the classic scheme. The APTT will generally be prolonged when a clotting factor level is less than 30-40%. Since the normal range for most clotting factors is 50-150% (and 70-130% for factor XI), a normal APTT does not rule out the possibility of a mild factor deficiency.

There are 6 causes of a prolonged APTT (with PT normal or slightly prolonged):

- Pre-analytical errors
- Heparin
- Coagulation factor deficiency associated with risk of hemorrhage
- Coagulation factor deficiency with no risk of hemorrhage
- Lupus anticoagulant
- Specific coagulation factor inhibitor

In the investigation of a prolonged APTT, pre-analytical errors should be ruled out first. The most common pre-analytical cause of a prolonged APTT is contamination with heparin in a sample drawn from an arterial or central line (APTT will often be >200 seconds). The APTT will be affected by an altered plasma to citrate ratio in blue top collection tubes, which may be seen with a high hematocrit (>55%), or a sample with a short or long draw. Other pre-analytical problems include dilution of a sample drawn above an IV, formation of clots in a sample due to inadequate mixing, delay in transport or processing of a sample (>4 hours), and inadequate centrifugation.

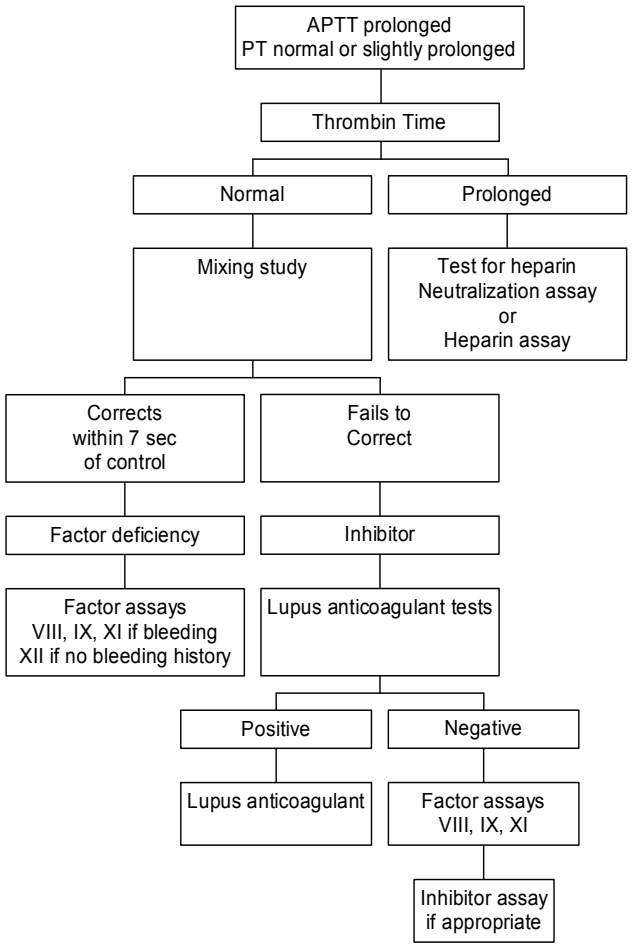
The APTT is used most frequently to monitor anticoagulation with unfractionated heparin. Each laboratory should set its own APTT therapeutic range for heparin, corresponding to a heparin level of 0.3-0.7 U/mL. In Saint Luke's Regional Laboratories this therapeutic range is currently 60-100 seconds. In cases of apparent heparin resistance where the APTT does not rise appropriately, a heparin assay is indicated to determine if a therapeutic amount of heparin is present. Low molecular weight heparin (LMWH) will cause only a mild prolongation of the APTT; if monitoring of LMWH is required, a specific LMWH assay is used. The APTT is prolonged by direct thrombin inhibitors such as Argatroban and lepirudin, and is used to monitor anticoagulation with these drugs.

Hereditary coagulation factor deficiencies which selectively prolong the APTT and are associated with a bleeding tendency include factors VIII, IX and XI. The common acquired coagulopathies such as liver dysfunction and DIC may cause prolongation of the APTT, however the PT will also be prolonged in these disorders, due to multiple clotting factor deficiencies. Hereditary coagulation factor deficiencies which selectively prolong the APTT but are not associated with a risk of hemorrhage include deficiencies of factor XII, prekallikrein and high molecular weight kininogen.

Lupus anticoagulants are acquired inhibitors directed against phospholipid-binding proteins, interfere in vitro with phospholipid-dependent coagulation tests, and are a common cause of APTT prolongation. In vivo, lupus anticoagulants do not interfere with coagulation factor complex formation on the platelet phospholipid surface, and are thus not usually associated with a bleeding tendency.

Approximately 15% of patients with severe factor VIII or IX deficiency develop alloantibodies (inhibitors) to transfused factor concentrate. Autoantibodies against clotting factors may also arise spontaneously, or associated with various diseases and drugs, most commonly directed against factor VIII. The inhibitor-factor complexes are rapidly cleared, resulting in factor deficiency and a severe bleeding tendency.

An approach to the evaluation of a prolonged APTT is outlined in the following algorithm.



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