



Saint Luke's Regional Laboratories Clinical Laboratory Letter



July 2007

Tick-Borne Disease Alert

The Missouri Department of Health issued an Advisory in mid-June regarding an increase in tick-borne disease in the state compared to the previous five years. Between January 1 and June 1, 2007, tick-borne rickettsial diseases (TBRD) including ehrlichiosis/anaplasmosis and Rocky Mountain spotted fever (RMSF) were noted to be increased. The Health Advisory can be accessed at <http://www.dhss.mo.gov>. *Ehrlichia chaffeensis* is the causative agent of human monocytic ehrlichiosis (HME), while *Anaplasma phagocytophilum* is responsible for human granulocytic ehrlichiosis (HGE). HME is more common in Missouri, although HGE is reported as well.

Signs and symptoms of TBRD are nonspecific and include fever, headache, myalgia, and rash, with rash more frequent in RMSF. Common laboratory findings that support the diagnosis of TBRD include leukopenia, thrombocytopenia and elevated liver enzymes in HME/HGE and hyponatremia in RMSF. Early treatment of suspected TBRD is strongly advised due to significant morbidity and potential mortality from these infections. Doxycycline is the drug of choice.

Specific testing, including serology and PCR for TBRD is available through Saint Luke's Regional Laboratories. Recommended testing for acute HME/HGE includes PCR and serology. HME/HGE serology includes IgG antibody for both organisms. Since IgG antibody may be negative in early infection, PCR for HME/HGE is recommended for suspected acute disease. Serology only is available for RMSF, but includes titers for both IgG and IgM antibodies. IgM is generally detectable within 1-2 weeks of RMSF symptom onset. Specimen requirement is one red top tube for serology and one lavender top tube, refrigerated, for PCR. Ticks should not be submitted for identification or testing.

Updated HIV Antibody Testing

Human immunodeficiency virus exists as two distinct viral species, designated HIV-1 and HIV-2. Each species is further subdivided into subgroups, including M, N, & O for HIV-1, and subgroups A-G for HIV-2. The vast majority (99.6%) of HIV infections worldwide are caused by HIV-1, group M. The less prevalent viral types are largely confined to West Africa.

Beginning in July, Saint Luke's Regional Laboratories will discontinue the current HIV-1 antibody test and begin using a new combination test for HIV-1 and HIV-2. Results will be reported as "HIV-1/2 antibody", with a reference range of non-reactive. The assay does not distinguish between HIV-1 and HIV-2. Specimens that test reactive to HIV-1/2 antibody are automatically forwarded to Mayo Medical Laboratories for confirmatory testing.

Mayo Medical Laboratories follows an algorithm for HIV confirmatory testing that initially includes a Western blot for antibodies to specific HIV-1 viral proteins. Any specimen that is reactive for HIV-1/2 antibody, but negative or indeterminate by HIV-1 Western blot is subsequently tested specifically for HIV-2.

Inherited Thrombophilia & Arterial Thrombosis

Arterial thrombosis is usually associated with acquired risk factors such as diabetes, dyslipidemia, hypertension, obesity and smoking. Thrombophilic defects known to predispose to arterial thrombosis include hyperhomocysteinemia and antiphospholipid antibodies. The inherited thrombophilic disorders, including factor V Leiden (FVL), prothrombin gene mutation (PGM), and deficiencies of protein C (PC), protein S (PS), and antithrombin (AT), are well established risk factors for venous thromboembolism, however their association with arterial thrombosis is controversial.

A recent review (Semin Hematol 44:106-113, 2007) addressed the prevalence and significance of these hereditary defects in relation to occlusive arterial disease (myocardial infarction, ischemic stroke, and peripheral arterial disease). Multiple studies and meta-analyses revealed conflicting results, however the authors concluded that the association between FVL and PGM and arterial occlusive disease is modest. PGM appears to be more often associated with arterial events than FVL, however results have been inconsistent. The very low prevalence of PC, PS, and AT deficiency has made it difficult to study the association of these genetic defects with arterial thrombosis. Routine screening for all these hereditary thrombophilic defects is not warranted in most cases of arterial thrombosis.

There are, however, sub-groups of patients in whom there is a stronger association between thrombophilic defects and arterial thrombosis, most notably younger patients with age of onset <45 years. In one study FVL was detected in 13.0% of patients with early presentation of myocardial infarction, significantly higher than the 3.8% prevalence in patients with older age presentation. In another study of myocardial infarction patients less than 36 years of age there was an increased prevalence of PGM (11.4%) compared with healthy young subjects (3.1%). Furthermore, in young patients environmental factors such as smoking and oral contraceptive use appear to have a synergistic effect with hereditary thrombophilia. One study reported an interaction between smoking and PGM for the risk of myocardial infarction in young women, with an odds ratio of 43 when both factors are present.

Another subgroup to consider is early arterial occlusion occurring after revascularization procedures. Inherited thrombophilias have been reported to predispose to failure of revascularization procedures in patients with peripheral arterial disease, with a failure rate more than three-fold higher than in patients without the defects. The authors recommend that thrombophilia be excluded prior to such procedures in patients with a personal or family history of thrombosis, or early age onset of disease (<45 years).

Saint Luke's Regional Laboratories offers an "arterial thrombosis panel" consisting of an antiphospholipid antibody panel and plasma homocysteine assay. Beyond this testing, current evidence does not support routine testing for the hereditary thrombophilic defects in most cases of

arterial thrombosis. Testing for FVL and PGM is recommended, however, in two sub-groups of arterial thrombosis patients: those with early onset of disease (<45 years, or <55 years in patients without the usual acquired risk factors for arterial disease), and those with early occlusion after revascularization procedures.

Phosphorus & CVD Risk

Data from the Offspring Cohort of the Framingham Study recently revealed an association between higher levels of serum phosphorus and increased cardiovascular disease (CVD) risk (Arch Intern Med 2007;167:879-885). With a sample size of 3,368 and a mean follow-up time of 16 years, investigators used statistical methods to relate serum phosphorus levels to the occurrence of a first CVD event. The data was adjusted for traditional CVD risk factors as well as standard risk factors that influence phosphorus levels including GFR, hemoglobin, albumin, proteinuria and CRP. Patients were divided into quartiles according to their phosphorus levels.

Quartile	Phosphorus
1	1.6-2.8 mg/dL
2	2.9-3.1 mg/dL
3	3.2-3.4 mg/dL
4	3.5 mg/dL or more

Analysis of the data showed that as phosphorus levels increased, there was a continuous increase in CVD risk. People falling in the 4th quartile had a 55% higher CVD risk compared to the 1st quartile. In this study, the normal range for serum phosphorus was 2.8–4.5 mg/dL, so patients in the top quartile were within the normal range. If this association is confirmed, it may be necessary to reevaluate the normal range for phosphorus.

While this study suggests an association between phosphorus levels and CVD risk, more research will be required to determine whether it truly causes CVD. Three pathogenic mechanisms have been proposed.

- High serum phosphorus is a marker of elevated PTH, which is proinflammatory
- High serum phosphorus directly injures endothelium and promotes calcification
- High serum phosphorus may be a biomarker for subclinical chronic kidney disease.

The last possibility appears less likely because CVD risk was adjusted for GFR.