



May 2006

## **Factor V Leiden Mutation and Risk of Infection**

The factor V Leiden mutation renders activated factor V relatively resistant to the proteolytic activity of activated protein C (APC) and is a well-described risk factor for thromboembolism. The potential role of factor V Leiden mutation in infection is intriguing, since activated protein C (Xigris) has therapeutic value in the treatment of adult severe sepsis.

In a recent Danish study (J Infectious Diseases 2005;192:1851-7), 719 individuals with factor V Leiden mutation (both heterozygotes and homozygotes) were investigated over a 7 year period for hospitalization for any infection. Among these subjects, 204 had a history of thromboembolism during the analysis period and 52 were hospitalized for an infectious disease. After adjustment for several factors, individuals with factor V Leiden mutation were found to be at increased risk for hospitalization from skin infections and at decreased risk for hospitalization from urinary tract infections compared to non-carriers. The investigators also analyzed risk of death associated with Factor V Leiden mutation. When mortality was defined as death within 28 days of admission to the hospital, patients with Factor V Leiden mutation were found to be at increased risk of death from sepsis, but not from pneumonia, meningitis, tuberculosis or diarrheal disease.

The findings from this analysis contradict an earlier report that fact V Leiden carriers had improved survival rates from sepsis, indicating that further studies are warranted.

## **The Significance of Mean Platelet Volume**

Platelet size can be measured directly by automated hematology analyzers, expressed as mean platelet volume (MPV). Platelet size is determined at the time of platelet production from megakaryocytes. There is evidence that MPV is increased when both platelet production and destruction are increased, probably mediated by cytokines such as interleukin-3, interleukin-6, and

thrombopoietin. There is also evidence that larger platelets are functionally more reactive, produce more thromboxane A<sub>2</sub>, aggregate more readily in vitro, contain more dense granules, and show increased expression of membrane receptors.

Elevated MPV has been associated clinically with cardiovascular and cerebrovascular morbidity. Elevated MPV has been identified as an independent risk factor for myocardial infarction in patients with coronary heart disease (Brit J Haematol, 2002, 1178,399-404), and for death or recurrent ischemic events after myocardial infarction (Lancet, 1991, 338:1409-1411). MPV has also been shown to be a strong independent predictor of impaired angiographic reperfusion and six month mortality in acute myocardial infarction treated with percutaneous coronary intervention (J Am Coll Cardiol, 2005, 46:284-290). An increase in MPV is independently associated with acute stroke (Stroke, 1995, 26:995-999), and an elevated MPV has been associated with a worse outcome in acute ischemic cerebrovascular events (Stroke, 2004, 35:1688-1691).

It is difficult to ascribe risk to a specific MPV value, however extrapolating from the above studies, an MPV of approximately 12.0fL or greater may be considered a risk factor for these vascular complications. Increased MPV values have also been reported in patients with vascular risk factors such as diabetes mellitus (especially when associated with microvascular complications), hypercholesterolemia, and smoking.

In a recent study (Brit J Haematol, 2005, 128:698-702) MPV was shown to be one of the laboratory values that may assist in elucidating the cause of thrombocytopenia. This parameter was significantly higher in patients with immune thrombocytopenic purpura (peripheral platelet destruction), than in aplastic anemia (decreased platelet production). An MPV greater than 12fL was only 59% sensitive, but was 95% specific for a diagnosis of immune thrombocytopenic purpura.

In summary, together with other clinical and laboratory parameters, the MPV may contribute useful information in individual patients regarding cardiovascular and cerebrovascular risk, and may also help in the evaluation of unexplained thrombocytopenia. Starting in mid-May 2006, Saint Luke's Regional Laboratories will begin reporting MPV together with all routine CBC's (one 5ml purple-top tube required.) The reference range is 9.4-12.3fL.

### **Treatment of Hypofibrinogenemia**

Conversion of fibrinogen into fibrin is the last stage of the coagulation sequence. Fibrinogen plays an important role in fibrin clot formation and platelet aggregation. If fibrinogen is decreased, bleeding may ensue.

Acquired hypofibrinogenemia is most commonly associated with:

- Severe liver disease
- Head trauma
- Acute DIC
- Tissue plasminogen activator (TPA) therapy
- Streptokinase & urokinase therapy
- Chemotherapy with asparaginase
- Plasma exchange with albumin

The blood bank often receives orders for fresh frozen plasma (FFP) to treat the prolonged protime (PT) and activated partial thromboplastin time (aPTT) associated with hypofibrinogenemia. Although FFP contains fibrinogen, it is not the optimal blood component because of the very large volumes of plasma that are required to increase fibrinogen to hemostatic levels. Cryoprecipitate is preferred because it contains the same concentration of fibrinogen as FFP in less than one-twentieth of the volume.

Cryoprecipitate refers to the proteins that precipitate out of solution when a unit of fresh frozen plasma is slowly thawed in the cold. Each bag contains a concentrated mixture of Factor VIII, fibrinogen, von Willebrand factor, and Factor XIII suspended in 10 to 15 mL of residual plasma. Since several bags of cryoprecipitate are transfused at a time, the blood bank pools them into a sterile plastic transfer pack prior to issue.

ABO compatible cryoprecipitate is desirable if large volumes will be transfused, but Rh compatibility is not important because no red blood cells are present. Cryoprecipitate should be infused through a standard blood filter at a rate of 4 to 10 mL/minute. At this rate, a pool of 10 bags can be infused in approximately 30 minutes.

Cryoprecipitate should be given when the fibrinogen level falls below 100 mg/dL, which is the minimal level needed for hemostasis. Each bag of cryoprecipitate contains 200 to 250 mg of fibrinogen and will increase the plasma fibrinogen level of a 70-kg adult by 6 to 8 mg/dL. Generally, 10 bags of cryoprecipitate are given if the fibrinogen level is between 50 and 100 mg/dL and 20 bags are given if it is less than 50 mg/dL. A fibrinogen level should be measured at 30 to 60 minutes after completion of the transfusion to determine if additional doses are needed. The therapeutic goal is to keep the plasma fibrinogen level above 100 mg/dL. The circulating half life of fibrinogen is 3 to 5 days.

Cryoprecipitate may be given prophylactically for head trauma because of the associated disseminated intravascular coagulation that can result in intracranial hemorrhage. In patients with either blunt or penetrating head trauma, 10 units of cryoprecipitate may be given empirically or when serial fibrinogen levels indicate a precipitous drop in fibrinogen level.

### **National Coverage Determinations (NCD)**

Please note that Medicare publishes quarterly updates to the NCDs. You may view these at:

[http://www.cms.hhs.gov/CoverageGenInfo/05\\_LabNCDs.asp#TopOfPage](http://www.cms.hhs.gov/CoverageGenInfo/05_LabNCDs.asp#TopOfPage)

Since the inception of strict requirements for Advance Beneficiary Notice (ABNs) several years ago, additional acceptable ICD-9 codes have been added to indicate medical necessity for various tests. Periodic review of the updates may decrease the number of ABNs you are asking your patients to sign. Please contact Tammy Thorne (932-3704) or Kristy Gibson (932-3171) with questions.