Salivary Cortisol to Screen for Cushing’s syndrome

Increasing numbers of obese, depressed, diabetic and hypertensive patients are presenting with clinical symptoms that mimic those of Cushing’s syndrome including weight gain, poor wound healing, immune suppression and mood changes. However, Cushing’s syndrome is extremely rare, occurring at a rate of only 5 cases per million individuals. With such a low incidence, establishing the diagnosis of Cushing’s syndrome is a very challenging clinical and laboratory problem.

One of the earliest biochemical abnormalities in Cushing’s syndrome is a failure to decrease cortisol secretion fully at its normal nadir late at night. However, obtaining a stress free blood sample at 11:00 pm or midnight for plasma cortisol determination is difficult in ambulatory patients. Recent studies in adults and children have convincingly demonstrated that an elevated late night or bedtime salivary cortisol sampling is an excellent screening test and has a sensitivity and specificity of greater than 90% (J Clin Endocrinol Metab 2006;91:3746-53).

False positive salivary cortisol results may be associated with hypertension, advanced age and psychiatric disorders. However, repeat testing is usually normal in these situations, but not in true endogenous Cushing’s syndrome.

Saint Luke’s Regional Laboratories is now providing Salivette tubes for collection of salivary cortisol samples along with a set of instructions. Patients should be instructed to not brush their teeth prior to collecting the saliva sample. They should also refrain from eating or drinking 15 minutes prior to specimen collection and should avoid using hydrocortisone creams which may contaminate the specimen.

The specimen is collected by:

- Removing the cap to expose the swab
- Tipping the tube so that the swab falls directly into the mouth.
- Rolling the swab in the oral cavity for one minute.
- Spitting the swab back into the tube
- Capping the tube tightly
- Recording collection time on the tube
- Refrigerating specimen until delivered to a SLRL patient Service Center

Specimens are sent to Mayo Medical Laboratories for testing by liquid chromatography – tandem mass spectrometry. Time dependent reference ranges are listed below.

<table>
<thead>
<tr>
<th>Time</th>
<th>Salivary Cortisol (ng/dL)</th>
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<tbody>
<tr>
<td>7 am – 9 am</td>
<td>100 – 750</td>
</tr>
<tr>
<td>3 pm – 5 pm</td>
<td>20 – 400</td>
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<tr>
<td>11 pm – midnight</td>
<td>&lt;100</td>
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Thrombosis in Plasma Cell Dyscrasias

Patients with plasma cell dyscrasias are at increased risk of developing thrombosis. The prevalence of venous thromboembolism (VTE) in MGUS is 6.1-7.5%. The prevalence in multiple myeloma was 10% in a retrospective study between 1998 and 2001, however this was prior to the use of thalidomide and lenalidomide.

General risk factors for thrombosis in patients with plasma cell dyscrasias include advanced age, immobility, and previous venous thromboembolism (VTE). Risk factors specific to plasma cell dyscrasias include prothrombotic effects of cytokines released from malignant plasma cells, including IL6. Monoclonal paraproteins may also contribute to a hypercoagulable state by interfering with fibrinolysis, inhibiting protein S, or exerting a lupus anticoagulant-like effect. Elevated levels of factor VIII, known to be an independent risk factor for VTE, have been reported in multiple myeloma. Furthermore, several authors have reported that a proportion of patients with myeloma have acquired resistance to activated protein C, in the absence of
factor V Leiden, also known to be an independent risk factor for VTE.

The immunomodulatory drugs thalidomide and lenalidomide were introduced in the late 1990’s for treatment of myeloma, and exert multiple effects, including inhibition of angiogenesis and promotion of apoptosis. These drugs have improved the response rate and survival of patients with myeloma, however they are associated with an increased risk of VTE. A number of studies have shown that thalidomide and lenalidomide administered alone are associated with a low risk of VTE (<5%). However, when either of these drugs is used in combination with dexamethasone, doxorubicin, melphalan and prednisone, and other chemotherapeutic agents, there is a significantly increased incidence of VTE in both newly-diagnosed and relapsed or refractory myeloma patients, varying in different studies from 14%-24%.

Venous thrombosis tends to occur during the induction phase in myeloma patients treated with thalidomide or lenalidomide combination therapy, usually during the first 6 months of therapy. Erythropoietin administered concurrently to patients with myeloma receiving lenalidomide combination therapy further increases the risk of VTE, and should therefore be used with caution.

In view of the significantly increased risk of VTE, prophylactic anticoagulation is recommended for myeloma patients receiving thalidomide or lenalidomide combination therapy. In the absence of randomized controlled trials addressing this issue, the optimal method of anticoagulation is currently not known, however warfarin (INR 2.0-3.0) or low molecular weight heparin are recommended by most authorities. Fortunately, the newer anti-myeloma drug bortezemib (a proteasome inhibitor) appears to be less thrombogenic than the immunomodulatory drugs, and in fact appears to protect against thrombosis when used in combination with thalidomide and dexamethasone.

Blood Donor Screening for Trypanosoma cruzi

Chaga’s disease is caused by the parasite, Trypanosoma cruzi. As many as 11 million persons in Mexico and in Central and South America carry the parasite and serve as a potential source of transfusion transmitted disease. The risk of T. cruzi transmission in the United States is increasing because of immigration of infected individuals from endemic countries. Estimates of the incidence of seropositive donors in the United States have ranged from 1 in 5400 to 1 in 25,000 donors.

Transfusion of red blood cells and platelets from infected donors carries the highest risk of transmission, approximately 38%. The risk of transmission from plasma components is considerably lower because T. cruzi is killed by freezing. The lifetime risk of severe heart or intestinal problems in infected individuals averages about 30% and usually occurs many years after the initial infection.

Because of this increasing risk of transfusion transmitted disease, Community Blood Center of Greater Kansas City began testing donors for antibodies to T. cruzi in June 2007. FDA requires hospitals to participate in a Look-back program which involves identification of all recipients of previously transfused blood components from confirmed positive donors. Physicians will be notified by a Saint Luke’s Hospital transfusion service if one of their patients has been transfused with a blood component from an implicated donor.

Cryoprecipitate Change

Cryoprecipitate is the preferred blood component for treatment of hypofibrinogenemia. 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.

Currently, hospital transfusion services pool 10 units of cryoprecipitate into a single transfer bag prior to sending the product to the nursing unit. Beginning February 15, Community Blood Center will begin providing pooled cryoprecipitate, which contains 5 units and has a total volume of 80 to 100 mL. Therefore, if a physician orders 10 bags of cryoprecipitate, two bags of pooled cryoprecipitate will be issued.