Erythropoietin

Erythropoietin (EPO) is a large glycoprotein hormone that regulates red blood cell production. More than 90% of circulating EPO is produced by the kidney and 10% by the liver. Normally, EPO levels vary inversely with hemoglobin or hematocrit. Hypoxia stimulates EPO release, which, in turn, stimulates bone marrow erythropoiesis. Elevated levels of RBC, hemoglobin, hematocrit or oxygen suppress the release of EPO.

Examples include iron deficiency, aplastic anemia, sickle cell anemia, thalassemia, megaloblastic anemia, and myelodysplastic syndromes.

Chronic renal failure may result in decreased renal EPO synthesis and, subsequently, anemia. In addition to renal failure, other conditions such as chronic infections (e.g. AIDS), chronic inflammation (e.g. rheumatoid arthritis & inflammatory bowel disease) malignancies (e.g. solid tumors, multiple myeloma & lymphoma) and prematurity are associated with anemia and deficient serum EPO levels. Patients suffering from EPO-deficient anemias have erythropoietin levels that are inappropriately low for the degree of anemia. Their EPO values fall within the darker shaded area of the graph. These patients may benefit from therapy with recombinant EPO.

Measurement of EPO is also useful in determining the cause of polycythemia. Polycythemia vera (P. vera) is a neoplastic clonal blood disorder with autonomous proliferation of red blood cells. Increased red blood cells result in a negative feedback suppression of EPO. Patients with P. vera have extremely elevated hemoglobin or hematocrit and decreased serum erythropoietin levels.

Secondary polycythemia is associated with disorders that cause tissue hypoxia such as living at high altitude, chronic obstructive pulmonary disease, cyanotic heart disease, sleep apnea, high affinity hemoglobinopathy, smoking, or localized renal hypoxia. In secondary polycythemia, EPO production is increased in an attempt to increase oxygen delivery to tissues by increasing the number of oxygen carrying red blood cells. Patients with secondary polycythemia have elevated hemoglobin or hematocrit and higher than normal serum EPO level.

Some tumors secrete EPO or EPO-like proteins and cause erythrocytosis. Examples include renal cell carcinoma, Wilm’s tumor, hepatoma, cerebellar hemangioblastoma, adrenal tumors, and leiomyoma.

In the work-up of polycythemia, an EPO assay is indicated if the hemoglobin level is greater than 18.5 g/dL in men or 16.5 g/dL in women, or if there is a lesser degree of hemoglobin elevation associated with P. vera-related features. A low serum EPO level indicates that P. vera is very likely. If the EPO level is elevated, the diagnosis is probably secondary erythrocytosis.

In July, Saint Luke’s Regional Laboratories will begin offering serum erythropoietin levels. CPT code is 82668. Reference range is 4 – 20 mIU/mL. Specimen requirement is a plain red top or SST
tube of blood. This assay cannot distinguish between endogenous and exogenous EPO.

**D-Dimer Level Is Associated With Risk Of Future Venous Thrombosis**

Although there have been significant recent advances concerning risk factors for venous thrombosis (including recognition of factor V Leiden and prothrombin gene mutation), approximately 40% of patients with venous thrombosis and a positive family history still have no identifiable risk factor. Plasma levels of D-dimer are elevated during acute venous thromboembolism as a result of fibrin formation and secondary fibrinolysis. There is significant variation in plasma D-dimer levels within the normal range among healthy individuals. A recent longitudinal population-based study evaluated the association between baseline D-dimer levels and the risk of future venous thrombosis (Blood 2003;101:1243-1248).

As part of a large population-based cardiovascular risk study, blood was drawn at baseline and at one to three year intervals thereafter in over 21,000 participants. Potential cases of venous thrombosis and pulmonary embolism were confirmed radiologically. D-dimer, factor V Leiden, prothrombin gene mutation, and factor VIII were assayed in the stored blood samples of 307 subjects who developed venous thromboembolism during 8 years of follow-up, and a further 616 who did not. The control group was matched to the cases by age, sex and race. The risk of subsequent venous thromboembolism increased substantially with increasing baseline levels of D-dimer. There was a 4.2-fold increased risk of thrombosis for D-dimer concentrations in the fifth quintile compared to the first. After adjustment for age, sex, race and other thrombotic risk factors the odds ratio for thrombosis for the fifth versus first quintiles was 3.0. The association of D-dimer level with thrombosis was greater in women than in men (odds ratio for fifth versus first quintiles 8.3 and 2.6 respectively). The relationship between D-dimer levels and thrombosis existed for idiopathic thrombosis and thrombosis secondary to trauma, surgery and immobility, but was not present for thrombosis associated with cancer.

The authors conclude that increasing baseline levels of D-dimer are associated with a graded increase in the future risk of venous thrombosis, independent of other common risk factors. Based on their data, they calculated that 13.3% of thrombotic events may be attributable to D-dimer levels in the highest quintile. It is unlikely that D-dimer is a causal factor in venous thrombosis. The authors hypothesize that it may be a marker for other hereditary or acquired prothrombotic factors, or more generally may reflect increased fibrin formation. It would be premature to include D-dimer levels in a hypercoagulability panel before this data is reproduced using more widely used commercially available D-dimer assays.

**The Microbiology of Bottled Water**

According to a recent publication, over half of Americans regularly drink bottled water and many believe that, unlike tap water, it contains no microorganisms. However, bottled water is rarely free of bacteria. Much of the bottled water sold in the U.S. (25-40%) comes from municipal water sources. Water originating from a spring acquires microorganisms indigenous to its source. Bottled water is considered a food product, which is regulated by the FDA. The FDA only tests for coliforms and allows the presence of 1 coliform bacteria in 10% of bottles tested. By comparison, European standards are much stricter, requiring the absence of coliforms, *Pseudomonas aeruginosa*, *E. coli*, and fecal streptococci. European water is tested in 250 mL aliquots and is also bottled directly from the source, whereas U.S. bottled water may be subject to additional processing that can lead to introduction of microorganisms. Although some states require disinfection, this process is not the same as sterilization and disinfected water should not be considered sterile.

Bacterial counts can increase rapidly in bottled water being stored at room temperature. Any organic matter present in the container provides a food source for bacteria, which adhere to the surface of plastic containers and multiply exponentially in a matter of days. Likewise, large water dispensers, such as those typically used in an office setting, may harbor abundant bacteria. Most of the organisms that may be found in bottled water are not pathogenic for healthy individuals. However, bacteria have been isolated from bottled water that would be of concern to an immuno-compromised host, including *Stenotrophomonas maltophilia* and *Burkholderia cepacia*. Immunocompromised individuals should consider using sterile water instead of common bottled water in order to avoid this potential source of infection.

F.V. Plapp, M.D., PhD, M.L. Zucker, M.D. C.E. Essmyer, M.D.