Warm Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemias (AIHA) are caused by autoantibodies directed against a patient's own red blood cells that result in accelerated red cell destruction. This disorder is relatively uncommon, with an incidence of 1 in 80,000 individuals. All ages are affected, with the peak incidence occurring in the fourth and fifth decades. Women are more often affected than men.

AIHA are divided into warm and cold autoantibody types based on the temperatures at which the antibodies maximally react with red blood cells in vitro. Warm autoantibodies are more reactive at 37°C than at lower temperatures, whereas cold autoantibodies react optimally at 5°C and less strongly at higher temperatures. These two principal types are further subdivided into primary, or idiopathic, and secondary forms which are associated with an underlying disease. Lymphoproliferative disorders are present in about half of the secondary warm and cold AIHA. Systemic lupus erythematosus and other autoimmune diseases account for the majority of the remaining warm types. Transient cold AIHA are associated with infections, especially mycoplasma pneumonia and infectious mononucleosis.

The clinical picture of warm type AIHA is highly variable. Most patients seek treatment for symptoms attributable to anemia, but occasionally massive hemolysis is seen at onset. Physical findings are related to the degree of anemia and include pallor, resting tachycardia, mild jaundice and occasionally fever. The spleen is usually only mildly enlarged.

Several common laboratory results suggest hemolysis. Hemoglobin is decreased, but the degree of anemia depends on the compensatory capacity of the bone marrow. Reticulocyte count is usually elevated and may result in a mildly elevated MCV. Spherocytes in the peripheral blood smear indicate ongoing red cell destruction. Unconjugated bilirubin is usually, but not always, elevated and urine urobilinogen is increased. Lactate dehydrogenase is usually elevated into the thousands. Serum haptoglobin levels are reduced or undetectable. Hemoglobinemia and hemoglobinuria are present in cases of severe hemolysis. Mild leukocytosis and thrombocytosis may be present.

The diagnosis of AIHA depends on the demonstration of a positive direct antiglobulin test (DAT), indicating the presence of immunoglobulin and/or complement on red blood cells. In warm autoimmune hemolytic anemia, red cells may be coated with IgG, IgG and complement, or complement alone. In warm AIHA, IgG is found alone in about 60% of cases and in association with complement in about 30% of cases. In contrast, cold autoimmune hemolytic anemia is caused by complement-fixing IgM antibodies that react more strongly in the cold than at higher temperatures. In these cases, the direct antiglobulin test detects only complement. Autoantibodies may appear to have specificity for a particular blood group antigen even though the patients’ red cells express that antigen.

The strength of the DAT does not predict the severity of disease. For instance, some patients with a strongly positive DAT have little hemolysis, while other patients with a weakly positive DAT hemolyze extensively. Also, the strength of the DAT often does not change following treatment, even though the clinical condition greatly improves.

Transfusion of patients with autoimmune hemolytic anemia is associated with unique risks. Autoantibody often complicates compatibility testing and makes it difficult to exclude the presence of co-existing alloantibodies, thus increasing the risk of a hemolytic transfusion reaction. In addition, the autoantibody itself may shorten the survival of transfused red cells. If possible, red blood cell transfusion should be avoided. However, a patient with life threatening anemia should never be denied blood even though the crossmatch is incompatible.

A critical aspect of transfusing patients with AIHA is to avoid over transfusion. The kinetics of red cell destruction always describe an exponential decay
curve, indicating that the number of cells removed during a unit of time is a percentage of the number of cells present at the start of this time interval. Raising the hemoglobin level abruptly is likely to increase the amount of hemolysis that is occurring and may precipitate DIC. Indeed, the most common cause of post transfusion hemoglobinemia and hemoglobinuria in AIHA may not be alloantibody induced hemolysis but rather the quantitative effect of increasing the red cell mass subjected to ongoing autoantibody hemolysis. Accordingly, transfusion of comparatively small volumes of blood is the optimal means of minimizing the danger of transfusion-induced intravascular hemolysis. The patient’s hemoglobin level should be maintained just above a tolerable level until more specific therapy becomes effective.

New Hepatitis C Report

The recommended initial laboratory test for hepatitis C virus (HCV) infection is an immunoassay for antibody to HCV. However, one of the shortcomings of HCV antibody testing is the significant number of false positive results among low-prevalence populations. For an immunocompetent population with HCV prevalence of <10%, the chance of a false positive antibody test reportedly ranges from 15-60%.

The CDC has recently published guidelines for reporting of HCV antibody (MMWR 2003;52 No. RR-3) based upon data review from thousands of tests from populations with HCV prevalence ranging from 2% to 25%. It is now recommended that HCV antibody reports should include the signal to cut-off (S/CO) ratio, which is calculated in the laboratory by dividing the value of the patient’s sample by the value of the negative-positive cut-off point for that run. The CDC has determined that samples with an S/CO ratio \( \geq 3.8 \) have a >95% probability of predicting true positive anti-HCV. Samples that are reactive for HCV antibody, but have an S/CO ratio <3.8 may be false positive and require supplemental testing to determine the true HCV status. False positive tests are seen most often in the elderly, dialysis patients, and patients with autoimmune disease.

Effective immediately, Saint Luke’s Regional Laboratory reports will include the S/CO ratio on specimens that are reactive for antibody to HCV. Samples with S/CO ratio \( \geq 3.8 \) are indicative of past or present HCV infection. Supplemental testing by qualitative or quantitative PCR on these patients allows assessment of viral activity. HCV genotyping can be performed simultaneously on samples with detectable virus by PCR. Samples with S/CO ratio < 3.8 should have confirmatory testing by qualitative HCV PCR. PCR & genotype testing can usually be performed on the residual serum sample used for the HCV antibody test.

Omega-3 Index: A Novel Test for Assessing Risk of Sudden Cardiac Death

Omega-3 fatty acids are the newest nutritional agents to be officially sanctioned by the American Heart Association (AHA) for reducing risk of death from CHD (Circulation 2002;106:2747-57). The AHA recommends that all patients with known CHD take about 1 g of EPA+DHA (the principal omega-3 fatty acids in fish oils) per day and that patients without known disease consume at least two (preferably oily) fish meals per week. This translates into about 500 mg of EPA+DHA per day. Recommending specific intakes is a start, but knowing whether or not patients have achieved target blood levels of omega-3 fatty acids would provide objective evidence of compliance and enable the physician to individually tailor omega-3 recommendations.

The Lipid and Diabetes Research Center of Saint Luke’s Hospital has developed and standardized a new blood test based on reports in the medical literature and recent studies from their laboratory. The test is called the Omega-3 Index, and it is used to stratify patients’ risk of death from CHD. The Omega-3 Index is the percent of total red blood cell fatty acids made up by EPA and DHA. An Omega-3 Index of 8% to 10% is associated with the lowest risk for death from CHD, while an Index of under 4% indicates high risk. In two major studies, risk for sudden cardiac death was 90% lower in those individuals with a high index compared to those with an index less than 4%. (JAMA 1995; 274:1363-1367; NEJM 2002; 346:1113-1118.)

The Omega-3 Index is unaffected by recent food intake and, because it is measured in red blood cells, reflects relatively long-term omega-3 exposure. A daily intake of 500 to 1,000 mg of EPA+DHA will, in most cases, produce an Omega-3 Index of 8%-10%.

Sample requirement is 5 mL of non-fasting blood in a purple top (EDTA) tube. The test is currently not covered by Insurance or Medicare; the cost is $80.

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