EDUCATIONAL COMMENTARY – UPDATE ON MARKERS FOR HEPATITIS VIRUSES

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Learning Outcomes
Upon completion of this exercise, the participant will be able to:

- Compare acute and chronic viral hepatitis infection.
- List the hepatitis virus infections which may become chronic.
- Describe the use of the signal to cut-off ratio.
- Discuss hepatitis B testing results expected in chronic disease and immunity.

Hepatitis is defined as inflammation of the liver. Inflammation of the liver may be the result of viral infection or exposure to various toxic agents. Viral hepatitis may be caused by several different viruses, the most common in the United States being hepatitis A (HAV), hepatitis B (HBV), or hepatitis C (HCV). Hepatitis D (HDV) is a defective virus and can only cause infection when the individual is also infected with hepatitis B. Hepatitis E (HEV) is another cause of inflammatory liver disease, but infection is rare in the United States.

The symptoms of all types of viral hepatitis are very similar and may include fatigue, jaundice, nausea, vomiting, diarrhea, anorexia, low grade fever, and headache. Hepatitis virus infection may be acute or chronic. In acute disease, the infected person recovers and produces protective antibodies which provide immunity to future infection. In chronic hepatitis, the patient continues to harbor the active virus and never produces protective antibodies. Also in chronic disease, the patient remains infectious due to the persistence of the virus in the body. Chronic hepatitis is very serious, sometimes leading to cirrhosis of the liver or hepatic cancer. Hepatitis B, hepatitis C, and hepatitis D may cause chronic infection.

Infection with hepatitis A was once called infectious hepatitis. It is transmitted primarily through food or water that is contaminated with feces of infected individuals. HAV most commonly occurs in countries where safe water supplies are not available and living conditions are crowded. In the United States, most cases occur in day care environments, in male homosexuals, or IV drug users.

Testing for hepatitis A includes ELISA testing for IgM and IgG antibodies to Hepatitis A (IgM anti-HAV and IgG anti-HAV). The presence of IgM anti-HAV in the patient's serum indicates an acute infection. If only IgG anti-HAV is present, the infection is probably a past infection and the person is immune. HAV infection does not become chronic. Vaccination to HAV is available.
Hepatitis B was formerly known as serum hepatitis. As indicated by its former name, it is transmitted through blood and body fluids of infected individuals. Patients infected with HBV produce specific antibodies to various components of the virus. These include antibody to the e antigen, antibody to the core antigen, and antibody to the surface antigen. In testing patients with suspected HBV, the laboratory can perform assays to detect HBV surface antigen (HBsAg), HBV e antigen (HBeAg) antigen, HBV core antibody (anti-HBc), antibody to HBeAg (anti-HBe), and antibody to HBsAg (anti-HBs). By evaluating which of these assays are positive, the stage of disease in a patient can be determined. In most cases, HBV infection is self-limiting and the patient recovers without future problems. These patients produce anti-HBs and are then immune.

In some cases, the infection may become chronic. In chronic disease the patient has continual damage to the liver. HBsAg remains detectable and antibody to HBsAg (anti-HBsAg) is not detectable. A repeatedly positive HBsAg over a 6-month period defines chronic HBV infection. The patient remains infectious.

Chronic HBV is treated with interferon or anti-viral drugs. According to the CDC, approximately 1.25 million people have chronic HBV. It is estimated that 4,000-5,000 people die each year. A recombinant vaccine is available to protect against HBV infection. The CDC reports that recent studies indicate the vaccine protects for at least 23 years even though levels of anti-HBs may be low or below detectable levels. In 2001, the FDA approved a combined HAV/HBV vaccine.

Hepatitis C is transmitted through blood and body fluids of an infected individual. It is estimated that 3.9 million (1.8%) Americans have been infected with HCV. Eighty percent of those infected have no signs or symptoms. If symptoms exist, they are similar to those seen in HBV infection. Each year there are approximately 30,000 new cases. This is a decrease from approximately 240,000 cases annually in the 1980s. After the screening of blood donations began in 1992, transfusion-associated cases of HCV have been reduced to less than one per 2 million transfused units of blood. Most cases of HCV result from injection of illegal drugs.

Chronic infection occurs in 55%-85% of infected patients and may lead to cirrhosis, scarring of the liver, or hepatic carcinoma. Most liver transplants are performed in response to damage caused by HCV infection. Increased levels of alanine aminotransferase (ALT) indicate liver damage. Patients with liver damage and high levels of the virus in their blood are treated with interferon and ribavirin, an anti-viral drug. This combination therapy can eliminate the HCV virus in 50%-80% of chronically infected patients.

Screening tests for antibodies to HCV include 3 FDA approved immunoassays, 2 ELISA procedures, and one chemiluminescent assay. The CDC recommends that all positive screening tests be repeated in duplicate. If one or both of the repeated assays is positive, CDC guidelines recommend confirmation with
recombinant immunoblot assay (RIBA) or HCV RNA testing also known as nucleic acid testing (NAT). RIBA is a more specific test for the detection of HCV antibodies than the screening antibody tests. HCV RNA assays measure the presence of the virus itself and may be qualitative or quantitative. These tests are also called viral load assays and may also be used to monitor therapy.

Most laboratories do not follow CDC recommendations and report positive HCV screening results without further confirmation. In 2003, the CDC published new guidelines for HCV testing. In the guidelines, performance of screening tests for antibody to HCV and confirmation of positive tests with a more specific assay continues to be recommended. To eliminate unnecessary confirmatory or reflex testing, the guidelines propose use of signal to cut-off ratios (s/co) for positive results. The s/co is calculated by dividing the absorbance value (OD) of the sample being tested in the screening assay by the absorbance value (OD) of the cut-off calibrator for that assay. A specific s/co ratio has been identified for each of the screening assays that predicts a true anti-HCV positive result in \(>95\%\) of cases. The s/co ratio for the predictive value for both of the ELISA screening assays is 3.8. The chemiluminiscent assay's s/co ratio predictive value is 8.0. For example, if the s/co ratio of a patient sample is \(<3.8\), the patient sample would test negative with 95\% certainty if the confirmatory test were performed. Therefore, it is not necessary to perform the confirmatory test. Use of the s/co ratio decreases the number of positive screening test results that must be confirmed and improves the reliability of reported results, thus, reducing the number of patients that require clinical evaluation and counseling. Currently, there is no available vaccination for HCV.

Hepatitis D infection only occurs as a co-infection with HBV. Co-infection may result in more severe acute infection and a higher risk of development of liver failure. Progression to chronic HBV/HDV is more common than with HBV alone. The virus is transmitted through infected blood and body fluids. HDV can be prevented by vaccination for HBV.

Viral hepatitis E is transmitted through the fecal-oral route. This infection is rare in the United States and is usually associated with travel to endemic areas such as the developing countries of North Africa and South Asia. There have been rare cases in the US that have not been connected to travel to endemic areas. Infection is more severe in pregnant women, particularly in the third trimester. The mortality rate in this group is approximately 20\%. Blood tests for HEV are not widely available. HEV does not progress to chronic disease. No vaccine is available, though several studies are being conducted to produce a protective vaccine.

Hepatitis is a serious health concern in the United States. Of most concern are those infections which may become chronic, i.e. Hepatitis B and Hepatitis C. Protection from infection with Hepatitis B has been available for many years. The primary focus in research now is to produce a vaccine for Hepatitis C.

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