EDUCATIONAL COMMENTARY – UPDATE ON MARKERS FOR VIRAL HEPATITIS

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Learning Outcomes

On completion of this exercise, the participant should be able to

• discuss the course of disease for each of the hepatitis viruses;
• describe the treatment for each of the hepatitis viruses;
• explain the laboratory testing used in the diagnosis and treatment of each virus and who should be tested; and
• discuss vaccinations available for hepatitis viruses.

Introduction

Hepatitis is defined as inflammation of the liver. The liver can be damaged by toxic chemicals, overuse of alcohol, certain medications, and other substances, but most cases of hepatitis are caused by viral infections. Hepatitis virus is responsible for a great disease burden worldwide. The World Health Organization adopted a strategy in 2016 to eliminate viral hepatitis as a public health problem, with the goal of reducing new infections by 90% and deaths due to viral hepatitis by 65% by 2030. In the United States, the most common hepatitis viral infections are caused by hepatitis A, hepatitis B, and hepatitis C viruses. Although some cases are asymptomatic, acute infections that are symptomatic have similar clinical characteristics regardless of the causative virus. Clinical manifestations include fever, malaise, headache, nausea, vomiting, abdominal pain, joint pain, jaundice, and elevated serum aminotransferase levels. Because all of the acute infections have similar clinical presentations, serologic testing must be performed to identify the causative virus.

Hepatitis A

Approximately 2500 new cases of hepatitis A virus (HAV) infection are diagnosed in the United States each year. In most cases, HAV causes mild liver disease followed by spontaneous recovery. The infection does not become chronic. Symptoms persist for a few weeks to a few months, during which time supportive treatment is provided for the patient. Usually, there is no permanent liver damage. Because the disease is transmitted through food or water contaminated with feces from an infected person, HAV is most common in countries with poor sanitation. Since the vaccine became available in 1995, the number of infections in the United States has decreased by 95%. Children are vaccinated at the age of 1 year. Vaccination is suggested for those traveling to countries where the infection is prevalent, for persons with clotting disorders or chronic liver disease, and for family members and close contacts of children adopted from countries with intermediate to high HAV prevalence. Because the
vaccine uses inactivated virus, it can be administered to immunocompromised individuals. Immune
globulin is available for short-term pre-exposure or post-exposure protection from the virus.³

Hepatitis B
Hepatitis B virus (HBV) is transmitted through infected blood and body fluids and usually causes an
acute, self-limiting liver infection. Hepatitis B can survive outside the body and remain infectious for at
least 7 days. Even dried blood continues to be infectious. It is extremely important for laboratorians to
strictly adhere to safety precautions. Hepatitis B virus can also be transmitted congenitally.²,⁴

The infection becomes chronic in 2% to 6% of infected adults and may lead to cirrhosis or hepatocellular
carcinoma. In contrast, the risk for chronic infection in infants is 90%.² Vaccination is available and
routinely administered to newborns. The vaccine is also recommended for susceptible household, sex,
and needle-sharing contacts of HBV-positive individuals. In the United States, these guidelines have
resulted in a 96% reduction in the incidence of acute HBV infection in children and adolescents and an
82% decrease overall (Figure 1). The Centers for Disease Control and Prevention (CDC) estimates that
there are approximately 850,000 to 2.2 million people living with chronic HBV in the United States, the
majority of whom were born outside of the United States before immunization became common. One in
12 Asian Americans are infected. Of these, one-third are not aware that they are infected, and overall
two-thirds of people with Hepatitis B do not know they are infected.²,⁵ The estimated number of new
cases annually is 19,200.²

Figure 1. Incidence of acute hepatitis B by year. United States, 1980-2014. Reprinted from Centers for Disease Control and Prevention.⁶
Hepatitis C

Hepatitis C virus (HCV) infection is considered the most serious of the viral hepatitis infections that commonly occur in the United States. Recent increases in occurrence (Figure 2) have been attributed to the increased use of injectable drug in individuals under 30 years of age. It is also transmitted by infected blood and body fluids. Only 20% to 30% of infected persons display the common symptoms of hepatitis. Compared with other viral hepatitis infections, HCV infection is much more likely to become chronic. The ability of the virus to mutate allows it to evade the immune response in approximately 75% to 85% of cases and develop into a chronic infection. Sixty percent to 70% of chronic infections lead to chronic liver disease. Of those with chronic liver disease, 5% to 20% will develop cirrhosis within 30 years and 1% to 5% will die of either cirrhosis or hepatocellular cancer. The CDC reports, “Chronic HCV infection is the leading indication for liver transplants in the United States.”

The CDC estimates that there were 33,900 new HCV infections in 2015, with approximately 3.5 million persons currently infected in the United States. Approximately one-half of all HCV-related deaths occurred in persons between the ages of 55 and 64 years. Because blood donations were not screened for HCV before 1992 and because the disease is often asymptomatic for up to 30 years, there is a greater likelihood that Baby Boomers are infected. The Centers for Disease Control and Prevention recommends one-time testing for all adults born between 1945 and 1965. Likelihood of infection for this population is five times that of other age groups. No effective vaccine or post-exposure immune globulin is available.
Hepatitis D
Infection with hepatitis D virus (HDV), also known as hepatitis delta virus, is rare in the United States. The infection can be acute or chronic, but only occurs in individuals who are also infected with HBV, as HDV is a defective virus that requires the presence of HBV to replicate. Individuals co-infected with HBV and HDV are more likely to develop chronic disease than those with HBV only. Transmission occurs through percutaneous contact with infected blood or body fluids.

Hepatitis E
Hepatitis E virus (HEV) infection rarely occurs in the United States. It is an enteric virus, transmitted through contaminated food or water. It is common in countries with poor sanitation. Infection with HEV is self-limiting and does not become chronic. The disease is much more severe in pregnant women.

Laboratory Testing
Final diagnosis of hepatitis infection requires serologic testing for the causative agent. A patient with suspected hepatitis is tested for alanine aminotransferase levels and screened using an enzyme immunoassay or chemiluminescent assay for antigens and antibodies directed against the causative virus. After the infectious agent is identified, nucleic acid testing may also be performed to confirm and quantify the virus. The status of the patient’s disease can be evaluated using algorithms available for each of the hepatitis viral infections.

Hepatitis A
Persons with acute HAV infection test positive for immunoglobulin M antibodies against HAV (IgM anti-HAV) and total anti-HAV (IgM anti-HAV and IgG anti-HAV). If only the IgG anti-HAV marker is present in the serum, the infection occurred in the past, and the patient has recovered and developed immunity from future infection. Nucleic acid testing is not usually performed on patients with HAV infections.

Hepatitis B
Various serologic tests may be performed to detect HBV markers (antigens and antibodies). Hepatitis B virus markers include hepatitis B surface antigen (HBsAg), IgM hepatitis B core antibody (IgM anti-HBc), total IgM and IgG core antibody (anti-HBc), and antibody to HBsAg (anti-HBsAg or anti-HBs). By evaluating the markers detected in the patient’s serum, one can determine the phase of the disease, whether the disease is acute or chronic, whether the patient is immune or susceptible, and whether immunity resulted from actual infection or vaccination (Table).
Table. Interpretation of markers in hepatitis infection.\textsuperscript{12}

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic “markers” or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

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<td>1. Resolved infection (most common)</td>
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<td>2. False-positive anti-HBc, thus susceptible</td>
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<td>3. “Low level” chronic infection</td>
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<td>4. Resolving acute infection</td>
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\textit{Hepatitis C}

Patients with suspected HCV infection are first screened with an enzyme immunoassay for HCV antibodies. If HCV antibodies are present, nucleic acid testing for HCV RNA (also known as \textit{viral load testing}) follows. If HCV RNA is present, it is determined that the patient is currently infected. If the result of the nucleic acid testing is negative but the physician still strongly suspects HCV infection, the patient should be retested at a later time. In that case, there are three possibilities: (1) the patient has not yet produced antibodies, (2) the patient had a past infection, or (3) the screening test result is false-positive. \textbf{Figure 3} shows the recommended testing algorithm.
Hepatitis D
Testing for HDV is not appropriate for persons who are not infected with HBV. Enzyme immunoassays are performed to detect antibodies to HDV in persons who are HBV positive.

Hepatitis E
Testing for HEV includes assays for IgM and IgG anti-HEV. Polymerase chain reaction testing for HEV RNA in serum and stool is also available.

Treatment
Hepatitis A
No medications are used in the treatment of HAV. Treatment includes only supportive therapy to relieve the symptoms, proper nutrition, and replacement of fluids if necessary.

Hepatitis B
Unvaccinated persons who have been exposed to HBV may be treated with hepatitis B immunoglobulin (HBIG) along with the HBV vaccine. This immunotherapy should occur within 7 days of exposure. HBIG provides temporary protection from acquiring the active infection. Individuals with diagnosed HBV
infection should be examined regularly by a physician. Many patients will spontaneously clear the virus and recover, requiring only supportive care. If the infection becomes chronic, continued medical care is necessary. Currently, there is no cure. Two classes of drugs are available for the treatment of HBV. These include immunomodulators, which enhance the immune response to eliminate the virus, and antiviral drugs, which decrease the virus’s ability to replicate, thereby reducing inflammation and liver damage. In 1991, interferon alfa was the first drug approved for the treatment of HBV. Lamivudine was introduced in 1998 as the first approved antiviral drug. Often, these two drugs were used in combination. Now there are two forms of interferon and five antiviral drugs available. Pharmacologic intervention is not always effective and may not be recommended for persons without active liver disease. In cases of severe liver damage, a liver transplant may be indicated.

**Hepatitis C**

Guidelines for the treatment of HCV infection have been established by the American Association for the Study of Liver Disease and the Infectious Disease Society of America. These organizations recommend that all persons with chronic HCV, except those persons with short life expectancies that cannot be remediated by HCV treatment, transplant, or other directed therapy, be treated with new direct-acting antiviral therapies. The goal of treatment for HCV is to achieve a cure, evidenced by sustained viral response (SVR) determined by a nucleic acid test with a minimum detection level of 25 IU/mL. **Sustained viral response** is defined as the continued absence of detectable HCV RNA for 12 weeks following treatment. Treatment regimens usually involve a combination of medications (interferons, ribavirin, and direct-acting antivirals) that vary according to the HCV genotype causing the infection. Comorbidities with other infections (e.g., HBV, HIV) and drug interactions also affect the selection of treatment modalities. Studies show a success rate of 99% in patients followed for five years post treatment. The evolution of therapy for HCV is represented in Figure 4.
Hepatitis D
There is no FDA-approved treatment for HDV infection. The only medication that has shown some degree of success is interferon-alfa. Clinical trials for new drugs are currently in progress. Also, there is no FDA-approved vaccination for HDV, but vaccination for HBV also prevents HDV.

Hepatitis E
Treatment for HEV is usually not necessary and only supportive therapy is administered. Immunosuppressed persons and pregnant women may require more careful attention. Often, ribavirin and interferon may be prescribed. Although there is no vaccine in the United States, a vaccine was recently introduced and available in China.

Conclusion
Viral hepatitis continues to be a serious health issue in the United States. Preventive vaccines are available for HAV and HBV infections. Currently, no vaccine for HCV infection is available. Great strides have been made in treatment, resulting in a cure for HCV. Although improvements have been made in
HBV therapies, there remains no cure. Hepatitis D and Hepatitis E are rare and pose minimal problems in the U.S.

References


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