Hepatitis B Virus Infection

Worldwide, approximately 350 million individuals are chronically infected with hepatitis B virus (HBV). HBV is the leading cause of cirrhosis globally (Figure 1). The United States is considered a low-prevalence region for HBV with less than 2% of the population infected. This still represents approximately 1.25 million people. The prevalence of chronic HBV is higher among individuals who have emigrated from endemic regions, as well as in populations at increased risk for transmission such as HIV-infected individuals, in whom the prevalence of chronic HBV infection is approximately 10%.

The presence of hepatitis B surface antigen (HBsAg) in the serum on 2 occasions at least 6 months apart defines chronic HBV infection. Hepatitis B surface antibody (anti-HBs) is the marker of immunity to HBV. Anti-HBs is found in individuals who have cleared their infection or responded to HBV vaccination.

The presence of HBV DNA indicates ongoing viral replication, with levels correlating with replication and infectivity. Hepatitis B core antibody (anti-HBc) is the antibody to hepatitis B core antigen and serves as a marker for prior exposure. Individuals who have been exposed to HBV are positive for anti-HBc regardless of whether or not they have cleared the virus or developed chronic infection. Thus, individuals who have immunity after exposure (ie, are anti-HBc positive) can be distinguished from those who have immunity due to vaccination (ie, are anti-HBs positive).

The hepatitis B e antigen (HBeAg) was traditionally used as an index of viral replication and infectivity but has been largely replaced in this regard by measuring HBV DNA. An individual can have HBeAg-negative disease with ongoing viral replication in the setting of hepatitis B core promoter or precore mutants that either do not produce the antigen or produce it at low levels.

Greater than 90% of infants with acute infection progress to chronic HBV infection, compared with less than 5% of adults. In adults, progression to chronic infection is more common in immunocompromised individuals, such as those who acquire HBV during

Figure 1. Prevalence of hepatitis B virus (HBV). HBsAg indicates HBV surface antigen. Adapted from the Centers for Disease Control and Prevention (CDC).
HIV infection. Once chronic infection is established, approximately 50% of patients will develop cirrhosis, and approximately one-quarter of patients with cirrhosis develop decompensated liver disease within 5 years. Cirrhosis also substantially increases the risk for hepatocellular carcinoma (HCC). Chronic HBV infection itself increases the risk for HCC even in the absence of cirrhosis and is the sixth leading cause of liver transplantation in the United States.

Table 1 summarizes treatment guidelines for chronic HBV infection from several liver organizations. There are subtle differences among the guidelines, but the general principles are the same. The decision whether to treat requires knowing HBeAg antigen status, HBV DNA levels, and alanine transaminase (ALT) levels. Liver biopsy provides decisive information but is not uniformly available. Patients can be categorized into HBeAg-positive or -negative disease. Among patients with HBeAg-positive disease, those with elevated HBV DNA levels, with a consensus threshold of 20,000 IU/mL, who have ongoing inflammation as manifested by elevated ALT meet the criteria for treatment. The ALT threshold used to determine whether a patient should be treated is somewhat controversial, with some experts believing that anyone with persistently elevated ALT warrants treatment and others requiring ALT to be greater than 2 times the upper limit of normal (ULN). It should be noted that ULN levels for ALT have been updated to 30 IU/L for men and 19 IU/L for women.

Among patients with HBeAg-negative disease, the same principle applies whereby those with ongoing viral replication and persistently elevated ALT meet the criteria for treatment. However, in these patients the HBV DNA threshold is lower, at greater than 2000 IU/mL. There are 7 US Food and Drug Administration (FDA)-approved treatment regimens for HBV infection, consisting of conventional interferon alfa, peginterferon alfa, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. Characteristics of these regimens, excluding conventional interferon alfa, are shown in Table 2. An advantage of peginterferon alfa is that it has a fixed-duration course, whereas the oral nucleos(t)ide analogues have somewhat indefinite treatment courses. Peginterferon alfa, entecavir, and tenofovir are used as initial antiretroviral agents. Treatment with peginterferon alfa is considered in patients with concomitant hepatitis C virus (HCV) infection and in patients with favorable predictors of response, including low HBV DNA level and high ALT, both of which are also predictors of response to nucleos(t)ide analogues, infection with genotype A or B rather than C or D, and absence of advanced disease. Peginterferon alfa may also be preferred in younger individuals, including women looking to become pregnant in the near future, and patients without comorbidities.

Entecavir and tenofovir have high potencies and high barriers to resistance. Reported 5-year resistance rates in treatment-naive patients are 70% for lamivudine, 29% for adefovir, and 17% (2-year rate) for telbivudine, compared with 1.2% for entecavir and 0% for tenofovir. Therefore, tenofovir and entecavir are the preferred initial oral agents. Notably, although

### Table 1. Treatment Criteria for Chronic Hepatitis B Virus Infection, Based on Antigen Status

<table>
<thead>
<tr>
<th>Guidelines/Algorithm</th>
<th>HBeAg Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA (IU/mL)</td>
<td>ALT (IU/L)</td>
</tr>
<tr>
<td>AASLD 2009&lt;sup&gt;7&lt;/sup&gt;</td>
<td>&gt;20,000</td>
<td>&gt;2x ULN&lt;sup&gt;a&lt;/sup&gt; or (+) biopsy</td>
</tr>
<tr>
<td>US Treatment Algorithm 2008&lt;sup&gt;8&lt;/sup&gt;</td>
<td>≥20,000</td>
<td>&gt;ULN&lt;sup&gt;b&lt;/sup&gt; or (+) biopsy</td>
</tr>
<tr>
<td>EASL 2009&lt;sup&gt;9&lt;/sup&gt;</td>
<td>&gt;2000</td>
<td>&gt;ULN&lt;sup&gt;b&lt;/sup&gt; or (+) biopsy</td>
</tr>
<tr>
<td>APASL 2008&lt;sup&gt;10&lt;/sup&gt;</td>
<td>≥20,000</td>
<td>&gt;2x ULN&lt;sup&gt;b&lt;/sup&gt; or (+) biopsy</td>
</tr>
</tbody>
</table>

AASLD indicates American Association for the Study of Liver Diseases; ALT, alanine transferase; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; ULN, upper limit of normal. Information derived from Lok and McMahon,<sup>7</sup> Keeffe et al,<sup>8</sup> EASL,<sup>9</sup> and Liaw et al.<sup>10</sup> <sup>a</sup>ULN for US Algorithm 2008 and AASLD 2009: 30 IU/mL (men), 19 IU/mL (women). <sup>b</sup>ULN for EASL 2009 and APASL 2008 is based on laboratory reference range.

### Table 2. Suggested Treatment Regimens for Hepatitis B Virus Infection

<table>
<thead>
<tr>
<th>Peginterferon alfa 2a&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Subcutaneous</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Dose</td>
<td>180 μg/wk</td>
<td>100 mg/day&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 mg/day&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.5 mg/day&lt;sup&gt;b&lt;/sup&gt;</td>
<td>600 mg/day&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Duration</td>
<td>48 wks</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Resistance</td>
<td>None</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Anti-HIV?</td>
<td>Weak</td>
<td>Yes</td>
<td>Weak</td>
<td>Weak</td>
<td>No</td>
</tr>
<tr>
<td>Initial Agent?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conventional (nonpegylated) interferon alfa is also approved for chronic HBV infection.<sup>a</sup> Renal dosing is necessary; a higher dose of entecavir may be required in cases of lamivudine resistance.

Anti-HIV indicates HIV antibody. Information derived from Lok and McMahon<sup>7</sup> and Keeffe et al.<sup>8</sup>
entecavir resistance is uncommon in previously untreated patients, in those with prior lamivudine treatment, the resistance rate for entecavir is approximately 50%.9,17

Figure 2 demonstrates the patterns of HBV virologic breakthrough and rebound as well as biochemical breakthrough. Virologic breakthrough is defined by increased HBV DNA after suppression and usually precedes biochemical breakthrough, which is indicated by increased ALT.12 When resistant mutants are initially selected, HBV DNA increases relatively slowly because mutant strains typically have diminished replication capacity. However, over time these strains develop compensatory mechanisms that increase replication fitness, resulting in a more severe virologic rebound that can precede severe hepatitis flare and even decompensation. Thus, it is important to recognize virologic breakthrough early in order to intervene appropriately and prevent hepatitis flare.

Figure 3 shows the HBV polymerase gene mutations that confer resistance to the various oral agents. Resistance to lamivudine, or emtricitabine, and telbivudine is conferred by mutations in the YMDD motif in the C domain of the polymerase. These mutations are often associated with compensatory mutations in the B domain that restore higher replication capacity.18 Entecavir resistance requires a 2-hit mechanism consisting of the YMDD M204V mutation and another mutation in the polymerase gene. Therefore, the barrier to entecavir resistance is lower in patients who have previously received lamivudine, because these patients are likely to harbor YMDD mutants from lamivudine exposure. This is an important factor when considering treatment regimens in patients with HIV/ HBV coinfection, many of whom have a history of lamivudine exposure. Lamivudine resistance does not confer cross-resistance to tenofovir and may even increase susceptibility to it. Thus, tenofovir may be preferred in patients with lamivudine resistance. Moreover, tenofovir is much more effective against HIV than is entecavir. It is recommended that initial antiretroviral agents include tenofovir and either emtricitabine or lamivudine. Some patients have contraindications to tenofovir, and in those cases, entecavir can be used, but not concomitantly with lamivudine or emtricitabine due to the overlapping resistance patterns.

**Hepatitis D Virus Infection**

Hepatitis D (delta) virus (HDV) is a small, defective RNA virus that requires HBsAg for transmission and packaging. Of the 350 million individuals with chronic HBV infection, approximately 15 million have also been exposed to HDV. In general, the highest rates of HDV infection are in areas where HBV is endemic, although that is not uniformly the case (Figure 4).19

Acquiring HBV and HDV during the same exposure (HBV/HDV coinfection) is associated with more severe acute hepatitis and higher mortality than that which occurs with acute HBV monoinfection. The fate of HDV is determined by the host response to HBV, and HDV is cleared if HBV is cleared. HDV superinfection in an HBV carrier can manifest as an acute hepatitis and usually results in chronic HDV infection. Compared with chronic HBV infection, chronic HBV/HDV coinfection is associated with a higher risk of cirrhosis and liver decompensation.

Figure 5 shows diagnostic markers of HDV infection and serologic profiles of HBV/HDV coinfection and superinfection.19 HBV DNA is usually low or negative in chronic HDV infection because HDV suppresses HBV replication. HDV immunoglobulin M antibody (anti-HDV IgM) is positive in acute infection and can persist in chronic infection; if it does persist, it can be used as a surrogate marker for HDV replication. Anti-HDV IgG is indicative of HDV exposure; it may persist or decline with viral clearance and persists in cases of chronic infection. Qualitative HDV RNA is a marker of viral replication that is positive in chronic infection. Quantitative

**Figure 2.** Indicators of antiviral resistance: virologic and biochemical breakthrough and rebound of hepatitis B virus (HBV) over time. ALT indicates alanine transaminase. Adapted from Lok and McMahon.12

**Figure 3.** Primary resistance mutations of hepatitis B virus (HBV). ADV/TDF indicates adefovir/tenofovir disoproxil fumarate; ETV, entecavir; LAM, lamivudine; LdT, telbivudine; Pol/RT, Pol/reverse transcriptase; RNaseH, ribonuclease H. Adapted from Allen et al.18 *Based on in vitro data and therapy switch following emergence of genotypic adefovir resistance. Adapted from Allen et al.18
HDV RNA is useful to monitor treatment response but is not readily available and the assays are not standardized. HBsAg is useful to monitor treatment response if quantitative HDV RNA is not available. Decreasing HBsAg titers often herald surface antigen loss and HDV clearance, although surface antigen loss is rare in treatment.

The mainstay of treatment for HDV infection is peginterferon alfa for at least 48 weeks. Conventional interferon alfa can also be used. In the most recent and largest treatment trial, 90 patients with HDV infection were randomized to receive peginterferon alfa with or without adeffovir or adefovir alone for 48 weeks. Sustained virologic response (SVR) rates at 6 months after treatment were 31% in the peginterferon alfa group, 26% in the combination group, and 0% in the adeffovir group. The oral nucleos(t)ides appear to have limited activity against HDV, because the virus uses host enzymes for replication and thus lacks enzyme targets. An ongoing 2-year trial is examining peginterferon alfa with or without tenofovir in 120 patients; evaluation of this longer treatment duration was prompted by the observation that in some patients response is observed only after prolonged treatment. Week 48 data presented at the 2012 American Association for the Study of Liver Diseases meeting showed undetectable HDV RNA in 42% of the combination patients and 34% of the peginterferon alfa monotherapy group. Final results are awaited. A National Institutes of Health phase II trial of lonafarnib, a prenylation inhibitor, is currently enrolling patients.

An algorithm for managing HDV infection is shown in Figure 6. Anti-HDV IgG should be measured in patients with chronic HBV infection, and if test results are positive, qualitative HDV RNA should be measured. Patients with chronic HBV/HDV coinfection should undergo biopsy to determine the stage of disease as ALT level does not correlate well with histology, and coinfection is associated with a much more severe disease progression. Based on biopsy results and individual patient characteristics, the risks and benefits of peginterferon alfa treatment should be weighed. Ribavirin should be added to treatment for individuals who also have HCV infection. If HBV DNA is greater than 2000 IU/mL, addition of a potent oral nucleos(t)ide analogue to peginterferon alfa should be considered. In patients who clear HDV, reactivation of HBV can occur, and an oral nucleos(t)ide analogue should then be considered for these patients.

**Hepatitis E Virus Infection**

Hepatitis E virus (HEV) is a single-stranded, nonenveloped RNA virus of the Hepeviridae family that enters the hepatocyte via an unknown mechanism. Five genotypes have been identified, the first 4 of which infect humans. HEV is endemic in many countries of Asia, Central America, and Africa (Figure 7). The genotype distribution of HEV varies geographically. Genotype 1 is most common in Asia, genotype 2 in Central America and Africa, and genotype 3 in the United States. Genotype 4 is seen in Eastern Europe and Asia.

Classic epidemic HEV infection is due to genotype 1 or 2 and is the most common cause of acute hepatitis in endemic areas. There is no known animal reservoir for these genotypes. Epidemic HEV infection is transmitted via the fecal-oral route and is associated with large waterborne outbreaks. Epidemic HEV infection typically occurs in adolescents and young adults and is clinically associated with a high rate of jaundice and cholestasis. Acute epidemic HEV infection is associated with an especially high fatality rate among pregnant women. Genotype 1

![Figure 4. Prevalence of hepatitis D (delta) virus (HDV). Adapted from Hughes et al.](image)

![Figure 5. Diagnostic markers of hepatitis D (delta) virus (HDV) infection and profiles of hepatitis B virus (HBV)/HDV coinfection and superinfection. ALT indicates alanine transaminase; anti-HDV IgG, HDV immunoglobulin G antibody; HBsAg, hepatitis B surface antigen. Adapted from Hughes et al.](image)
or 2 HEV infection should be considered in individuals with acute hepatitis who have recently traveled to an endemic area.

Autochthonous cases of HEV infection acquired in the United States and Europe are due to genotype 3 or 4 infections. The clinical course is generally transient and asymptomatic. Autochthonous HEV infection was believed to occur very infrequently in the United States until recently, when seroprevalence studies showed that a substantial proportion of the population has anti-HEV IgG but has never presented with clinical symptoms. In autochthonous HEV infection, as opposed to epidemic HEV infection, the fatality rate is not increased in pregnant women. Also unlike epidemic HEV infection, autochthonous HEV infection can become chronic in immunocompromised patients.

Genotype 3 HEV should be considered in persons with unexplained hepatitis, especially if they are older (older men in particular), solid organ transplant recipients, or HIV-infected or present with acute or chronic liver failure. Acute HEV infection accounts for a small proportion of unexplained liver injury. Individual cases and small outbreaks have been linked to zoonotic spread, with swine being the main reservoir. There have been case reports of acquisition from undercooked deer, undercooked pig liver, and shellfish. HEV RNA has been isolated from commercially available pig liver and sausage. Case reports have also linked HEV transmission to blood transfusions and organ donations.

However, most individuals in the United States with evidence of HEV exposure have no recognized risk factors. Diagnostic markers for HEV infection and the biochemical profile of acute infection are shown in Figure 8. The clinical course of acute HEV infection is characterized by a 3-week to 8-week incubation period, during which HEV RNA can be detected in the stool or serum. After 8 weeks, symptoms develop in some patients and are usually accompanied by a rise in ALT and the appearance of anti-HEV IgM. IgM persists for months and declines with the resolution of infection. Anti-HEV IgG can persist for years. A diagnostic test that measures HEV IgM is commercially available, although it has not been approved by the FDA and sensitivities and specificities of the assays vary widely. The confirmatory test is HEV RNA, which is not commercially available but can be requested through the National Institutes of Health. In immunocompromised patients, IgM and IgG may be falsely negative. Suspected HEV infection in such patients should also be confirmed by an HEV RNA test.

Initial reports of autochthonous acute HEV infection were in the setting of solid organ transplantation. Subsequently, reports of acute HEV infection in HIV-infected patients in the United States began to appear, including the first case report of HEV genotype 3 as the cause of acute hepatitis in a patient in 2008, another report of HEV genotype 3 and jaundice in a pregnant woman in the same year, and a third report in 2009. Later in 2009, Dalton and colleagues reported the first case of chronic HEV infection in a patient with HIV infection. The patient was a 48-year-old man who had first been diagnosed with HIV infection in 2001. He started antiretroviral therapy in January 2007, with a CD4+ cell count of 30/μL, an ALT level of 51 IU/mL, and serologic tests negative for hepatitis A virus (HAV), HBV, and HCV. His ALT remained elevated for 2 years. After a report of chronic infection in a solid organ transplant recipient, the patient’s physicians performed HEV RNA testing and detected HEV RNA in serum and feces. Testing of 18-month-old samples also showed HEV RNA in
serum and feces, with one enzyme immunoassay showing positive anti-HEV IgG and IgM results and another showing negative results.

In chronic HEV infection, HEV RNA is positive in the stool and plasma and remains persistently positive. ALT levels usually rise and remain elevated. Anti-HEV IgG levels also typically rise and remain elevated, but patients with advanced immunosuppression may not produce anti-HEV IgG. In many of the case reports of chronic infection in HIV patients, IgG was negative; thus, concern about potential chronic HEV infection in an HIV-infected patient should prompt confirmatory HEV RNA testing. Chronic HEV infection is associated with rapid development of cirrhosis, observed in both solid organ transplant recipients and HIV-infected individuals. Cirrhosis can develop within 2 years to 5 years. In patients who are successfully treated, however, posttreatment liver biopsies demonstrate a reduction in inflammation and fibrosis.22,24

Most experience in treating HEV infection has been in solid organ transplantation. In this setting, reduction of immunosuppression leads to spontaneous clearance in approximately one-third of patients; in the remaining two-thirds, peginterferon alfa or ribavirin monotherapy or the combination results in clearance in most cases.

HIV-infected individuals are not likely to spontaneously clear HEV infection even with immune reconstitution with antiretroviral therapy. A small number of case reports indicate successful treatment with peginterferon alfa with or without ribavirin or with ribavirin monotherapy, but as of yet, there are no established guidelines or approved regimens for treating these patients.29-32

Figure 8. Diagnostic markers of hepatitis E virus (HEV) and profile of acute infection. ALT indicates alanine transaminase; anti-HEV IgG, HEV immunoglobulin G antibody; anti-HEV IgM, HEV immunoglobulin M antibody. Adapted from Hoofnagle et al.24

Summary

Non-HCV viral hepatitis is an important cause of morbidity and mortality, particularly among HIV-infected individuals. HBV is the leading cause of cirrhosis worldwide, and coinfection with HDV causes accelerated progression of liver disease. Autochthonous cases of HEV have been reported among HIV-infected and -uninfected persons and can lead to chronic infection in the setting of immunosuppression. Chronic HEV infection is associated with rapid development of cirrhosis. Reliable antibody assays and molecular tests for HDV and HEV are needed. Peginterferon alfa continues to have a role in treating viral hepatitis, even as we move toward newer, peginterferon alfa–free regimens in the treatment of HCV infection.

Presented by Dr Price in June 2013. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Price in December 2013.

Financial Affiliations: Dr Price has no relevant financial affiliations to disclose. Her spouse has held stock options for Bristol-Myers Squibb and Johnson & Johnson.

Additional Suggested Reading


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