Chronic Hepatitis B Virus and Hepatitis D Virus

New Developments

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KEYWORDS

• Hepatitis B • Hepatitis D • Hepatitis delta • Vaccination • Antivirals

KEY POINTS

- Hepatitis B remains a leading cause of liver-related morbidity and mortality globally, and increased efforts are needed to improved screening and linkage to care.
- The Centers for Disease Control and Prevention recommends universal adult hepatitis B vaccination for infants through adults 59 years of age, which could increase vaccination coverage and decrease overall hepatitis B cases.
- Existing therapies for hepatitis B are highly effective at suppressing viral replication, and novel therapies with greater potential for functional cure are on the horizon.
- Hepatitis delta infection occurring in the setting of chronic hepatitis B is associated with the most severe form of viral hepatitis, leading to a significantly greater risk of cirrhosis, hepatocellular carcinoma, and death.
- There are currently no Food and Drug Administration-approved therapies for hepatitis delta in the United States, but novel therapies effective at suppressing hepatitis delta virus RNA are soon to become available, pending results of ongoing phase 3 clinical trials.

EPIDEMIOLOGY OF HEPATITIS B VIRUS

The prevalence of hepatitis B virus (HBV) is underestimated in many regions, due to lack of epidemiologic data from many regions where its prevalence is highest. It is estimated that 272 million people were living with chronic hepatitis B (CHB) infection in 2020, with 1.5 million new infections each year.[1,2] The highest prevalence of the

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disease is noted to be in the Western Pacific (116 million), Africa (81 million), Eastern Mediterranean (18 million), and South East Asia (16 million).[1,3]

In the United States, it was estimated that only 850,000 persons were living with HBV infection based on survey data.[4,5] However, when considering foreign-born populations and changing immigration patterns, one recent study estimates the prevalence of CHB infection to be as high as 2.4 million in the United States.[6] In addition, the incidence of acute HBV infection is increasing as noted in a study reporting an increase of 114% in three states (Kentucky, Tennessee, and West Virginia) from 2009 to 2013; this increase is thought to be related to an increase in injection drug use.[7]

VACCINATION FOR HEPATITIS B VIRUS

As of 2021, the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommendation expands the indicated age range for universal HBV vaccination to now include all adults aged 19 to 59 years.[8] This removes the previous recommendation for risk factor assessment in this age group to determine vaccine eligibility. In addition, it is now recommended that universal vaccination be provided to those 60 years and older if they have increased risk factors for HBV, including being men who have sex with men, those having sex partners who are positive for hepatitis B surface antigen (HBsAg), those having more than 1 sex partner in 6 months, persons at risk for percutaneous or mucosal exposure to blood, those who travel to countries with high or intermediate endemic HBV ($\geq$2% HBsAg seroprevalence), persons with hepatitis C virus (HCV) or human immunodeficiency virus (HIV), those with chronic liver disease, or those who are incarcerated, as well as anyone who wishes to be vaccinated against HBV.[8] In addition, the new recommendations state that health care providers should offer HBV vaccination to all adults, including those 60 years and older, even without known risk factors, which differs from prior language suggesting that vaccination should be provided when requested by the patient. This shifts the responsibility of initiating the consideration of HBV vaccination from the patient to the provider.[8]

The World Health Organization (WHO) recommends that all infants receive the HBV vaccine as soon as possible after birth, preferably within 24 hours.[1] The vaccination is typically given as three doses administered at 0, 1, and 6 months as in the single-antigen vaccinations available with Recombivax and Energix-B or the combination hepatitis A and B vaccination, Twinrix. In addition, Twinrix may be administered on an accelerated schedule before travel, potential exposure, or immunosuppression at 0, 7, and 21 to 30 days, followed by a dose at 12 months.[4] Heplisav-B is a two-series vaccination for HBV administered at 0 and 1 months, approved for adults 18 years and older. Heplisav-B was approved by the Food and Drug Administration (FDA) in 2017; when compared with Energix-B, there was no difference in the occurrence of serious adverse events.[9] In addition, PreHevbrio is the first 3-antigen-containing vaccine, which is also a three-series vaccination, approved for HBV.[10] PreHevbrio was approved by FDA in 2021 and there is little or no difference in seroprotection or occurrence of mild or serious adverse events when compared with Engerix-B.[8]

The presence of anti-HBs $\geq$10 IU/L 1 to 2 months after three doses of vaccine is considered to be reflective of immunity. Literature suggests that the protection against HBV from full vaccination is at least 30 years and potentially lifelong due to the persistence of immunologic memory even if anti-HBs is negative.[4,11] Persons who have completed an HBV vaccination series at any point or who have a history of HBV infection should not receive additional HBV vaccination, although there is no evidence that receiving additional vaccine doses is harmful.[12] In addition, the CDC notes that there

are cases where revaccination might be indicated, as in nonresponder infants born to persons testing positive for HBsAg, health care providers, and persons receiving hemodialysis.[4,8] The CDC also recommends that health care providers only accept dated records as evidence of HBV vaccination.[8]

Screening/Testing Before Vaccination

Testing is not a requirement for vaccination, and in settings where testing is not feasible, vaccination of persons recommended to receive the vaccine should continue.[4,8] However, in settings in which the patient population has a high rate of previous HBV infection, pre-vaccination testing should be performed concomitantly with the administration of the first dose of vaccine. This may reduce costs by avoiding the complete vaccination of persons who are already immune.[8] It may also reduce the risk of providing false reassurance of vaccine-induced protection in patients who have undiagnosed CHB or past exposure to HBV, as evidenced by the presence of hepatitis B core antibody (anti-HBc) total.

Serologic markers for HBV infection include HBsAg, antibody to HBsAg (anti-HBs), hepatitis B core antibody (anti-HBc), immunoglobulin M and immunoglobulin G (IgM anti-HBc, IgG anti-HBc).[4] At least 1 serologic marker is present during the different phases of acute and chronic HBV infection. The CDC recommends screening all pregnant women for HBV with HBsAg. In addition, they recommend universal screening at least once in a lifetime for all persons 18 years and older with the following 3-panel test: HBsAg, anti-HBs, and anti-HBc.[13] This replaces prior risk factor-based screening and will help differentiate persons who have a current HBV infection from those who have immunity from a prior infection but may be susceptible to reactivation, and those who are susceptible and need vaccination.[4] The Proposed Updated Recommendations from the CDC also expand existing risk-based testing recommendations to include the following populations, activities, exposures, or conditions associated with increased risk for HBV infection: persons currently or formerly incarcerated in a jail, prison, or other detention setting; persons with a history of sexually transmitted infections or multiple sex partners; and persons with a history of HCV infection.[13]

TREATMENT GUIDELINES FOR CHRONIC HEPATITIS B

The goal of CHB treatment is to prevent liver-related morbidity and mortality.[14,15] Guidelines for the treatment vary by organization, whether following the 2018 Updates on the Treatment of Hepatitis B from the American Association for the Study of Liver Diseases (AASLD), the 2017 Clinical Practice Guidelines from the European Association for the Study of the Liver (EASL), or the 2015 Update of the Asia Pacific Clinical Practice Guidelines from the Asian Pacific Association for the Study of the Liver (APASL). When deciding on timing of the initiation of therapy, it is also important to consider additional risk factors for hepatocellular carcinoma (HCC) and cirrhosis, such as the patient's age and their family history of HCC. Below are the indications for treatment in those patients who have CHB (sorted by recommending society).

American Association for the Study of Liver Diseases

The AASLD recommends treating HBV infection with antiviral therapy in patients with compensated cirrhosis if HBV DNA greater than 2000 IU/mL regardless of the alanine aminotransferase (ALT) level, and treating patients with decompensated cirrhosis with any detectable HBV DNA.[14] For CHB with HBeAg positivity, the AASLD recommends that if the ALT is lower than the upper limit of normal (<35 IU/L for men and <25 IU/L for women), and HBV DNA $\geq$20,000 IU/mL, the ALT and HBV DNA of these patients can

be monitored every 3 to 6 months.[16] If there is a rise in ALT, but less than 2 times the upper limit of normal, with a falling HBV DNA level, this may signify seroconversion, so monitoring should be increased in frequency. Lastly, if these patients have an elevated ALT greater than 2 times the upper limit of normal, with HBV DNA ≥20,000 IU/mL, then they should be treated. For CHB with negative HBeAg activity and ALT lower than the upper limit of normal, the ALT and HBV DNA of these patients can be monitored every 3 to 6 months. If ALT increases but is less than 2 times the upper limit of normal with HBV DNA less than 2000 IU/mL, then ALT and HBV DNA can be monitored every 3 months for a year, then every 6 months. If ALT is greater than 2 times the upper limit of normal with HBV DNA ≥2000 IU/mL, then patients should be treated. The AASLD also recommends considering factors like age (>40 years), a family history of cirrhosis or HCC, previous treatment history, presence of cirrhosis, or presence of extrahepatic manifestations when deciding whether to treat patients with CHB with ALT less than two times the upper limit of normal and HBV DNA ≤2000 IU/mL in HBeAg-negative patients or ≤20,000 IU/mL in HBeAg-positive patients.

European Association for the Study of the Liver

EASL recommends that all patients with CHB who are HBeAg-positive or -negative with HBV DNA ≥2000 IU/mL, ALT at the upper limit of normal (normal is approximately 40 IU/L for men and women), or at least moderate liver necroinflammation or fibrosis be treated.[15] If patients have a normal ALT but high HBV DNA levels, they may be treated if they are older than 30 years, regardless of the severity of liver histologic lesions. Patients with both compensated and decompensated cirrhosis need treatment. Lastly, patients that have a family history of HCC or cirrhosis, and extrahepatic manifestations can be treated even if the above treatment indications are not fulfilled.[15]

Asian Pacific Association for the Study of the Liver

APASL recommends treating everyone with compensated or decompensated cirrhosis.[17] For non-cirrhotic HBeAg-positive CHB, with ALT less than 2 times the upper limit of normal (normal ≤40 IU/L for men and women) and HBV DNA less than 20,000 IU/mL, patients may be monitored every 3 months. If testing reveals moderate to severe inflammation or significant fibrosis, then treat. If ALT is ≥2 times the upper limit of normal and HBV DNA is >20,000 IU/mL without seroconversion for 3 months, then these patients should be treated. For non-cirrhotic HBeAg-negative CHB, these patients can be monitored unless ALT is 2 times the upper limit of normal with HBV DNA greater than 2000 IU/mL, in which case therapy should be initiated.

Antiviral medications can suppress HBV replication, decrease liver injury, and prevent transmission to susceptible persons.[18] Despite this, WHO estimates that only 16.7% of those diagnosed with CHB are receiving treatment.[19] In addition, some experts argue that treatment guidelines should be expanded, citing rising evidence that high viremia and persistent presence of HBeAg are associated with increased risk of cirrhosis, HCC, and liver-related mortality.[18,20–22] One US study of 41 HBeAg-positive patients with ALT ≤40 IU/L found that despite having normal ALT, many patients in the immune-tolerant phase have significant disease on liver biopsy (fibrosis stage ≥2 or fibrosis stage 1 plus grade ≥2 inflammation); this was noted in 29% of all patients, in 0% of those 35 years or younger, in 22% of those aged 36 to 50, and in 45% of those older than 50 years.[23] Overall, they report that there is data to support expanding treatment to immune tolerant and those in the indeterminate phenotype (commonly HBeAg-negative with HBV DNA <10,000 IU/mL but ALT greater than the upper limit of normal) who have evidence of active or advanced liver disease as well as treatment

to immune tolerant patients older than 40 years and even possibly those older than 30 years.

PREFERRED THERAPIES FOR HEPATITIS B VIRUS

The 2018 AASLD Updates on Hepatitis B reports the preferred therapies for HBV include entecavir, tenofovir dipovoxil fumarate (TDF), tenofovir alafenamide (TAF), and pegylated -interferon (PEG-IFN).[16] Entecavir, TDF, and TAF are nucleoside/nucleotide analogs, which can be administered orally.[15] They are long-term treatments, until HBsAg loss, with early stopping considered in select cases. They are tolerated well and have good viral suppression, with minimal to no risk of viral resistance.[15] For entecavir and TDF, there are dosage adjustments based on renal function. TAF is more stable than TDF in plasma and delivers the active metabolite to hepatocytes more efficiently, allowing a lower dose to be used with similar antiviral activity, less systemic exposure, and decreased renal and bone toxicity.[16] PEG-IFN is given as subcutaneous injections for 48 weeks.[15] It is less well tolerated and has more adverse effects, namely in those with psychiatric, neurologic, and endocrine dysfunction. It provides moderate viral suppression and no risk of viral resistance.[15]

When comparing entecavir and TDF, prior studies have shown that TDF was superior to entecavir in suppressing HBV viral load while having a similar safety profile to TDF.[24] In addition, a 2019 meta-analysis comparing tenofovir monotherapy with entecavir monotherapy in patients with CHB found that the incidence of HCC was significantly lower in the tenofovir group than the entecavir group (rate ratio [95% CI] of 0.66 [0.49, 0.89]; $P = .008$), while there was no statistical significance in incidence of death or transplantation (rate ratio [95% CI] of 0.78 [0.55, 1.13]; $P = .19$), encephalopathy (risk ratio [95% CI] of 0.72 [0.45, 1.13];, $P = .15$) or variceal bleeding (risk ratio [95% CI] of 0.71 [0.34, 1.50], $P = .37$) between the 2 groups.[25]

NEW HEPATITIS B VIRUS THERAPIES ON THE HORIZON

The therapeutic goals of current antivirals are mainly virologic and biochemical responses that may prevent disease progression and improve survival; however, these therapies do not generally promise a functional cure, or sustained loss of HBsAg.[26,27] Future therapies for HBV cure include agents that target the virus life cycle or those that indirectly modulate host factor/host immune responses including entry inhibitors; core protein allosteric modulators; those that cause RNA interference, inhibition, or neutralization of HBsAg; inhibitors of cccDNA; toll-like receptor agonists; immune checkpoint inhibitors; and therapeutic vaccines.[27] While none of these novel therapies are currently available, several agents undergoing clinical trials look promising and the field continues to anxiously await interim data readouts on the efficacy of these potential agents.

COINFECTION AND SUPERINFECTION WITH HEPATITIS D

Hepatitis D, also known as “delta hepatitis,” is a liver infection caused by the hepatitis D virus (HDV) and only occurs in people who are also infected with the HBV.[28] People can become infected with both hepatitis B and hepatitis D viruses at the same time, referred to as “coinfection,” or get hepatitis D after first being infected with HBV, known as “superinfection.”[28] Once chronicity is established, HDV can rapidly progress to cirrhosis in 10% to 15% of patients within 2 years and in 70% to 80% of patients within 5 to 10 years.[29,30]

Several recent studies have attempted to provide updated estimates of global HDV prevalence but have been limited by lack of high-quality population-level data. HDV

prevalence estimates have ranged from 15 million to 72 million, although most experts believe the prevalence is likely closer to 20 million affected globally.[31–34] Like HBV, these variations in prevalence estimates likely stem from incomplete population testing due to less clinical awareness, but also may reflect a lack of availability of HDV testing.[35] Hepatitis D is most common in Eastern Europe, Southern Europe, the Mediterranean region, the Middle East, West and Central Africa, East Asia, and the Amazon Basin in South America.[28] In the United States, prevalence data for HDV is lacking, with prior studies citing a range from 2% to 50%.[35–37] In one study of 1191 patients with CHB, 499 had been tested for HDV, and 42 (8%) were determined to be coinfected; half of these were also HCV-infected. Cirrhosis was present in 73% of the coinfected, 80% of the tri-infected, but only 22% of the mono-infected. Twenty-nine patients (69%) were Caucasian/non-Hispanic; 10 (24%) were Asians and Pacific Islanders.[37] In addition, another study showed that the seroprevalence of HDV was increasing from 29% in 1988 to 1989 to 50% in 2005 to 2006 in one US city among people who inject drugs.[35,38]

The AASLD recommends testing of HBsAg-positive persons at risk for HDV, including those with HIV infection, persons who inject drugs, men who have sex with men, those at risk for sexually transmitted disease, and immigrants from areas of high HDV endemicity.[14] However, given the severity of disease caused by HDV, as well as more recent prevalence data suggesting a higher-than-expected prevalence, some experts recommend universal testing for HDV in anyone with CHB.[37,39,40] The recommended screening test for HDV is serum anti-HDV IgG followed by HDV RNA PCR if positive.[35]

The goal of HDV treatment is HDV RNA clearance or suppression with the ultimate goal of reducing progression to cirrhosis, hepatic decompensation, and HCC.[39] For persons with HDV infection, the only effective treatment currently available in the United States is pegylated-interferon-α (PEG-α).[14] In patients with active hepatitis D with elevated liver enzymes, histologic evidence of hepatitis, or persistently elevated HDV RNA or anti-HDV IgM who do not have contraindications to PEG-α, PEG-α treatment can be initiated.[39] However, the rate of sustained HDV RNA suppression after 1 year of PEG-α therapy is only 15% to 20%, and this is not a well-tolerated drug.[41,42]

Owing to the current limitations of interferon-α-based therapies, there has been interest in novel therapies for HDV.[35] Current investigational therapies target various stages of the HDV lifestyle, and include the following classes: interferon-lambda (IFN-λ), prenylation inhibitors (lonafarnib), entry inhibitors (hepcludex B), and nucleic acid polymers.[35]

CLINICS CARE POINTS

- The prevalence of hepatitis B and D are underestimated in many regions of the world, including the United States.
- The US Centers for Disease Control and Prevention (CDC) has expanded the indicated age range for universal hepatitis B virus (HBV) vaccination to now include all adults aged 19 to 59 years.
- Although antiviral medications can suppress HBV replication, decrease liver injury, and prevent transmission to susceptible persons, few with chronic hepatitis B (CHB) are receiving therapy.
- Given the severity of disease caused by hepatitis D virus (HDV), as well as a higher-than-expected prevalence, some experts recommend universal testing for HDV in anyone with CHB.

- While current therapies do not generally promise a functional cure, future therapies for HBV cure include agents that target the virus life cycle or those that indirectly modulate host factor/host immune responses.

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