

CLINICAL REVIEWS

Selecting Appropriate Management Strategies for Chronic Hepatitis B: Who to Treat

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BACKGROUND: Hepatitis B virus (HBV) infection is a significant problem. In the United States estimates indicate that 0.3% of the population (1.25 million individuals) have chronic hepatitis B infection.

METHODS: Review of published practice guidelines and literature on management of hepatitis B to determine: 1) Which persons in Western populations are at the highest risk for HBV infection and should be screened for HBV seromarkers to identify those who are chronically infected and those who need to be protected with hepatitis B vaccine; 2) The importance of regular monitoring in persons with chronic hepatitis B, the frequency of monitoring, and which tests should be performed; 3) How to identify the patients who are appropriate candidates for antiviral therapy.

RESULTS: Recommendations for screening, diagnosis, monitoring, and treatment of chronic HBV infection are reviewed. Important differences are discussed between the Practice Guidelines for chronic hepatitis B developed by the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Asian Pacific Association for the Study of the Liver (APASL). In addition, this article reviews which patients who are not covered by these Guidelines might be candidates for antiviral therapy.

DISCUSSION: Established practice guidelines provide direction to providers for the diagnosis and management of chronic HBV infection to reduce the risk of serious sequelae. However, not all patients with chronic hepatitis B are identified, and many of those who are diagnosed do not receive adequate management and follow-up.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a significant problem worldwide. Of the 6 billion worldwide population, an estimated 2 billion have been infected by HBV (1). Of those, it is estimated that between 350,000 and 400,000 persons have chronic hepatitis B (CHB) infection. There is clear epidemiologic evidence that chronic HBV infection can result in the development of hepatocellular carcinoma (HCC) and cirrhosis (2-4). The Centers for Disease Control and Prevention (CDC) estimates that 1.25 million persons in the United States, 0.3% of the population, are chronically infected with HBV (5). The majority of those persons chronically infected may be unaware that they have HBV infection. Furthermore, of those who have been identified as having chronic HBV infection, the majority are not receiving regular, routine follow-up. There are several reasons for this. Patients with chronic HBV infection may not be aware that the status of their disease could change from inactive chronic infection to active chronic hepatitis, that they are at risk for the development of complications of HBV, or that effective antiviral therapy is available to treat their disease if needed, and that screening techniques for detecting HCC are available which may change the outcome if HCC develops (6). Health-care

providers may be unaware of the natural history of HCC, and the need for continuous lifetime monitoring of HBV infection status (7).

SCREENING HIGH RISK POPULATIONS FOR CHB

In the United States, Western Europe, and Japan, there are groups of individuals in whom epidemiologic studies have found the prevalence of hepatitis B surface antigen-positivity (HBsAg) is high. These groups are identifiable and should be screened for evidence of HBV infection. Table 1 outlines the current recommendations for screening for HBV seromarkers. Most of these groups were initially identified by the CDC and the Advisory Council for Immunization Practices (ACIP) in a report in 1991 (8). However, since then other groups of individuals were found to be at high risk, such as inmates of correctional institutions and persons coinfecting with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), and these groups should be added to the list of those to test. Table 2 summarizes the tests for HBV and how they should be interpreted.

Immigrants from countries with a high prevalence of HBV infection include persons from Asia, sub-Saharan Africa, the South Pacific Islands, Amazon Basin of South America, the

Table 1. High-Risk Groups Who Should Be Screened for HBV Infection and Vaccinated if Seronegative

Pregnant women
Health-care workers
Hemodialysis patients
Recipients of clotting factor concentrates
Individuals from areas where there are high prevalence rates of HBV, including immigrants and adopted children
Asia
Sub-Saharan Africa
South Pacific islanders (Samoans, Tongans, etc.)
Middle East
Indigenous populations of the Arctic
Amazon Delta of South America
Eastern Europe including Russia
Household and sexual contacts of persons who are HBsAg-positive
Injection drug users
Sexually active men, women, adolescents, and adults, with multiple partners
Inmates of correctional facilities
Individuals with abnormal LFTs of unknown cause
Individuals infected with HCV or HIV

Middle East, Eastern Europe including Russia, and indigenous populations of the Arctic. Individuals who were born in one of these geographic regions where HBV is endemic should be tested and if an HBsAg-positive person is identified in a first-generation immigrant family, then screening should include second- and third-generation family members. Individuals then found to be seronegative should be vaccinated. For example, if in an extended family of Asian descent, a grandmother from China is found to be HBsAg-positive, then her children and grandchildren should be screened. High rates of HBV infection have been found in incarcerated persons in the United States, and HBV screening and vaccination programs, as well as screening programs for HIV and HCV, should be a part of all Prisoner Health Programs in the United States.

In high-risk individuals, serologic testing can be performed with either HBsAg and antibody to hepatitis B surface antigen (anti-HBs), or with anti-HBc as a screening test, and further testing of those who are positive for anti-HBc with both HBsAg and anti-HBs. Individuals found to be HBsAg-positive should be evaluated for CHB infection, while those who are anti-HBs positive should be considered immune. Persons found to be negative for both HBsAg and anti-HBs, or

negative for anti-HBc should receive a full three-dose immunization schedule of hepatitis B vaccine.

PHASES OF CHRONIC HBV INFECTION AND RISK FACTORS FOR PROGRESSION

At a National Institutes of Health (NIH) Workshop on HBV, three phases of chronic HBV infections were defined: the immune tolerant phase, the CHB phase, and the inactive hepatitis B phase (9).

The immune tolerant phase is usually seen in persons infected at birth. Hepatitis B “e” antigen (HBeAg) acts as an immune modulator allowing HBV to avoid recognition by the immature immune system and consequently cytotoxic T-cell activity against HBV antigens are absent. In immune competent persons, HBV itself is not cytotoxic but hepatocellular damage is due to activity of the host’s immune system. In the immune tolerant phase, HBeAg is positive, HBV DNA is elevated, ALT is usually normal, and liver inflammation is absent or minimal. During this phase liver disease is uncommonly progressive and treatment is usually not effective. Eventually most patients infected at birth progress to the CHB phase. Persons infected in later childhood or as adults may not experience the immune tolerant phase and manifest the CHB phase shortly after infection. The CHB phase is characterized by a present but weak cytotoxic T-cell response resulting in ALT elevation, HBV DNA levels >10⁵ copies/mL, and active liver inflammation of various degrees varying from mild inflammation with no or mild fibrosis to moderate to severe liver inflammation and fibrosis.

In most patients, a more vigorous cytotoxic T-cell response eventually occurs, resulting in seroconversion from HBeAg to anti-HBe during the CHB phase. After seroconversion, most patients go into the inactive hepatitis B phase characterized by normal ALT levels, low levels of HBV DNA (<10⁵ copies/mL), and improvement of liver inflammation, and even improvement of liver fibrosis over time provided they remain in the inactive hepatitis B phase. Treatment is not indicated in the inactive hepatitis B phase and patients usually do not develop progressive liver fibrosis or need treatment. However, some individuals develop anti-HBe CHB, characterized by the absence of HBeAg but HBV DNA levels above 10⁵ copies/mL and active liver inflammation. In addition, patients may move from the inactive hepatitis B phase back to the CHB phase, either by experiencing a reversion from anti-HBe to

Table 2. Serological and Molecular Markers of HBV Infection and Their Interpretation

	Acute Hepatitis B	Recovery from Acute Hepatitis B	Chronic HBeAg+ Disease	Chronic HBeAg- Disease	Successful Vaccination	Resistance to Antiviral Agents
HBsAg	✓ (may clear)		✓	✓		
Anti-HBs		✓			✓	
Anti-HBc IgM	✓					
Anti-HBc	✓	✓	✓	✓		
HBeAg	✓		✓			
Anti-HBe		✓ (in some cases)		✓		
DNA (PCR if required)	✓ (may be only marker during incubation period)		✓	✓		✓ (sequence <i>pol</i> region)

Table 3. Factors Associated with the Progression of Chronic HBV Infection

Viral
HBV
Genotype
Precore mutant
Core promoter mutations
Other: HIV, HDV, HCV
Demographic
Age
Male sex
Ethnicity
Environmental and social
Alcohol
NAFLD
Aflatoxin

HBeAg or having flares of anti-HBe CHB characterized by episodes of elevated HBV DNA levels followed by flares of ALT elevation (4, 10). Some patients in the inactive hepatitis B phase eventually clear HBsAg at a rate of about 0.5% per yr (7).

Individuals in any of the three phases of CHB infection can develop HCC. For these reasons, all persons chronically infected with HBV, even those in the inactive hepatitis B phase, need lifelong monitoring of ALT to assess for disease reactivation and the complications of HBV infection (6).

RISK FACTORS FOR PROGRESSION OF LIVER DISEASE AND HCC IN HBV INFECTION

Table 3 lists the risk factors that may accelerate the course of HBV infection or contribute to the development of HCC. These include viral, demographic, and social/environmental factors. Recently, there has been much interest in the role of HBV genotypes in the development of HBV-related liver disease. Eight genotypes of HBV have been identified, A through H, and they differ in HBV DNA sequences by 8% or more; several sub-genotypes, varying between 4% and 8%, have also been identified (11, 12). Some genotypes appear to be less frequently associated with severe complications, for example, genotypes Ae and Bj, while others, such as genotypes Aa, Ba, C, and D, appear to be linked to more aggressive chronic hepatitis or higher risk of HCC. More definitive data defining the role of HBV genotypes in subsequent liver disease is needed before HBV genotype testing or genotype-driven therapeutic choices become part of clinical practice.

Important mutations in the HBV genome appear to increase the risk of complications in HBV infected persons. A common mutation that occurs in certain HBV genotypes around the time of HBV seroconversion, the "precore" (PC) mutation, can be associated with anti-HBe positive CHB. This mutation, at base pair 1896 from tyrosine to guanine, results in the creation of a stop codon that prevents the formation of HBeAg. Although there is down-regulation of HBV DNA replication with this mutation, replication can still occur at a sufficiently high rate to result in liver inflammation

and ongoing fibrosis (CHB phase) (12). Another mutation, a double mutation in the basal core promoter (BCP) area, or the core gene, downgrades HBV DNA replication but has been associated with more severe liver disease and HCC in some studies (12).

Coinfection with HCV may increase the risk of progression of CHB. Furthermore, multiple studies clearly show that HCV/HBV coinfection increases the risk of developing HCC (3). Coinfection with hepatitis delta virus (HDV) also increases the risk of progression of hepatic injury (13). In persons coinfecting with HIV and HBV, HBV titers may be higher and liver disease may progress more rapidly (14). It is important to note that in some patients who have HBV/HIV coinfection, serum may be negative for HBsAg but positive for anti-HBc. It is prudent to measure HBV DNA level in such patients.

Males who are chronically infected with HBV have a three to four times higher risk of subsequently developing HCC than females (3, 4). In males, the risk of complications, especially HCC, increases with age and is much higher in those aged 45 years or older. There is not enough data to determine the relationship between increasing age and risk of HCC in females. Data on the role of ethnicity in risk of complications from HBV is also lacking. Several studies have suggested that alcohol consumption is a risk factor for developing chronic liver disease and possibly HCC (15). Unfortunately, no studies have been conducted to determine the effect of hepatic steatosis due to nonalcoholic fatty liver disease (NAFLD) as a risk factor for disease progression in HBV. However, in HCV liver steatosis has been associated with an increased risk of liver fibrosis (16). With the epidemic of obesity, insulin resistance, and the metabolic syndrome that is currently taking place in the United States, such studies are badly needed. Finally, exposure to aflatoxin, present in grains and nuts from developing countries, is a synergistic risk factor of developing HCC in persons with HBV infection (3).

MONITORING PERSONS CHRONICALLY INFECTED WITH HBV

Initial Evaluation

Individuals with chronic HBV infection need lifelong monitoring for the development of active chronic hepatitis and HCC (6). Table 4 provides a list of recommended clinical

Table 4. Evaluation of Newly Identified Persons Chronically Infected with HBV

History and physical examination, with emphasis on liver examination
Screen and vaccinate household/sexual contacts
Biochemistry tests
Complete liver panel, CBC
AFP
HBeAg and anti-HBe
HBV DNA if HBeAg is positive or ALT or AST are elevated
Screen for hepatitis A and vaccinate if anti-HAV-negative
Consider baseline liver ultrasound

Test	Units	Conversion
Liquid hybridization (Abbott)	pg/mL	1pg HBV DNA = 383,000 copies/mL (~3X 10 ⁵ copies)
Hybrid capture (Digene)	pg/mL	1pg HBV DNA = 383,000 copies/mL
Branched DNA (Bayer)	copies/mL	
PCR-amplicor (Roche)	copies/mL	
TaqMan PCR	IU/mL	1 IU = 5.1 copies (10 ⁵ copies = ~20,000 IU)

Figure 1. Commercially available tests for HBV DNA.

examination and laboratory tests for their initial evaluation. The initial evaluation is important to identify the current stage of the individual's chronic HBV infection and thus what testing should be subsequently performed and how frequently the patient should be evaluated. In addition to a pertinent history and physical examination, a complete liver panel should be performed to identify if active inflammation, evidenced by elevated ALT and/or AST, may be present, and whether liver synthetic function, measured by bilirubin and albumin, is normal. If either bilirubin or albumin is abnormal, prothombin time should also be measured to determine if decompensated cirrhosis might be present. A CBC is useful to determine the platelet count, which if below 130,000 may suggest the presence of portal hypertension resulting in splenomegaly (which can cause a fall in platelet count due to sequestration).

Initially, all patients should have HBeAg, anti-HBe, and HBV DNA levels measured to classify the phase of chronic HBV infection. Since there are many different methods commercially available for measuring HBV DNA, interpretation of results can be a challenge for health-care providers. Figure 1 lists the available tests and how to convert the results in other units into copies/mL (the usual unit used in guidelines). Figure 2 indicates the range of HBV DNA that each of these tests is able to measure. It is important to note

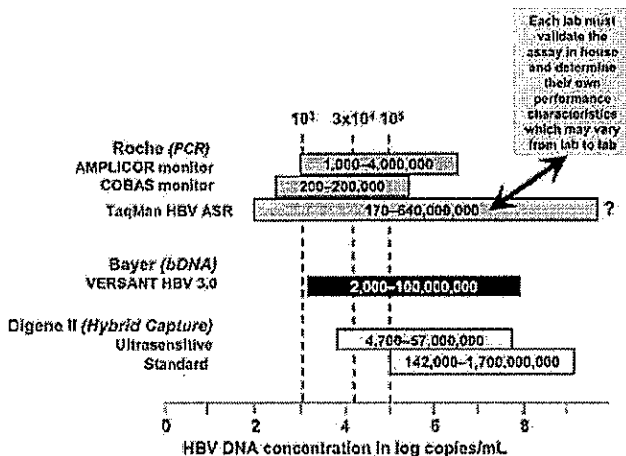


Figure 2. Ranges of quantitative HBV DNA assays.

Table 5. AASLD Recommendations for Monitoring Patients Chronically Infected with HBV

HBeAg-positive persons with normal ALT levels
Monitor ALT/AST levels every 3 months for first year then every 6 months thereafter
HBeAg-positive patients with elevated ALT levels
Perform liver biopsy
Inactive HBsAg carrier state
Perform liver chemistries every 6–12 months to assess development of active disease
If ALT rises above upper limit of normal and HBV DNA > 10 ⁵ copies/mL, perform liver biopsy

that tests that give results in picograms (pg/mL) are unable to detect HBV DNA below approximately 100,000–150,000 copies/mL, so tests employing this technology can miss some individuals with levels above 100,000, *i.e.*, 10⁵ copies/mL.

Follow-Up Evaluation

Table 5 outlines the frequency of monitoring and types of laboratory testing that should be considered for individuals with chronic HBV infection. Individuals in the immune tolerant phase who are HBeAg-positive and have normal ALT levels should be evaluated with ALT and AST testing every 3 months for the 1st yr, then every 6 months. If ALT becomes elevated, then liver biopsy should be considered. For those with CHB who are either HBeAg or anti-HBe positive and have elevated ALT and HBV DNA levels, a liver biopsy should be considered.

For those in the inactive hepatitis B phase, with low HBV DNA levels and normal ALT, ALT and AST levels should be tested every 6–12 months indefinitely. If ALT and or AST become elevated, HBeAg, anti-HBe, and HBV DNA testing should be performed. If HBV DNA is < 10⁵ copies/mL and liver aminotransferase levels are elevated, then another cause of liver function elevations should be sought. This should include a history of alcohol use and a review of current medications (prescribed, over-the-counter, and herbal), testing for anti-HCV and, if possible, anti-HDV. Additional possible causes of liver enzyme elevations are insulin resistance and NAFLD, so risk factors for these conditions should also be assessed.

GUIDELINES FOR THE TREATMENT OF CHB

Evidence-based guidelines for the treatment of CHB have been developed by three of the worlds' major specialist liver societies, the American Association for the Study of Liver Diseases (AASLD) (6), the European Association for the Study of the Liver (EASL) (17), and the Asian Pacific Association for the Study of the Liver (APASL) (18). The AASLD guidelines were developed using three key stages: (1) a thorough review of the literature to identify evidence-based studies on hepatitis B; (2) a guideline document prepared by experts in the field; and (3) a thorough review of the guidelines

Table 6. AASLD Recommendations for Treatment in Patients Chronically Infected with HBV

HBeAg-positive CHB	
HBV DNA	>10 ⁵ copies/mL, elevated ALT >1.5 × upper limit normal (ULN)
Consider biopsy	
Wait 3–6 months to see if spontaneous HBeAg seroconversion occurs if patient has compensated liver disease	
If seroconversion does not occur, then treat if moderate liver inflammation or moderate fibrosis present on biopsy	
HBeAg-negative CHB	
HBV DNA	>10 ⁵ copies/mL, elevated ALT
Consider biopsy	
Treat if moderate liver inflammation or moderate fibrosis present	
Long-term therapy usually required in persons with HBeAg-negative chronic HBV as withdrawal of therapy frequently results in relapse	
Patients on treatment should be evaluated with periodic HBV DNA levels to monitor response and detect emergence of resistance	

by a panel of experts in liver disease. The guidelines developed by EASL and APASL used similar criteria and a similar development process. These guidelines are reviewed and updated every 2–3 yr. Evidence-based guidelines require sufficient evidence to support any recommendations that are made and thus may not cover all situations which a clinician caring for patients with HBV may encounter. These guidelines are not meant to represent “standards of care” and should rather be used to help clinicians rationally care for their patients with HBV.

Table 6 summarizes the AASLD recommendations for selecting patients for treatment for CHB. Individuals in the immune tolerant phase should not be treated, as treatment infrequently results in HBeAg seroconversion and, in patients receiving nucleos(t)ide inhibitors such as lamivudine and adefovir, the risk of developing resistance increases over time. Similarly, those in the inactive hepatitis B phase should not receive treatment, as they already have low levels of HBV DNA and normal ALT levels. Patients in the immune tolerant phase whose ALT level rises to >2 × ULN for 3–6 months should be considered for treatment. Also, persons who are HBeAg-positive and have fluctuating ALT levels that rise above the normal range but do not rise above 2 × ULN should be considered for a liver biopsy and treated if they have moderate/severe necroinflammation. Persons in the inactive phases should have a liver biopsy if ALT levels rise above the normal limit and HBV DNA becomes or remains >10⁵ copies/mL. In patients who are anti-HBe positive who initially have or later develop CHB, evidenced by abnormal ALT and HBV DNA >10⁵ copies/mL, treatment should be considered if liver biopsy shows moderate/severe hepatitis or moderate/severe fibrosis. In HBeAg-positive patients with compensated liver disease, treatment should be delayed for 3–6 months in case spontaneous HBeAg seroconversion occurs.

The AASLD’s 2004 guidelines recommend interferon alpha, lamivudine, and adefovir as first-line treatments. In

HBeAg-positive patients, if interferon is chosen, it should be given for 4–6 months; if an oral nucleos(t)ide inhibitor such as lamivudine or adefovir is used, treatment should continue for 6 months after HBeAg seroconversion occurs to ensure the best chances, about 80%, that seroconversion will be sustained. In anti-HBe-positive patients with CHB, the criteria for initiating treatment are similar: the presence of moderate hepatitis, moderate fibrosis, or persistent ALT levels >2 × ULN. Now that entecavir and peginterferon alfa-2a are licensed, the AASLD guidelines will soon be revised. Both of these agents should also be considered as first-line medications for both HBeAg-positive and HBeAg-negative (anti-HBe positive) CHB.

Two other important treatment recommendations should be considered when caring for patients with HBV. Several studies have clearly shown that there is a risk of up to 50% that individuals with chronic HBV infection will develop an exacerbation of hepatitis during chemotherapy treatment for malignancies (19). The prophylactic use of lamivudine has been shown to significantly reduce this risk (20). Therefore, when beginning chemotherapy all HBsAg-positive patients, regardless of their ALT or HBV DNA levels, should be treated with nucleoside analogs and this medication should be continued for at least 4 months after completing chemotherapy. Similar risk has been shown in persons treated with tumor necrosis factor alpha inhibitors for rheumatic disorders or inflammatory bowel disease, and these individuals should also be given lamivudine prophylaxis (21, 22).

The guidelines developed by EASL and APASL are very similar to the AASLD guideline (17, 18). The EASL guideline has a specific recommendation against treating persons with mild hepatitis (17).

The use of the HBV DNA level of >10⁵ copies/mL to define CHB is based on one study from the NIH published in 1989 using dot blot hybridization to measure HBV DNA, an older, less sensitive methodology than we have today (23). Recently, three studies have suggested that CHB may occur at lower levels of HBV DNA in some patients, levels between 10⁴ and 10⁵ copies/mL (24, 25). One of these studies correlated HBV DNA levels with liver biopsy findings and found that 30,000 copies/mL was a more sensitive cutoff, with no participants below this level having biopsy evidence of CHB (24). However, this study also found that the level of >10⁵ copies/mL had a diagnostic accuracy of 91%, indicating that it is still a useful level. Another study by Chu *et al.* found that some patients who were anti-HBe positive with HBV DNA levels between 10⁴ and 10⁵ copies/mL also had elevated ALT levels and therefore may not have truly been in the inactive hepatitis B phase (25). However, in this study not all participants with elevated ALT levels underwent a liver biopsy to confirm their CHB status and, furthermore, investigations for other possible causes of ALT elevation were not reported.

A third study showed that one of eight patients with anti-HBe and HBV DNA levels between 10⁴ and 10⁵ copies/mL had significant fibrosis on liver biopsy. However, in this study

several persons with HBV DNA levels $>10^5$ copies/mL in their sera had no or minimal fibrosis found at liver biopsy (26).

A panel of experts recently published an opinion on the management of hepatitis B (27). They recommended that individuals with elevated ALT levels who had HBV DNA levels of 10^4 – 10^5 copies/mL should be treated. However, before treatment is undertaken in these patients, it seems prudent to first perform a liver biopsy and to then treat only if moderate to severe inflammation or fibrosis are present.

CONCLUSION

Chronic infection with HBV is lifelong in most infected individuals. It is important to detect undiagnosed HBV-infected persons by screening high-risk individuals, and to vaccinate those who are found to be seronegative. Individuals with chronic HBV infection need lifelong monitoring to determine if/when treatment is needed and for surveillance to detect HCC at a potentially treatable stage. Excellent antiviral therapy is now available that can suppress (but not eradicate) this virus and individuals who might benefit from treatment should be identified and offered appropriate antiviral therapy.

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