

# Internist Diagnosis and Management of Chronic Hepatitis B Virus Infection

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## ABSTRACT

Chronic infection with the hepatitis B virus can lead to hepatocellular carcinoma and cirrhosis in up to 25% of infected individuals. As many as 2 million individuals in the US may have chronic hepatitis B infection, most of whom immigrated to the US from hepatitis B-endemic regions of the world. A 2010 report from the Institute of Medicine noted that two thirds of patients with hepatitis B are unaware of their infection, and most health care providers do not screen for hepatitis B or know how to manage hepatitis B-positive patients. In 2010, the Hepatitis B Foundation convened a group of primary care providers to consider the existing evidenced-based recommendations and strategies for implementation of hepatitis B screening into routine practice. The group designed an easy-to-use algorithm for screening, initial evaluation, ongoing management, and referral to a subspecialist when appropriate. Internal medicine specialists, including primary care providers and subspecialists, need to understand the steps they can take to address this often under-recognized disorder.

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**KEYWORDS:** Chronic; Disease management; Hepatitis B; Liver; Screening

The hepatitis B virus is responsible for one of the most common chronic infectious liver diseases, affecting some 350-400 million individuals worldwide.<sup>1</sup> Without interven-

**Funding:** The workshop described was convened and funded by the Hepatitis B Foundation ([www.hepb.org](http://www.hepb.org)) from its general operating funds. The Hepatitis B Foundation is a 501(c)3 nonprofit research and disease advocacy organization supported by federal, state, corporate, and private foundation grants, and individual charitable donations. No commercial support was provided for the March 10-11, 2010 workshop.

**Conflict of Interest:** Brian McMahon, the Liver Disease Program at the Alaska Native Tribal Health Consortium has received support from Gilead; Barbara A. Haber, research support from Bristol-Myers Squibb, Gilead, Roche; W. Thomas London, spouse owns shares of Merck & Co. Inc.; Robert Perrillo, serves on the Speaker's Bureau for Bristol-Myers Squibb and Gilead Sciences, consultant for Roche Pharmaceuticals and Gilead; All others, no conflict of interest.

**Authorship:** All authors had access to the data and played a role in writing this manuscript.

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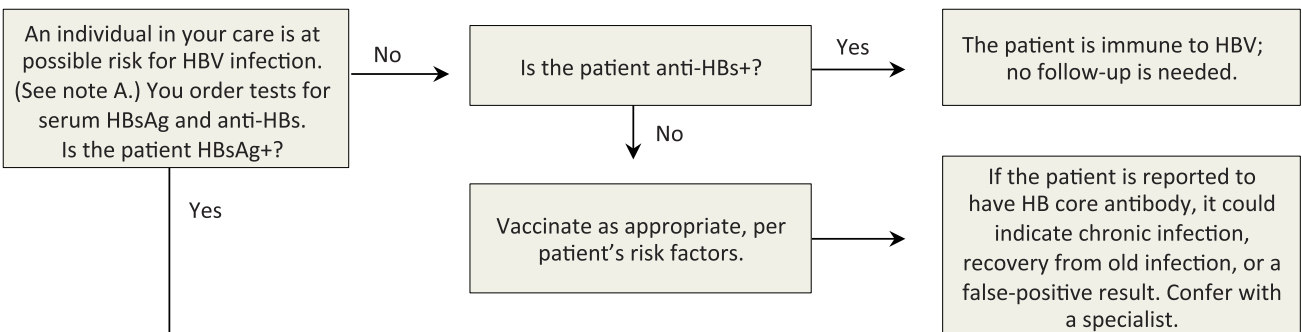
tion, 15%-25% of those infected will die prematurely from complications including cirrhosis or hepatocellular carcinoma. The Third National Health and Nutrition Examination Survey (NHANES III) estimated that 1.25 million people in the US have chronic hepatitis B infection. However, the survey under-represents Asian and Pacific Islander Americans.<sup>2-4</sup> When such under-represented populations are taken into account, as many as 2 million Americans may be chronically infected with hepatitis B.<sup>2</sup>

## PROVIDER AWARENESS ABOUT CHRONIC HEPATITIS B INFECTION

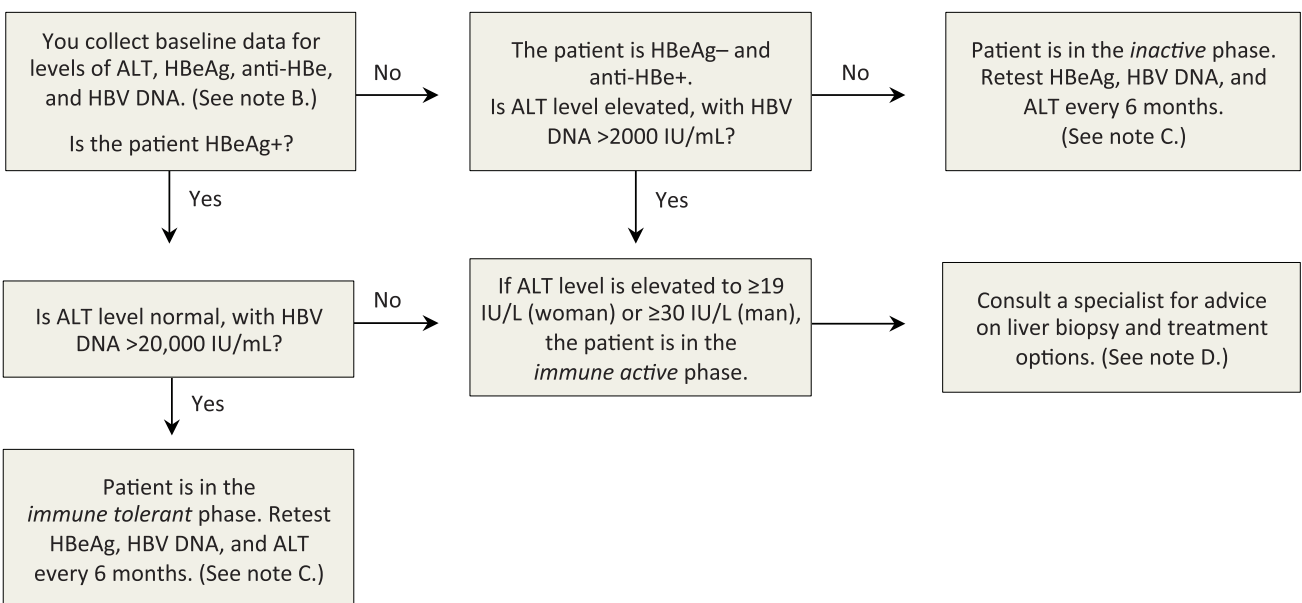
In 2010, at the request of the US government, the Institute of Medicine (IOM) published a comprehensive report to draw attention to the unmet need of those with viral hepatitis.<sup>5</sup> This report found that more patients in the US die yearly of chronic viral hepatitis than of human immunodeficiency virus infection. Furthermore, while 75% of those with human immunodeficiency virus infection in the US were aware of their infection, only 35% of those with hepatitis B knew they were infected. Of those aware

## Suspect HBV infection? Use this algorithm to screen and intervene

### Screening at-risk patients



### Evaluating and monitoring HBsAg+ patients



**Figure** Hepatitis B screening algorithm for at-risk patients.<sup>12</sup> McHugh JA, Cullison S, Apuzzio J, et al. Chronic hepatitis B infection: a workshop consensus statement and algorithm. *J Fam Pract.* 2011;60(9):E1-E8. ALT = alanine aminotransferase; anti-HBe = antibody to HBeAg; anti-HBs = antibody to HBsAg; AST = aspartate aminotransferase; DNA = deoxyribose nucleic acid; HBeAg = hepatitis B e-antigen (protein produced by HBV, indicating heightened viral activity); HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HIV = human immunodeficiency virus.

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of their infection, <50% received regular follow-up care. Because effective antiviral agents are available for those with active liver disease, the IOM concluded that there is an urgent need to inform and educate primary care providers of the importance of hepatitis B screening and follow-up. The IOM report found that primary care providers, including internal medicine physicians, had significant gaps in their knowledge of hepatitis B, including knowing who should be screened, what tests to order, how to evaluate individuals found to be infected, the long-term management of those infected, and when to refer patients to specialists for treat-

ment. As a result of the IOM report, the US Department of Health and Human Services issued an action plan in May 2011 entitled "Combating the Silent Epidemic: the U.S. Department of Health and Human Services Action Plan for the Prevention and Treatment of Viral Hepatitis" (<http://www.hhs.gov/ash/initiatives/hepatitis/>).<sup>6</sup> The internal medicine specialist plays a crucial role in the implementation of this plan through the identification of infected individuals by screening patients in their practices who are at high risk for contracting hepatitis B, and through participation in the care, management, and treatment of infected individuals.

*(continued)* Algorithm notes

<b>A</b> Individuals at risk for HBV infection	
<ul style="list-style-type: none"> <li>• Blood or tissue donors</li> <li>• Hemodialysis patients</li> <li>• HIV-positive patients</li> <li>• Household members or sexual contacts of infected individuals</li> <li>• Individuals with conditions that may require immunosuppressive or immune-modifying therapy (beyond 2 weeks of corticosteroids)</li> <li>• Individuals with elevated ALT/AST of unknown cause</li> <li>• Infants born to HBV-infected mothers</li> <li>• Injection drug users</li> <li>• Men who have sex with men</li> <li>• Pregnant women</li> </ul>	<ul style="list-style-type: none"> <li>• Individuals born in regions where HBV prevalence is <math>\geq 2\%</math>:                         <ul style="list-style-type: none"> <li>– Africa</li> <li>– Asia</li> <li>– Caribbean: Antigua-Barbuda, Dominica, Grenada, Haiti, Jamaica, St. Kitts-Nevis, St. Lucia, Turks and Caicos</li> <li>– Central America: Guatemala and Honduras</li> <li>– Eastern Europe, except Hungary</li> <li>– Middle East, except Cyprus and Israel</li> <li>– North America: indigenous peoples of Alaska, Northern Canada, and Mexico</li> <li>– South America: Amazonian areas of Bolivia; Brazil, Columbia, Ecuador, Guyana, Peru, Suriname, Venezuela</li> <li>– South Pacific, except Australia and New Zealand</li> </ul> </li> </ul>
<b>B</b> Postdiagnosis education and counseling	
<ul style="list-style-type: none"> <li>• Screen close family members, household contacts, and sexual partners</li> <li>• Vaccinate uninfected close family members, household contacts, and sexual partners</li> <li>• Provide infected individuals with disease-management information and consult with a specialist</li> </ul>	
<b>C</b> Recommended management of chronic HBV infection	
<ul style="list-style-type: none"> <li>• Measure ALT every 6 months, HBV DNA at baseline and every 6 months if ALT is elevated <math>\geq 19</math> IU/L (women) or <math>\geq 30</math> IU/mL (men)</li> <li>• Measure HBeAg yearly</li> <li>• Measure alpha-feto protein and perform liver ultrasound every 6-12 months for those at high risk for HCC:                         <ul style="list-style-type: none"> <li>–Family history of HCC</li> <li>–Cirrhosis</li> <li>–Man <math>\geq 40</math> years or woman <math>\geq 50</math> years</li> <li>–<math>&gt;20</math> years old and born in Africa</li> <li>–Co-infection with HCV or HIV</li> </ul> </li> </ul>	
<b>D</b> Potential candidates for referral	
<ul style="list-style-type: none"> <li>• HBeAg-positive, ALT elevated; with or without advanced fibrosis or cirrhosis</li> <li>• HBeAg-negative, ALT elevated, HBV DNA <math>&gt;2000</math> IU/mL; with or without advanced fibrosis or cirrhosis</li> <li>• Patients undergoing immunosuppressive or sustained immune-modifying therapy (eg., <math>&gt;2</math> weeks of corticosteroids or other modifying agents)</li> </ul>	

**Figure** Continued

**IMPLEMENTING NATIONAL SCREENING, MANAGEMENT, AND VACCINATION RECOMMENDATIONS**

In response to the IOM report and the Action Plan, the Hepatitis B Foundation organized a meeting of primary care providers, including participants specializing in internal medicine, pediatrics, family medicine, and obstetrics/gynecology, as well as a physician assistant and a nurse practitioner (no commercial support was received for the meeting, nor honoraria provided for participants). Three experts in viral hepatitis presented background information and the

current evidenced-based practice guidelines for hepatitis B infection developed by the American Association for the Study of Liver Diseases (AASLD),<sup>7</sup> a National Institutes of Health (NIH) Consensus Conference,<sup>8</sup> and the Centers for Disease Control and Prevention.<sup>9-11</sup> With this knowledge, the primary care participants developed a simple, easy-to-use algorithm to assist primary care providers in implementing the evidenced-based guidelines from AASLD and others.<sup>12</sup> The algorithm will assist internists in screening of patients at high risk for contracting hepatitis B, identifying chronically infected patients, ordering appropriate labora-

tory tests to determine the phase of chronic infection, and alerting the physician about timing of referral to a specialist. The first section of the algorithm covers screening for hepatitis B infection (serologic testing for the hepatitis B surface antigen [HBsAg]) and vaccination of those at risk who are found to be negative for hepatitis B seromarkers. The second section of the algorithm addresses initial evaluation and management, and when referral might be appropriate for those found to be chronically infected (Figure).

## IDENTIFYING PATIENTS WITH CHRONIC HEPATITIS B INFECTION

Chronic hepatitis B infection is a complicated and, at times, confusing condition. Infection can progress rapidly or slowly and may suddenly regress to an inactive phase associated with subsequent improvement in liver inflammation and even reversal of fibrosis.<sup>1</sup> In some patients, the disease can reactivate years later. In most individuals with chronic hepatitis B infection, these progressions and regressions occur while patients are asymptomatic, or have non-specific symptoms such as fatigue. Significant clinical disease may not occur until liver failure or hepatocellular carcinoma develops. Chronic hepatitis B infection is generally classified into 4 immunologic phases: the immune tolerant, immune active, and inactive phases, and the HBsAg clearance phase, as defined at an NIH workshop on hepatitis B.<sup>13</sup> The algorithm (Figure) can assist internal medicine providers in defining the phase of chronic hepatitis B infection a patient may be experiencing.

## MANAGEMENT OF DISEASE

Chronic hepatitis B infection cannot be cured but can generally be kept under control with current treatment strategies. Patients in the immune-tolerant and inactive phases generally do not need treatment, and providers are advised to retest all individuals with chronic hepatitis B infection every 6 months for life, to monitor for progression of disease. The algorithm also calls for internal medicine providers to conduct surveillance for hepatocellular carcinoma in those with chronic hepatitis B infection, per AASLD evidenced-based guidelines for hepatocellular carcinoma<sup>14</sup> (see algorithm note B, Figure). Individuals with a family history of hepatocellular carcinoma, those with cirrhosis, men over age 40 years, and women over age 50 years should have liver ultrasound performed every 6 months. Many providers also test for serum alpha-fetoprotein, although this test is not specifically recommended by the AASLD practice guideline. This routine surveillance is supported by strong evidence outlined in the AASLD guideline that screening can detect hepatocellular carcinoma early, while the individual is in a treatable stage and when interventions such as surgical resection, radiofrequency ablation of small tumors, or liver transplantation may cure many patients.

Although hepatitis B vaccination is routine in the US, there are gaps in care regarding both administration of vaccine,

especially in the immigrant community, and appropriate post-vaccination measurement of protective titers for those at risk. Hepatitis B is highly transmissible from mother to child, and by close contact within a household, particularly via sexual exposure. It is important for the internist to screen not only patients at high risk (eg, first-generation immigrants from hepatitis B-endemic areas) but to recommend screening of their children and close contacts (see algorithm note B).

## CONCLUSION

Morbidity and mortality due to chronic hepatitis B infection can be greatly reduced if internal medicine and other primary care providers are aware of and routinely implement national screening, management, and vaccination recommendations; this includes identification of chronically infected patients, initial evaluation of disease, and life-long monitoring of patients with chronic hepatitis B infection. Strong evidence suggests that a 3-pronged prevention strategy will have a significant and lasting effect on the reduction of morbidity and mortality of hepatitis B infection:

1. Prevention of hepatitis B infection in at-risk adults by screening and vaccination of susceptible (HBsAg/anti-HBs-negative) individuals (which has been shown to prevent subsequent development of hepatitis B-related hepatocellular carcinoma);
2. Prevention of cirrhosis and hepatocellular carcinoma by identifying individuals with chronic hepatitis B infection who would benefit from treatment; and
3. Prevention of death from hepatocellular carcinoma in patients with chronic hepatitis B infection by early detection of hepatocellular carcinoma when curative therapy is possible.

Internal medicine physicians and other primary care providers must play a key role in instituting these important measures in the US health care system.

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