

# Evaluation and Management of Hepatitis B Virus Infection

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## Program Audience

Primary care physicians.

## Educational Needs Addressed

It is estimated that there are 1.25 million patients in the United States chronically infected with hepatitis B virus (HBV). Chronic HBV infection, if undiagnosed, can result in progressive liver disease and increased risk for developing hepatocellular carcinoma. It is critical for patients at higher risk for HBV, particularly those from endemic regions, to receive the appropriate screening and follow-up. Treatment has been shown to slow disease progression and reduce the risk of hepatocellular carcinoma.

## Educational Objectives

After participating in this CME activity, primary care physicians should be able to

1. Identify patients who should be screened for chronic HBV infection
2. Know the appropriate approach to screening and follow-up testing
3. Describe the natural history of chronic hepatitis B
4. Describe the available options for treatment and endpoints for therapy

## CASE STUDY

### Initial Presentation



A 46-year-old Asian male who came to the United States 2 years ago presents for primary care.

- What is the role for screening for hepatitis B in this patient?

It is estimated that there are 1.25 million patients in the United States chronically infected with hepatitis B virus (HBV), defined as testing positive for the hepatitis B surface antigen (HBsAg) for more than 6 months [1]. These patients are at increased risk for progressive liver disease and hepatocellular carcinoma [2]. Asian Americans shoulder a heavy burden of infection with HBV; they are 2.4 times more likely to die of hepatocellular carcinoma than are Caucasian Americans and are often unaware they are infected [3]. Furthermore, self-reporting of vaccine status is an unreliable measure of protection because a significant percentage of such patients are either chronically infected or lack protective antibody [3].

Patients who should be screened for HBV include those born in high- and intermediate-prevalence areas as well as those with historical or other risk factors (Table 1) [4]. For patients from endemic areas, a strategy of screening all patients, treating patients found to be chronically infected, and vaccinating contacts of infected patients was the most cost-effective strategy of those assessed [5].

- How is HBV transmitted?

HBV is transmitted by exposure to infectious body fluids; it has been detected in every bodily fluid except stool. HBV is transmitted with greater efficiency than is either hepatitis C

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**Table 1.** Patients Who Are Candidates for Screening for Chronic HBV

Persons born in areas with high and intermediate prevalence rates of HBV:

- South Asia and South Pacific Islands
- Africa
- Middle East
- Mediterranean Europe
- Indigenous population of the Arctic
- South America
- Eastern Europe
- All states of the former Soviet Union
- Caribbean nations


Miscellaneous candidates for screening:

- Persons with a history of drug injection
- Men who have sex with men
- Persons with a history of sexually transmitted diseases
- Patients with a history of hepatitis C and/or HIV
- Household and sexual contacts of HBsAg-positive patients
- Patients on hemodialysis
- Patients with chronically elevated aminotransferases
- Pregnant women
- Prisoners in correctional facilities
- Persons with past exposure to blood products

HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus. (Adapted with permission from Lok A, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007;45:508.)

or HIV. It is transmissible through perinatal, sexual, or percutaneous exposure, close person-to-person contact with open cuts and sores, and through shared household articles such as razors and toothbrushes. The risk of transmission increases with the level of HBV DNA in serum [6]. The likelihood of progression to chronicity is in large part determined by the age at exposure; neonates have a greater than 90% chance of progressing to chronicity, whereas this chance is less than 5% in adults [7].

## Case Continued

 This patient relates that his mother had hepatitis B and passed away from hepatocellular carcinoma several years ago. His physical examination is unremarkable. Testing reveals the following:

- HBsAg, positive
- Hepatitis B surface antibody (HBsAb), negative
- Hepatitis B core antibody (HBcAb), positive
- Alanine aminotransferase (ALT), 150 U/L
- Aspartate aminotransferase (AST), 105 U/L

- Total bilirubin, 0.6 mg/dL
- Alkaline phosphatase, 66 U/L

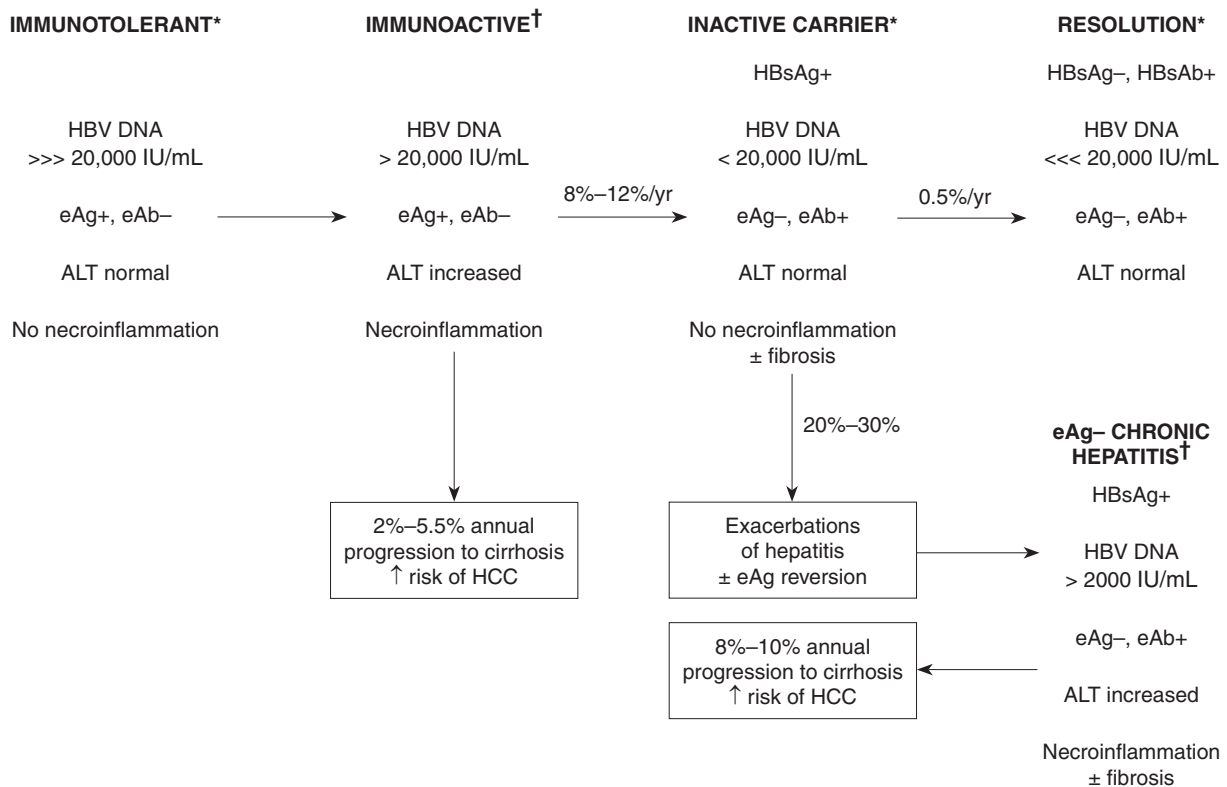
- **What additional follow-up testing is indicated in patients found to be HBsAg-positive, and how is this testing used to determine whether or not a patient with chronic HBV is a candidate for treatment?**

Patients found to be HBsAg-positive should undergo testing to assess the status of their liver disease. Serum albumin and prothrombin time assess hepatic synthetic function. A complete blood count assesses for hypersplenism; both thrombocytopenia and leukopenia are potential indicators of hypersplenism. The viral replication status is assessed with hepatitis B e antigen (HBeAg) and HBV DNA. The viral replication data, in combination with the ALT and hepatitis B e antibody (HBeAb), allows the clinician to start the process of determining where a patient falls along the natural history continuum shown in **Figure 1**.

## Natural History of HBV

Patients infected via vertical transmission begin in the immunotolerant stage, a stage marked by normal aminotransferases, very high HBV DNA levels, and no necroinflammation in the liver. At an undefined point in time, all patients will transition into the immunoinactive stage of disease, a stage marked in the majority of patients by elevated aminotransferases, high viral loads, and hepatic necroinflammation. In Asian patients infected via vertical transmission, this transition often occurs in the third to fourth decade of life. It is critical to differentiate between these 2 stages, as patients in the immunoinactive stage are at increased risk of progression to cirrhosis and end-stage liver disease and are candidates for therapy. The aminotransferases do not perfectly correlate with necroinflammation; a liver biopsy is sometimes required in patients with normal aminotransferases to confidently differentiate between these 2 stages.

Patients in the immunoinactive stage of disease will spontaneously seroconvert the e antigen (lose e antigen and develop e antibody) at a rate of 8% to 12% per year (Figure 1) [8]. In general, the higher the serum ALT, the more likely seroconversion will occur; seroconversion is often preceded by a flare of hepatitis with a marked elevation of the aminotransferases [9]. Seroconversion of the e antigen is a desirable development, as it heralds the onset of the inactive carrier stage of disease, which is marked by reduced, if not undetectable, HBV DNA levels, normalization of the aminotransferases, and resolution of necroinflammation. Patients in the inactive



**Figure 1.** Natural history of hepatitis B virus (HBV). ALT = alanine aminotransferase; eAb = e antibody; eAg = e antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma. \*Not a candidate for therapy. †Candidate for therapy.

carrier state have reduced risk of progressive liver disease as well as hepatocellular carcinoma [10,11].

Unfortunately, e antigen seroconversion does not have 100% durability; 20% to 30% of patients in the inactive carrier state will have reinitiation of viral replication, either through e antigen reversion or, more commonly, through the development of precore or core promoter mutations that allow for viral replication in the absence of e antigen (Figure 1) [12–14]. For this reason, it is critical that patients in the inactive carrier state be monitored indefinitely for evidence of reactivation.


HBeAg-negative chronic hepatitis is characterized by elevated aminotransferases, HBV DNA levels that are often lower than in the immunoactive stage (> 2000 IU/mL), and hepatic necroinflammation [15]. Patients with HBeAg-negative chronic hepatitis B are at even higher risk of progression of disease than patients in the immunoactive stage. For this reason, it is critical that they are identified. The challenge for the clinician is to differentiate between an inactive carrier with minimal replication and a patient with HBeAg-negative hepatitis with normal aminotransferases.

A liver biopsy can differentiate between the 2 scenarios and should be pursued if there is any doubt.

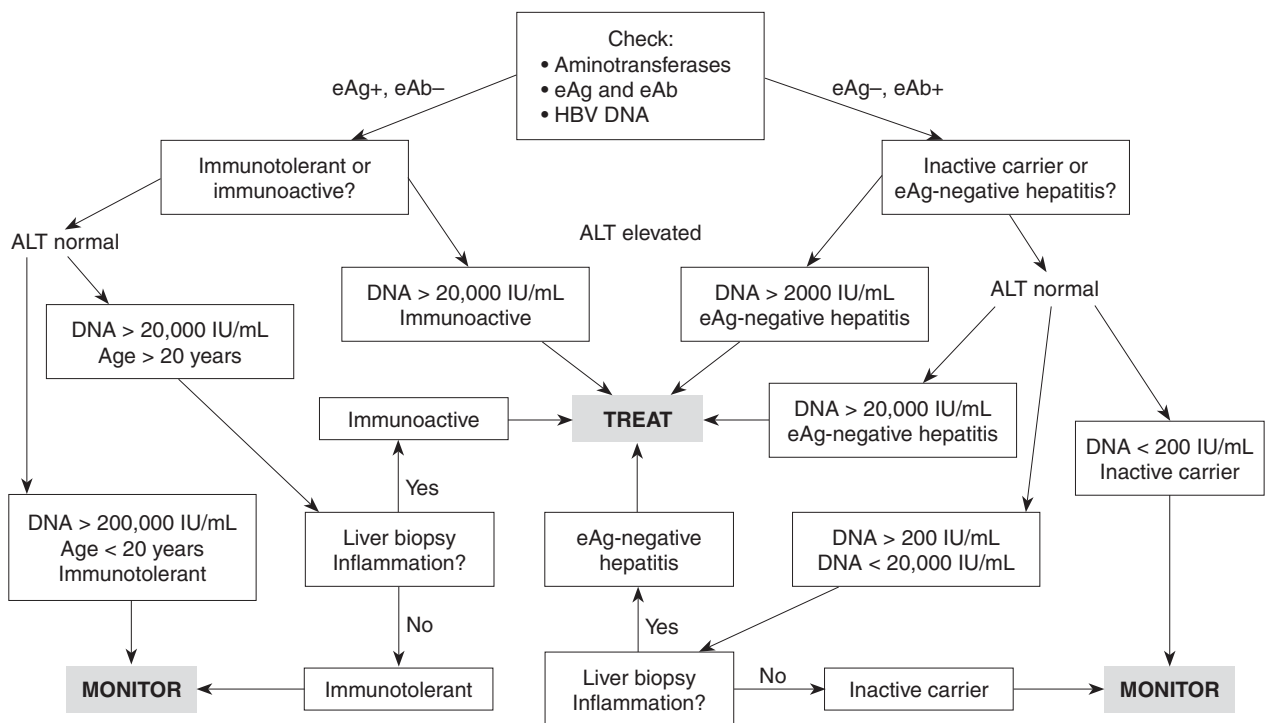
The final stage in the natural history of chronic hepatitis B is the development of surface antigen seroconversion marked by the loss of HBsAg and development of HBsAb (Figure 1). While the prognosis of these patients is improved, low levels of HBV DNA are detectable in the serum of some of these patients and hepatocellular carcinoma has been reported, particularly in patients who had progressed to cirrhosis prior to seroconversion [16,17].

The clinician's role is to determine where an individual patient falls along the continuum and using that information to determine if treatment is indicated.

### Case Continued

 This patient's follow-up laboratory test results are as follows:

- HBeAg, positive
- HBeAb, negative



**Figure 2.** Evaluation of the hepatitis B surface antigen–positive patient. ALT = alanine aminotransferase; eAb = e antibody; eAg = e antigen; HBV = hepatitis B virus.

- HBV DNA, 800,000 IU/mL
- Albumin, 4.2 g/dL
- Prothrombin time, 11.2 seconds
- White blood cell count,  $7.2 \times 10^9$ /L
- Platelet count, 283,000 cells/mm<sup>3</sup>

• **Where does this patient fall on the chronic HBV continuum? Is a liver biopsy indicated?**

Based on this patient’s elevated aminotransferases, HBeAg positivity, and elevated HBV DNA, he is in the immunoactive stage of disease (Figure 2); he is at increased risk for disease progression and hepatocellular carcinoma and is therefore a candidate for therapy. A liver biopsy is not absolutely required in this case, although it would provide information regarding the degree of liver damage, most specifically the stage of fibrosis. The stage of fibrosis would help guide the clinician in determining the endpoints of therapy and also the frequency of screening for hepatocellular carcinoma.

Patients with advanced fibrosis may be candidates for treatment beyond the accepted endpoints of therapy and the presence of advanced fibrosis should prompt surveillance for hepatocellular carcinoma at a shortened interval (every 6 months).

A liver biopsy can be essential for differentiating between patients in the immunotolerant or immunoactive stage of disease, or differentiating between patients in the inactive carrier state and those with HBeAg-negative chronic hepatitis. While the aminotransferases are often helpful in this regard (Figure 1 and Figure 2), they are not necessarily a perfect indicator of histologic activity; a percentage of patients in the immunoactive stage of disease or with e antigen–negative HBV will have normal aminotransferases. The age of the patient should be factored into decision making; the older the patient, the greater the likelihood of necroinflammation on liver biopsy [4]. Ultimately, if there is any doubt regarding a patient’s disease status, a liver biopsy should be performed.

• **What are the available treatment options for HBV?**

The therapies approved by the U.S. Food and Drug Administration for HBV are listed in **Table 2**. The interferons are prescribed for a defined period of time, whereas the nucleoside and nucleotide analogues (NAs) are continued until a specific endpoint of therapy is reached. For immunoreactive patients, the goal is e antigen seroconversion—loss of e antigen and development of e antibody. Seroconversion of e antigen is associated with sustained viral suppression in the majority of patients. For patients with e antigen–negative chronic hepatitis, there is no seroconversion equivalent and relapse is the rule even after prolonged viral suppression. Thus, therapy in these patients is often continued indefinitely.

The choice of therapy is based on patient-specific factors. Interferon is most effective in immunoreactive patients with a pretreatment ALT greater than 2 times the upper limit of normal and lower levels of HBV DNA [18]. Pegylated interferon has greater ease of administration and is slightly more effective than standard interferon. Forty eight weeks of pegylated interferon results in a seroconversion rate of 27% at the end of treatment and 32% 24 weeks after the completion of therapy, with a durability of 80% to 90% [19,20]. Interferon is much less effective in patients with normal aminotransferases and very high viral loads. Disadvantages of interferon include an extensive side effect profile and the fact that it is poorly tolerated in patients with advanced liver disease. An advantage of interferon is that viral resistance has not been reported.

When administered to immunoreactive patients, the NAs produce seroconversion rates of 12% to 21% at 1 year with durability of response somewhat less than those seen with interferon [21–24]. The most effective NA combines high potency with low likelihood of viral resistance. The NAs are continued for 6 to 12 months after e antigen seroconversion has occurred. Patients need to be aware before initiating therapy that there is no defined time endpoint; there is no way to predict how long seroconversion will take, although it is likely to occur more quickly in patients with elevated aminotransferase levels.

Emerging viral resistance is a significant concern when NAs are used as a monotherapy. Among the approved NAs, entecavir has the lowest rate of drug resistance, while lamivudine has the highest rate in patients naive to NA therapy.

The development of viral resistance has significant clinical implications, as it limits treatment options and, if unnoticed, results in disease progression and increased risk of hepatocellular carcinoma. Strategies to avoid the development of resistance include reinforcing the need for compliance and careful monitoring of the viral response on therapy. Factors associated with an increased risk of resistance include very high pretreatment HBV DNA and even more importantly, persistence of viremia on therapy.

**Table 2.** FDA-Approved Therapies for Hepatitis B Virus Infection

Interferons	
Interferon alpha 2b (5 million units once/day or 10 million units 3 times/week for 12–24 weeks)	
Pegylated interferon alpha 2a (180 µg once/week for 48 weeks)	
Nucleoside analogues	
Lamivudine (100 mg once/day)	
Entecavir (0.5 mg once/day; 1 mg once/day in patients with lamivudine resistance)	
Telbivudine (600 mg once/day)	
Nucleotide analogues	
Adefovir (10 mg once/day)	

Studies have documented a correlation between viral load at 6 months and the likelihood of emerging viral resistance [25,26]. Patients started on NA monotherapy should have their response to therapy monitored every 3 months and if there is not a sufficient virologic response, an alternative therapy should be implemented.

Another potential strategy to reduce the risk of emerging viral resistance would be to use de novo combination therapy. Studies have documented a reduction in the development of lamivudine resistance when lamivudine was combined with a second agent, but have not shown any improvement in virologic endpoints of therapy [19,27].

Lamivudine resistance has cross-resistance with telbivudine, and lamivudine resistance is required to develop entecavir resistance. There is no cross-resistance between lamivudine and adefovir. While it seems likely to be the case, there are no data to suggest combination therapy will further reduce the risk of emerging resistance in drugs with low resistance rates to begin with, such as entecavir. For patients who have developed lamivudine resistance, there are data that show add-on therapy with adefovir is superior to sequential monotherapy in reducing the risk of adefovir resistance [28]. Sequential monotherapy has been shown to result in multidrug resistance and should be avoided [29].

### Case Resolution



The patient is treated with 48 weeks of pegylated interferon and ribavirin. He seroconverts by the end of treatment. He remains an inactive carrier 3 years later.

### CONCLUSION

Chronic hepatitis B, if undiagnosed, can result in progressive liver disease and an increased risk of hepatocellular carcinoma. It is critical for patients at higher risk for HBV, particularly those from endemic regions, be screened initially

with HBsAg, HBsAb, and HBeAb. Patients who are HBsAg-positive should have follow-up testing, including aminotransferases, HBeAg, HBeAb, and HBV DNA. A thoughtful interpretation of this testing, in combination with a liver biopsy in some circumstances, will allow the clinician to determine where the patient falls in the natural history of chronic hepatitis B. This determination allows the clinician to identify candidates for therapy, choose the best option for therapy with an understanding of the risk of emerging viral resistance, and know the endpoints of therapy. Treatment has been shown to slow disease progression and reduce the risk of hepatocellular carcinoma.

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## CME EVALUATION: Evaluation and Management of Hepatitis B Virus Infection

**DIRECTIONS:** Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. The immunotolerant stage of hepatitis B virus infection (HBV) is characterized by all of the following EXCEPT
  - A. Normal aminotransferases
  - B. Very high HBV DNA levels
  - C. No necroinflammation in the liver
  - D. Increased risk of progression to cirrhosis
  
2. In most patients, the immunoactive stage of HBV is characterized by all of the following EXCEPT
  - A. Normal aminotransferases
  - B. High viral loads
  - C. Hepatic necroinflammation
  - D. Increased risk of progression to cirrhosis
  
3. The inactive carrier stage of HBV is characterized by all of the following EXCEPT
  - A. High HBV DNA levels
  - B. Normalization of the aminotransferases
  - C. Resolution of necroinflammation
  - D. Reduced risk of progressive liver disease
  - E. Reinitiation of viral replication in 20% to 30% of patients
  
4. Patients with hepatitis B e antigen–negative chronic hepatitis have all the following EXCEPT:
  - A. Elevated aminotransferases
  - B. HBV DNA levels that are often lower than in the immunoactive stage
  - C. Hepatic necroinflammation
  - D. Lower risk of progression of disease than patients in the immunoactive stage
  
5. Which of the following statements about interferon therapy for HBV is FALSE?
  - A. It is continued until a specific endpoint is reached
  - B. It is most effective in immunoactive patients with a pretreatment alanine aminotransferase level greater than 2 times the upper limit of normal and lower levels of HBV DNA
  - C. Pegylated interferon is slightly more effective than standard interferon
  - D. It is less effective in patients with normal aminotransferases and very high viral loads
  - E. Viral resistance has not been reported



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