

Diagnosis and Management of HBV in Managed Care

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Summary

Hepatitis B virus infection is a common infection that can result in cirrhosis, liver cancer, and death. Vaccination of at-risk groups and screening for infection are two ways to limit the spread of this disease. Antivirals can alter the progression of the disease through suppression of virus replication but virologic resistance and disease rebound can occur. Strategies to control resistance are being developed.

Key Points

- Hepatitis B virus infection is very common and can become a chronic condition.
- The consequences of chronic infection are cirrhosis, liver cancer, and death.
- The primary goal of hepatitis B therapy is the prevention of consequences through durable suppression of HBV replication with antiviral agents.
- Medication resistance occurs with hepatitis B infection.
- Strategies to combat HBV resistance are evolving.

HEPATITIS B VIRUS (HBV) IS CLASSIFIED into eight genotypes (A-G). Genotype appears to have an impact on the natural history of the disease and response to treatment. Genotype B is associated with less active and more slowly progressive liver disease than C. Genotypes A and B respond better to interferon (IFN) than C and D. Genotypes G and A are the primary genotypes found in patients from the United States.¹

HBV infection is very common, with more than 2 billion people worldwide having been infected with the virus at one time. Approximately 350 million are chronically infected and are at high risk of serious illness and death from cirrhosis and primary liver cancer. Worldwide, hepatitis B kills 500,000 to 750,000 persons each year.²

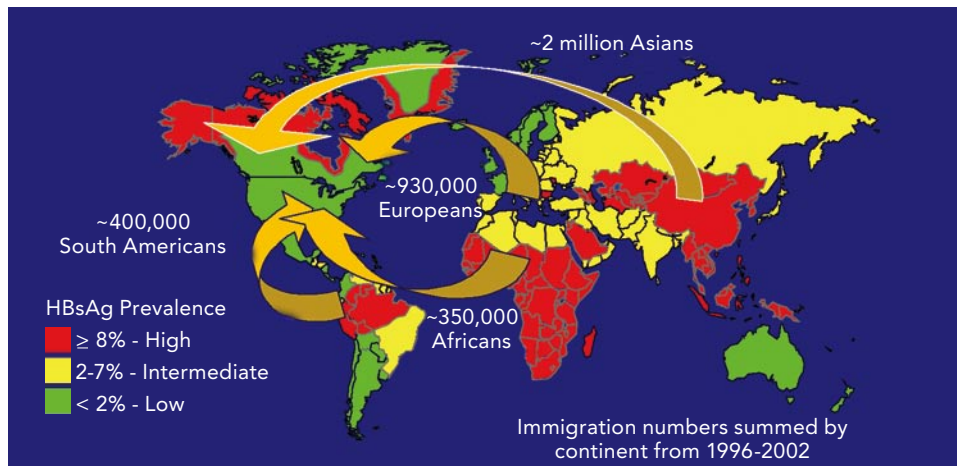
It is estimated that there are 1.25 million chronically infected Americans, of whom 20 to 30 percent acquired their infection in childhood. Many of these cases are among people who have emigrated from areas of the world where HBV is endemic. In the United States alone, there are 140,000 to 320,000 new cases per year. HBV results in 4,000 to 5,000 deaths per year. The premature mortality from cirrhosis or liver cancer is 20 to 25 percent.

The frequency of HBV infection and patterns of HBV transmission vary dramatically in different parts of the world (Exhibit 1).³⁻⁵ Approximately 45 percent of the world's population live in areas where the prevalence of chronic HBV infection is high (>8 percent of the population are HBsAg positive), 43 percent live in areas of intermediate prevalence (2 to 7 percent of the population are HBsAg positive), and only 12 percent of the world's population live in areas of low endemicity (<2 percent of the population are HBsAg positive).

In areas of high endemicity, the lifetime risk of HBV infection is greater than 60 percent. Such areas include most of Asia (except Japan and India), most of the Middle East, the Amazon Basin of South America, most Pacific Island Groups, Africa, and other special populations such as Native Alaskans, Australian Aborigines, and Maoris in New Zealand. Most infections in these areas occur at birth or during early childhood when the risk of acquiring chronic infection is the greatest. There is little recognition of acute disease, as most early childhood HBV infections are asymptomatic. However, the rates of chronic liver disease and liver cancer are high.

In areas of intermediate endemicity, the lifetime

Exhibit 1: Geographic Prevalence of Chronic Hepatitis B May Be Impacted by Migration



References: 3-5

risk of HBV infection is 20 percent to 60 percent and infections occur in all age groups. Acute disease is commonly recognized as many infections occur in adolescents and young adults. Additionally, high rates of HBV-related chronic liver disease occur due to the high prevalence of chronic HBV infection.

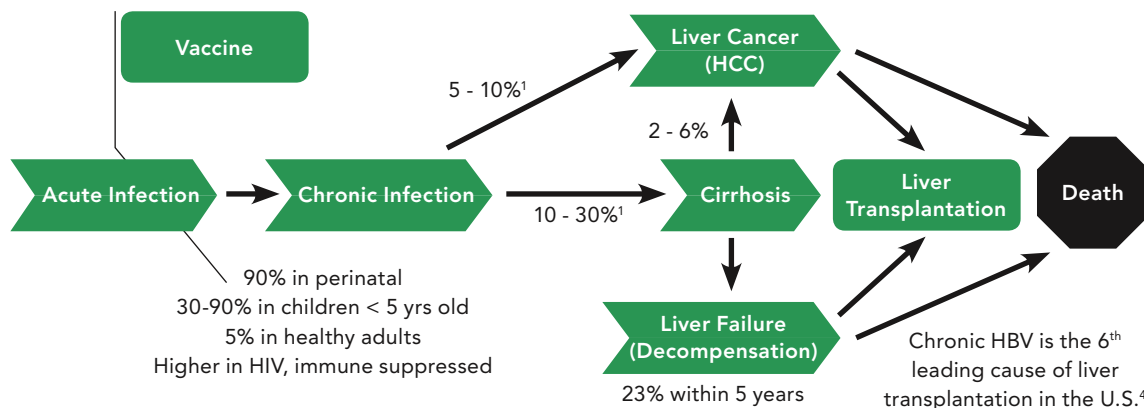
Exhibit 2 illustrates the possible progression of HBV infection.⁶⁻⁹ In many patients, the initial acute infection is not detected. Whether one develops chronic hepatitis B depends on when the infection was originally acquired. If it is contracted before age 1, the rate of chronic infection is 90 percent. This vertical transmission does not occur in the United States because of prenatal screening and infant vaccination. In the United States, HBV is a sexually

transmitted disease in adolescents or adults. The rate of conversion to chronic infection in a sexually transmitted population is only 5 percent.

The consequences of chronic infection include cirrhosis and liver cancer. HBV infection is the only liver disease that predisposes humans to liver cancer where the patient does have to have cirrhosis. The risk of liver cancer is higher if the patient does develop cirrhosis. The development of cirrhosis and liver cancer appear to be related to the patient's viral load.^{10,11} Serum levels of HBV DNA greater than 100,000 copies/ml significantly increase risk.

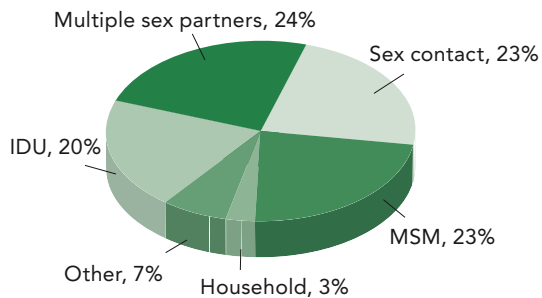
The most common ways by which HBV is acquired in the United States are shown in Exhibit 3.¹² The majority of transmission occurs through sexual

Exhibit 2: Hepatitis B: Disease Progression



1. Torresi J et al. Gastroenterology. 2000.
 2. Fattovich G et al. Hepatology. 1995.
 3. Moyer LA et al. Am J Prev Med. 1994.
 4. Perrillo R et al. Hepatology. 2001.
 References: 6-9

Exhibit 3: HBV Sources of Infection



Many patients do not reveal IDU as source of infection.

MSM, men having sex with men; IDU, intravenous drug use; household, household contact with blood

References: 12

Exhibit 4: Who to Test for Hepatitis B Risk Factors

- Persons born in hyperendemic areas
- Men who have sex with men
- Injecting drug users
- Dialysis patients
- Other parenteral viruses HIV, HCV
- Patients with abnormal LFT's
- Pregnant women
- Family members, household members, and sexual contacts of HBV-infected persons
- Persons with unexplained abnormal ALT levels
- Health care, emergency medical, and public safety workers after needlestick or mucosal exposures or blood

Reference: 14

contact whether that is multiple sexual partners or men having sex with other men. There is a very high rate of transmission with anal intercourse.

During acute infection, about 30 percent of persons have no signs or symptoms. If symptoms are present, they are generally nonspecific, including jaundice, fatigue, abdominal pain, loss of appetite, nausea, vomiting, joint pain, dark urine, and/or clay-colored bowel movements.¹³

Exhibit 4 lists those patients who should be screened for possible HBV infection.¹⁴ When choosing patients for screening, it is important to note that the incubation period for HBV can be two to six months. HBV testing determines whether the patient has an acute infection, chronic infection, or is a chronic hepatitis B carrier.

In order to reduce transmission of HBV, it is recommended that three groups be vaccinated against hepatitis B: 1) all babies at birth, 2) all children 0 to 18 years of age who have not been vaccinated, and 3) people of any age whose behavior or job puts them at high risk for HBV infection.¹⁵ There is no medical reason not to give hepatitis B vaccine to anyone who wants to be protected against HBV infection. The various hepatitis B vaccines are shown in Exhibit 5. The most popular is the combination vaccine for both hepatitis A and B.

If patients have HBV, abstinence or limited use of alcohol is recommended. Sexual contacts of infected patients should be tested. Because perinatal transmission is very efficient, infants born to HBV positive mothers require hepatitis B immune globulin and vaccination. Another general recommendation is treatment with substance abuse. Because household transmission is responsible for 3 percent of cases, HBV positive patients should not share personal articles, which could be contaminated with blood (i.e., toothbrush, razor blades). These

patients should also be vaccinated against hepatitis A, because they do not need any additional assaults on their liver.

The primary goal of hepatitis B therapy is the prevention of cirrhosis, liver cancer, and death through durable suppression of HBV replication. Although there are good medications for HBV infection, nothing can cure the disease. Like HIV, medications suppress the virus but do not completely eliminate the virus from the body.

Exhibit 6 is a treatment algorithm for patients with HBV.¹⁵ Patients with low viral loads are monitored and not treated. The outcome measures, which can be used to measure success of therapy, are liver histology, liver function tests, serum HBV DNA, and seroconversion (conversion to carrier state).

For patients who are treated, there are six medications currently FDA approved for hepatitis B treatment. Two are injectable (interferon alfa-2b [Intron A[®]] and peginterferon alfa-2a [Pegasys[®]]). The intravenous agents are given for a specific course but do not have a very high rate of efficacy. The four oral agents are lamivudine (Epivir-HBV[®]), adefovir dipivoxil (Hepsera[®]), entecavir (Baraclude[®]), and telbivudine (Tyzeka[®]). Tenofovir, already approved

Exhibit 5: Vaccination for Hepatitis A and B

Monovalent:

- Hepatitis A Vaccine, Inactivated
 - HAVRIX[®]
 - VAQTA[®]
- Hepatitis B Vaccine, (Recombinant)
 - ENERGIX-B[®]
 - RECOMBIVAX HB[®]

Bivalent:

- Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine
 - TWINRIX[®]

for HIV, is likely to be approved for use in HBV infection in the near future.

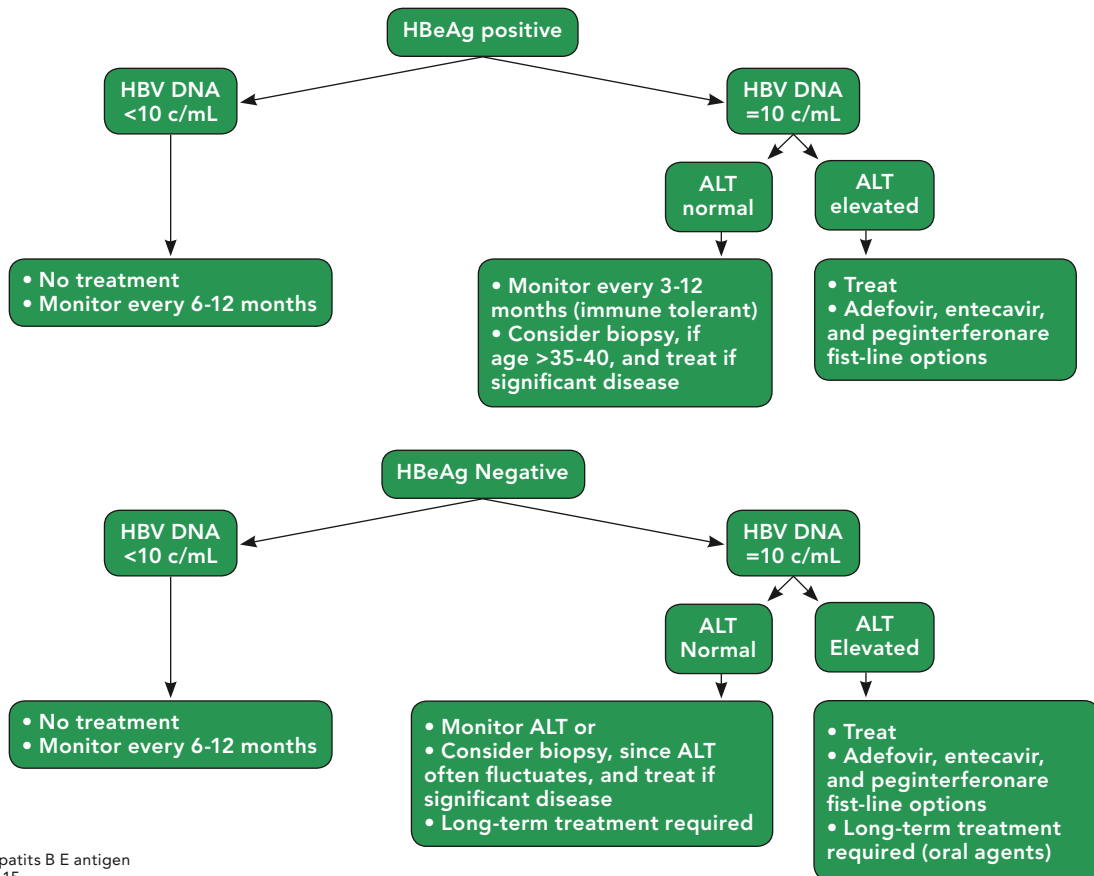
Entecavir and adefovir appear slightly more effective than telbivudine and lamivudine.¹⁶⁻¹⁹ In patients who do not yet have cirrhosis, lamivudine can alter disease progression by reducing viral load (Exhibit 7).²⁰ Alteration of disease progression has not yet been shown with the other agents.

Like HIV, resistance of HBV to medications does occur, particularly if one medication is used. The emergence of resistant virus is associated with rebound of serum HBV DNA, increased rate of disease progression, elevated serum ALT (including acute exacerbation), decreased rate of seroconversion, reversion of liver histological improvement, re-infection of liver grafts, and transmission of drug resistance. Resistance rates increase the longer a patient is exposed to a particular medication. By four years of therapy, resistance developed to lamivivudine in 70 percent of patients in one study compared with 24 percent at one year.²¹ Eighteen and 29 percent of patients who received adefovir developed resistance by four and five years, respectively.²²

There are two possible strategies to diminish resistance. This includes oral monotherapy with regimen adjustment based on individual response or combination therapy. With oral monotherapy, emerging data reveal that patients with substantial early viral suppression are less likely to develop resistance (by weeks 24 to 48).²³ It is important to evaluate HBV load early in the course of therapy. If there is an excellent response, monotherapy can be continued. If there is a poor viral reduction, medication should be switched or a medication added. Combination therapy may be more effective than monotherapy in suppressing viral replication. It may decrease or delay the incidence of drug resistance. Because there is cross-resistance among some of the antivirals, selection of medications for combination therapy requires using medications with different resistance profiles.

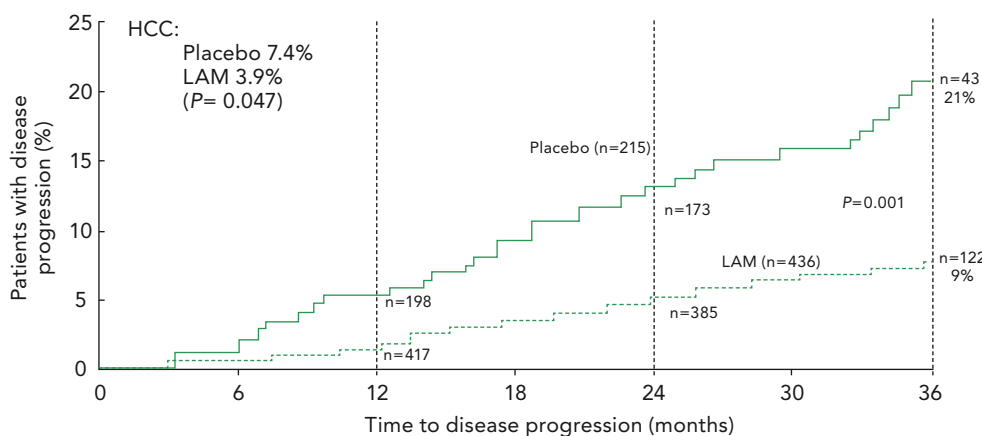
Candidates for combination therapy are those patients in whom long-term therapy is anticipated, those with advanced cirrhosis, and possibly those with less advanced cirrhosis. Patients with advanced cirrhosis can ill afford virologic resistance with clinical rebound. How to identify those patients who would benefit the most from combination therapy is yet to be determined.

Exhibit 6: Updated Treatment Algorithm: Patients with Concentrated Disease



HBeAg, hepatitis B E antigen
Reference: 15

Exhibit 7: Lamivudine for Patients with HBV and Advanced Liver Disease: Effect on Disease Progression



HCC, hepatocellular carcinoma
Reference: 20

Conclusion

Hepatitis B infection is common and causes significant consequences. Management may include monitoring alone or antivirals and monitoring. The management of HBV medication resistance is evolving as more is learned about how viruses develop resistance. The current strategy is to adapt therapy when virologic breakthrough occurs based on laboratory testing. In the future, hopefully there will be better strategies to prevent or delay medication resistance. **JMCM**

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References

- Norder H, Courouce AM, Coursaget P, et al. Genetic diversity of hepatitis B virus strains derived worldwide: genotypes, subgenotypes, and HBsAg subtypes. *Intervirology*. 2004;47:289-309.
- World Health Organization. Hepatitis B. Fact Sheet No. 204. August 2008. Available at <http://www.who.int/mediacentre/factsheets/fs204/en/>. Accessed August 22, 2008.
- World Health Organization. Geographic Prevalence of HBsAg. Data from 1996 (unpublished). <http://www.who.int/vaccinesurveillance/graphics/htmls/hepbprev.htm>. Accessed August 22 2008.
- DHS, Office of Immigration Statistics, 2002 Yearbook of Immigration Statistics, October 2003.
- Mahoney FJ. Update on diagnosis, management, and prevention of hepatitis B virus infection. *Clin Microbiol Rev*. 1999;12:351-66.
- Torresi J, Locarnini S. Antiviral chemotherapy for the treatment of hepatitis B virus infections. *Gastroenterology*. 2000;118:S83-103.
- Fattovich G, Giustina G, Schalm SW, et al. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EUROHEP Study Group on Hepatitis B Virus and Cirrhosis.

Hepatology. 1995;21:77-82.

- Moyer LA, Mast EE. Hepatitis B: virology, epidemiology, disease, and prevention, and an overview of viral hepatitis. *Am J Prev Med*. 1994;10 Suppl:45-55.
- Perrillo RP, Wright T, Rakela J, et al. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology*. 2001;33:424-32.
- Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology*. 2006;130:678-86.
- Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006;295:65-73.
- Centers for Disease Control and Prevention. Hepatitis B. In: Atkinson W et al, eds. *Epidemiology & Prevention of Vaccine-Preventable Diseases*. 8th ed. Washington DC: Public Health Foundation; 2005:191-212.
- Centers for Disease Control and Prevention. Hepatitis B FAQs for Health Professionals. Available at <http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#treatment>. Accessed August 22, 2008.
- Lok ASF, McMahon BJ. Chronic hepatitis B. *Hepatology*. 2001;34:1225-41.
- Keefe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clin Gastroenterol Hepatol*. 2006;4:936-62.
- Lok AS. The maze of treatments for hepatitis B. *N Engl J Med*. 2005;352:2743-6.
- Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2005;352:2673-81.
- Gish RG, Lok AS, Chang TT, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. *Gastroenterology*. 2007;133:1437-44.
- Lai CL, Gane E, Liaw YF, Hsu CW, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med*. 2007;357:2576-88.
- Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004;351:1521-31.