

Diagnosis and Management of Hepatitis B in Managed Care

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Summary

Hepatitis B virus (HBV) infection is a common problem around the world. Within the U.S., Asian-Pacific islander immigrants have the highest prevalence. Universal screening of pregnant women and the vaccination of infants and children has a positive impact on the prevalence of chronic infection in the U.S. Screening, proper diagnosis, and treatment are key to preventing long term HBV complications such as cirrhosis and liver cancer.

Key Points

- Chronic HBV infection is common
- Asian-Pacific islanders have highest prevalence
- Geographic migration from countries with high rates of HBV has an impact on who has HBV in the U.S.
- HBV can progress over time, resulting in irreversible liver damage, cancer, and death
- Viral load is strongly associated with progression of disease, both in terms of cirrhosis and liver cancer.
- Many of these patients are currently in your practice or plan.
- The FDA has approved six different treatments to suppress viral replication and decrease risk of liver disease.

HEPATITIS B IS A DNA VIRUS. DNA VIRUSES incorporate into human chromosomes and become a part of us. Consequently, it is very difficult to eradicate them. Even when DNA viruses appear quiescent, they are still in the body and can cause damage. Hepatitis B is a member of the Hepadnaviridae family that primarily infects liver cells; it is 50 to 100 times more infective than the human immunodeficiency virus (HIV), and is able to survive in dried blood for longer than one week. Attempts to control hepatitis viruses almost always rest in trying to suppress the virus, rather than to kill it. Hepatitis B, unlike hepatitis C (HCV), cannot be eradicated.

Hepatitis B is a much larger problem for the rest of the world than for the U.S. More than 2 billion people worldwide have been infected with the virus. Approximately 350 million are chronically infected and are at high risk of serious illness, cirrhosis, and primary liver cancer. Around the world, HBV kills 500,000 to 750,000 people annually. In the U.S., hepatitis C is a more significant problem than hepatitis B.

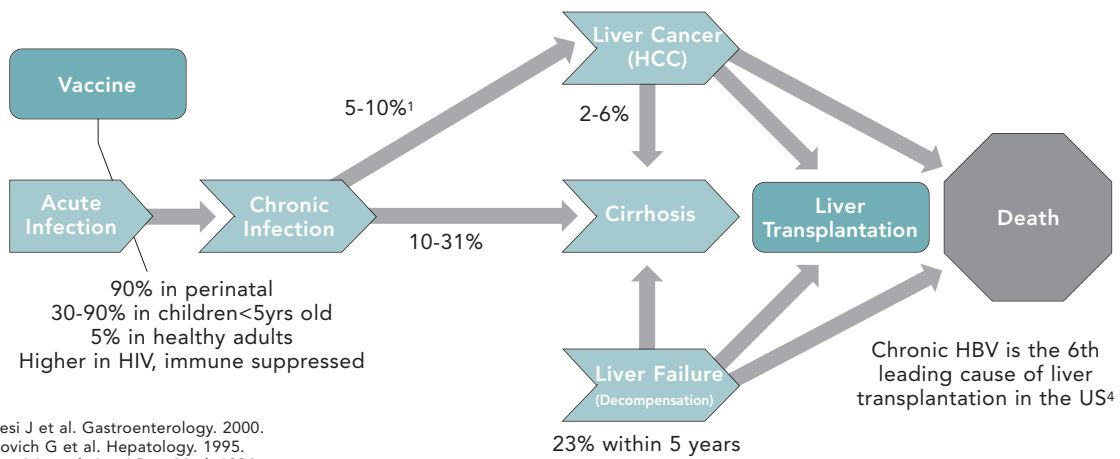
It is estimated that there are about 1.25 million people who are chronically infected with HBV in this country as opposed to the 4 million people infected with HCV. A reported 4,000 or 5,000 HCV deaths occur each year in the U.S., secondary to HBV.¹

In the U.S., the overall prevalence rate of HBV infection is only 1/3 of 1 percent. Many of those infected with hepatitis B in the United States are immigrants, or the children of immigrants, coming from countries with a high prevalence of the disease. Geographic migration has a continuing impact on HBV prevalence in the U.S.²

Depending on the country of origin, anywhere from five to fifteen percent of Asian-Pacific islanders immigrating to the U.S. are carriers of hepatitis B.³ This is important because one in four carriers of hepatitis B will die and can silently transmit the virus to family and strangers. Because of the high prevalence, all patients of Asian origin should be screened for hepatitis B.

Exhibit 1 illustrates the natural history of hepatitis B infection.^{4,5} A person exposed to HBV can develop an

Exhibit 1: Hepatitis B: Disease Progression



acute infection that resolves or develops into a chronic infection. If one gets hepatitis B as an infant, which is how it is transmitted in Asia, the Pacific Islands and sub Saharan Africa, the chance of having chronic hepatitis B is in excess of ninety percent. Perinatal transmission is very efficient. If the viral levels in the mother are high, ninety percent of infants will be infected with the virus at birth. If the viral levels are low, about twenty percent of mothers transmit the virus. Because of the high rate of chronic infections that develop from exposure at birth, this cycle of transmitting the virus to the next generation continues.

This generational transfer of the virus does not occur in the U.S. because all pregnant women are screened for hepatitis B. If a mother has hepatitis B, the baby is treated with hepatitis B immunoglobulin and a vaccine, which decreases risk of infection to less than 5 percent.

Predominantly, hepatitis B is transmitted sexually in the U.S. The chance of converting to chronic disease when HBV is acquired in adulthood is five percent. In the U.S., not as much chronic disease is seen compared to countries where the disease is passed primarily from generation to generation at birth.

Once chronic infection is acquired, liver cancer with or without cirrhosis can develop. Hepatitis B is a known human carcinogen.⁶ Eighty percent of hepatocellular carcinoma cases in the world are caused by hepatitis B. In the U.S., hepatitis C, fatty liver, and hepatitis B are the primary causes of hepatocellular carcinoma.

With all the other causes of liver disease (alcohol, autoimmune hepatitis, hepatitis C, and fatty liver), which can lead to cancer, cirrhosis must develop before cancer occurs. Cirrhosis does not have to be present for HBV infected patients to develop liver cancer. But, patients who are infected and do develop cirrhosis are at the highest risk for hepatocellular carcinoma.⁷

The likelihood of liver cancer and other complications in individuals with hepatitis B is related to viral load or the amount of virus detectable in the body.⁸⁻¹⁰ Such data support the possibility of reducing long-term cancer risk by inducing sustained suppression of HBV replication.

The premature mortality from cirrhosis or liver cancer resulting from hepatitis B is thought to be at least 20 to 25 percent. Liver cancer secondary to HBV can develop as early as age 30. This is particularly prominent in the sub Saharan/African people. This early development of liver cancer may be a factor of the HBV genotype predominant in that population.

Seven genotypes of HBV have been discovered, (A-G). Specific genotypes may respond differentially to the various treatment options and also have different natural histories and lead to different risks of developing liver cancer.¹¹ Genotype B is associated with a less active and slower progressive liver disease than C. Genotypes A and B respond better to interferon treatment than C and D. The distribution of the various genotypes differs throughout the world and within regions of the United States.¹² An HBV genotype test is not commercially available yet but should be soon.

To identify cases of hepatitis B, the following groups should be screened:

- Patients who were born in endemic areas and their children
- Family, household and sexual contacts of HBV-infected persons
- Homosexual men
- Injection drug use
- Dialysis patients
- HIV infected patients
- Pregnant women

- Persons with unexplained abnormal ALT levels.
- Health care, emergency medical, and public safety workers after needle stick or mucosal exposures or blood.¹³

Homosexual men have a particularly high rate of hepatitis B. Anal intercourse is an exceedingly efficient mechanism of sexually transmitting hepatitis B. The blood-to-blood transfer with used needles makes injection drug use another risk factor. The breaks in universal precautions during dialysis remain a mechanism of transfer of hepatitis B. Because two of highest risk factors, homosexuality and injection drug use, are the same for both viruses, HIV infected patients also have a higher risk of having hepatitis B than the general population.

Since 1999, the incidence of acute hepatitis B in the U.S. has risen about 5 percent among men ages 20 to 39, 20 percent among men older than 40, and 31 percent among women over 40. Because of the universal vaccination of school age children, this number should begin declining. However, there is a whole cadre of people that are older who are still at risk and are still getting acute hepatitis B.

The symptoms of HBV infection are usually very mild and not considered serious by many infected patients so they do not seek care. Thirty percent or more of patients with acute hepatitis B have no signs or symptoms. If symptoms are present, they are very non-specific including jaundice, fatigue, abdominal pain, loss of appetite, nausea, vomiting, joint pain, dark urine, and clay colored bowel movements.

Once someone has chronic hepatitis B, it cannot be cured. The best that can be done is to treat patients with the active disease to control their viral loads. Once treated, the active disease patient is like the hepatitis B carrier who has a low viral load and does not develop significant liver damage.

Patients who are infected with hepatitis B need to be educated about their disease, how to prevent its spread, and how to minimize the long-term damage to their liver. Ideally, patients should abstain from drinking any alcohol. Any substance abuse should be treated. If substance abuse continues, the patient is at an increased risk for acquiring other viruses such as HIV, which can complicate the hepatitis B infection. Household transmission is responsible for a very small number of cases, so patients should be advised not to share articles that have possible contact with blood such as toothbrushes, nail clippers, and razor blades. Infected patients should be vaccinated for hepatitis A because if one has chronic liver disease, of any cause, and another viral hepatitis is acquired, the prognosis is worse.

There are effective strategies to eliminate hepatitis B in the U.S. Vaccination is the primary strategy. Vaccination against hepatitis B is recommended for

babies at birth, children between the ages of zero and 18 who have not been vaccinated, and people of any age whose behavior or job puts them at high risk for hepatitis B infection. The Immunization Action Coalition states that there is no medical reason not to give hepatitis B vaccinations to anyone who wants to be protected against hepatitis B.¹⁴ There are vaccines that cover hepatitis B (Engerix-B[®] and Recombivax HB[®]), hepatitis A (Havrix[®] and Vaqta[®]), and both hepatitis B and hepatitis A (Twinrix[®]). Use of the combination vaccine is an opportunity to vaccinate against two types of hepatitis at one time.

Deciding who should receive treatment is determined by surrogate markers for clinical outcomes such as ALT, viral load, and antigen and antibodies against HBV status. After an acute infection, some patients will convert to a carrier state (seroconversion) and not require further treatment because their immune system is keeping the virus in check. Others will not seroconvert and will have chronic disease, which requires indefinite treatment to suppress the viral load.

As shown in Exhibit 2, a person with hepatitis B surface antigen positivity for more than six months is considered to have chronic hepatitis B.¹⁵ The viral level is then considered. If the viral level is greater than 10⁴ copies /ml, the ALT level is then considered. People in the carrier state, with low viral counts and normal liver enzymes, are monitored every three to six months but do not need specific treatment. All other patients will need a liver biopsy.

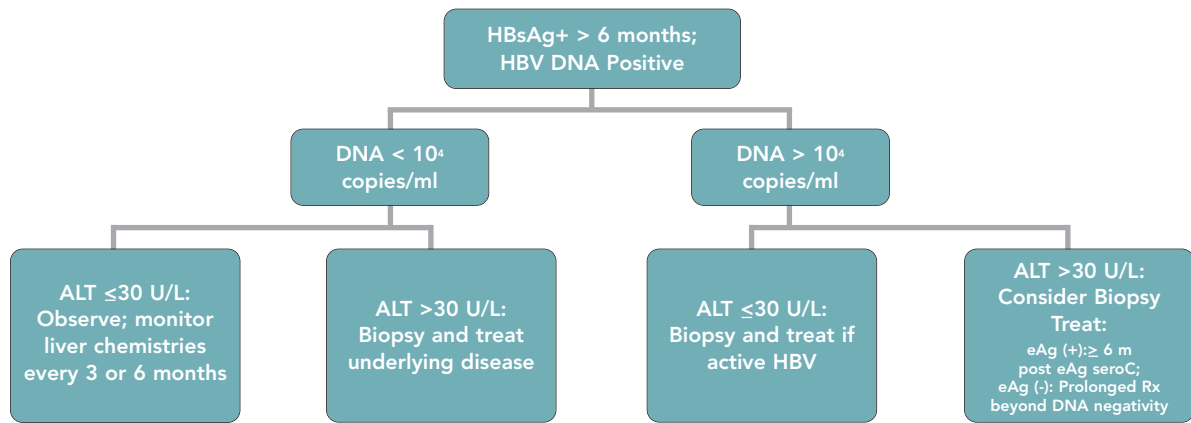
Although a liver biopsy can be used over time to assess response to treatment, this is primarily only done in studies. There are ongoing attempts to try to replace the invasive expensive liver biopsy with less invasive and possibly less expensive ways to measure damage to the liver. These include technologies such as ultrasound and various blood tests.

Patients are evaluated with history and physical examination, laboratory tests to assess liver function, and tests for viral replication. Other liver diseases like hepatitis C and hepatitis D are also ruled out. Hepatitis D requires concomitant infection with hepatitis B but is very uncommon in the U.S. The presence of liver cancer is ruled out with laboratory tests and ultrasounds in some patients.

The long-term goals of chronic hepatitis B treatment are to suppress viral replication and to prevent cirrhosis and liver cancer. The treatment endpoints that are desired include an undetectable serum viral load, normalization of liver function tests, and loss of hepatitis B antigens.¹³ Improvements in liver histology are measured in studies but not typically in clinical practice.

There are now six FDA approved treatments for hepatitis B. These include interferon alfa-2b

Exhibit 2: HBV Diagnostic Criteria Chronic Hepatitis B



Gish RG. Clin Liver Dis 2005;9:541-565.

(Intron[®] A), peginterferon alfa-2a (Pegasys[®]), lamivudine (Epivir-HBV[®]), adefovir (Hepsera[™]), entecavir (Baraclude[™]), and telbivudine (Tyzeka[™]). The interferons are injectable and the others are oral medications. All of these agents are inhibitors of hepatitis B polymerase, which is the enzyme that allows the virus to replicate. They do not kill the virus but suppress replication.

A study using lamivudine showed that reducing viral replication has been shown to substantially decrease the number of patients who develop advanced liver disease over three years (9 percent versus 21 percent).¹⁶ Unfortunately the virus can develop resistance to medications. The emergence of a resistant virus is associated with the rebound of serum viral load, increased rate of disease progression, elevated serum ALT, decreased rate of seroconversion, reversion of histological improvement, reinfection of liver grafts, and transmission of drug resistance. After four years of treatment, seventy percent of people become resistant to lamivudine.

Rates of resistance to adefovir and entecavir are very low during the first two to three years of therapy. Rates increase after that, but are still lower than those seen with lamivudine. Resistance does develop to telbivudine, which is the newest agent, at a rate of twenty-one percent during the first two years. This is not as high as with lamivudine, but is much worse than the other two oral products.

At this time, none of the treatments for hepatitis B have been compared head-to-head. In general, the efficacy measures such as viral load response at one year are about the same with each agent. The oral medications all appear to be well tolerated in patients. Injections of interferon can cause flu like symptoms and local reactions in many patients.

Conclusion

Hepatitis B is a common viral infection. People who emigrate to the U.S. from areas of high endemicity have a higher prevalence. Hepatitis B can progress over time resulting in irreversible liver damage, liver cancer and/or death. The viral load is strongly associated with the progression of the disease, both in terms of cirrhosis and liver cancer. Many of these people are seen in general medicine practices but their disease is not detected, because often they have no symptoms. For chronic disease, treatment must be continued indefinitely to maintain viral suppression. **JMCM**

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