

WILLIAM D. CAREY, MD

Professor of Medicine, Cleveland Clinic Lerner College of Medicine
Staff, Digestive Disease Institute, Cleveland Clinic
Cleveland, OH

The prevalence and natural history of hepatitis B in the 21st century

■ ABSTRACT

The prevalence of chronic hepatitis B virus (HBV) infection varies by geographic region. Most of North America is a low-prevalence (< 2%) area. Certain high-prevalence pockets exist, especially areas with a high proportion of Asian immigrants and Alaskan and northern Canadian native populations, where rates of chronic HBV are as high as 5% to 15%. In most low-prevalence areas, HBV infection is acquired mainly during adolescence and midadulthood, whereas perinatal transmission is the main route in high-prevalence (\geq 8%) areas. Up to 40% of patients with chronic HBV infection develop liver complications. Age at acquisition affects the likelihood of chronicity and the development of liver complications. The risk of each is greatest with perinatal transmission; the disease is usually self-limiting when exposure to HBV occurs during adolescence or young adulthood. Viral load predicts progression to cirrhosis and hepatocellular carcinoma; therefore, reducing viral load is the major goal of treatment.

■ KEY POINTS

The prevalence of chronic HBV infection in the United States is expected to increase as Asian immigrants constitute a larger proportion of the US population.

The chance of chronic infection is 90% or greater with perinatal transmission; conversely, the risk of chronic disease is less than 10% with adult-acquired infection.

In addition to viral load, predictors of disease progression include age at onset, male sex, and comorbidities.

Hepatitis B virus (HBV) infection is highly prevalent worldwide and is a major cause of morbidity and death. Two billion people globally have been infected with HBV, 350 to 400 million are chronic carriers, and tens of millions of new cases occur annually. Of those infected, 15% to 40%

develop HBV complications, namely cirrhosis or hepatocellular carcinoma (HCC).¹⁻³

The high prevalence of HBV infection represents an enormous failure of public health, considering that HBV immunization has been available for an entire generation, and where it has been employed it has been highly effective at reducing the incidence of HBV infection. Immunization, however, has been underused.

This supplement to the *Cleveland Clinic Journal of Medicine*, derived from a live symposium, aims to enhance awareness of the natural history of HBV infection and clarify its management recommendations with illustrative case histories. The supplement starts with a brief review of HBV terminology, natural history, and epidemiology.

■ CHRONIC HBV INFECTION TERMINOLOGY

Familiarity with the terms commonly used to describe chronic HBV infection will help clinicians in the management of the disease⁴:

- **Chronic HBV infection** is defined as presence of hepatitis B surface antigen (HBsAg) for more than 6 months. Those with infection may also express another antigen, HB e antigen (HBeAg), a marker of heightened infectivity. At the same time, those who are HBeAg positive are better responders to antiviral therapy compared with those who are HBeAg negative.

- **An inactive HBsAg carrier** is an individual who is HBsAg positive with a very low level of circulating virus, liver enzyme levels within normal limits, and a low likelihood of having chronic progressive disease.

- **Resolved HBV infection** is defined as previous HBV infection with no remaining evidence of active disease. Such individuals test negative for HBsAg and positive for antibody to HBsAg (anti-HBs) and to HB core antigen (anti-HBc). They also have no detectable viral load, or HBV DNA, in their blood. In most instances, they are protected from reinfection.

- **Reactivation** is the reappearance of HBV infection in someone who is known to be an inactive HBsAg carrier or whose previous HBV infection had resolved (see “Case: Recurrence despite anti-HBs and HBsAg negativity,” page S3).

- **HBeAg seroconversion** is the transition from

See end of article for author disclosures. doi:10.3949/ccjm.76.s3.01

HBeAg-positive to HBeAg-negative status and development of antibody to HBeAg (anti-HBe), usually accompanied by less active liver disease and lower viral loads.

- **HBeAg clearance** is disappearance of HBeAg without the development of anti-HBe; **reactivation** or **reversion** to HBeAg-positive status can occur.

■ GEOGRAPHIC DISTRIBUTION OF CHRONIC HBV INFECTION

The global prevalence of HBV varies widely. Regions are divided into areas of low, intermediate, and high prevalence, defined as follows⁴:

- **High prevalence** implies that at least 8% of the population is currently infected, with a lifetime likelihood of active or resolved infection greater than 60%. About 45% of the world's population lives in regions of high prevalence. Among this group, early childhood infections are common, with the virus usually transmitted from mother to infant during the perinatal period.

- **Intermediate prevalence** is defined as 2% to 7%, with a lifetime risk of infection of 20% to 60%. These regions represent about 43% of the global population. In intermediate-prevalence areas, infections occur in all age groups.

- **Low prevalence** is defined as less than 2% and represents only 12% of the global population. In these regions, the lifetime risk of infection is less than 20%.

North America is a low-prevalence area except for the northern rim, where Inuit and Yupik Eskimos have a high prevalence, and communities that have a substantial immigrant population from high-prevalence areas, such as sub-Saharan Africa and many parts of Asia.

Chronic HBV infection in the United States

Approximately 1.25 million individuals in the United States are HBsAg carriers.^{2,4} In Asian Americans and Alaskan natives, the prevalence of HBsAg positivity, or chronic disease, is 5% to 15%.^{5,6} Similarly, US health statistics sources estimate that among those who are chronically infected, approximately half are Asian American.⁷ As the Asian American population continues to increase (1.5 million to 7 million from 1970 to 1990^{5,8}; 11.9 million in the 2000 US Census⁸), the total prevalence of chronic HBV infection will increase as well.

■ NATURAL HISTORY OF CHRONIC HBV INFECTION

The progression to chronic HBV infection characteristically starts with an acute infection, indicated by the presence of HBsAg (**Figure 1**). Serum tests for HBsAg remain positive as long as chronic infection is present. Positivity for HBeAg, a marker of higher viral load and heightened infectivity, also develops, and may remain for months to years. Resolution of infection is heralded by disappearance of HBsAg. In this case, the anti-HBc and anti-HBs are positive.

Case: Recurrence despite anti-HBs and HBsAg negativity

A 55-year-old man previously treated for lymphoma was referred in March 2008 for evaluation following recent discovery of an abnormality in liver enzyme levels. His lymphoma had been treated successfully in 2002 with a combination of radiation therapy and chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisolone] and rituximab). There is no evidence of residual lymphoma. The patient had been well until 2 weeks before his referral, when he developed abdominal distention found to be ascites.

In 2002, his laboratory values were essentially normal except for a trivial elevation of alanine aminotransferase (ALT). At that time, he was hepatitis B surface antigen (HBsAg) negative and had antibody to HBsAg (anti-HBs), consistent with resolution of chronic hepatitis B virus (HBV) infection.

On presentation in March 2008, the patient was HBsAg positive. IgM anti-HBc, a marker of recent infection or reactivation, was positive. Anti-HBs was not measured. Computed tomography to assess tumor burden showed no tumor; however, ascites was present.

A laboratory evaluation in 2006 had shown marked elevation of transaminase levels; now, in 2008, evaluation shows startlingly elevated levels of ALT (1,023 U/L) and aspartate aminotransferase (472 U/L). The patient is also profoundly jaundiced.

What can explain the recurrence of chronic HBV infection in this patient?

Chronic HBV usually causes microinflammatory changes that evoke a fibrotic response in the liver, and many infected individuals will eventually develop cirrhosis and are at risk for the development of HCC. Inactive HBsAg carriers often bypass the development of cirrhosis but remain at risk for HCC if their viral load is very high. This is particularly true when infection is acquired in infancy.

The age at acquisition of HBV has a large impact on the likelihood of the disease becoming chronic. The chance of chronic infection is 90% or greater among neonates who become infected with HBV through perinatal transmission. Exposure during adolescence or young adulthood is associated with a 95% or greater likelihood that the disease will be self-limiting.

The typical North American patient with HBV acquires the infection as an adolescent or young adult and is not at risk of HCC unless cirrhosis develops. In most patients who acquire the disease in adolescence or adulthood, the infection resolves after weeks or a few months and they are not at risk of either cirrhosis or

From acute to chronic infection

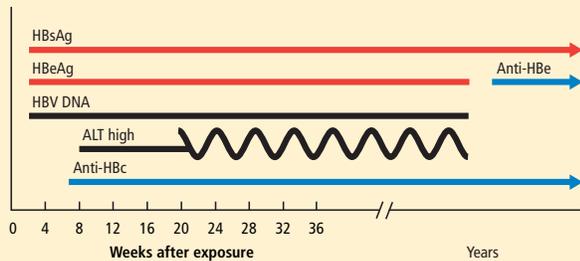


FIGURE 1. The progression from acute to chronic hepatitis B virus (HBV) infection starts with detectable hepatitis B surface antigen (HBsAg) and viral load (HBV DNA). The presence of these markers may precede the onset of symptoms and the elevation of alanine aminotransferase (ALT). Typically, HB e antigen (HBeAg), a marker of infectivity, also becomes positive; in some instances, HBeAg is replaced by its antibody (anti-HBe). The development of immunoglobulin M antibody to HB core antigen (anti-HBc) indicates resolution of infection and, in most instances, lifelong immunity.

Adapted, with permission, from *Cleveland Clinic Journal of Medicine* (Elgouhari HM, et al. Hepatitis B virus infection: understanding its epidemiology, course, and diagnosis. *Cleve Clin J Med* 2008; 75:881–889).

HCC. However, an individual such as the one described in the accompanying case, who becomes immunocompromised, is at risk of reactivation of HBV infection (see “Case revisited”).

HBV MODES OF TRANSMISSION

In low-prevalence areas, such as most of North America, most cases of HBV infection are acquired during adolescence to midadulthood, a period during which behaviors that increase the risk of HBV infection (ie, intravenous drug abuse or unprotected sexual activity) are most likely.^{9,10} Sex workers and homosexuals are at particular risk of sexual transmission of HBV. Intravenous drug abusers and health workers are at risk of parenteral transmission.

In high-prevalence areas, HBV is mostly transmitted during the perinatal period from mother to infant, conferring a high likelihood of chronicity.^{9,10} Mothers who are HBsAg positive, particularly those who are also HBeAg positive, are much more likely than others to transmit HBV to their offspring.

FACTORS THAT INFLUENCE THE COURSE OF HBV INFECTION

Viral load has emerged as the most significant factor implicated in the development of cirrhosis or HCC. Iloeje et al¹¹ found that viral load predicted progression to cirrhosis among a cohort of nearly 4,000 Taiwanese. Other factors that can influence the course of HBV infection include age at onset, male sex, and comor-

Case revisited

The patient had resolved HBV infection in 2002, as measured by negative HBsAg and positive anti-HBs. Nevertheless, he experienced reactivation of the virus under the influence of potent immunosuppression, induced not only by his lymphoma but also by its treatment. The reactivation had serious consequences; he experienced an elevation in liver enzyme levels and developed ascites, evidence of hepatic decompensation. Chemotherapy-induced reactivation of HBV infection that appeared completely resolved is increasingly recognized among oncologists. Fortunately, with active antiviral treatment, his liver function tests are normal and his ascites is gone.

bidities (ie, alcohol use, human immunodeficiency virus infection, hepatitis C virus infection). Core promoter and precore mutants may affect the likelihood of developing HCC. A genetic signature that predisposes liver cells to proliferate, termed *field effects*, may also lead to the development of HCC. The influence of smoking and diabetes on the development of HCC in HBV-infected individuals is not well documented.

Reduction or elimination of measurable virus is the current holy grail of treatment; available antiviral therapies are potent tools that lower viral load with the hope of reducing the likelihood of either cirrhosis or HCC.

HBV genotypes may be implicated in the progression of liver disease or the risk of development of HCC. HBV genotypes differ by region and may correlate with ethnicity and disease progression. In a study of 694 US patients with chronic HBV, Chu et al¹² found that genotypes A and C were associated with a higher prevalence of HBsAg positivity than other genotypes. Genotypes B and C were the most common among Asian American patients, while genotype A was the most common among Caucasian and African American patients. The authors suggested that HBV genotypes may explain the heterogeneity in the manifestation of the disease.

DISCLOSURES

Dr. Carey reported that he has no financial interests or relationships that pose a potential conflict of interest with this article.

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Correspondence: William D. Carey, MD, Professor of Medicine, Cleveland Clinic Lerner College of Medicine, 9500 Euclid Ave., A30, Cleveland, OH 44195; careyw@ccf.org