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# Hepatitis B virus infection: Understanding its epidemiology, course, and diagnosis

## ABSTRACT

Although hepatitis B virus (HBV) infection is not as common in the United States as in some countries, 5,000 Americans die from it every year. This number can be significantly decreased with proper screening and by vaccinating people at risk. Internists should be aware of the natural history of HBV infection, a vital prerequisite to correctly assessing disease severity and subsequently determining the need for antiviral therapy.

## KEY POINTS

HBV infection is much more likely to persist and become chronic if it is acquired at birth or in early childhood rather than during adulthood.

Chronic HBV infection is defined as persistence of HBV surface antigen in the serum for more than 6 months.

Although many cases of chronic HBV infection resolve spontaneously, some progress to cirrhosis, hepatocellular carcinoma, and death.

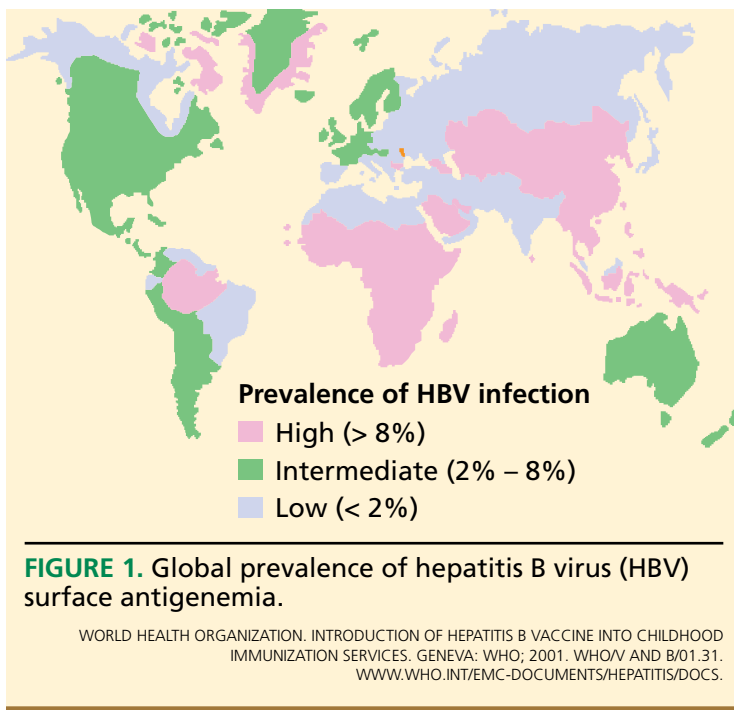
**O**UR KNOWLEDGE about hepatitis B and related diseases has dramatically increased since the discovery of the causative virus, HBV, in 1963. Despite effective vaccination, hepatitis B still constitutes a major public health problem.

In two parts, this comprehensive review will highlight a practical clinical approach to HBV infection. In this first part, we discuss the epidemiology, natural history, and diagnosis of HBV infection. In the second part, to be published in the next issue of this journal, we will review the general principles of its management, its management in patients on immunosuppressant therapy and in pregnant women, and HBV vaccination.

## COMMON IN ASIA, LESS SO IN AMERICA

More than 2 billion people—one-third of the world's population—alive today have been infected with HBV at some time in their life, and of these, about 350 million remain infected.<sup>1</sup> Every year, 1 million people die of HBV-related cirrhosis or hepatocellular carcinoma, which means that HBV takes a life every 30 seconds.<sup>2</sup>

HBV infection is highly prevalent in Asia, sub-Saharan Africa, and other parts of the developing world, but less so in the United States, except in Alaskan natives and immigrants from regions of high prevalence (FIGURE 1). By some estimates, 1.25 million carriers, defined as those positive for the HBV surface antigen for more than 6 months, live in the United States, and about half of them are Asian-American.<sup>3,4</sup> Other estimates put the



**Parenteral or mucosal exposure to infected blood poses a high risk of HBV**

number as high as 2 million, taking into account the prevalence of HBV in immigrant populations.

The incidence of acute hepatitis B in the United States has declined from 8.5 per 100,000 population in 1990 to 2.1 per 100,000 population in 2004, with the greatest declines (94%) in children and adolescents, coincident with an increase in hepatitis B vaccination in these age groups.<sup>5</sup> Despite these advances, HBV still causes a considerable number of cases of cirrhosis, cancer, and death—about 5,000 deaths each year in the United States.

### ■ HBV HAS FOUR GENES, EIGHT GENOTYPES

HBV is a DNA virus of the Hepadnaviridae family. Its genome is double-stranded with four genes, each one encoding a specific structural protein or proteins<sup>6,7</sup>:

- S gene, for the viral envelope (surface antigen)
  - C gene, for both the nucleocapsid (core) antigen and the pre-core (e) antigen
  - X gene, for two regulatory proteins required for HBV replication
  - P gene, for DNA polymerase.
- Several clinically important mutations in

the HBV genome are known (TABLE 1).<sup>7-12</sup>

Eight genotypes of HBV (labeled A through H) have been identified.<sup>13,14</sup> All eight have been found in the United States, but genotype A accounts for 35% of cases, genotype B for 22%, and genotype C for 31%.<sup>15</sup>

The clinical significance of HBV genotypes is not as clear as that of hepatitis C virus genotypes. Although recent data have suggested that different HBV genotypes may be associated with different rates of progression of liver disease and different rates of response to interferon therapy,<sup>13</sup> these data were not enough to recommend routine testing for HBV genotypes in clinical practice.<sup>16</sup>

In HBV infection, the virus itself does not injure liver cells. Rather, the damage of hepatitis is immune-mediated and begins to appear as the host's immune system attempts to clear the virus.

### ■ MARKERS OF HBV INFECTION

HBV produces several antigens that can be detected in the blood and that disappear as the body produces antibodies against them. The patterns of these and other markers provide clues to the phase of infection (FIGURE 2).

**HBV surface antigen** and **HBV DNA** are often the first detectable markers of acute infection, appearing before the onset of symptoms or before elevation of **alanine aminotransferase (ALT)** occurs. By definition, an HBV infection is chronic if surface antigen persists longer than 6 months.

**HBV e antigen**, derived from pre-core protein, is considered a marker of HBV replication and infectivity. In chronic infection, e antigen can persist for years or decades.

**HBV core antigen** cannot be detected in the serum, but antibodies against it can, first **immunoglobulin M (IgM)** and later **immunoglobulin G (IgG)**.

### ■ TRANSMISSION: VERTICAL OR HORIZONTAL

Because HBV replicates profusely and produces high titers in the blood (108 to 1,010 virions/mL), any parenteral or mucosal exposure to infected blood poses a high risk of HBV acquisition. The risk of HBV transmission from

TABLE 1

**Clinically important hepatitis B virus (HBV) mutations**

MUTATION	LOCATION IN THE HBV GENOME	RISK FACTORS FOR MUTATION	SIGNIFICANCE
<b>YMDD and multiple others</b>	P (polymerase) gene	Previous treatment with nucleoside analogues (or, rarely, naturally)	Development of drug resistance
<b>Precore or core</b>	C (core) gene	More common in Asia and Southern Europe (30%–90%) than in the United States (10%–40%)	Failure of HBV e antigen secretion but with a remaining risk for progressive liver disease
<b>Vaccine escape</b>	"a" determinant of the S gene	HBV vaccine or immune globulin recipients	Possibly increased risk of hepatocellular carcinoma or prolonged HBV infection
			Occult HBV infection*

\*Defined as detectable HBV DNA with undetectable HBV surface antigen. The existence and clinical significance of occult HBV infection with surface mutants remains controversial, however.<sup>12</sup>

a single needlestick is 1% to 6% if the blood is positive for HBV surface antigen but negative for HBV e antigen, and 22% to 40% if positive for both antigens.<sup>17–19</sup> Saliva, nasopharyngeal fluid, breast milk, semen, urine, and cervical secretions can also harbor HBV.<sup>20</sup>

Worldwide, perinatal (vertical) transmission is the predominant mode of HBV transmission, whereas intravenous drug abuse and unprotected sexual intercourse are the main routes of infection in areas of low prevalence, such as the United States. In sub-Saharan Africa, Alaska, and Mediterranean countries, transmission of HBV usually occurs horizontally during childhood, presumably via contact with nonintact skin.<sup>21–24</sup> Saliva has also been thought to be the route of HBV transmission in sporadic cases through human bites.<sup>25</sup>

**People at risk of HBV infection include:**

- Parenteral drug users
- People with multiple sexual partners
- Household contacts and sexual partners of people who are positive for HBV surface antigen
- Infants born to HBV-infected mothers
- Patients and staff in custodial institutions for the developmentally disabled
- Recipients of certain plasma-derived products (including patients with congenital coagulation defects)
- Hemodialysis patients
- Health and public-safety workers who have

contact with blood

- People born in areas where HBV is endemic, and their children.

These people—as well as all pregnant women, patients infected with hepatitis C virus or human immunodeficiency virus, and patients with chronically elevated ALT or aspartate aminotransferase (AST) levels—should be screened for HBV infection with serologic markers.

**CLINICAL MANIFESTATIONS VARY**

HBV infection, acute or chronic, has variable manifestations. During the acute stage, HBV infection can manifest as anicteric (subclinical) hepatitis, icteric hepatitis, or, rarely, acute fulminant hepatitis. Chronic HBV infection can be asymptomatic (the HBV surface antigen carrier state), or it can be manifested by symptoms and signs of cirrhosis or hepatocellular carcinoma or both. Extrahepatic manifestations, including serum sickness, polyarteritis nodosa, essential mixed cryoglobulinemia, membranous glomerulonephritis, and aplastic anemia, have been reported in patients with HBV infection.<sup>26</sup>

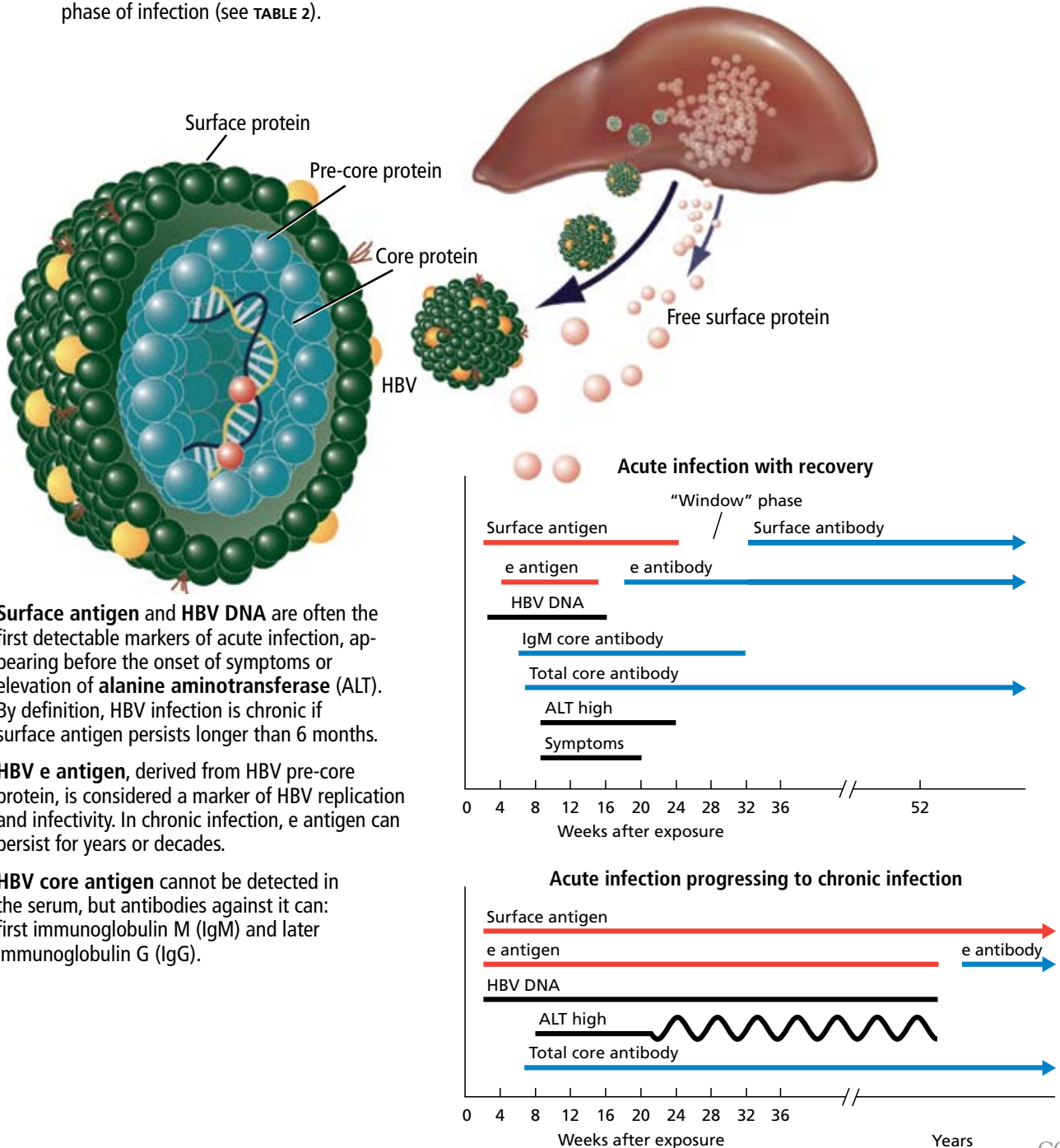
**Acute hepatitis B**

The incubation period of HBV ranges from 2 weeks to 4 months. Initially, patients complain of fatigue, malaise, anorexia, right upper quad-

**In chronic HBV infection, high serum HBV DNA is a strong predictor of cirrhosis**

## Markers of acute and chronic HBV infection

Most cases of hepatitis B virus (HBV) infection acquired in adulthood resolve spontaneously within 6 months. In contrast, most infections acquired at birth or in early childhood persist and become chronic. HBV produces several proteins (antigens) that can be detected in the blood and that disappear as the body produces antibodies against them. The patterns of these and other markers provide clues to the phase of infection (see TABLE 2).

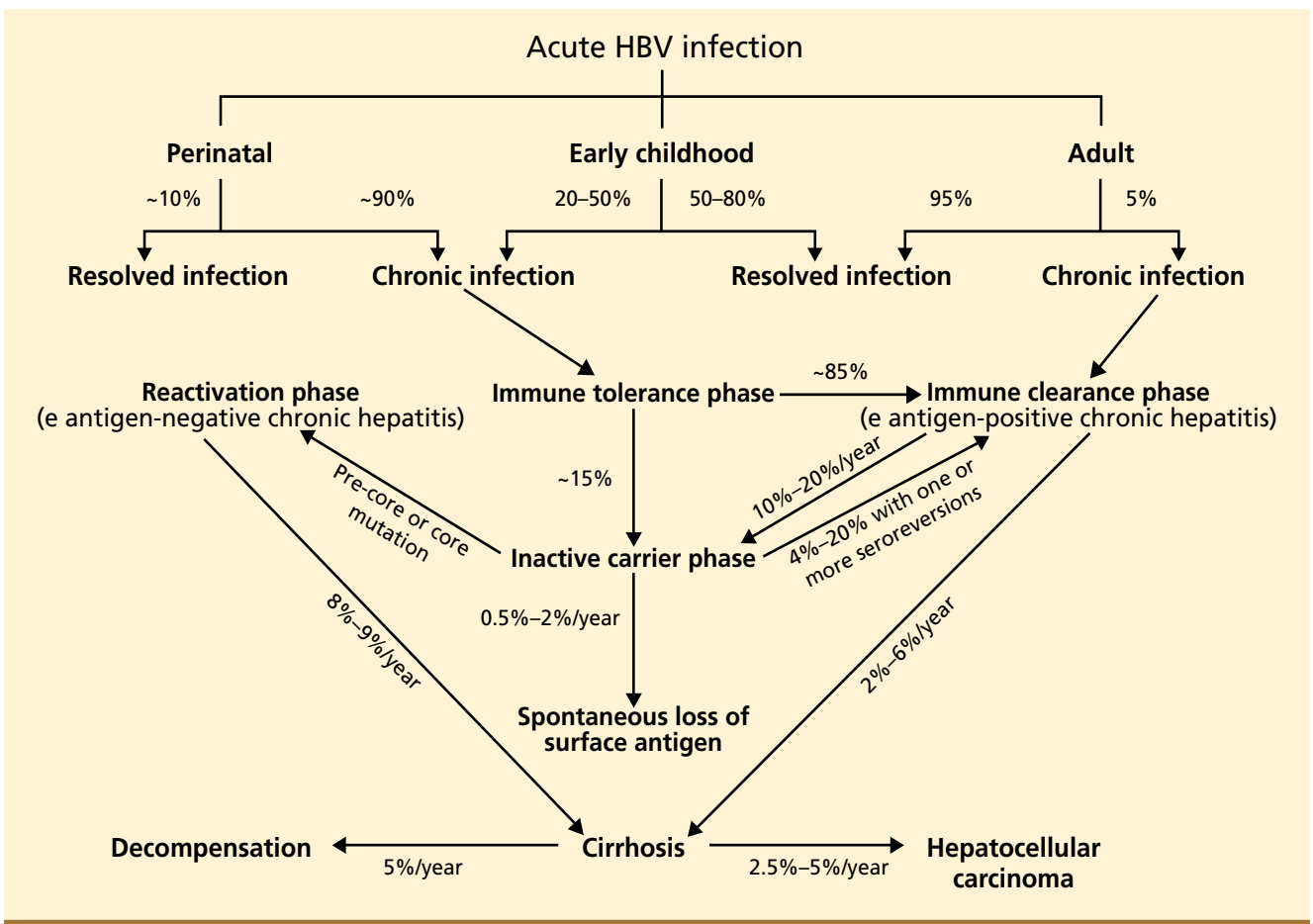


**Surface antigen** and **HBV DNA** are often the first detectable markers of acute infection, appearing before the onset of symptoms or elevation of **alanine aminotransferase (ALT)**. By definition, HBV infection is chronic if surface antigen persists longer than 6 months.

**HBV e antigen**, derived from HBV pre-core protein, is considered a marker of HBV replication and infectivity. In chronic infection, e antigen can persist for years or decades.

**HBV core antigen** cannot be detected in the serum, but antibodies against it can: first immunoglobulin M (IgM) and later immunoglobulin G (IgG).

FIGURE 2



**FIGURE 3.** Natural history of HBV infection.

rant discomfort, or flu-like symptoms (coryza, photophobia, headache, and myalgia); then jaundice becomes apparent, usually within 10 days of the onset of symptoms. Low-grade fever, jaundice, and mildly tender hepatomegaly are the most common signs. Generalized lymphadenopathy is not a feature of acute HBV infection. If the patient also has hepatitis D virus infection or underlying liver disease (eg, alcoholic liver disease), then acute HBV infection may be more severe.

In the acute phase, ALT and AST levels rise, sometimes to values above 1,000 IU/L. In icteric hepatitis, bilirubin levels also rise, usually after the ALT level does. Although the peak ALT level reflects the hepatocellular injury, it has no prognostic value. With recovery, ALT levels normalize in 1 to 4 months.

**Acute fulminant hepatitis B** occurs in 0.1% to 0.5% of patients, and causes about 10% of cases of acute liver failure in the Unit-

ed States.<sup>27</sup> Patients typically present with rapidly progressive acute hepatitis characterized by signs of liver failure, such as coagulopathy, encephalopathy, and cerebral edema.

In the so-called window phase, laboratory testing may not reveal HBV surface antigen because of early clearance but shows IgM antibody against the HBV core antigen. HBV DNA may be low or undetected.

### Chronic hepatitis B

Chronic hepatitis B is usually diagnosed as a result of a workup for abnormal liver function tests or as a result of screening patients at risk for HBV infection. Many patients with chronic hepatitis B have no symptoms or have nonspecific symptoms such as fatigue or right upper quadrant discomfort.

Acute exacerbations due to HBV e antigen seroreversion (ie, in which e antigen reappears) occasionally occur in patients with

TABLE 2

**Phases of chronic hepatitis B virus infection**

PHASE	E ANTIGEN	E ANTIBODY	HBV DNA	ALT	LIVER BIOPSY FINDINGS
<b>Immune tolerance</b>	Positive	Negative	High	Normal	Normal or nonspecific
<b>Immune clearance</b>	Positive	Negative	Moderately high	Elevated	Chronic hepatitis
<b>Inactive carrier</b>	Negative	Positive	Absent or low	Normal	Nonsignificant hepatitis (usually)
<b>Reactivation</b>	Negative or positive	Positive or negative	Moderate	Elevated	Chronic hepatitis

chronic hepatitis B. Most of these exacerbations are asymptomatic, but occasionally an acute hepatitis-like clinical picture with detectable IgM antibody against the core antigen occurs, leading to misdiagnosis of acute HBV infection in patients not previously known to have chronic HBV infection.<sup>28</sup>

In late cases, signs of cirrhosis such as jaundice, ascites, splenomegaly, pedal edema, encephalopathy, or variceal bleeding can be present.

Hepatocellular carcinoma should be suspected in cirrhotic patients with new-onset right upper quadrant pain, rapidly developing ascites, a palpable liver mass, or hepatic encephalopathy. Other nonspecific features of hepatocellular carcinoma include watery diarrhea, hypoglycemia, and certain cutaneous manifestations such as acanthosis nigricans and the Leser-Trelat sign (multiple pruritic seborrheic keratoses of sudden onset).

In chronic hepatitis B, liver enzyme levels can be normal, even in patients with well-compensated cirrhosis. ALT levels may range from normal to five times higher than normal. Thrombocytopenia, hypoalbuminemia, direct hyperbilirubinemia, and prolonged prothrombin time suggest cirrhosis.

Findings of chronic hepatitis B on liver biopsy range from minimal inflammation to cirrhosis. The most characteristic histologic feature of chronic HBV infection is the “ground-glass hepatocyte,” which is due to intracellular accumulation of HBV surface antigen.<sup>29</sup>

### ■ FEW ADULTS (BUT MANY CHILDREN) REMAIN CHRONICALLY INFECTED

The natural history of HBV infection has become better defined, thanks to extensive epidemiologic studies and highly sensitive HBV DNA assays (FIGURE 3). It is crucial for clinicians to understand the natural history of HBV infection to appropriately decide which infected patients need antiviral therapy. This will be discussed in our second article.

HBV surface antigen can be detected in the blood approximately 2 to 4 weeks after inoculation. Simultaneously, HBV DNA, usually in very high levels, is also detectable in the blood. However, in the rare cases of acute fulminant hepatitis, HBV DNA levels can be low or undetectable at the time of presentation because the immune system mounts a robust response with extensive damage to HBV-infected hepatocytes.

The rate of spontaneous recovery from acute HBV infection varies, depending on the patient’s age at the time of HBV acquisition and the patient’s immune status. Fewer than 5% of immunocompetent adults infected with HBV remain chronically infected, defined as being positive for HBV surface antigen for more than 6 months. On the other hand, 80% to 90% of infected infants and about 20% to 50% of children 1 to 5 years old at the time of acute infection remain chronically infected.<sup>21</sup>

### Four phases of chronic HBV infection

Four phases of chronic HBV infection have been outlined (TABLE 2),<sup>30</sup> although all patients

**People at risk of HBV—and pregnant women—should be screened**

TABLE 3

**Serologic patterns of hepatitis B virus (HBV) infection**

INTERPRETATION	SURFACE ANTIGEN	SURFACE ANTIBODY	E ANTIGEN	E ANTIBODY	IgM CORE ANTIBODY	IgG CORE ANTIBODY	HBV DNA
Acute HBV, early phase	Yes	No	Yes	No	Yes	Yes or no	High
Acute HBV, window phase	No	No	No	Yes	Yes	Yes or no	Low
e antigen-positive chronic hepatitis	Yes	No	Yes	No	No	Yes	High
e antigen-negative chronic hepatitis	Yes	No	No	Yes	No	Yes	Moderate
Inactive carrier state	Yes	No	No	Yes	No	Yes	Absent or low
Resolved hepatitis B	No	Yes or no	No	Yes	No	Yes	Absent

do not go through all phases. HBV surface antigen is detectable in all of them.

The **immune tolerance phase**, the initial phase of chronic HBV infection, is seen almost exclusively in those who acquired HBV infection vertically or during early childhood. Although patients have high HBV DNA levels, they do not have significant liver disease. This discrepancy is thought to be related to the immune tolerance to HBV; however, the exact mechanism of that tolerance is unclear.<sup>31</sup>

Only 15% of those with immune tolerance have spontaneous HBV e antigen seroconversion (ie, loss of e antigen and appearance of anti-e antibody) within 20 years after infection.<sup>32</sup>

The **immune clearance phase** (HBV e antigen-positive chronic hepatitis) appears about 20 to 30 years after the onset of the immune tolerance phase in patients who acquire HBV early in life. It is also often seen in patients with infections acquired late in childhood or in adulthood.

This phase marks the start of an immune-mediated process aimed at clearing the viral infection, but it also leads to concomitant hepatocellular injury. Spontaneous clearance of the e antigen increases in this phase to an annual rate of 10% to 20%.<sup>32,33</sup> The strongest predictors of spontaneous e antigen seroconversion are old age, an elevated ALT level, and an acute exacerbation.<sup>26</sup>

Although ALT levels are elevated and there is evidence on liver biopsy of chronic active hepatitis, this phase is usually asymptomatic. Rarely, however, it presents with an acute flare of hepatitis, sometimes accompanied by IgM antibodies against the HBV core antigen (in low titer), leading to an incorrect diagnosis of acute HBV infection.

Depending on the duration of the chronic hepatitis and the frequency and severity of flares, about 12% to 20% of patients in the immune-clearance phase develop serious liver disease within 5 years.<sup>31</sup>

The **inactive carrier phase** following HBV e antigen seroconversion is characterized by undetectable or low HBV DNA levels (< 1,000 copies/mL), normal ALT levels, and minimal or no necroinflammation on liver biopsy.<sup>30</sup> Such patients should be followed with serial testing, as 4% to 20% of them spontaneously revert to being positive for e antigen at least once.<sup>16</sup> On the other hand, only 0.5% to 2% of surface antigen carriers in western countries clear themselves of surface antigen yearly, but up to half of those who clear the surface antigen have low-level HBV viremia.<sup>34</sup>

The **reactivation phase** (HBV e antigen-negative chronic hepatitis) is seen in some HBV-infected patients, especially those from Asia and southern Europe, in whom the virus has a spontaneous pre-core or core mutation that makes infected cells unable to secrete the

**HBV surface antigen and DNA can be detected 2–4 weeks after inoculation**

TABLE 4

### Risk factors for cirrhosis and hepatocellular carcinoma in patients with HBV infection

#### Risk factors for cirrhosis

Longer duration of infection  
Male sex  
High levels of HBV DNA  
HBV genotype C (more than B)  
Habitual alcohol consumption  
Concurrent infection with hepatitis C or D virus  
or human immunodeficiency virus  
Obesity  
Diabetes mellitus

#### Risk factors for hepatocellular carcinoma

High level of HBV DNA  
Longer duration of infection  
Male sex  
Family history of hepatocellular carcinoma  
Presence of cirrhosis  
Race (Asian, African)  
HBV genotype C (more than B)  
HBV variant (core promoter)  
Reversion from e antibody to e antigen  
Hepatitis C virus coinfection  
Heavy alcohol consumption  
Cigarette smoking  
Obesity  
Diabetes mellitus

Signs of acute HBV: low-grade fever, jaundice, mildly tender hepatomegaly

e antigen. Although these patients have no e antigen in their blood, they do have intermittent or persistent elevation of ALT, elevated HBV DNA, and histopathologic findings of chronic hepatitis. Compared with those in the immune clearance phase, patients in the reactivation phase tend to be older and to have lower HBV DNA levels but advanced hepatic damage.

Immunity to HBV infection is characterized by loss of HBV surface antigen, DNA, e antigen, and anti-core antigen IgM with development of anti-surface antigen antibody and anti-core antigen IgG (total anti-core antigen antibody). The presence of anti-surface antigen antibody and anti-core antigen IgG together differentiates natural immunity through resolved infection from that which is acquired through vaccination, which is denoted by isolated anti-surface antigen antibody.

FIGURE 2 illustrates the typical serologic course of HBV infection, and TABLE 3 summarizes how to interpret the various serologic patterns.

### Cirrhosis, liver failure, cancer

Cirrhosis, hepatic decompensation, and hepatocellular carcinoma are the major long-term complications of HBV infection. In untreated patients, the annual rate of progression to cirrhosis has been estimated to be 2% to 6% in patients with HBV e antigen-positive chronic hepatitis and 8% to 9% in those with e antigen-negative chronic hepatitis.<sup>30</sup>

The likely explanation for these surprising cirrhosis rates is that e antigen-negative chronic hepatitis usually represents a late stage of the disease, and patients in this phase are usually older and have more advanced liver disease.

Subsequently, the annual rate of progression from compensated cirrhosis to hepatic decompensation has been estimated to be about 5%.<sup>35</sup>

Across all the stages described above, a high serum HBV DNA level has been shown to be a strong predictor of progression to cirrhosis in patients with chronic HBV infection. In a population-based prospective cohort study of 3,582 untreated HBV-infected patients in Taiwan, Iloeje et al<sup>36</sup> found that, compared with patients with serum HBV DNA levels lower than 104 copies/mL, those with levels of 104 or higher had an adjusted relative risk of cirrhosis of 2.5. The relative risk rose to 5.9 with HBV DNA levels of 105 or higher, and 9.8 with levels of 106 copies/mL or higher. More studies in different patient populations are needed for confirmation.

HBV is a strong carcinogen, and the risk of hepatocellular carcinoma is 100 times higher in patients with HBV infection than in uninfected ones.<sup>31</sup>

The most important risk factor for hepatocellular carcinoma in HBV-infected patients is cirrhosis, but this cancer can also develop in noncirrhotic livers.<sup>37</sup> The annual rate of hepatocellular carcinoma has been estimated to be higher (2.5%–3%) in patients with cirrhosis than in noncirrhotic carriers (0.5%–1%).<sup>30,35–38</sup> Risk factors for cirrhosis and hepatocellular carcinoma are summarized in TABLE 4.<sup>16,30</sup> ■



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