

SCREENING AND DIAGNOSING HEPATITIS B VIRUS INFECTION:
IMMIGRANT AND SPECIAL POPULATIONS*

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ABSTRACT

Chronic infection with the hepatitis B virus (HBV) is considered to be prevalent in historically endemic areas (eg, Eastern Europe, Asia, Africa, the Middle East, and Pacific basin), where it is the leading cause of cirrhosis and hepatocellular carcinoma. In these areas, HBV is mostly transmitted perinatally or in early childhood (<5 years) and, therefore, follows a pattern that is somewhat distinct from adulthood-acquired infections, which are more commonly transmitted via sexual and injection-drug use exposure and tend to occur more frequently in the United States and Western Europe. This article explores the different phases in the life cycle of HBV, as they relate to perinatal or childhood-acquired infection. A considerable portion of the discussion is centered on diagnostic and screening strategies, including the recently updated recommendations from *Morbidity and Mortality Weekly Report* that now call for screening of all persons born in geographic regions with hepatitis B surface antigen (HBsAg) prevalence of at least 2%, men who have sex with other men, past/current

intravenous drug users, persons receiving cytotoxic or immunosuppressive therapy, and those with elevated alanine aminotransferase or aspartate aminotransferase levels of unknown etiology. Also discussed are public health implications of treating HBsAg (+) persons, particularly with respect to destigmatizing HBV as a disease that is solely transmitted via sexual contact and addressing common misconceptions held by at-risk immigrant groups. (*Adv Stud Med.* 2009;9(3):82-88)

Considered a DNA virus, hepatitis B belongs to the hepadnaviridae family of viruses, which contain several avian and mammalian variants. All hepadnaviruses share a similar life cycle in their hosts, and therefore as expected in humans, the hepatitis B virus (HBV) has been known to result in chronic hepatitis and hepatocellular carcinoma (HCC) in such species as ducks, woodchucks, and ground squirrels.¹ As illustrated in the Figure, the infectious (“Dane”) particle of the HBV virus is a 42-nm sphere that contains a core (nucleocapsid) that encloses the DNA and an outer shell (or envelope) that is composed of several proteins known collectively as HBs (ie, surface proteins).¹ This outer shell (ie, surface coat) surrounds an inner protein shell (referred to as core particle or capsid) that is composed of HBc protein and surrounds the viral DNA and the enzyme DNA polymerase.¹ Despite its compact nature, the virus induces a wide clinical spectrum of disease, which is highly influenced by mode/timing of transmission and the interaction between HBV and the host immune system.

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Modes of transmission include perinatal, percutaneous, sexual exposure, and close person-to-person contact (eg, open cuts and sores). More casual contact such as kissing, coughing, or even breast-feeding is not known to lead to transmission.² In the human host, HBV is generally not cytopathic (ie, does not kill hepatocytes); instead, it indirectly causes various degrees of hepatic injury by inducing the host's immune system to attack viral proteins that are present on the hepatocyte surface. The severity of hepatic injury is dependent on the strength of the immune system, with the most complete immune response being associated with the most severe acute liver injury, but the greatest likelihood of viral clearance.³ Because infected neonates tend to have an immature immune system, the majority (95%) are not able to clear the virus and, therefore, become asymptomatic chronic HBV carriers. Individuals with chronic HBV infection may have no evidence of liver disease, or they may develop chronic hepatitis, which carries a 30% risk of progression to cirrhosis, leading to liver cancer and liver failure.³

Those infected later in life have a considerably lower risk of developing chronic HBV infection, with 30% of children infected between infancy and the age of 6 and only 3% to 5% of those infected as adults becoming chronic carriers. The remainder experience acute infection that results in viral clearance.¹ Acute HBV infection manifests 2 to 3 months after viral exposure and lasts 2 to 4 months, producing symptoms such as fatigue, poor appetite, nausea, vomiting, abdominal pain, low-grade fever, jaundice, dark urine, and light stool color. As a result of the aforementioned weakened immune response, infection tends to be asymptomatic in infants, children aged younger than 5 years, and immunocompromised adults with newly acquired HBV infection.²

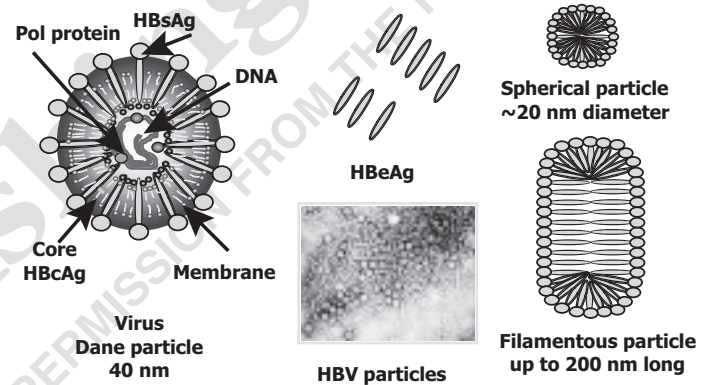
LIFE CYCLE OF HBV

As stated in the introduction by Ahmet Gurakar, MD, chronic HBV infection is considered to be prevalent in historically endemic areas, including much of Eastern Europe, Asia, Africa, the Middle East, and the Pacific basin, where it is the leading cause of cirrhosis and HCC. In these areas, HBV is mostly transmitted perinatally or in early childhood (<5 years) and, therefore, follows a pattern that is somewhat distinct from adulthood-acquired infections, which are more com-

monly transmitted via sexual and injection-drug use exposure and tend to occur more frequently in the United States and Western Europe.

For purposes of this discussion, it useful to understand the life cycle of HBV as it relates to perinatal or childhood-acquired infection. Broadly, the 4 sequential phases of chronic HBV infection (Table 1) can be defined as: (1) immune tolerance; (2) immune activity/clearance (hepatitis B envelope antigen [HBeAg]

Figure. HBV Particles: HBV Virion, e-Antigen, and S Proteins



HBcAg = hepatitis B core antigen; HBeAg = hepatitis B envelope antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus. Reprinted with permission from Professor Arie J. Zuckerman. Published in Lee. *N Engl J Med.* 1997;337:1733-1745.¹

Table 1. Four Phases of Chronic HBV Infection (HBsAg (+) Patients)

<p>Immune Tolerant Phase</p> <ol style="list-style-type: none"> 1. HBeAg (+) 2. HBV DNA >200 000 IU/mL 3. ALT normal 	<p>Immune Active Phase</p> <p>HBeAg (+)</p> <ol style="list-style-type: none"> 1. HBV DNA >20 000 IU/mL 2. ALT levels high or fluctuating 3. Active inflammation on liver biopsy
<p>Inactive Phase</p> <ol style="list-style-type: none"> 1. HBeAg (-) 2. HBeAb (+) 3. HBV DNA <2000 IU/mL 4. Normal ALT 	<p>HBeAg negative (-)</p> <ol style="list-style-type: none"> 1. HBV DNA >2000 IU/mL 2. ALT levels high or fluctuating 3. Active inflammation on liver biopsy

ALT = alanine aminotransferase; HBeAb = hepatitis B envelope antibody; HBeAg = hepatitis B envelope antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

(+) chronic hepatitis); (3) inactive; and (4) precore mutation or reactivation (HBeAg (-) chronic hepatitis).^{1,4} It is important to consider that infected patients do not always experience every phase, may not transition into phases in the aforementioned sequence, and may remain in one phase indefinitely.

In the immune tolerance phase (typically during infancy), there is minimal immune activity against the virus, viral replication is high (ie, high serum HBV DNA levels), serum alanine aminotransferase (ALT) levels are normal, and patients are generally asymptomatic. Histology in this phase shows minimal inflammatory activity. In contrast to the healthy adult, in whom this incubation phase lasts 2 to 4 weeks, perinatally infected persons experience an incubation period that often lasts for decades, with a low rate of immune clearance.^{1,4}

In the immune activity/clearance phase, the patient is usually in his or her second or third decade of life and the immune system now attempts to clear the virus. As a result, previously inactive HBV carriers begin to have recurrent episodes of clinical reactivation as immune-mediated destruction of infected hepatocytes occurs, leading to elevated liver enzymes, decreasing HBV DNA levels, and active inflammation on liver biopsy. In this phase, perinatally infected patients often become symptomatic for the first time, presenting with elevated ALT levels, which are believed to be a manifestation of immune-mediated lyses of infected hepatocytes.⁴ The duration of this phase is variable (months to years), and reactivation can be clinically severe enough to mimic fulminant acute infection. In patients with chronic disease, this stage may persist for 10 or more years, leading to cirrhosis and its complications.¹ The duration of this phase, as well as the frequency and severity of the flares, are known to correlate with the risk of cirrhosis and HCC.⁴

Once the host's immune system is able to eliminate or diminish infected cells, active viral replication ends. In the inactive phase, HBV DNA levels have fallen, seroconversion from HBeAg (+) to HBeAg (-)/anti-HBe (+) status occurs, ALT levels normalize, and liver inflammation is reduced. This inactive carrier state may persist indefinitely, in which case the prognosis tends to be favorable (although HCC may still develop) or it may lead to reactivation of HBV replication via development of an HBeAg (-) strain. HBeAg (-) infection involves genetic mutations at precore or core promoter

regions and is associated with poorer long-term clinical outcome and lack of spontaneous remission.^{5,6}

Reactivation (HBeAg (-) chronic hepatitis phase) may occur spontaneously or as a result of immunosuppression and is usually associated with elevated ALT and HBV DNA levels and active inflammation on liver biopsy.⁴ Patients in this latter phase of chronic HBV infection are usually older and have more advanced liver disease.⁴

DIAGNOSIS

The diagnostic goals in HBV infection include identifying infected patients, determining whether these patients have active viral replication and ongoing liver damage, and assessing whether they are appropriate candidates for treatment.⁷ The diagnostic tools used to characterize the state of HBV infection include serologic, virologic, biochemical, and histologic tests.

The serologic patterns of chronic HBV infection are varied and complex, with at least one serologic marker present during each of the different phases of HBV infection.² Hepatitis B surface antigen (HBsAg) is one of the first serologic markers to appear after infection, and its persistence for more than 6 months indicates chronic HBV infection.^{7,8} Serum HBV DNA is used to establish a baseline viral level before treatment, to monitor response to therapy, and to survey for development of drug resistance. The presence of antibody to HBsAg (anti-HBs) is associated with recovery and/or immunity to HBV, or immunity after HBV vaccination.⁷ Individuals who are HBsAg (+) and anti-HBs (-) are considered chronically infected, those who are HBsAg (-) and anti-HBs (+) are immune to HBV, and individuals who are HBsAg (-) and anti-HBs (-) have no evidence of immunity or current infection and should be vaccinated.^{5,6}

Although the presence of HBeAg indicates active HBV replication, its absence does not necessarily signify cessation of viral replication, because HBeAg may not be detectable in HBeAg (-) chronic HBV due to potential precore or core promoter mutations. Antibody to HBeAg (anti-HBe) generally indicates conversion from HBeAg to anti-HBe, but it can also be found in patients with precore or core promoter mutant HBV infection. HBeAg seroconversion is considered a therapeutic end point for HBeAg (+) patients because it is associated with decreased viral replication and a lower risk of disease progression, but it is not

always protective against later reactivation or development of HCC.⁸

From a biochemical perspective, increased serum ALT levels have traditionally indicated necroinflammation of liver cells, whereas normal or mildly elevated ALT levels have been associated with mild or no inflammation on liver biopsy. But as several studies have indicated, the degree of ALT elevation and extent of liver damage do not always correlate.⁷ Certain patients with chronic HBV infection who had persistently normal ALT levels have been found to have stage 2 (or greater) hepatic fibrosis. These patients tend to be older (>40 years of age), have increased HBV DNA levels, and may be erroneously considered “healthy” inactive carriers.⁵ Moreover, the upper limit of normal (ULN) for ALT levels is known to vary widely and may be overestimated, as evidenced by studies indicating an increased risk of liver disease-related mortality in association with a redefined ULN for ALT values.⁷ As a result of these limiting factors, the ALT level should be interpreted in combination with HBV DNA levels, age, and histologic findings.⁷

In considering histologic markers, a liver biopsy is invasive but critical in confirming the diagnosis of chronic HBV infection, grading the severity of necroinflammation, staging the degree of fibrosis, and determining the need for therapy in patients with normal ALT levels and high serum HBV DNA levels.⁷ Liver biopsy may also be useful in excluding other causes of liver disease, particularly alcoholic or nonalcoholic liver disease.⁷ As a general guideline, when interpreting HBV-related tests in patients with perinatally acquired infection, it is important to remain cautious in response to an absence of symptoms and seemingly nonalarming test results, such as normal ALT levels and low HBV DNA levels.

INITIAL EVALUATION

For patients who present with diagnosed chronic HBV infection, an initial evaluation should include a family history of HBV and HCC, risk factors for coinfection (eg, HIV and hepatitis C), and alcohol use.⁸ Laboratory tests should include assessment for liver disease, markers of HBV replication, and tests for hepatitis C (HCV) and hepatitis A. Periodic monitoring of patients with chronic HBV includes twice-yearly (or more frequent) physical examination and blood work, including liver function, complete blood

count, HBV DNA, HBeAg, anti-HBe, and α -fetoprotein (AFP; for patients >30 years). Annual liver imaging studies generally involve ultrasound, although computed tomography (CT) or magnetic resonance imaging (MRI) may be used in certain patients.

SCREENING

Individuals who should undergo screening for chronic HBV (Table 2) include those who have historically been considered at high risk for active infection with HBV, as well as new populations that have been recently added to the *Morbidity and Mortality Weekly Report (MMWR)* recommendations for HBV testing (discussed in the next section; Table 3).^{2,3}

Table 2. Initial Screening for HBV

HBcAb	HBsAg	HBsAb	
-	-	-	Vaccine recommended
-	-	+	Vaccinated: passive immunity
+	(IgM)	+	Acute HBV infection
+	-	+	Previous infection; recovering from acute infection; undetectable HBsAb
+	(IgG)	+	Chronic infection

HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; Ig = immunoglobulin.

Table 3. HBV: Who to Screen

- Persons born in high endemic areas ($\geq 2\%$ prevalence)
- US-born children of immigrants from high-risk areas
- Household and sexual contacts of HBsAg (+) persons
- Persons who have ever injected drugs
- Persons with multiple sexual partners, or history of STDs
- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT/AST
- Individuals infected with HIV or HCV
- Patients undergoing dialysis
- All pregnant patients

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; STD = sexually transmitted disease.

PERSONS BORN IN GEOGRAPHIC REGIONS WITH HBsAg PREVALENCE OF AT LEAST 2%

Persons born in these regions (eg, much of Eastern Europe [Russia, the Ukraine, Poland, Romania, and Bulgaria], Asia, Africa, Amazon Basin of South America, the Middle East, and the Pacific Islands) and special populations (eg, Native Alaskans, Australian Aborigines, and Maoris in New Zealand) should be tested for chronic HBV infection.² This population includes immigrants, refugees, asylum seekers, and internationally adopted children born in these regions, regardless of vaccination status in their country of origin.² Asian and Pacific Islander Americans (APIAs) include Asian Americans, native Hawaiian, and other Pacific Islander Americans. Based on the US Census data, "Asian" refers to people having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent.⁹ "Native Hawaiian and other Pacific Islander" refers to people having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.⁹ APIAs have been known to be underrepresented in most nationwide population surveys and data on population-based prevalence of HBV infection in APIAs is either varied or lacking. One screening program conducted among a predominantly immigrant Asian population found that 15% of newly tested positive New York City residents had chronic HBV infection, with the rate of HCC being 5- to 11- fold higher compared to other ethnic groups.¹⁰ In general, Asian patients have a more complicated course of HBV infection, with disease progression being documented despite HBeAg seroconversion, very low HBV DNA levels, and persistently normal ALT levels. HBV screening programs in Asian communities are thus critical in identifying infected persons and initiating interventions to reduce long-term complications and widespread transmission.

The prevalence of chronic HBV infection in Middle Eastern and African communities ranges from 5% to 15%, with men (vs women) being more affected. Among immigrants from Eastern European countries (except Hungary), the prevalence is between 2% and 7%.²

Other high-risk populations that have been added to the *MMWR* recommendations for HBV screening include men who have sex with other men, past/current intravenous drug users, persons receiving cytotoxic or immunosuppressive therapy, and those with elevated ALT or aspartate aminotransferase levels of unknown etiology.

SCREENING INDIVIDUALS WITH A HISTORY OF VACCINATION

Because some individuals may have been infected with HBV prior to receiving HBV vaccination, HBsAg testing is recommended regardless of vaccination history for persons born in geographic regions with HBV prevalence of at least 2%. The fact that individuals from these regions of high or intermediate endemicity of HBV infection may have been born before full implementation of routine infant HBV vaccination or during the early stages of vaccination programs is further compounded by the overall difficulty in verifying the vaccination status of these foreign-born persons and the reported high rate of perinatal and early childhood HBV transmission prior to implementation of routine vaccination programs.²

HBsAg testing is also recommended for US-born individuals who were not vaccinated as infants and whose parents were born in regions with high HBV endemicity ($\geq 8\%$) because prevalence of chronic HBV infection is high in this population. Although persons with HBsAg (-) mothers who completed the vaccine series as infants in the United States do not need to be tested, those vaccinated through catch-up programs as children or adolescents should be tested if they were likely to have had HBV exposure before vaccination. Those who received HBV vaccination as adolescents or adults after the initiation of risk behaviors (eg, intravenous drug use) may have been exposed to HBV prior to vaccination, and therefore should be tested as well.²

PUBLIC HEALTH IMPLICATIONS OF HBsAg (+) PERSONS

HBsAg (+) laboratory results are indicative of chronic HBV infection and should be reported to the state or local health department. Past and present sex partners and household and needle-sharing contacts of HBsAg (+) persons should be identified and, if not vaccinated, should be tested for HBsAg and anti-HBc and/or anti-HBs. These individuals should receive the first dose of the HBV vaccine as soon as the blood sample for serologic testing has been collected and be scheduled to complete the vaccine series.²

Patient education regarding ways to reduce the risk of transmission is essential (Table 4), as is destigmatization of HBV as a disease that is solely transmitted via sexual contact.² Because US immigrants become

infected when they are infants or young children, these individuals are particularly prone to transmitting the virus during early childhood through direct contact with blood of infected individuals (ie, contact between open wounds, sharing contaminated toothbrushes or razors, and tattooing). Parents and children should, therefore, be thoroughly educated regarding these particular modes of transmission.

If an HBsAg (+) person is identified in a first-generation immigrant family, then screening should include second- and third-generation family members. Individuals then found to be seronegative should be vaccinated.² For example, if in an extended family of Asian descent, a grandmother from China is found to be HBsAg (+), then her children and grandchildren should be screened.⁸

From a public health perspective, it is important to develop strategies to improve communication and relationships with patients and to gain their trust. In doing so, it is vital for clinicians to be able to address common beliefs and communication barriers specific to various ethnic groups that may impact patient compliance with screening and prevention programs.

With respect to Asian patients, it is important to understand that if these individuals hold strong, culturally rooted health beliefs, they may not seek out preventive screening because, in traditional Chinese culture, if a person feels well, there is no need to see a doctor. Also, because blood is considered a nonrenewable vital energy source for the body, patients may resist having blood tests. Some patients may hold beliefs that HBV can be spread by sharing food or chopsticks, the vaccine can transmit HBV infection, a cure for HBV exists, and HCC is only caused by alcohol. Some HBV (-) individuals, who are unaware of the preventive benefits of vaccination, believe that there is no way of preventing liver cancer.

With regard to other at-risk immigrant groups, one survey examining cultural problems that prevent immigrants residing in California from participating in HBV immunization programs found that numerous European Americans believe in anti-vaccine ideas and many East Africans have little knowledge of the English language and the American system.¹¹ According to East African community leaders, some East Africans do not understand that their children need to receive a series of injections to complete the HBV immunization series, while others do not understand the concept of healthy people getting injections

to prevent potential future problems. Many East Africans are having difficulty learning another language and adapting to a new social system (including obtaining immunizations) as a result of suffering from posttraumatic stress disorder, stemming from civil wars fought within their countries.¹¹

Limited proficiency in English is a healthcare barrier that is common among all US immigrants, and as such, it may be useful to have in place bilingual signs that aid in making appointments, filling prescriptions, and obtaining laboratory tests; a bilingual list of common phrases, medical terms, and questions; and a 24-hour telephone interpreter service. Use of family members as interpreters may be counter-productive due to the potential for poor paraphrasing, lack of linguistic equivalence, impatience, and interpreter beliefs/bias.¹²

Table 4. Reducing Transmission of HBV

- To prevent or reduce the risk for transmission to others, HBsAg (+) persons should be advised to:
 - Notify their household, sex, and needle-sharing contacts that they should be tested for markers of HBV infection, vaccinated against hepatitis B, and, if susceptible, complete the hepatitis B vaccine series.
 - Use methods (eg, condoms) to protect nonimmune sex partners from acquiring HBV infection from sexual activity until the sex partners can be vaccinated and their immunity documented.
 - Cover cuts and skin lesions to prevent the spread of infectious secretions or blood.
 - Clean blood spills with bleach solution.
 - Refrain from donating blood, plasma, tissue, or semen.
 - Refrain from sharing household articles (eg, toothbrushes, razors, or personal injection equipment) that could become contaminated with blood.
 - Dispose of blood and body fluids and medical waste properly.
 - Inform medical or dental care professionals of HBsAg (+) status.
- HBsAg (+) pregnant women should be advised of the need for their newborns to receive hepatitis B vaccine and hepatitis B immune globulin beginning at birth and to complete the hepatitis B vaccine series according to the recommended immunization schedule.

HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

Another major barrier is access to healthcare. In general, immigrants are among the poorest citizens in Western countries and are prominent among the approximately 15% of the US population that lacks health insurance.¹² As a result, the concept of preventive care through screening programs, the importance of prompt, reliable follow-up for healthcare appointments, and an understanding about reimbursement systems are lacking and must be addressed, possibly through community outreach programs and ethnic news media.

SCREENING FOR HCC

Evidence indicating that liver cancer is one of the most common tumors in regions where HBV is highly endemic (particularly the Far East and sub-Saharan Africa) attests to the fact that chronic HBV is a well-established risk factor for HCC.^{7,13} As such, screening for HCC should be considered for those carriers at high risk, including Asian men older than age 40, Asian women older than age 50, Africans older than age 20, persons with cirrhosis, those with a family history of HCC, and those with high HBV DNA levels and/or active hepatic inflammatory activity.⁷ It is important to note that HCC may develop in patients with HBV infection without cirrhosis and it may also develop at an alarmingly young age in persons born in endemic regions with presumed HBV infection at the time of birth. Screening for HCC involves ultrasound studies every 6 months and monitoring of AFP levels. MRI and CT scan, which are more sensitive but more expensive, may be preferred for patients who have cirrhosis.

CONCLUSIONS

Perinatal infection with HBV follows a pattern that is distinct from the common cases of adulthood-acquired infection that healthcare providers are accustomed to observing among US-born citizens. Perinatal transmission of HBV is considered a major risk factor in development of chronic HBV infection and is highly prevalent in the ever-expanding population of US immigrants from highly endemic regions such as Eastern Europe, Asia, Africa, the Middle East, and Pacific basin. As a result of the considerable public health implications (eg, cirrhosis, liver cancer, and

widespread transmission) associated with chronic HBV infection and the availability of effective therapies, it is important for healthcare providers to be able to recognize at-risk patients and employ proper screening and diagnostic techniques.

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