



HBV SCREENING MADE EASY TOOLKIT

A CME/CE-CERTIFIED ACTIVITY FOR THE SUCCESSFUL SCREENING
OF PATIENTS AT RISK FOR HBV INFECTION

PROVIDER INFORMATION



This activity is jointly sponsored/co-provided
by Postgraduate Institute for Medicine and the
Asian Health Foundation.

This activity is supported by independent
educational grants from Bristol-Myers Squibb
and Gilead Sciences Medical Affairs.



LETTER FROM THE ASIAN HEALTH FOUNDATION

Dear Health Care Professional:

Chronic hepatitis B (CHB) is a serious and prevalent disease that accounts for substantial morbidity and mortality from liver cancer, cirrhosis, and liver failure, both globally and nationally. About 350 million persons worldwide currently have CHB, and 600,000 deaths related to hepatitis B virus (HBV) infection occur annually. In the United States, CHB affects an estimated 2 million individuals and causes 2000 to 4000 deaths each year. Much of the burden of CHB in the United States is borne by Asians and Pacific Islanders, and the disease represents an important health disparity for this population. However, nearly two-thirds of those with CHB, including Asian Americans, are unaware of their infection and, therefore, are untreated and are at significant risk for the severe long-term consequences of the disease.

The availability of both valid and accessible screening tests and safe and effective treatments for those who need them provides a solid rationale for early identification of those persons at greatest risk in order to bring them into care. Screening is also essential to reduce HBV transmission through vaccination of those susceptible to infection. This program provides guidance and practical tools for primary care providers (PCPs) on the early identification of patients at risk for CHB through screening and testing, prevention through vaccination, and general information for counseling patients on HBV infection and the risks of CHB. Although this program focuses on immigrant populations most at risk, particularly Asian Americans, much of the information presented is applicable to persons from other regions of intermediate or high HBV endemicity as well.

This continuing medical education/continuing education (CME/CE) activity will benefit PCPs by offering current information on screening, diagnosis, and prevention of transmission for their patients at high risk for CHB. In turn, this CME/CE activity will benefit patients with CHB by expanding the knowledge about this disease among PCPs, thereby promoting screening, earlier diagnosis, and vaccination, along with contributing to the optimal care of patients in populations at highest risk.

It is our sincere hope that you will find the components in this program to be a useful part of both your clinical practice and continuing education about this serious disease.

Sincerely,

The Asian Health Foundation

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CME/CE INFORMATION

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Bristol-Myers Squibb



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PROGRAM OVERVIEW

The AHF HBV Screening Made Easy Toolkit is a CME/CE-certified program designed to give health care providers and their patients relevant clinical tools and resources to optimize recognition, diagnosis, and prevention of chronic hepatitis B (CHB). The AHF HBV Screening Made Easy Toolkit includes Provider Information, an Office Wall Poster, a coordinating Front Desk Initial Screening Card, and a Hepatitis B Screening Patient Information Card.

The Provider Information presents up-to-date information and guidance on the epidemiology of hepatitis B virus (HBV) infection and best practices in screening, testing, vaccination, prevention, and patient counseling. Because many unanticipated developments arise in the long-term care of patients with CHB that cannot be addressed in one program, additional sources and Website links are included throughout the Provider Information that direct the reader to more detailed information, guidance, or Web-based tools. In addition, the Provider Information includes coordinated sections for training office staff on implementation of the HBV Screening Made Easy Toolkit, specifically use of the Front Desk Initial Screening Card, the Patient Information Card, and the Office Wall Poster. The Front Desk Initial Screening Card will help determine whether the patient needs HBV screening. The Patient Information Card coordinates with both the information presented in the Provider Information and the world map of HBV endemicity shown on the Office Wall Poster. The Patient Information Card can be photocopied for distribution to patients.

TARGET AUDIENCE

This activity has been designed to meet the educational needs of primary care providers, including physicians, physician assistants, nurse practitioners, and registered nurses.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Implement the Centers for Disease Control and Prevention screening and testing recommendations for HBV
- Educate office staff to screen patients on initial presentation for HBV and facilitate the process for testing, vaccination, and patient counseling

- Counsel patients on the need for screening, testing, and vaccination
- Provide appropriate care and counsel for patients and their families

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PHYSICIAN CONTINUING MEDICAL EDUCATION INFORMATION

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Postgraduate Institute for Medicine and the Asian Health Foundation. The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

The Postgraduate Institute for Medicine designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credit(s)*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NURSING CONTINUING EDUCATION INFORMATION

Credit Designation

This educational activity for 1.1 contact hours is provided by Postgraduate Institute for Medicine.

Accreditation Statement

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Consulting Fees: Bristol-Myers Squibb; Gilead Sciences, Inc.
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Media: Screening Toolkit

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DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

HOW TO USE THE SCREENING TOOLKIT

How the screening toolkit is used in individual practices will vary; however, counseling on chronic hepatitis B (CHB) treatment and monitoring should always be provided by the health care practitioner. In this suggested approach to using the screening tool, the health care practitioner provides counseling on treatment and prevention of hepatitis B virus (HBV) infection, the front desk staff takes responsibility for initial screening of patients, and

the office medical staff, such as medical assistants and nurses, orders HBV tests and provide general counseling.

The following color-coded chart shows the individual steps for the implementation of the toolkit and the responsibilities of each individual in using the toolkit components.

Responsibilities:

Health care practitioner: Counseling on treatment and prevention of HBV infection

Front desk staff: Initial screening

Medical assistant/nurse: HBV tests and general counseling

HEALTH CARE PRACTITIONER			
PREP P	PREPARATION HBV provider trains front desk and office medical staff on Screening Toolkit components and use		
FRONT DESK STAFF			
STEP 1	INITIAL SCREENING <ul style="list-style-type: none"> • Screens each patient using a photocopy of the Initial Screening Card • Affixes test sticker to a photocopy of the Initial Screening Card, if appropriate • Refers patient to medical staff 		
MEDICAL ASSISTANT/NURSE			
STEP 2	GENERAL HBV COUNSELING AND TESTING <ul style="list-style-type: none"> • Counsels patient on the need for testing using a photocopy of the Hepatitis B Screening Patient Information Card • Explains what testing involves • Orders tests 		
STEP 3	HBV TEST RESULTS COUNSELING <table border="0" style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> ⊖ Negative test results: <i>Counseling by medical assistant or nurse</i> <ul style="list-style-type: none"> • Counsels patient on the negative test results and the need for vaccination if susceptible </td> <td style="width: 50%; vertical-align: top;"> ⊕ Positive test results: <i>General counseling by medical assistant or nurse</i> <ul style="list-style-type: none"> • Counsels patient on the positive test results and what can be done to help patient stay as healthy as possible • Reassures patient that the HBV provider will offer a full discussion of management and prevention </td> </tr> </table>	⊖ Negative test results: <i>Counseling by medical assistant or nurse</i> <ul style="list-style-type: none"> • Counsels patient on the negative test results and the need for vaccination if susceptible 	⊕ Positive test results: <i>General counseling by medical assistant or nurse</i> <ul style="list-style-type: none"> • Counsels patient on the positive test results and what can be done to help patient stay as healthy as possible • Reassures patient that the HBV provider will offer a full discussion of management and prevention
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CALL TO ACTION: EPIDEMIOLOGY OF CHB

HBV infection is a significant cause of morbidity and mortality worldwide.¹ According to the World Health Organization, an estimated 2 billion individuals have been infected with HBV, 350 million individuals live with CHB, and 600,000 individuals die annually due to complications from acute or chronic infection.^{1,2} CHB is a major cause of cirrhosis and hepatocellular carcinoma (HCC).^{3,4} CHB is also a significant problem in the United States and represents an important health disparity among immigrant populations.⁵⁻⁷ For example, individuals who immigrated to the United States from China, Taiwan, Vietnam, and Korea between 1974 and 2008 had estimated hepatitis B surface antigen (HBsAg) prevalence rates of 12%.⁵ In comparison, the US general population between 1999 and 2006 had an HBsAg prevalence rate of less than 3%.⁸ Estimates suggest that at least 2 million persons in the United States have CHB, and the disease causes 2000 to 4000 deaths each year.⁹⁻¹¹ However, safe and effective treatments for CHB are now available that can reduce the risk of progression to serious hepatic complications, thereby improving quality of life and survival.¹²

RATIONALE FOR HBV SCREENING

Given the prevalence of HBV infection, the serious long-term consequences of chronic infection, and the availability of safe and effective treatment for those who need it, early screening of persons at high risk is essential to bring those who are infected into care. However, despite the availability of accurate screening tests and the release of Centers for Disease Control and Prevention (CDC) screening recommendations, an estimated two-thirds of persons with CHB remain unaware of their infection.^{7,13} In

the United States, about 420,000 to 600,000 individuals have undiagnosed CHB and, therefore, are untreated and remain at risk for HCC, cirrhosis, and liver failure.^{7,9,11} An estimated 25% of all persons with untreated CHB who were infected as infants or young children as well as 15% of those who were infected when they were older eventually develop HCC, cirrhosis, and/or liver failure.^{7,11} Although HBV immunization programs instituted worldwide in the past have lowered the prevalence of HBV carriers in younger age groups, the incidence of HBV-related HCC is expected to increase for the next several decades because of the high prevalence of chronic infection and the long latency period between infection and development of cancer.³ Screening is also needed to identify persons with CHB because they are the primary sources of HBV transmission, and those who remain unaware of their infection cannot take precautions to prevent transmission.¹¹ Greater efforts in screening and diagnosis of HBV infection are needed to bring all those affected into care to reduce their risk of progression to serious complication, to prevent transmission, and to lower the overall burden of CHB in the United States.

WORLD MAP OF HBV PREVALENCE

HBV endemicity, as measured by prevalence of HBsAg, varies by region around the world and forms the basis for screening immigrants from endemic regions.¹⁴ For clinics with a high number of patients who are Asians and members of immigrant populations, focusing on the patients' place of birth produces the highest yield in identifying those who need to be screened. As shown in **Figure 1**, on the basis of the HBsAg-positive preva-

Figure 1. World map of HBsAg prevalence rates, 2006.^a



^aFor multiple countries, estimates of HBsAg prevalence are based on limited data and might not reflect current prevalence in countries that have implemented childhood HBV vaccination. HBsAg prevalence may vary within countries by subpopulation and locality.

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

Source: Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR*. 2008;57(RR-8):1-20.

lence rate, the world is divided into 2 regions of intermediate and high endemicity ($\geq 2\%$) and low endemicity ($< 2\%$).¹¹ **Table 1** lists regions and countries with HBsAg prevalence rates $\geq 2\%$. High endemic areas include countries in central Asia, Southeast Asia, Sub-Saharan Africa, and the Amazon basin; areas of intermediate endemicity include countries in the Middle East and Eastern Europe, as well as the Mediterranean basin. As described in the next section, individuals who were born in these regions or whose parents were born in these regions should be routinely screened for CHB.¹¹

The primary routes of HBV transmission also vary by world region and determine a person's risk of developing CHB¹⁴ (see **Sidebar: HBV Transmission Routes and Risk of CHB**). In areas of intermediate or high HBV endemicity, such as Southeast Asia, transmission predominantly occurs perinatally or during early childhood when the risk of developing CHB is greatest. In these areas, rates of chronic liver disease and liver cancer are very high. In areas of low endemicity, such as the United States, HBV transmission predominantly occurs in adults through sexual contact or needle sharing, and the risk of developing CHB is low.^{11,14}

HBV TRANSMISSION ROUTES AND RISK OF CHB

HBV is transmitted through mucosal or percutaneous exposure to HBV-infected blood or body fluids via sexual contact, needle sharing by injection drug users (IDUs), perinatal exposure to a mother with CHB, prolonged household contact, or needle stick injuries in health care settings.¹¹ While most cases of acute HBV infection in adults are self-limited and patients recover completely, a small proportion of adults ($< 5\%$) will develop chronic infection, with ongoing viral replication in the liver.⁴ Infants and young children are at much greater risk for CHB than adults, with an estimated 90% of children infected perinatally and 50% of those infected aged 1 to 5 years progressing to CHB.⁴

IMMIGRANT POPULATIONS AT HIGHEST RISK FOR CHB

Because the burden of CHB in the United States falls disproportionately on immigrant populations, screening efforts targeted to individuals in these groups may help reduce existing health

disparities.⁵⁻⁷ The CDC estimates that about 47% to 70% of all persons who were HBsAg-positive in 2006 were foreign-born.¹¹ However, these estimates are based on data from the National Health and Nutrition Examination Survey (NHANES), which has serious limitations in terms of measuring viral hepatitis because Asian and Pacific Islander populations are underrepresented.⁷ A more recent analysis by the CDC using estimates of country-specific HBsAg-positive prevalence rates reported that 63% of the nearly 30 million individuals who immigrated to the United States between 1974 and 2008 were born in regions with a CHB prevalence rate $\geq 2\%$. The analysis also showed that imported CHB cases accounted for a total of 1.3 million new cases or about 95% of all new cases occurring in the United States during that time span.⁵ The overall estimated prevalence of CHB among new immigrants between 1974 and 2008 was 4.6%, which is higher than the US general population prevalence rate of 0.3%.⁵ **Table 2 on page 7** lists the estimated prevalence rate of seropositive status for HBsAg and the number of imported CHB cases among immigrants to the United States between 1974 and 2008. The majority (55.2%) of estimated imported CHB cases were from the Western Pacific Region.⁵ As shown in Table 2, the leading 3 countries of birth for imported cases were from the Western Pacific Region: the Philippines, China, and Vietnam. When combined, these 3 countries alone accounted for 37% of the estimated total burden of CHB among immigrants.⁵

Asian Americans and Pacific Islanders also bear a significant portion of the long-term consequences of CHB in the United States, accounting for half of the deaths that result from CHB.¹⁵ Asian Americans have the highest rate of HCC among all ethnic groups.^{16,17} According to an analysis based on data from the CDC National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) surveillance system, the annual incidence rate of HCC increased significantly from 2.7/100,000 persons in 2001 to 3.2/100,000 in 2006, with the highest average annual HCC rate for 2001 to 2006 occurring among Asians/Pacific Islanders (7.8/100,000), followed by blacks (4.2/100,000), American Indians/Alaska Natives (3.2/100,000), and whites (2.6/100,000).¹⁷

Table 1. Geographic regions with intermediate to high HBsAg prevalence.

Region	HBsAg Prevalence $\geq 2\%$
Africa	All countries
Southeast Asia, East Asia, and Northern Asia	All countries
Australia and South Pacific	All countries except Australia and New Zealand
Middle East	All countries except Cyprus and Israel
Eastern Europe	All countries except Hungary
Western Europe	Malta, Spain, and indigenous populations in Greenland
North America	Alaska Natives and indigenous populations in Northern Canada
Mexico and Central America	Guatemala and Honduras
South America	Ecuador, Guyana, Suriname, Venezuela, and Amazonian areas of Bolivia, Brazil, Columbia, and Peru
Caribbean	Antigua-Barbuda, Dominica, Grenada, Haiti, Jamaica, St. Kitts-Nevis, St. Lucia, and Turks and Caicos Islands

HBsAg, hepatitis B surface antigen.

Source: Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR*. 2008;57(RR-8):1-20.

Furthermore, Asians and Pacific Islanders account for more than two-thirds of births to women with CHB but account for only 5.7% of all US births.⁷ Like the general population, however, most Asian Americans are undiagnosed and are not in care;

available data suggest that an estimated two-thirds of all Asian Americans with CHB in the United States are unaware of their infection.¹³

Table 2. Prevalence of HBsAg and CHB among immigrants to the United States by region or country of origin between 1974 and 2008.

Region or Country of Origin	Immigrants, N	HBsAg-Positive, %	CHB Cases, N (%)
Region			
Africa	939,183	11.1	104,698 (8.0)
Americas	13,201,197	1.6	207,800 (15.8)
Eastern Mediterranean	1,695,778	5.0	85,565 (6.5)
Europe	3,994,078	2.9	117,335 (8.9)
Southeast Asia	1,847,292	4.0	73,360 (5.6)
Western Pacific	6,604,083	11.0	724,002 (55.2)
Total	28,281,611	4.6	1,312,760 (100)
Top 10 Countries			
Philippines	1,765,203	10.0	176,520 (13.4)
China	1,372,025	12.0	164,643 (12.5)
Vietnam	1,200,863	12.0	144,103 (11.0)
Korea	918,505	12.0	110,221 (8.4)
Mexico	5,807,590	1.0	58,076 (4.4)
India	1,323,110	3.0	39,693 (3.0)
Taiwan	313,643	12.0	37,637 (2.9)
Dominican Republic	940,769	4.0	37,631 (2.8)
Haiti	532,968	5.0	26,648 (2.0)
Hong Kong	211,472	12.0	25,377 (1.9)

CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen.

Source: Mitchell T, Armstrong GL, Hu DJ, et al. The increasing burden of imported chronic hepatitis B—United States, 1974-2008. *PLoS One*. 2011;6:e27717.

IMPLEMENTING THE HBV SCREENING MADE EASY TOOLKIT

In 2008 the CDC revised recommendations for HBV infection screening.¹¹ The CDC recommends screening based on risk rather than universal screening because the prevalence rate of HBsAg-positive status is low in the US general population.¹¹ The objective of screening for HBV infection is twofold: to prevent or delay serious complications of untreated CHB and to reduce HBV transmission.¹¹

Table 3 lists population groups in the United States recommended for routine screening for HBV infection.¹¹ Screening is recommended for immigrants born in countries of intermediate or high HBV endemicity and unvaccinated children of persons from countries with high HBV endemicity (**Figure 1**). In addition, screening is recommended for IDUs, men who have sex with men, all pregnant women, patients undergoing hemodialysis, and persons infected with human immunodeficiency virus (HIV); any patients scheduled for immunosuppressive therapy or chemotherapy should be tested for CHB.

Table 3. HBV screening recommendations for US populations.

Persons born in countries with HBsAg prevalence ≥2% (intermediate to high HBV endemicity)
Unvaccinated children of persons from countries with ≥8% prevalence (high HBV endemicity)
Blood, organ, plasma, semen, tissue donors
Hemodialysis patients
All pregnant women
Infants born to HBsAg-positive mothers
Household contacts, needle sharing partners, or sex partners of HBV-infected persons
Sources of blood or body fluid exposures that might warrant postexposure prophylaxis
HIV-infected persons
Persons with select medical conditions (eg, elevated ALT or AST levels of unknown etiology)
Persons with behavioral exposures (eg, IDUs, MSM)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B virus surface antigen; HIV, human immunodeficiency virus; IDU, injection drug user; MSM, men who have sex with men.

Source: Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR*. 2008;57(RR-8):1-20.

TRAINING FRONT DESK STAFF ON SCREENING/TESTING

- ✓ Describe to the front desk staff how to use the **Initial Screening Card** on initial contact with the patient. They should make a photocopy of the laminated card for each patient
- ✓ Explain that at the first encounter with each patient, they present the photocopy and ask the 3 questions on the page. Explain that answers to the 3 questions will help determine whether the patient needs HBV testing
- ✓ Point out the color-coded world map on the **Initial Screening Card** to the front desk staff. Explain that the need for HBV testing is indicated by the place of birth of the patient or patient's parents
- ✓ If patients indicate that they or their parents were born in a **red** country, **testing is needed**. The front desk staff member should place the sticker indicating the need for testing on the patient's photocopy of the **Initial Screening Card**
- ✓ If patients or their parents were born in a **grey** country, testing is not needed
- ✓ Point out the section, "Let Me Explain Why We Ask" on the Initial Screening Card. Explain to the front desk staff that this section describes the reason we ask patients where they or their parents were born, which is because it indicates the risk for HBV infection, and individuals with CHB are at a high risk for developing serious liver disease. We want to test individuals at risk so that we can work with them to protect their health
- ✓ Describe to the front desk staff that all they need to do next is give the photocopy of the ✓ to the designated office medical staff member who will counsel the patient on testing

ORDERING HBV TESTS

A number of different tests can assess for specific serologic markers of HBV infection. Measurable serologic markers of HBV infection are described in **Table 4**.^{11,18}

Table 4. Serologic markers of HBV infection.

Serologic Marker	Description
HBsAg	<ul style="list-style-type: none"> • Protein on the surface of HBV • Can be detected at high levels in serum during acute HBV infection or in CHB • Presence indicates the patient is infected
Anti-HBs	<ul style="list-style-type: none"> • Antibody to HBsAg • Presence may indicate recovery and immunity from HBV infection • Also develops in patients successfully vaccinated against HBV
Anti-HBc	<ul style="list-style-type: none"> • Antibody to core antigen of HBV (core antigen is not detectable in blood) • Appears at the onset of symptoms in acute HBV infection and remains throughout life • Presence indicates previous or ongoing HBV
IgM anti-HBc	<ul style="list-style-type: none"> • Immunoglobulin M class antibody to the core antigen of HBV • Presence indicates recent acute infection with HBV (≤ 6 months)
HBeAg	<ul style="list-style-type: none"> • Protein produced by HBV when it is actively replicating • Can be detected in serum during acute HBV infection and CHB • Some strains of HBV do not make e antigen • Active replication
Anti-HBe	<ul style="list-style-type: none"> • Antibody to HBeAg • Inactive infection except strains of HBV that do not make e antigen
HBV DNA	<ul style="list-style-type: none"> • Genetic material of HBV • Number of HBV DNA copies in the blood is used to detect active HBV infection and to monitor response to antiviral therapy (10,000 copies/mL = 2000 IU/mL)

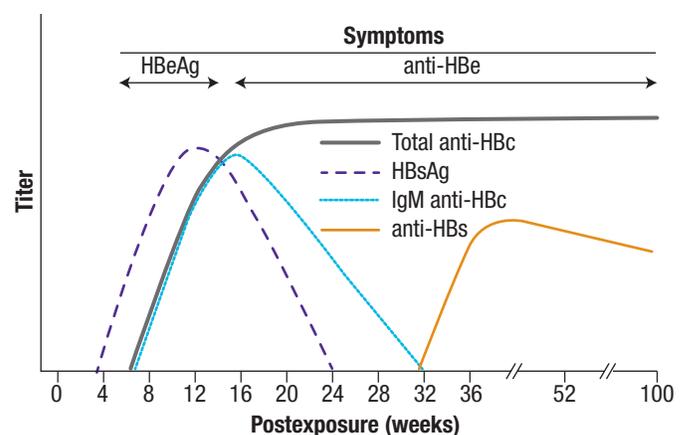
Anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B e antibody; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgM anti-HBc, immunoglobulin M class antibody to hepatitis B core antigen.

Sources: Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR*. 2008;57(RR-8):1-20; Centers for Disease Control and Prevention. Hepatitis B FAQs for health professionals. <http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#>. Accessed March 19, 2012.

CHANGES IN SEROLOGIC MARKERS THROUGH THE COURSE OF INFECTION

The levels of serologic markers change as HBV infection progresses from acute infection to either recovery or to CHB.¹¹ During the first few weeks after acute infection with HBV, HBsAg is the only serologic marker detected. Total hepatitis B core antibody (anti-HBc) appears about 1-2 months after the initial acute infection and persists for the duration of life in most patients. Immunoglobulin M class antibody to hepatitis B core antigen typically can be detected within 6 months of acute infection. Patients who recover from HBV infection develop hepatitis B surface antibody (anti-HBs) and clear HBsAg and HBV DNA from the blood (**Figure 2**).

Figure 2. Typical serologic course of acute HBV infection with recovery.



Anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B e antibody; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; IgM anti-HBc, immunoglobulin M class antibody to hepatitis B core antigen.

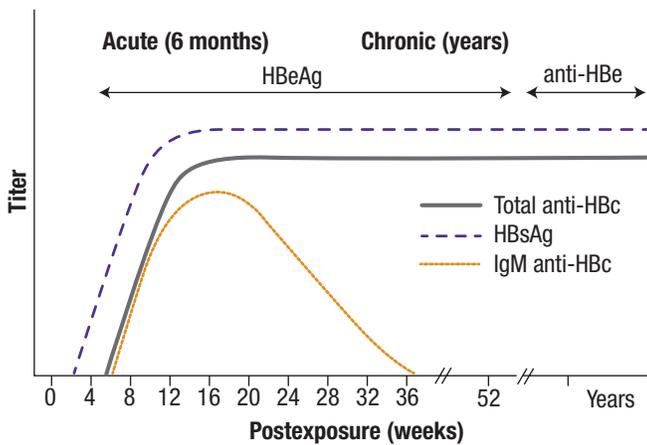
Source: Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR*. 2008;57(RR-8):1-20.

Patients who progress from acute infection to CHB do not develop anti-HBs and do not clear HBsAg and HBV DNA from the blood (**Figure 3**). Hepatitis B e antigen (HBeAg) can be present during both acute infection and in CHB. The presence of HBeAg is generally associated with more active disease.¹¹ Although most CHB patients will eventually develop hepatitis B e antibody (anti-HBe) and clear HBeAg from the blood, HBeAg-negative status does not mean that the disease is inactive. Patients with HBeAg-negative CHB can have detectable HBV DNA and active disease.¹⁹ In fact, worldwide, HBeAg-negative CHB is more common than HBeAg-positive CHB.

PRIMARY SCREENING TOOL FOR CHB

The American Association for the Study of Liver Diseases (AASLD) recommends testing for both HBsAg and anti-HBs as a primary screening tool for CHB.²⁰

Figure 3. Typical serologic course of acute HBV infection with progression to CHB.



Anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B e antibody; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; IgM anti-HBc, immunoglobulin M class antibody to hepatitis B core antigen.

Source: Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR*. 2008;57(RR-8):1-20.

Anti-HBc can be used only if positive test results are followed up with testing for both HBsAg and anti-HBs. This is necessary to differentiate patients who have active infection from those who have immunity. For additional information on the role of testing for anti-HBc, see **Sidebar: Occult HBV Infection and Anti-HBc**. Tests that are not to be used for screening include HBeAg, anti-HBe, and HBV DNA levels. However, testing for blood levels of these serologic markers may be used to evaluate patients for treatment, to monitor disease progression, and to assess response.²⁰

OCCULT HBV INFECTION AND ANTI-HBc

Occult HBV infection refers to patients who are negative for HBsAg but have persistent HBV DNA replication in the liver.²¹ Typically, HBV DNA is not detectable in the blood, but anti-HBc antibodies with or without anti-HBs are detectable in patients with occult infection.¹² Patients with occult infection are at risk for reactivation during immunosuppressive therapy or chemotherapy and, therefore, all patients scheduled to undergo these types of treatments should be tested for anti-HBc and HBsAg before initiation of therapy.¹² Occult HBV can also occur in patients with HIV infection, and the American Association for the Study of Liver Diseases (AASLD) advises clinicians to test all patients with HIV for both HBsAg and anti-HBc.²⁰ If the patient is positive for either HBsAg or anti-HBc, then a test for serum HBV DNA should be performed.²⁰

TRAINING MEDICAL ASSISTANT/NURSE ON ORDERING TESTS

- ✓ Explain to the office medical staff that they should make a photocopy of the laminated *Patient Information Card* for each patient
- ✓ Point out to the office medical staff the coordinating section on testing, *“What’s involved in testing?”* on the *Patient Information Card* that they can use with the patient. This section explains that only a simple blood test is needed
- ✓ Explain to the office medical staff that tests for both HBsAg and anti-HBs are required to screen for CHB
- ✓ Provide the office medical staff with the American Medical Association (AMA) billing codes to use for ordering tests:
 - 87340: HBsAg
 - 86706: Anti-HBs

INTERPRETING HBV TEST RESULTS

CHB is indicated by test results that are positive for HBsAg and negative for anti-HBs. The usual interpretation of common serologic tests for HBV infection is shown in **Table 5**.^{11,22}

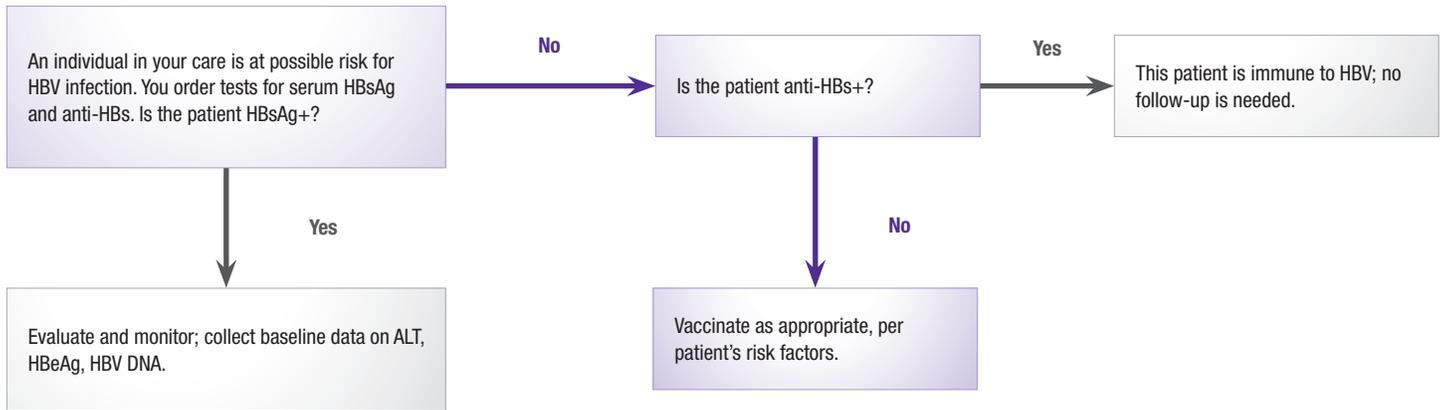
A positive test result for HBsAg should be followed by collection of baseline data for alanine aminotransferase (ALT), HBeAg, anti-HBe, and HBV DNA levels.²³ Screening and vaccination of household contacts, family members, and sexual contacts of HBsAg-positive patients are also recommended.²³ Test results that are negative for HBsAg and anti-HBs indicate that the patient is susceptible to HBV infection and should trigger vaccination, which is discussed further below. Patients who are negative for HBsAg but positive for anti-HBs are immune and do not require vaccination. **Figure 4 on page 10** presents an algorithm for screening patients at risk for HBV infection.

Table 5. Interpretation of HBsAg and anti-HBs tests for HBV infection.

Patient Status	HBV Serologic Marker	Test Result
Susceptible	HBsAg	Negative
	Anti-HBs	Negative
Immune	HBsAg	Negative
	Anti-HBs	Positive
Infected	HBsAg	Positive
	Anti-HBs	Negative

Anti-HBs, hepatitis B surface antigen antibody; HBsAg: hepatitis B surface antigen; HBV, hepatitis B virus.
 Sources: Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR*. 2008;57(RR-8):1-20; Centers for Disease Control and Prevention (CDC). Interpretation of hepatitis B serologic test results. <http://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf>. Accessed June 3, 2012.

Figure 4. Algorithm for screening patients at risk for HBV infection.



ALT, alanine aminotransferase; anti-HBs, hepatitis B surface antigen antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Source: Adapted from McHugh JA, Cullison S, Apuzzo J, et al. Chronic hepatitis B infection: a workshop consensus statement and algorithm. *J Fam Pract.* 2011;60:E1-E8.

TRAINING MEDICAL ASSISTANT/NURSE ON COUNSELING PATIENTS ON TEST RESULTS

- ✓ Explain to the office medical staff how you would like them to discuss both positive and negative results with patients
- ✓ Point out the coordinating section on test results, **“What if I don’t have the virus?”** on the **Patient Information Card**
- ✓ Patients do not have CHB if test results are **negative** for both HBsAg and anti-HBs, but they are susceptible to infection and candidates for vaccination
- ✓ Patients who test negative for HBsAg and positive for anti-HBs are immune and do not require vaccination
- ✓ Point out the coordinating section on test results, **“What if I have the virus?”** on the **Patient Information Card**. The office medical staff should explain to patients that the treating physician will discuss this section with them
- ✓ Point out the coordinating section, **“What treatment is available if I have the virus?”** on the **Patient Information Card**. The office medical staff should explain to patients that the treating physician will discuss this section with them

VACCINATION: PROVEN SAFE AND EFFECTIVE

The HBV vaccine is highly effective and safe, and since 1982 more than 1 billion doses have been given worldwide.^{24,25} The 3-dose vaccine series (administered over a 6-month period) provides protection against HBV infection in 98% to 100% of infants and 90% to 95% of adolescents and adults.¹⁴

Vaccination is a key step in preventing acquisition of HBV infection and transmission.¹¹ Universal HBV vaccination of newborns in the United States has markedly reduced the incidence of acute cases of HBV (Figure 5).⁴ Between 1990 and 2007, the rate of new acute HBV cases decreased by more than 80%.²⁶ Consequently the estimated incidence of new, domestically acquired cases of CHB has fallen from about 10 cases/100,000 population in 1991 to the current rate of 1.2 cases/100,000 population.⁵

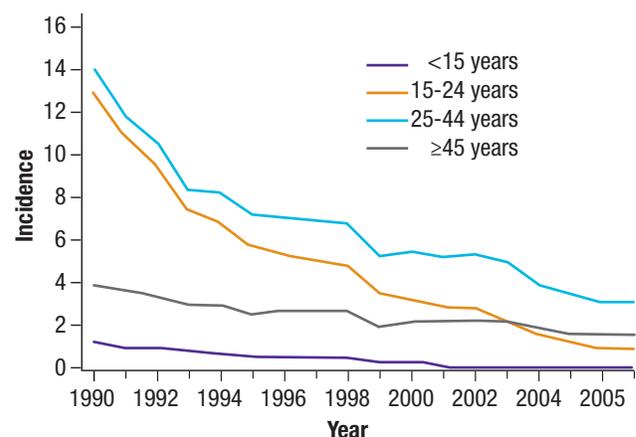
GROUPS RECOMMENDED FOR VACCINATION

Vaccination is particularly important for family members and other household contacts of patients who are HBsAg-positive, in addition to other individuals who are at risk of exposure to HBV.²⁷ The CDC currently recommends HBV vaccination for all newborns and children up to age 18, and all adults at risk for HBV infection (Table 6 on page 11).^{27,28} Pregnancy is not a contraindication for vaccination, and all susceptible pregnant women at risk for HBV exposure should be vaccinated.²⁷⁻²⁹ Additional measures are required for infants born to HBsAg-positive

women, which include the administration of hepatitis B immune globulin (HBIG) and the first dose of HBV vaccination to the newborn within 12 hours of delivery.²⁸

For more information on immunoprophylaxis to reduce perinatal transmission in HBeAg-positive women, please consult the recommendations from the CDC, *A Comprehensive Immu-*

Figure 5. Incidence of acute HBV, by age group and year—United States, 1990-2007.^a



^a Per 100,000 population.

Source: Centers for Disease Control and Prevention. Surveillance for acute viral hepatitis—United States, 2007. Surveillance summaries, May 22, 2009. *MMWR.* 2009;58(SS-3):1-27.

Table 6. Adult groups recommended for HBV vaccination.

Persons at risk for HBV infection through sexual exposure	<ul style="list-style-type: none"> • Sex partners of HBsAg-positive persons • Sexually active persons who are not in a long-term, mutually monogamous relationship (eg, persons with more than one sex partner during the previous 6 months) • Persons seeking evaluation or treatment for a sexually transmitted disease • MSM
Persons at risk for HBV infection through percutaneous or mucosal exposure to blood	<ul style="list-style-type: none"> • Current or recent IDUs • Household contacts of HBsAg-positive persons • Residents and staff of facilities for developmentally disabled persons • Health care workers and public safety workers with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids • Persons with end-stage renal disease (eg, predialysis, hemodialysis, peritoneal dialysis, and home dialysis)
Others	<ul style="list-style-type: none"> • International travelers to regions with HBsAg prevalence of ≥2% (see Figure 1) • Persons with chronic liver disease • Persons with HIV infection • Unvaccinated adults (aged 19-59 years) with diabetes mellitus; unvaccinated adults with diabetes mellitus (aged ≥60 years) at discretion of clinician • All other persons seeking protection from HBV infection

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IDU, injection drug user; MSM, men who have sex with men.

Sources: Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP); Part 2: Immunization of Adults. *MMWR*. 2006;55(RR-16):1-33; Centers for Disease Control and Prevention. Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2011;60(50):1709-1711.

nization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States, available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5416a1.htm>

VACCINE SCHEDULES FOR ADULT PATIENTS

The HBV vaccine schedule for adults is shown in **Table 7**.¹⁴ The typical vaccination schedule for adults is 3 intramuscular injections, with the second and third dose administered 1 and 6 months, respectively, after the first. Patients who do not complete the vaccine series within the recommended timeframe need to receive only the remaining shots; they do not need to

restart the dose series.¹⁴ Patients who are immunocompromised or are undergoing hemodialysis require a higher dose and/or a different dosing schedule.²⁷ **Table 7** also includes the dosing schedule for combination HBV and hepatitis A virus (HAV) vaccines. A combination vaccine is recommended for adults aged 18 years and older who have risk factors for both HAV and HBV.²⁷

Post-vaccine testing for anti-HBs

After completion of the vaccine series, testing of anti-HBs levels is not needed for most adults; however, it is recommended for those at high risk for HBV exposure, such as health care and public safety workers, as well as needle sharing or sexual contacts of HBsAg-positive individuals.²⁷ Post-vaccination testing should be conducted 1 to 2 months after the last dose in these individuals.²⁰ In addition, annual testing for anti-HBs levels is recommended for chronic hemodialysis patients.²⁰ According to the CDC, revaccination of those individuals who do not initially respond is effective; among individuals who did not respond to the first 3-dose vaccine series with anti-HBs concentrations of >10 mIU/mL, an additional vaccine dose led to a response in 25% to 50% of patients, and a revaccination with the 3-dose revaccination series led to a response in 44% to 100% of patients.²⁷

Vaccine booster shots

Booster shots of the HBV vaccine are not recommended for previously vaccinated adults and children with normal immune status.¹⁴ Booster doses are recommended for hemodialysis patients when anti-HBs levels decline to <10 mIU/mL.¹⁴ The role of HBV vaccine booster shots in other immunocompromised persons, such as those undergoing chemotherapy, persons with HIV infection, or hematopoietic stem-cell transplant recipients, has not been determined. According to the CDC recommenda-

Table 7. HBV vaccine recommended dosing and schedules for adults.

Single-Antigen HBV Vaccine				Combination Vaccine (HBV and HAV)	
Recombivax HB		Engerix-B®		Twinrix®	
Dose (µg) ^a	Volume (mL)	Dose (µg) ^a	Volume (mL)	Dose (µg) ^a	Volume (mL)
Adults (aged ≥20 years)					
10	1.0	20	1.0	20	1.0
Hemodialysis and other immunocompromised patients aged <20 years					
5	0.5	10	0.5	NA	NA
Hemodialysis and other immunocompromised patients aged ≥20 years					
40 ^b	1.0	40 ^c	2.0	NA	NA

^a Recombinant hepatitis B surface antigen protein dose.

^b Dialysis formulation administered on a 3-dose schedule at 0, 1, and 6 months.

^c Two 1.0 mL doses administered at one site, on a 4-dose schedule at 0, 1, 2, and 6 months.

HAV, hepatitis A vaccine; HBV hepatitis B vaccine; NA, not applicable.

Source: Centers for Disease Control and Prevention. Hepatitis B epidemiology and prevention of vaccine-preventable diseases. *The Pink Book*, 12th edition. April 2011. <http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/hepb.pdf>. Accessed April 21, 2012.

tions, however, when anti-HBs levels decline to <10 mIU/mL in immunocompromised patients, booster doses should be considered for those at continued risk of HBV exposure.¹⁸

Additional preventative measures for persons with CHB

Individuals with CHB are the primary source of new HBV infections; therefore, patients diagnosed with CHB need to take precautionary measures to prevent transmission of HBV to susceptible individuals (**Table 8**).^{11,20} Patients should be informed that they can participate in all types of social activities involving casual contact, including contact sports, and that they can share food and utensils.²⁰

Table 8. Preventive measures for all persons who are HBsAg-positive to reduce HBV transmission.

- Have sexual contacts vaccinated
- Use barrier protection during sexual intercourse if partner is not vaccinated or naturally immune
- Cover open cuts and scratches
- Do not share toothbrushes or razors
- Clean blood spills with bleach or detergent
- Do not donate blood, organs, or semen

Sources: Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR*. 2008;57(RR-8):1-20; Lok A, McMahon B. Chronic hepatitis B update: 2009. *Hepatology*. 2009;50:1-36.

TRAINING MEDICAL ASSISTANT/NURSE ON COUNSELING PATIENTS ON VACCINATION AND PREVENTION

- ✓ Point out the coordinating section, **“What’s involved in getting vaccinated?”** on the *Patient Information Card* to the office medical staff. Explain to the staff members that patients who are susceptible to HBV infection need to be vaccinated
- ✓ Describe to the office medical staff what they need to tell patients about the vaccine:
 - Three doses are needed within 6 months. Alternative schedules may be available for patients who need them
 - The vaccine is safe and effective. More than 1 billion doses have been given worldwide, and the vaccine provides complete protection from infection if the person is exposed to HBV
 - If a vaccine dose is missed, the entire series does not have to be restarted. The patient needs to receive only the remaining doses
 - Individuals at continued risk for HBV exposure need post-vaccination testing for anti-HBs about 1 to 2 months after completion of the vaccine series to confirm an immune response. This includes all health care and public safety workers, as well as needle sharing or sexual contacts of HBsAg-positive individuals. Annual testing for anti-HBs levels is recommended for chronic hemodialysis patients
- ✓ Provide the office medical staff with the AMA billing codes to use for the vaccine to ensure insurance coverage:
 - 90740: HBV vaccine, dialysis, or immunosuppressed-patient dosage (3-dose schedule), for intramuscular use
 - 90746: HBV vaccine, adult dosage, for intramuscular use
 - 90747: HBV vaccine, dialysis, or immunosuppressed-patient dosage (4-dose schedule), for intramuscular use
- ✓ Provide the office medical staff with information on where patients can get vaccinated if the clinic does not carry the vaccine, such as a list of local public health clinics, community health centers, and community pharmacies that provide HBV vaccination
- ✓ Point out to the office medical staff the coordinating section, **“How can I protect my family?”** on the *Patient Information Card*
- ✓ Review with the office medical staff the precautionary measures listed in the section that those patients with CHB need to take to prevent spreading the virus. Also review with the staff members the list of activities that patients can continue, including all social activities involving casual contact
- ✓ Explain to the office medical staff that they can reassure the patient that the treating physician will provide more information on precautionary measures and permitted activities

CLINICAL STAGES OF CHB

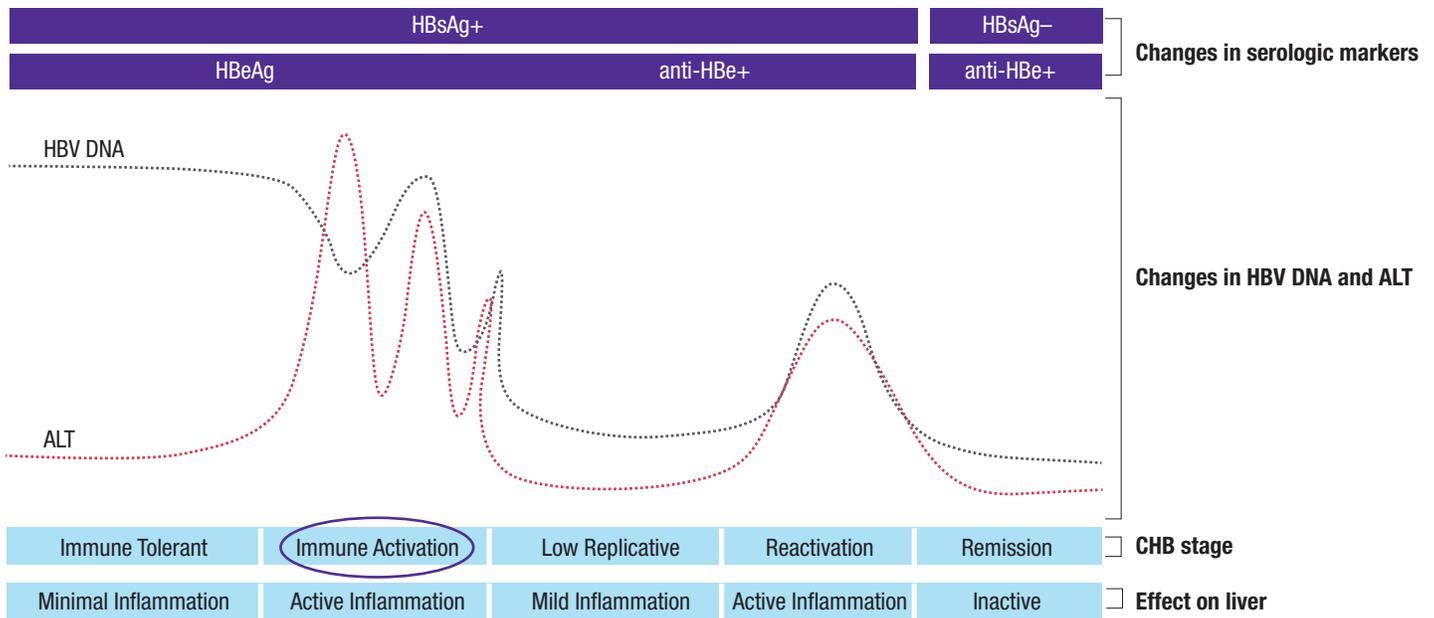
HBV infection can be categorized into several different clinical stages based on HBeAg status, ALT levels, and HBV DNA levels.³¹ Patients who are in certain stages require only monitoring and do not need antiviral therapy.²⁰ However, it is important to note that patients with CHB, including inactive carriers, are at risk for HCC.^{32,33} For more information on HCC screening and surveillance, please consult the *AASLD Practice Guideline on Management of Hepatocellular Carcinoma*, available at: <http://www.aasld.org/practiceguidelines/Documents/HCCUpdate2010.pdf>

The clinical stages of CHB are summarized in **Figure 6 on page 13**.³¹ Serologic markers, HBV DNA levels, and ALT levels fluctuate with each stage. Patients who fall into the immune-activation stage are those most likely to require treatment.³¹

Immune-tolerant stage. Patients in the immune-tolerant stage were infected perinatally and are HBsAg-positive and HBeAg-

positive, with normal ALT levels but high HBV DNA levels (see **Sidebar: Interpreting ALT Levels on page 13**).^{4,20} Later in life, patients can progress to HBeAg-positive CHB with elevated ALT levels. It is uncommon to find a patient in the immune-tolerant stage in developed countries where CHB usually evolves from acute infection acquired in adulthood through sexual transmission and injection drug use.^{2,20} The immune-tolerant phase can last for decades.⁴

Immune-activation stage. Patients in this stage are usually HBeAg-positive and have elevated HBV DNA levels, elevated ALT levels, and indications of liver inflammation.^{4,34} This is the stage in which patients are most likely to meet criteria for antiviral treatment.²⁰ Individuals who acquired HBV infection as adults through person-to-person transmission often enter into the immune-activation stage after experiencing no or only a short immune-tolerant stage.^{4,20} Many HBeAg-positive patients in the

Figure 6. Clinical stages of CHB.

ALT, alanine aminotransferase; anti-HBe, hepatitis B e antibody; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Source: Tong MJ, Pan CQ, Hann HW, et al. The management of chronic hepatitis B in Asian Americans. *Dig Dis Sci.* 2011;56:3143-3162.

INTERPRETING ALT LEVELS

The upper limit of normal (ULN) values for ALT currently used as upper reference limits by laboratories are typically set at 40 U/L for men and 30 U/L for women.³⁶ However, an Italian study found that ULN values for ALT levels that are now considered healthy are lower (<30 U/L for men and <19 U/L for women) than the values currently used as upper reference limits by laboratories.³⁶ Similar findings were reported in a Korean study among healthy potential liver donors with normal liver histology.³⁷ In the Korean study, serum ALT ULNs were found to be lower for healthy subjects than previously accepted ULNs (45 IU/L for men and 34 IU/L for women).³⁷ When clinicians evaluate ALT levels, they should take into consideration these lower limits.²³ In addition, clinicians must take into account other factors that influence ALT levels, including medical history, age, cholesterol levels, and body mass index.^{36,37}

immune-active phase will eventually clear HBeAg, develop anti-HBe, and enter into the inactive-carrier stage.⁴

Inactive-carrier (low-replicative) stage. Patients can move from the immune-activation stage to a period of low HBV DNA replication, sometimes called the *low-replicative stage*.³¹ Some

patients will then become inactive carriers and exhibit persistent HBV infection of the liver in the absence of significant necro-inflammatory disease.^{20,31} Inactive carriers typically eventually become HBeAg-negative and develop anti-HBe.²⁰ Carriers usually have a favorable prognosis; however, reversion to active liver disease remains a possibility.³⁵ In addition, inactive carriers are also at continued risk for HCC.³²

Reactivation stage. Patients can also experience reactivation.^{20,31} Patients in this stage have HBeAg-negative CHB. Their HBV DNA and ALT levels are elevated, and there is recurrent liver inflammation. Reversion to HBeAg-positive serostatus is possible in patients experiencing reactivation.²⁰

Remission or resolved-hepatitis-B stage. Patients in this stage have an established history of acute HBV infection or CHB, are negative for HBsAg, are positive for anti-HBc, and may be positive or negative for anti-HBs.^{20,31} They have undetectable HBV DNA levels and normal ALT levels.

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