Hepatitis B virus: Screening and diagnosis in adults

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INTRODUCTION

It is estimated that approximately two billion people worldwide have evidence of past or present infection with HBV, and 257 million individuals are chronic carriers (ie, positive for hepatitis B surface antigen [HBsAg]) [1]. In the United States, an estimated 880,000 persons are living with chronic HBV [2], although studies that account for immigrants from endemic countries estimate this figure to be up to 2.2 million [3,4].

The identification of hepatitis B virus (HBV) infection was revolutionized by the discovery of Australia antigen, now called hepatitis B surface antigen (HBsAg). During the ensuing two decades, serologic assays were established for HBsAg and other HBV antigens and antibodies. Advances in molecular biology techniques led to the development of hybridization and polymerase chain reaction (PCR) assays for direct determination of hepatitis B virus DNA (HBV DNA). The diagnosis of HBV infection can also be made by the detection of HBsAg or hepatitis B core antigen (HBcAg) in liver tissues by immunohistochemical staining and of HBV DNA by Southern hybridization, in-situ hybridization, or PCR.

This topic will focus on the approach to testing and screening for HBV infection in adults and will review the changes in hepatitis B antigens, antibodies, and DNA levels that occur during acute and chronic infection and how these tests can be used clinically. Topic reviews that discuss HBV diagnosis and screening in children, and the epidemiology, clinical manifestations, natural history, and treatment of HBV infection are presented separately. (See "Clinical manifestations and diagnosis of hepatitis B virus infection in children and adolescents" and "Hepatitis B virus

immunization in infants, children, and adolescents" and "Epidemiology, transmission, and prevention of hepatitis B virus infection" and "Hepatitis B virus: Clinical manifestations and natural history" and "Hepatitis B virus: Overview of management".)

APPROACH TO SCREENING AND TESTING

Adults without history or evidence of liver disease — Many patients with chronic HBV infection have no history or evidence of liver disease. Although there are no studies that have specifically evaluated the effects of screening versus not screening on clinical outcomes, screening can lead to vaccination and counseling of high-risk uninfected individuals, as well as linkage to appropriate medical care and treatment for those who have chronic infection or are at risk for reactivation of resolved infection [5,6]. In patients who are eligible for treatment, antiviral therapy can lead to reductions in cirrhosis, hepatic decompensation, mortality, and hepatocellular carcinoma. (See "Hepatitis B virus immunization in adults" and "Hepatitis B virus: Overview of management" and "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Screening persons for HBV is supported by the American Association for the Study of Liver Diseases, the American College of Physicians, the United States Centers for Disease Control and Prevention, the World Health Organization, and the United States Preventative Task Force [5,7-14].

Individuals without known risk for HBV infection — We suggest screening for HBV in the following groups of patients, even if there is no known risk for HBV infection:

- **Persons ≥18 years of age** – All persons ≥18 years of age should be screened for HBV infection at least once in their lifetime, unless there is documentation that an HBV vaccine series has been completed **and** there is serologic evidence of immunity (anti-HBs ≥10 milli international units/mL).

- **Pregnant persons** – Pregnant persons should be screened during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing. This is discussed in detail in a separate topic review. (See "Hepatitis B and pregnancy", section on 'Maternal screening'.)

Universal screening was adopted by the United States Centers for Disease Control (CDC) in 2023 given the low vaccination rates among adults, the harms of missed infection, and the prevalence of HBV infection in adults [14]. In a systematic review of 17 studies conducted by the

CDC, the median prevalence of chronic HBV infection in the United States general population was 0.4 percent.

For individuals without risk factors for HBV, our approach to screening is similar to the CDC. However, for those with documentation of vaccination, the CDC suggests screening unless the person was screened for HBV prior to vaccination, whereas we determine the need for screening based on immunity after vaccination. In other countries screening practices may differ depending upon the prevalence of HBV infection. (See 'Society guideline links' below.)

For most patients who remain without risk factors for acquiring HBV, repeat screening is not warranted. However, screening prior to blood, plasma, organ, tissue, or semen donation is routinely performed, regardless of the person's prior history. In addition, screening is warranted prior to initiating immunosuppressive therapy (eg, corticosteroids, biologics, cancer chemotherapy, anti-rejection therapies) or direct acting antiviral therapy for hepatitis C, since patients with HBV infection are at risk for HBV reactivation. Screening in these populations is discussed separately. (See "Blood donor screening: Laboratory testing", section on 'Infectious disease screening and surveillance' and "Prevention of infections in hematopoietic cell transplant recipients", section on 'Donor selection' and "Kidney transplantation in adults: Hepatitis B virus infection in kidney transplant recipients", section on 'Donors' and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Evaluation for conditions that might affect therapy'.)

Individuals with risk factors for HBV infection — We recommend screening individuals for HBV infection if they endorse risk factors for HBV infection (table 1). In these populations, the median prevalence of chronic HBV infection ranges from approximately 1 to 12 percent, depending upon the population [14]. Screening is warranted even in those with documentation of prior vaccination, unless they were screened prior to vaccination **and** there was evidence of immunity after vaccination (anti-HBs ≥10 milli international units/mL).

Individuals at increased risk for HBV include:

- Persons born in countries with HBV prevalence ≥2 percent (table 2) (see "Epidemiology, transmission, and prevention of hepatitis B virus infection")
- Persons born in the United States but whose parents were born in regions with HBV prevalence ≥8 percent (table 2)
- Persons with HIV or hepatitis C virus infection (see "Primary care of adults with HIV" and "Screening and diagnosis of chronic hepatitis C virus infection")

- Persons who have ever injected drugs (see "Opioid use disorder: Epidemiology, clinical features, health consequences, screening, and assessment", section on 'Assessment')
- Men who have sex with men (see "Primary care of gay men and men who have sex with men")
- Individuals with multiple sexual partners and/or a history of sexually transmitted diseases (see "Screening for sexually transmitted infections")
- Patients with end-stage kidney disease (including those undergoing dialysis) (see "Hepatitis B virus and dialysis patients")
- Household and sexual contacts of HBV-infected persons (see "Epidemiology, transmission, and prevention of hepatitis B virus infection")
- Persons currently or previously incarcerated in a jail, prison, or detention setting. (see "Clinical care of incarcerated adults")

Screening should be repeated in unvaccinated patients without evidence of prior hepatitis B who continue to engage in behaviors that put them at increased risk for HBV infection. There are no data to support when screening should be repeated; we typically rescreen patients every one to two years or sooner if they have had a known exposure. However, we prefer to vaccinate these patients to prevent infection.

What to test — When screening persons for HBV, we test for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and total hepatitis B core antibody (anti-HBc) [11,14]. Special considerations for testing in pregnant persons are discussed elsewhere. (See "Hepatitis B virus immunization in infants, children, and adolescents", section on 'Postvaccination serology' and "Hepatitis B and pregnancy", section on 'Maternal screening'.)

Previously, testing for anti-HBc was only indicated for certain groups. However, guidelines now recommend anti-HBc testing for all persons to differentiate immunity from HBV vaccination versus recovery from past HBV infection (table 3B) and to identify those with occult infection. (See 'Serologic markers' below and 'Occult HBV infection' below.)

Based on the results of this testing patients may have:

- No evidence of prior infection or immunity (negative for all three serologic markers).
- Evidence of immunity due to prior infection (anti-HBs positive, anti-HBc total positive, HBsAg negative). (See 'Prior HBV infection' below.)

- Evidence of immunity due to immunization (anti-HBs positive, anti-HBc total negative, HBsAg negative).

- Chronic HBV infection (HBsAg positive and anti-HBc total positive). (See 'Chronic HBV infection' below.)

Some patients who endorse prior vaccination may have a detectable but low anti-HBs (<10 milli international units/mL) or undetectable anti-HBs. This is most likely due to waning antibody response. Although most immunocompetent persons have immune memory if they had mounted an immune response after completing the vaccine series, a booster or repeat vaccine series is typically suggested. (See "Hepatitis B virus immunization in adults", section on 'When a booster dose should be administered'.)

Adults with evidence of liver disease — Patients with clinical signs or symptoms consistent with acute or chronic liver disease (eg, elevated alanine aminotransferase or aspartate aminotransferase) should be tested for HBV regardless of their vaccination history. Testing includes HBsAg, anti-HBc total and anti-HBs, and anti-HBc IgM in patients with acute liver disease. (See 'Diagnostic algorithms' below.)

TYPES OF TESTS

Serologic markers — Infection with HBV is associated with characteristic changes in the serum levels of hepatitis B antigens and antibodies (table 3A-B and figure 1). These markers are used to define different clinical states (table 4).

Hepatitis B surface antigen and antibody — Hepatitis B surface antigen (HBsAg) is the serologic hallmark of HBV infection. It can be detected using an enzyme immunoassay (EIA).

HBsAg appears in serum 1 to 10 weeks after an acute exposure to HBV, prior to the onset of clinical symptoms characteristic for acute hepatitis or elevation of serum alanine aminotransferase (ALT) (figure 1). In patients who subsequently recover, HBsAg usually becomes undetectable after four to six months. Persistence of HBsAg for more than six months implies chronic infection. It is estimated that less than 5 percent of immunocompetent adult patients with genuine acute hepatitis B progress to chronic infection [15]. Among patients with chronic HBV infection, the rate of clearance of HBsAg is approximately 0.5 percent per year [16].

The disappearance of HBsAg is followed by the appearance of hepatitis B surface antibody (anti-HBs). In most patients, anti-HBs persists for life, thereby conferring long-term immunity from

reinfection. However, over time, anti-HBs may disappear in some patients, and they may have only isolated hepatitis B core antigen (anti-HBc) IgG. (See 'Isolated anti-HBc' below.)

In some patients, anti-HBs may not be detectable until after a window period of several weeks to months, during which **neither** HBsAg nor anti-HBs can be detected (figure 2). At this time, the serologic diagnosis may be made by the detection of IgM antibodies against hepatitis B core antigen (IgM anti-HBc) (see below).

HBV can be classified into at least eight genotypes and four major serotypes. All HBV serotypes share one common antigenic determinant: "a." These serotypes have epidemiologic significance. Antibodies to the "a" determinant confer protection to all HBV serotypes [17].

Coexistence of HBsAg and anti-HBs has been reported. In early studies, rates ranging from 5 to 30 percent of HBsAg-positive individuals were reported [18]; however, subsequent studies have described lower rates, varying from 1 to 10 percent [19]. In most instances, the antibodies are unable to neutralize the circulating virions. These individuals should therefore be regarded as carriers of the hepatitis B virus.

Hepatitis B core antigen and antibody — Hepatitis B core antigen (HBcAg) is an intracellular antigen that is expressed in infected hepatocytes. It is **not** detectable in serum with available commercial assays. Anti-HBc can be detected throughout the course of HBV infection.

During acute infection, anti-HBc is predominantly of IgM class (figure 1). IgM anti-HBc is the sole marker of HBV infection during the window period between the disappearance of HBsAg and the appearance of anti-HBs (figure 2). The detection of IgM anti-HBc is usually regarded as an indication of acute HBV infection.

However, IgM anti-HBc may remain detectable up to two years after the acute infection. Furthermore, the titer of IgM anti-HBc may increase to detectable levels during exacerbations of chronic hepatitis B [20]. This can present a diagnostic problem: incorrectly suggesting acute hepatitis B, particularly in endemic areas in which many HBsAg-positive patients presenting with acute hepatitis actually have exacerbations of chronic hepatitis B [15,21]. Other common causes of acute exacerbation of chronic hepatitis B are superinfection with hepatitis D virus (delta virus) or hepatitis C virus [15,21]. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection".)

IgG anti-HBc persists along with anti-HBs in patients who recover from acute hepatitis B (table 3A-B and figure 1). It also persists in association with HBsAg in those who progress to chronic HBV infection. Tests for IgG anti-HBc are not commercially available, so total anti-HBc is measured when screening or testing for chronic HBV.

Some investigators have noted a correlation between the titer of IgM anti-HBc and serum alanine aminotransferase, serum HBV DNA levels and histologic inflammation in patients with chronic hepatitis B. However, the studies correlating IgM anti-HBc titer with HBV replication or activity of liver disease were performed using quantitative IgM anti-HBc assays that have lower cutoffs than the qualitative assays available in the United States. The latter assays were designed for diagnosis of acute HBV infection and have higher cutoffs.

Isolated anti-HBc — The isolated presence of antibody to hepatitis B core antigen (anti-HBc) in the absence of HBsAg and anti-HBs has been reported in 0.4 to 1.7 percent of blood donors in low prevalence areas and in 10 to 20 percent of the population in endemic countries [22]. Isolated detection of anti-HBc can occur in several settings:

- During the window period of acute hepatitis B when the anti-HBc is predominantly IgM class. (See 'Acute hepatitis' below.)
- When anti-HBs has fallen to undetectable levels many years after recovery from acute hepatitis B. (See 'Hepatitis B surface antigen and antibody' above.)
- When the HBsAg titer has fallen below the cutoff level for detection in those with chronic hepatitis B (approximately 0.5 percent per year [16]). (See 'Hepatitis B surface antigen and antibody' above and 'Occult HBV infection' below.)
- In the setting of HBsAg mutations where testing leads to false-negative HBsAg results. This occurs when monoclonal instead of polyclonal hepatitis B surface antibodies are used in enzyme immunoassays for capture and/or detection of HBsAg [23,24]. (See "Hepatitis B virus immunization in adults", section on 'Vaccine-induced HBV S escape mutants'.)
- In some cases, isolated anti-HBc may be due to a false-positive test result. This is most likely seen in patients who are at low risk for disease. In the late 1980s, it was suggested that as many as 50 to 80 percent of persons with isolated anti-HBc had false-positive test results, based upon studies that demonstrated the development of a primary anti-HBs response to hepatitis B vaccination of asymptomatic individuals with isolated anti-HBc [22,25]. However, improvements of enzyme immunoassays in the past decade have decreased the rate of false-positive results.

To help determine the etiology of an isolated anti-HBc, the evaluation should include repeat testing for anti-HBc, HBsAg, anti-HBs, and hepatitis B e antibody (anti-HBe). Additional testing is warranted in certain patients:

- Patients who remain positive for isolated anti-HBc IgG, have evidence of a recent HBV exposure, have symptoms of acute hepatitis, and/or have markedly elevated ALT levels should be tested for the presence of anti-HBc IgM to rule out recent HBV infection. (See "Hepatitis B virus: Clinical manifestations and natural history", section on 'Acute hepatitis'.)

- Individuals with evidence of chronic liver disease, those who need immunosuppressive therapy, and persons with HIV should be tested for HBV DNA to exclude low-level chronic HBV infection. HBV DNA has been detected in the serum of individuals with isolated anti-HBc when tested by polymerase chain reaction (PCR) assays; however, the frequency of detection varies from 0 to 20 percent, with most studies showing <5 percent detection [26-28]. (See 'Occult HBV infection' below.)

The clinical significance of isolated anti-HBc can vary depending upon the cause. As an example, occult HBV infection (ie, isolated anti-HBc with a detectable HBV DNA in the liver and occasionally in the serum) has been associated with chronic liver disease and hepatocellular carcinoma. In addition, reactivation of HBV replication with reverse seroconversion (ie, reappearance of HBsAg) can occur in patients with isolated anti-HBc in the setting of intense immunosuppression, regardless of baseline HBV DNA detection. Prophylactic antiviral therapy may reduce the risk of reactivation in such patients. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Transmission of HBV infection has also been reported from blood and organ donors with isolated anti-HBc. Although the incidence ranges widely (from 0.4 to 78 percent) [26,29-31], the risk is highest when a liver from anti-HBc-positive donors is transplanted. This may be due in part to the high percentage of patients with isolated anti-HBc (>70 percent) who have HBV DNA detected in the liver. Transmission can occur even when the serum HBV DNA is negative. As an example, de novo HBV infection developed in 9 out of 64 (14 percent) liver transplant recipients who were anti-HBc negative and received a liver from a donor who was anti-HBc positive, but HBsAg and HBV DNA negative [31]. A discussion of how to prevent HBV infection in this setting is found elsewhere. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients".)

Hepatitis B e antigen and antibody — Hepatitis B e antigen (HBeAg) is a secretory protein that is processed from the precore protein. It is an early antigen and not an envelope antigen. It is generally considered to be a marker of HBV replication and infectivity. The presence of HBeAg is usually associated with high levels of HBV DNA in serum and higher rates of transmission of HBV infection from carrier mothers to their babies [32-34] and from patients to health care workers [35].

HBeAg to anti-HBe seroconversion occurs early in patients with acute infection, prior to HBsAg to anti-HBs seroconversion (figure 1). However, HBeAg seroconversion may be delayed for years to decades in patients with chronic HBV infection. In such patients, the presence of HBeAg is usually associated with the detection of high levels of HBV DNA in serum and active liver disease. However, HBeAg-positive patients with perinatally acquired HBV infection may have normal serum ALT concentrations and minimal inflammation in the liver during the first two to three decades of life [36,37].

Seroconversion from HBeAg to anti-HBe is usually associated with a decrease in serum HBV DNA and remission of liver disease [38,39]. However, some patients continue to have active liver disease after HBeAg seroconversion [40-42]. Such individuals may have low levels of wild-type HBV or HBV variants with a stop codon in the precore or dual nucleotide substitutions in the core promoter region that prevent or decrease the production of HBeAg [43].

Serum HBV DNA assays — Qualitative and quantitative tests for HBV DNA in serum have been developed to assess HBV replication. The sensitivity limit of these assays depends upon the techniques used. The range of linearity also varies. Currently, most HBV DNA assays use real-time PCR techniques, report results in international units/mL, have lower limit of detection around 10 to 20 international units/mL and a range of linearity up to 8 log(10) international units/mL.

Recovery from acute hepatitis B is usually accompanied by the disappearance of HBV DNA in serum as determined by hybridization or branched DNA (bDNA) assays. However, HBV DNA may remain detectable in serum for many years if tested by PCR assays [44]. This observation suggests that the virus persists after "recovery" but is controlled by the immune system.

Similar findings have been noted in patients with chronic HBV infection. Spontaneous or treatment-induced HBeAg seroconversion is usually accompanied by the disappearance of HBV DNA from serum by hybridization methods, but PCR assays usually remain positive except in patients with HBsAg seroconversion [45]. A study of 49 patients who had spontaneous/interferon-induced HBeAg clearance found a wide range in HBV DNA levels at the time HBeAg first became undetectable, implying that there is no threshold HBV DNA level for HBeAg clearance/seroconversion [46]. By contrast, most patients who develop HBeAg seroconversion during nucleos(t)ide analog therapy have undetectable serum HBV DNA. In fact, many patients receiving nucleos(t)ide analog therapy remain HBeAg positive despite having undetectable serum HBV DNA for months or years. The explanation for this phenomenon is likely related to the lack of direct effect of nucleos(t)ide analogs on covalently closed circular HBV DNA (ccc DNA) and viral RNA transcription and viral protein expression.

HBV DNA levels are also detectable in patients with HBeAg-negative chronic hepatitis, although levels are generally lower than in patients with HBeAg-positive chronic hepatitis. A serum HBV DNA level of >2,000 international units/mL has been proposed as a cutoff level to differentiate patients with HBeAg-negative chronic hepatitis from those in an inactive carrier state (ie, HBeAg-negative, persistently normal ALT) [47,48]. Two studies confirmed that serum HBV DNA levels of patients in the inactive carrier state were persistently below 2000 international units/mL, but serum HBV DNA levels were highly variable among patients with HBeAg-negative hepatitis [46,48]. Because of the fluctuations in HBV DNA levels in the latter patients, there is no absolute cutoff level that is reliable for differentiating patients in the inactive carrier state from those with HBeAg-negative chronic hepatitis B [46]. Some studies suggest that quantitative HBsAg levels <1000 international units/mL help in differentiating inactive carriers from those with HBeAg-negative chronic hepatitis [49].

Clinical use — The major clinical role of serum HBV DNA assays in patients with chronic HBV infection is to assess HBV replication and candidacy for antiviral therapy. Indications for HBV treatment are based upon the presence of active liver disease and high HBV DNA levels (table 5). A cutoff of 20,000 international units/mL has been proposed for treatment initiation in HBeAg-positive patients, and a lower threshold of 2000 international units/mL for HBeAg-negative patients. (See "Hepatitis B virus: Overview of management".)

Several large cohort studies reported that persistently high HBV DNA (>4 log(10) copies/mL or ~2000 international units/mL in patients who have been infected for more than four decades) is independently associated with an increased risk of cirrhosis and hepatocellular carcinoma (HCC) [50,51]. Data from these studies suggest that in patients who have been infected for several decades, high serum HBV DNA (on repeat tests) alone may be a consideration for initiating antiviral therapy. (See "Hepatitis B virus: Overview of management", section on 'Indications for antiviral therapy'.)

Patients with high pretreatment serum HBV DNA levels are less likely to respond to interferon [52,53]. In contrast, pretreatment serum HBV DNA levels do not appear to predict response to nucleos(t)ide analog therapy. However, it may take longer for the HBV DNA to become undetectable in patients treated with nucleos(t)ide analog therapy if pretreatment levels are high. (See "Entecavir in the treatment of chronic hepatitis B virus infection" and "Tenofovir and adefovir for the treatment of chronic HBV infection".)

Suppression of serum HBV DNA is also used as one of the end-points in assessing response to antiviral treatment and to detect virologic breakthrough. With the availability of potent antiviral agents, suppression of HBV DNA to undetectable levels by PCR is the goal. Monitoring of serum HBV DNA using sensitive quantitative assays such as real-time PCR assays with a lower limit of

detection of <20 international units/mL will identify patients who have virologic breakthrough (>1 log increase in HBV DNA from nadir while on treatment) [54]. (See appropriate topic reviews.)

Rarely, tests for HBV DNA in serum help to identify HBV as the etiology of liver disease in HBsAg-negative patients [55]. This is especially important in patients with fulminant hepatitis B, who may have cleared HBsAg by the time they present [56]. (See "Clinical significance of hepatitis B virus genotypes" and "Clinical significance and molecular characteristics of common hepatitis B virus variants".)

DIAGNOSTIC ALGORITHMS

Tests for HBV markers are useful in confirming the diagnosis of HBV infection and in the selection and monitoring of patients for antiviral therapy.

Acute hepatitis — The diagnosis of acute hepatitis B is based upon the detection of hepatitis B surface antigen (HBsAg) and IgM hepatitis B core antibody (anti-HBc) (table 3A-B and figure 1). During the initial phase of infection, markers of HBV replication, hepatitis B e antigen (HBeAg) and HBV DNA, are also present. Recovery is accompanied by the disappearance of HBV DNA, HBeAg to hepatitis B e antibody (anti-HBe) seroconversion, and subsequently HBsAg to hepatitis B surface antibody (anti-HBs) seroconversion.

Rarely, patients present during the window period when HBsAg has become negative but anti-HBs is not yet positive. In this setting, which is more common in patients with fulminant hepatitis B in whom virus clearance tends to be more rapid, IgM anti-HBc is the sole marker of acute HBV infection (figure 2).

The differential diagnosis of HBsAg-positive acute hepatitis includes acute hepatitis B, exacerbations of chronic hepatitis B (eg, around the time of HBeAg seroconversion), reactivation of chronic hepatitis B, superinfection of a hepatitis B carrier with hepatitis A, C, D, or E virus [15,21,57], and acute hepatitis due to drugs and other toxins in a hepatitis B carrier.

Prior HBV infection — Previous HBV infection is characterized by the presence of anti-HBs and IgG anti-HBc (figure 1). This pattern differs from immunity to HBV infection after vaccination, which is indicated by the presence of anti-HBs only.

Chronic HBV infection — The diagnosis of chronic HBV infection is based upon the persistence of HBsAg for more than six months (table 3A-B and figure 1). Additional tests for HBV

replication, HBeAg and serum HBV DNA and ALT, should be performed to determine if the patient should be considered for antiviral therapy.

All patients with chronic HBV infection should be regularly monitored because HBV DNA and alanine transaminase (ALT) levels vary during the course of infection to monitor for progression of liver disease (table 6). In addition, patients who are not candidates for treatment at the time of presentation may become candidates for treatment during follow-up. (See "Hepatitis B virus: Overview of management".)

HBeAg-negative patients who have normal serum ALT and low (<2000 international units/mL) or undetectable HBV DNA are considered to be in an inactive carrier state. These patients generally have a good prognosis and antiviral treatment is not indicated. However, serial tests are necessary to accurately differentiate them from patients with HBeAg-negative chronic hepatitis who have fluctuating ALT and/or HBV DNA levels. Thus, it is recommended that these patients have repeat ALT +/- HBV DNA tests at three-month intervals during the first year [58]. Patients who are truly inactive carriers should continue to be monitored, but at less frequent intervals. HBeAg-negative patients with elevated serum ALT concentrations should be tested for serum HBV DNA to determine if the liver disease is related to persistent HBV (wild-type or HBeAg-negative variants with mutations in the precore or basal core promoter region that abolish or decrease HBeAg production) replication. Quantification of HBsAg levels can help to differentiate inactive carriers from patients with HBeAg-negative chronic hepatitis [59].

Additional tests for hepatitis C (HCV) and hepatitis D (HDV) should also be performed to rule out superinfection with other hepatitis virus(es). (See "Hepatitis B virus: Clinical manifestations and natural history" and "Screening and diagnosis of chronic hepatitis C virus infection" and "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection".)

Occult HBV infection — There exists a subset of patients with occult HBV infection, which is defined as the presence of detectable HBV DNA by polymerase chain reaction (PCR) in patients who are negative for HBsAg. Such patients have been further subclassified as having "seropositive" or "seronegative" occult HBV depending upon whether they are positive or negative for other HBV markers, most commonly anti-HBc [60-63]. Seronegative occult HBV is rarely seen in humans, although it has been described in woodchucks [64,65].

Most patients with occult HBV have very low or undetectable serum HBV DNA levels, accounting for the failure to detect HBsAg. Infections with HBV variants that decrease HBsAg production or have mutations in the S gene with altered S epitopes that evade detection in serology assays for HBsAg are uncommon.

However, HBV DNA is often detected in the liver, and transplantation of livers from these persons can result in de novo HBV infection [30,63]. In addition, patients with occult HBV infection, particularly those who are anti-HBc positive, are at risk of HBV reactivation if they receive potent immunosuppressive therapy such as anti-CD20 or myeloablative therapies for bone marrow or stem cell transplant. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Occult HBV infection has been associated with chronic liver disease and should be considered in the differential diagnosis of patients with apparent cryptogenic chronic liver disease, especially those with risk factors for HBV infection [63]. One study identified 56 of 591 (9 percent) patients seronegative for HBsAg with evidence of chronic liver disease who were HBV DNA positive by PCR in sera for at least two different regions in the HBV genome (surface and core) [66]. Patients were seen at a single institution in a region where HBV was endemic, and they had a negative evaluation for all other known causes of liver disease. The complete HBV genome from nine of these patients was compared with five controls who were positive for HBsAg. All but one patient with occult infection had a low HBV DNA titer. Compared with controls, those with occult infection had a variety of HBV variants leading to alterations in HBsAg expression. (See "Clinical significance of hepatitis B virus genotypes" and "Clinical significance and molecular characteristics of common hepatitis B virus variants".)

The presence of occult HBV infection may also be associated with an increased risk of hepatocellular carcinoma, particularly in patients with chronic HCV infection, as well as those who are from countries with a high prevalence of HBV infection [63]. However, the role of occult HBV in hepatocellular carcinoma remains controversial, as an association has not been uniformly found in all studies, most of which are cross-sectional in design and cannot prove etiological relationship. (See 'Approach to screening and testing' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diagnosis of hepatitis B".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading

level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hepatitis B (The Basics)")
- Beyond the Basics topic (see "Patient education: Hepatitis B (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Overview** – Approximately two billion people worldwide have evidence of past or present infection with hepatitis B virus (HBV), and 257 million individuals have chronic HBV infection. Many patients with chronic HBV infection have no history or evidence of liver disease.

  Hepatitis B surface antigen (HBsAg) is the serologic hallmark of HBV infection (acute and chronic). Hepatitis B e antigen (HBeAg) is a secretory protein that is processed from the precore protein. It is generally considered to be a marker of HBV replication and infectivity. Hepatitis B core antibody (anti-HBc) can be detected throughout the course of HBV infection and persists in those with chronic or past HBV infection. (See 'Serologic markers' above.)

- **Screening for HBV infection** – Among adults without a history or evidence of liver disease, screening is important to identify those with chronic HBV infection and those who would benefit from vaccination. In some settings (eg, prior to the use of immunosuppressive therapy) it is also useful to identify those who are at risk for reactivation of chronic or resolved infection.

  - **Whom to screen** – For most adults without risk factors for HBV, we suggest one time HBV screening for those ≥18 years of age (**Grade 2C**). One exception is persons who have documentation of completing a hepatitis B vaccine series and have evidence of

immunity (anti-HBs ≥10 milli international units/mL). (See 'Individuals without known risk for HBV infection' above.)

For adults at increased risk for acquiring HBV (table 1), we recommend HBV screening (**Grade 1B**). In these persons, the prevalence of chronic HBV infection ranges from approximately 1 to 12 percent, depending upon the population. Screening should be repeated periodically in unvaccinated patients without evidence of prior hepatitis B who continue to engage in behaviors that put them at increased risk for HBV infection, although we prefer to vaccinate these persons. (See 'Individuals with risk factors for HBV infection' above.)

Screening in selected settings (eg, pregnancy; prior to donating blood, plasma, organs, tissue, or semen; prior to receiving immunosuppressive therapy; and prior to receiving direct-acting antiviral therapy for treatment of HCV) is discussed in separate topic reviews. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy" and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'HBV coinfection' and "Hepatitis B and pregnancy", section on 'Maternal screening'.)

- **What tests to order** – When screening for HBV, individuals should be tested for HBsAg, hepatitis B surface antibody (anti-HBs), and total anti-HBc. (See 'What to test' above.)

- **Evaluating patients with evidence of liver disease** – Adults with signs and symptoms of acute or chronic liver disease (eg, elevated alanine aminotransferase or aspartate aminotransferase) should be tested for HBV infection. Testing should include HBsAg, total anti-HBc and anti-HBs, and IgM anti-HBc for those presenting with acute liver disease. (See 'Adults with evidence of liver disease' above and 'Diagnostic algorithms' above.)

- **Interpretation of serologic test results**:

  - **Acute HBV** – The diagnosis of acute HBV infection is based upon the detection of HBsAg and IgM anti-HBc (table 3A-B and figure 1). (See 'Acute hepatitis' above.)

  - **Prior HBV** – Previous HBV infection is characterized by the presence of anti-HBs and IgG anti-HBc (figure 1). This differs from immunity to HBV infection after vaccination, which is indicated by the presence of anti-HBs only. (See 'Prior HBV infection' above.)

  - **Chronic HBV** – The diagnosis of chronic HBV infection is based upon the persistence of HBsAg for more than six months (table 3A-B and figure 1). (See 'Chronic HBV infection' above.)

HBeAg and serum HBV DNA should be performed in those with chronic HBV infection to determine if the patient should be considered for antiviral therapy. (See 'Chronic HBV infection' above and 'Clinical use' above.)

- **Occult HBV infection** – Occult HBV infection is defined as the presence of detectable HBV DNA by polymerase chain reaction (PCR) in patients who are negative for HBsAg. Such patients have been further subclassified as having "seropositive" or "seronegative" occult HBV depending upon whether they are positive or negative for other HBV markers, most commonly anti-HBc. Most of these patients have very low or undetectable serum HBV DNA levels though HBV DNA is often detected in the liver. (See 'Occult HBV infection' above.)

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Topic 3680 Version 30.0

GRAPHICS

Groups at increased risk for hepatitis B virus

Individuals at risk for HBV due to vertical transmission (ie, mother to child transmission)
▪ Individuals born in regions with high (≥8%) or intermediate (≥2%) prevalence rates for HBV, including immigrants and adopted children* ▪ Infants born to pregnant persons who are HBsAg-positive¶ ▪ US-born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (≥8%)*
Individuals at risk due to horizontal transmission (ie, percutaneous or mucosal exposure to blood or body fluids contaminated with blood)Δ
▪ Household contacts of HBsAg-positive persons ▪ Needle sharing or sexual contacts of HBsAg-positive persons ▪ Individuals who have ever injected drugs ▪ Individuals with multiple sexual partners and/or history of sexually transmitted infections ▪ Men who have sex with men ▪ Inmates of correctional facilities or other detention settings ▪ Individuals with HIV infection◇ ▪ Individuals with current or past HCV infection§ ▪ Individuals with end-stage kidney disease on maintenance renal dialysis
Other individuals
▪ Individuals with elevated alanine aminotransferase or aspartate aminotransferase levels of unknown origin ▪ Individuals who request HBV testing

In the United States, screening for HBV includes[4]:

- **Risk-based screening** – For all individuals (including children and adolescents), screen those who have any of the risk factors listed in the table if they might have been susceptible during the period of increased risk¥. For those with ongoing risk factors (ie, for horizontal transmission) who remain susceptible, continue to test periodically.Δ
- **Universal screening** – For individuals ≥18 years of age, screen at least once in a lifetime. However, for those without risk factors for HBV, screening is generally not needed if there is documentation of completing a hepatitis B vaccine series and evidence of immunity (anti-HBs ≥10 milli-international units/mL) after vaccination.‡
- **Pregnancy screening** – Screen all pregnant people during each pregnancy, regardless of vaccination status of history of prior testing.

Refer to UpToDate content on screening and diagnosis of HBV, HBV immunization, and HBV and pregnancy for more detailed information on screening and vaccination.

HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; US: United States; HIV: human immunodeficiency virus; HCV: hepatitis C virus; anti-HBs: hepatitis B surface antibody; anti-HBc: hepatitis B core antibodies; HBIG: hepatitis B immune globulin.

* If HBsAg-positive persons are found in first-generation immigrants of a family, subsequent generations should be tested.

¶ To reduce the risk of perinatal transmission, infants born to HBsAg-positive mothers should receive HBIG and hepatitis B vaccine as soon as possible and within 12 hours of birth and then complete the hepatitis B series. Post-vaccination serology should be obtained at 9 to 12 months. Refer to the UpToDate topic that discusses HBV immunization in infants.

Δ In unvaccinated individuals with ongoing HBV risk through percutaneous or mucosal exposure, hepatitis B vaccine should be initiated at the time of screening; the need for subsequent doses will depend upon the results. Post-vaccination serology should be performed to ensure immunity. For at-risk persons who do not complete the vaccine series, repeat testing should be performed periodically (eg, every 1 to 2 years).

◇ The presence of HBV coinfection informs the choice of antiretroviral regimen. In addition, patients with HIV who are not immune should be vaccinated regardless of age or risk factors, since HBV infection has an accelerated course in coinfected patients.

§ Patients with chronic HBV are at risk for HBV reactivation with direct-acting antiviral therapy for hepatitis C. Refer to the UpToDate topic that provides an overview of the management of hepatitis C infection.

¥ Susceptible persons include those who have never been infected with HBV (ie, HBsAg-negative, total anti-HBc-negative, and anti-HBs-negative) and either did not complete a HepB vaccine series per the Advisory Committee on Immunization Practices recommendations or who are known to be vaccine nonresponders.

‡ For most patients who remain without risk factors for acquiring HBV, repeat screening is not warranted. However, screening prior to blood, plasma, organ, tissue, or semen donation is routinely performed, regardless of the person's prior history. In addition, screening is warranted prior to initiating immunosuppressive therapy (eg, corticosteroids, biologics, cancer chemotherapy, anti-rejection therapies) since persons with HBV are at risk for HBV reactivation. Refer to the UpToDate topic on HBV reactivation.

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Graphic 55052 Version 18.0

Epidemiology and modes of transmission of hepatitis B virus infection

	High	Intermediate	Low
Carrier rate	≥8%	2 to 7%	<2%
Geographic distribution	Parts of sub-Saharan Africa (eg, Western Africa, South Sudan)	Mediterranean basin; Eastern Europe; Central Asia; Southeast Asia; China; Japan; parts of Latin and South America (eg, Peru, Colombia); Middle East	United States; Canada; Western Europe; Mexico; Australia; New Zealand
Predominant age at infection	Perinatal and early childhood	Early childhood	Adult
Predominant mode of infection	Mother to child; percutaneous	Percutaneous; sexual	Percutaneous; sexual

For updated information on the prevalence of chronic hepatitis B virus infection, refer to the United States Centers for Disease Control and Prevention and the World Health Organization websites.

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Graphic 51820 Version 9.0

Interpretation of the hepatitis B serologic panel

Tests	Results	Interpretation
HBsAg	Negative	Susceptible
anti-HBc	Negative	
anti-HBs	Negative	
HBsAg	Negative	Prior infection (inactive)
anti-HBc	Positive	
anti-HBs	Positive	
HBsAg	Negative	Immune due to hepatitis B vaccination*
anti-HBc	Negative	
anti-HBs	Positive	
HBsAg	Positive	Acutely infected
anti-HBc	Positive	
IgM anti-HBc	Positive	
anti-HBs	Negative	
HBsAg	Positive	Chronically infected
anti-HBc	Positive	
IgM anti-HBc	Negative	
anti-HBs	Negative	
HBsAg	Negative	Four interpretations possible¶
anti-HBc	Positive	
anti-HBs	Negative	

HBsAg: hepatitis B surface antigen; anti-HBc: hepatitis B core antibody; anti-HBs: hepatitis B surface antibody; IgM: immunoglobulin M; HBV: hepatitis B virus.

* Antibody response (anti-HBs) can be measured quantitatively or qualitatively. A protective antibody response is reported quantitatively as 10 or more milli-international units (≥10 mIU/mL) or qualitatively as positive. Postvaccination testing should be completed one to two months after the third vaccine dose for results to be meaningful.

¶ Four interpretations:

1. Might be recovering from acute HBV infection.
2. Might have had prior infection and test not sensitive enough to detect very low level of anti-HBs in serum.
3. Might be susceptible with a false positive anti-HBc.

4. Might be undetectable level of HBsAg present in the serum, and the person is actually chronically infected.

Centers for Disease Control and Prevention, Hepatitis B information for health professionals: Interpretation of hepatitis B serologic test results. Available from the CDC website.

Graphic 60827 Version 7.0

Diagnostic tests to determine phase of acute or chronic hepatitis B virus infection[1]

HBsAg	HBeAg	IgM anti-HBc	Total anti-HBc*	Anti-HBs	Anti-HBe	HBV DNA	ALT¶	Interpretati
Acute HBV infection								
+	+	+	±			+++	Elevated	Early phase
		+	±			+	Elevated	Window phase
			+	+	+	±	Normal	Recovery phas
Chronic HBV infection (HBsAg-positive for >6 months)								
+	+		+	-	-	+++ (Serum HBV typically >1 million international units/mL)	Normal or mildly elevated	Immune-tolera phase[Δ]
+	+		+	-	-	+++ (Serum HBV >20,000 international units/mL)	Persistently elevated	Immune-active HBeAg-positive
+	-		+	-	+	++ (Serum HBV >2000 international units/mL)	Elevated	Immune-active HBeAg-negativ
+	-		+		+	- to ++ (Serum HBV ≤2000 international units/mL)	Normal or mildly elevated	Inactive chroni HBV[§]
-	-		± (generally +)	±	±	+ in liver; - to + in serum	Normal	Occult HBV

ALT: alanine aminotransferase; anti-HBc: antibody to hepatitis B core antigen; anti-HBe: antibody to hepatitis B e antigen; anti-HBs: antibody to hepatitis B surface antigen; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

* This test is typically ordered as total anti-HBc, which includes IgM and IgG.

¶ The upper limits of normal for ALT in healthy adults are reported to be 29 to 33 units/L for males and 19 to 25 units/L for females. For healthy children after infancy, the upper limits of normal are 25 to 38 units/L and 22 to 31 units/L for boys and girls, respectively.

Δ For patients with immune-tolerant chronic hepatitis B, liver biopsy or noninvasive tests show no fibrosis and minimal inflammation. This is the initial phase seen in patients with perinatally acquired HBV infection.

◇ For patients with immune active chronic hepatitis B, liver biopsy or noninvasive tests show chronic hepatitis with moderate or severe necroinflammation with or without fibrosis. For patients who are HBeAg positive, immune-active chronic hepatitis B (also known as the clearance phase) can last for 10 to 20 years, and may be associated with the loss of HBeAg. For patients who are HBeAg negative, immune-active chronic hepatitis B is associated with immune reactivation and is also referred to as HBeAg-negative chronic hepatitis B or HBeAg-negative replicative phase.

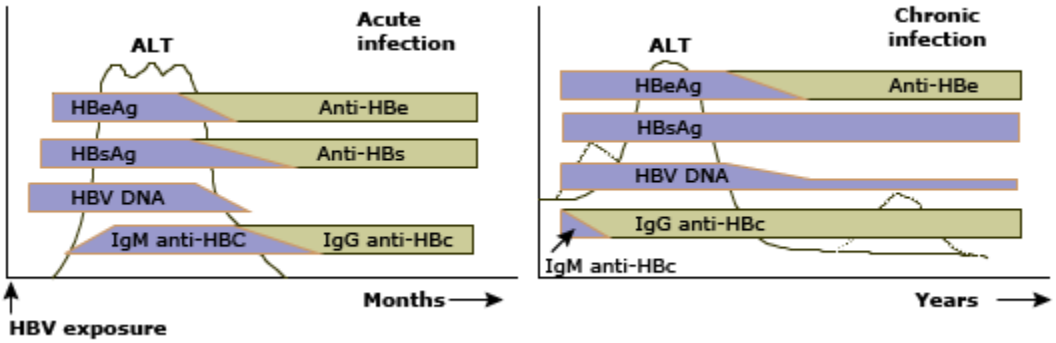
§ Patients with inactive chronic hepatitis B are HBeAg negative. In such patients, liver biopsy confirms the absence of significant necroinflammation, but biopsy or noninvasive testing show variable levels of fibrosis. This stage has also been referred to as the nonreplicative or carrier phase.

References:

1. *Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.*

Graphic 60627 Version 8.0

Serologic responses to hepatitis B virus infection



Schematic representation of the serologic responses to acute and chronic HBV infection in relation to the serum ALT concentration.

(Left panel) Acute infection is characterized initially by the presence of HBeAg, HBsAg, and HBV DNA beginning in the preclinical phase. IgM anti-HBc appears early in the clinical phase; the combination of this antibody and HBsAg makes the diagnosis of acute infection. Recovery is accompanied by normalization of the serum ALT, disappearance of HBV DNA, HBeAg to anti-HBe seroconversion, and subsequently HBsAg to anti-HBs seroconversion and switch from IgM to IgG anti-HBc. Thus, previous HBV infection is characterized by anti-HBs and IgG anti-HBc.

(Right panel) Chronic infection is characterized by persistence of HBeAg (for a variable period), HBsAg, and HBV DNA in the circulation; anti-HBs is not seen (in approximately 20% of patients, a non-neutralizing form of anti-HBs can be detected). Persistence of HBsAg for more than 6 months after acute infection is considered indicative of chronic infection.

HBV: hepatitis B virus; ALT: alanine aminotransferase; HBeAg: hepatitis B e-antigen; anti-HBe: antibody to hepatitis B e-antigen; HBsAg: hepatitis B surface antigen; anti-HBs: antibody to hepatitis B surface antigen; IgM: immunoglobulin M; anti-HBc: antibody to hepatitis B core antigen; IgG: immunoglobulin G.

Graphic 69344 Version 5.0

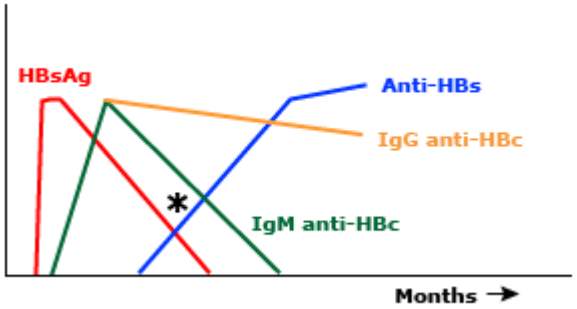
Glossary of clinical terms used in HBV infection

Definitions
Chronic hepatitis B
Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. Chronic hepatitis B can be subdivided into HBeAg-positive and HBeAg-negative chronic hepatitis B.
Inactive HBsAg carrier state
Persistent HBV infection of the liver without significant, ongoing necroinflammatory disease.
Resolved hepatitis B
Previous HBV infection without further virological, biochemical, or histological evidence of active virus infection or disease.
Acute exacerbation or flare of hepatitis B
Intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal and more than twice the baseline value.
Reactivation of hepatitis B
Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B.
HBeAg clearance
Loss of HBeAg in a person who was previously HBeAg positive.
HBeAg seroconversion
Loss of HBeAg and detection of anti-HBe.

HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; anti-HBe: hepatitis B e antibody.

Graphic 81182 Version 2.0

Window period of acute HBV infection



Schematic representation of the serologic findings during the window period of acute hepatitis B virus infection. The disappearance of HBsAg (hepatitis B surface antigen) is followed by the appearance of anti-HBs. In some patients, however, anti-HBs may not be detectable until after a window period of several weeks to months. At this time, neither HBsAg nor anti-HBs can be detected, the serologic diagnosis may be made by the detection of IgM antibodies against hepatitis B core antigen (IgM anti-HBc).

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* Window period.

Graphic 65368 Version 5.0

Recommendations for initial treatment of chronic hepatitis B in nonpregnant adults

HBeAg	HBV DNA (PCR)	ALT	Treatment strategy
Patients without cirrhosis*			
+	>20,000 international units/mL	≤2 x ULN[¶]	Treatment is not recommended, because current treatment has low efficacy in inducing HBeAg seroconversion. Treatment may be considered in older patients (>40 years) and in those with family history of HCC.
			Patients should be monitored[Δ] and treatment considered if ALT becomes elevated >2 x ULN, liver biopsy shows moderate/severe inflammation or fibrosis[◇] (eg, METAVIR score ≥F2), and/or noninvasive testing suggests moderate/severe fibrosis.
+	>20,000 international units/mL	>2 x ULN[¶]	Observe for 3 to 6 months if compensated and treat if no spontaneous HBeAg loss.
			Immediate treatment if severe hepatitis flare (eg, icteric or clinical decompensation).
			ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.[§ ¥]
			End-point of treatment – Seroconversion from HBeAg to anti-HBe.[‡]
			Duration of therapy:
			▪ PegIFN alfa: 48 weeks.
			▪ ETV, TAF, or TDF: Continue for at least 12 months after HBeAg seroconversion.
–	>2000 international units/mL	>2 x ULN[¶] OR 1 to 2 x ULN[¶] if liver biopsy shows moderate/severe necroinflammation or significant fibrosis[◇] (eg, METAVIR score	ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.[§ ¥]
			End-point of treatment – HBsAg loss.
			Duration of therapy:
			▪ PegIFN alfa: One year.

		≥F2) or non-invasive testing shows significant fibrosis	
			▪ ETV, TAF, or TDF: Several years or indefinite.[†]
–	≤2000 international units/mL	≤ULN[¶]	Monitor and treat if HBV DNA and ALT increase as described above.
Patients with cirrhosis*			
+/–	Detectable	Any ALT	Compensated:
			▪ HBV DNA >2000 international units/mL – Treat with ETV, TAF, or TDF.[§ ¥] Treatment should be continued indefinitely.**
			▪ HBV DNA <2000 international units/mL – Consider treatment particularly if ALT elevated; close monitoring if treatment is not initiated.
			Decompensated:
			▪ Treat immediately, regardless of ALT or HBV DNA levels. ETV preferred.[§ ¥] TDF may be used with close monitoring of renal function. Refer for liver transplant.
+/–	Undetectable	Any ALT	Compensated: Observe, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis if HBV DNA remains undetectable.
			Decompensated: Refer for liver transplant, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis.

ALT: alanine aminotransferase; anti-HBe: antibody to hepatitis B e antigen; ETV: entecavir; HBeAg: Hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; PegIFN alfa: pegylated interferon alfa; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; ULN: upper limit of normal.

* Based upon findings on noninvasive testing or liver biopsy performed during the initial evaluation. Patients with advanced fibrosis determined by noninvasive methods should be evaluated using a second method, and if results are concordant, consider managing the same way as patients with cirrhosis.

¶ The American Association for the Study of Liver Diseases (AASLD) recommends using an ALT >35 U/L for men and >25 U/L for women as the upper limit of normal (ULN) rather than local laboratory values.

Δ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of monitoring.

◇ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of indications for biopsy.

§ Adefovir, lamivudine, and telbivudine are not recommended due to a high rate of resistance after the first year and/or weak antiviral activity.

¥ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of which agent to use.

‡ Up to 50% of patients who achieve HBeAg seroconversion can experience a virologic relapse after discontinuing treatment with oral agents. Thus, some providers prefer to treat until HBsAg-loss.

† For most patients, antiviral therapy should be continued indefinitely. However, treatment discontinuation may be considered in persons without cirrhosis who have demonstrated loss of HBsAg and in selected patients who have had undetectable serum HBV DNA for >3 years and agree to close monitoring after stopping treatment. Persons who stop antiviral therapy should be monitored every month for the first six months. Refer to the UpToDate topic on management of hepatitis B virus infection for a detailed discussion of the risks and benefits of stopping antiviral therapy in this setting.

** This includes HBeAg-positive adults with cirrhosis who seroconvert to anti-HBe on therapy.

References:

1. *Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.*

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Evaluation of patients with chronic HBV infection

Initial evaluation
1. History and physical examination*
2. Family history of HBV infection, liver disease, HCC
3. Laboratory tests to assess liver disease – complete blood counts with platelets, aminotransferase levels, total bilirubin, alkaline phosphatase, albumin, and INR
4. Tests for HBV replication – HBeAg, anti-HBe, HBV DNA
5. Tests to rule out viral coinfections – anti-HCV, anti-HDV (in persons from countries where HDV infection is common and in those with history of injection drug use), and anti-HIV[¶]
6. Tests to screen for HCC[Δ] – (eg, ultrasound)
7. Tests to screen for fibrosis[◇] – vibration-controlled transient elastography, serum fibrosis panel, or liver biopsy[§]
Suggested follow-up for patients not considered for treatment: HBeAg+, HBV DNA >20,000 international units/mL, and normal ALT without cirrhosis[¥]
ALT every 3 to 6 months and HBeAg every 6 to 12 months.
If ALT levels increase between 1 to 2 × ULN:[‡] ▪ Recheck ALT every 1 to 3 months and HBeAg every 6 months. ▪ Consider liver biopsy or noninvasive assessment of fibrosis if ALT levels remain persistently elevated, age >40 years, and/or family history of HCC. Recommend treatment if biopsy shows moderate/severe inflammation or significant fibrosis (eg, METAVIR score ≥F2).
If ALT increases to >2 × ULN[‡] for 3 to 6 months and HBeAg+, HBV DNA >20,000 international units/mL, recommend treatment.
Screen for HCC in relevant population.[Δ]
Suggested follow-up for patients not considered for treatment: HBeAg-, HBV DNA <2000 international units/mL, and normal ALT without cirrhosis[¥]
ALT and HBV DNA every 3 months for 1 year, if persistently normal, ALT and HBV DNA every 6 to 12 months.[†]
If ALT increases between 1 to 2 × ULN:[‡] ▪ Check serum HBV DNA level and exclude other causes of liver disease. ▪ Monitor ALT and HBV DNA every 3 months. ▪ Consider liver biopsy or noninvasive assessment of fibrosis if ALT remains elevated on serial tests or if HBV DNA persistently ≥2000 international units/mL. Recommend treatment for patients with moderate/severe inflammation or significant fibrosis.

If ALT increases to >2 × ULN, recommend treatment if HBV DNA >2000 international units/mL.
If HBV DNA increases to >2000 international units/mL, recommend treatment if ALT > 2 × ULN. If ALT <2 × ULN, assess liver fibrosis by biopsy or noninvasive tests. Recommend treatment if moderate/severe inflammation or significant fibrosis is present.[§]
Screen for HCC in relevant population.

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; INR: international normalized ratio; HBeAg: hepatitis B e antigen; anti-HBe: antibody to HBeAg; HCV: hepatitis C virus; HDV: hepatitis delta virus; ALT: alanine aminotransferase; ULN: upper limit of normal.

* Patient should be evaluated for signs and symptoms of cirrhosis, risk factors for coinfections, alcohol use, and information on vaccination status.

¶ In patients who have not undergone one-time screening and those with ongoing risk factors for HIV-infection.

Δ Refer to the topic that discusses screening of hepatocellular carcinoma.

◇ Refer to the topics in UpToDate that discuss noninvasive assessment of hepatic fibrosis.

§ Liver biopsy can also assess severity of inflammation and help rule out other causes of liver disease, information that will not be provided by noninvasive assessment of liver fibrosis. Refer to the UpToDate topic on management of hepatitis B virus for additional information on the role of liver biopsy.

¥ Cirrhosis is based upon findings from the initial evaluation. Patients with advanced fibrosis determined by noninvasive methods should be evaluated using a second method, and if results are concordant, consider managing the same way as patients with cirrhosis.

‡ The AASLD recommends using an ALT >35 U/L for men and >25 U/L for women as the upper limit of normal rather than local laboratory values.

† If cost is a concern, ALT alone can be monitored.

References:

1. *Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.*

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