HEPATITIS B VIRUS (HBV) QUANTITATION

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Table of Contents

GUIDELINES
BACKGROUND
CLINICAL EVIDENCE
Guidelines and Recommendations
US FOOD AND DRUG ADMINISTRATION (US FDA)
CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)
APPLICABLE CODING
REFERENCES
POLICY HISTORY/REVISION HISTORY

INSTRUCTIONS FOR USE

Physician Decision Support (PDS) is a lab ordering tool operated by BeaconLBS. This Clinical Guideline supports the Questions and Answers that appear in PDS for tests referenced in this document. UnitedHealthcare reserves the right, in its sole discretion, to modify its Clinical Guidelines as necessary. This Clinical Guideline is provided for informational purposes. It does not constitute a Medical Policy or medical advice.

GUIDELINES

BeaconLBS recommends the use of Hepatitis B virus (HBV) quantitative testing to be used in conjunction with clinical presentation and other laboratory markers as an indicator of HBV infection to:

- assess disease prognosis in chronic HBV infection;
- assist in decision making regarding when to initiate therapy;
- assess viral response to treatment as measured by changes in HBV DNA levels.

These recommendations are consistent with current evidence, expert opinion, and guidelines from the American Association for the Study of Liver Diseases (AASLD), Asian Pacific Association for the Study of the Liver (APASL), and European Association for the Study of the Liver (EASL).

BACKGROUND

Hepatitis B virus (HBV) is a blood-borne virus and one of the most common infectious diseases in the world. HBV can cause a life-threatening liver infection. HBV can cause chronic liver disease, cirrhosis, and liver cancer.¹
In the United States, an estimated 800,000 to 1.4 million persons have chronic HBV infection. HBV also has a global impact and is endemic in Asia and sub-Saharan Africa. Often in these endemic areas, people become infected with HBV during childhood. About 2 billion people worldwide have been infected with the virus and about 350 million live with chronic infection. An estimated 1 million persons die each year due to the acute or chronic consequences of hepatitis B.

HBV is a DNA virus belonging to the Hepadnaviridae family. There are 8 HBV subgroups (A-H) that are based on genetic differences and may be associated with disease progression and response to treatment. Genotype A is the most common in the US.

HBV transmission if similar to that for the human immunodeficiency virus (HIV), however HBV has been found to be 50 to 100 times more infectious than HIV. HBV is transmitted via several common infection routes and through contact with blood and other body fluids. In developing countries the common modes of transmission include: perinatal, vertical (from mother to child), early childhood infections, unsafe injection practices, blood transfusions, and sexual contact. In many developed countries, the majority of infections are transmitted by sexual contact and unsafe injection practices. Additionally, HBV remains a major infectious occupational hazard for health care workers.

There are multiple risk factors for HBV infection including: parenteral drug abuse, multiple sexual partners, sexual transmission from HBV-positive partners, infants of HBV-infected mothers, HIV infection, and hemodialysis. Occupational needlesticks (health care workers) are also considered risk factors.

The WHO recommends that all infants should receive the hepatitis B vaccine as this is the mainstay of hepatitis B prevention. The complete vaccine series induces protective antibody levels in more than 95% of infants, children and young adults. After age 40, protection following the primary vaccination series drops below 90%. At 60 years old, protective antibody levels are achieved in only 65 to 75% of those vaccinated.

Since 1982, over one billion doses of hepatitis B vaccine have been used worldwide. In many countries where 8% to 15% of children used to become chronically infected with HBV; vaccination has reduced the rate of chronic infection to less than 1% among immunized children. As of 2006, 164 countries vaccinate infants against hepatitis B, a major increase compared with 31 countries in 1992, the year that the World Health Assembly passed a resolution to recommend global vaccination against hepatitis B.

Serological Markers of HBV

The incubation period (time from the acquisition of HBV to the onset of clinical symptoms) typically consists of 8-12 weeks. Serologic testing for the diagnosis of HBV infection involves measurement of several HBV specific antigens and antibodies. In general, the results can be used to identify different phases of HBV infections and determine whether a patient is susceptible to infection, immune as a result of resolved infection, immune as a result of vaccination, acutely infected, or chronically infected. Diagnosis is confirmed by demonstration of specific antigens or antibodies. The three most clinically useful antigen-antibody systems that have been indentified are:

- Hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs)
- Antibodies to HBCAg (anti-HBC IgM and anti-HBC IgG)
- Hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe)

HBsAg is a protein on the surface of HBV; and the first serological marker to appear. It can be detected in high levels in serum usually 1 to 12 weeks after infection. HBsAg is detectable during acute or chronic HBV infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is also the antigen used to make HBV vaccine.

Shortly thereafter, HBeAg becomes evident. The presence of HBeAg is associated with relatively high infectivity and severity of disease. Very early in the incubation period, HBsAg, HBV virions, HBV DNA, DNA polymerase, and HBeAg are detectable. Even though, serum HBV DNA assays will show the presence of HBV DNA, this test is generally not used for the diagnosis of acute HBV infection.

Anti-HBc is the first antibody to appear. Demonstration of anti-HBc in serum indicates HBV infection, current or past. This antibody appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with HBV in an undefined time frame. IgM anti-HBc positivity indicates recent infection with HBV (<6 months). IgM anti-HBc is present in high titer during acute infection and usually disappears within 6 months, although it can persist in some cases of chronic hepatitis. This test may therefore reliably diagnose acute HBV infection. IgG anti-HBc generally remains detectable for a lifetime.

Anti-HBe appears after anti-HBc and its presence correlates to a decreased infectivity. Anti-HBe replaces HBeAg in the resolution of the disease. Anti-HBs is generally interpreted as indicating recovery and immunity from HBV infection. Anti-HBs also develops in a person who has been successfully vaccinated against HBV. Anti-HBs replaces HBsAg as the acute HBV infection is resolving. Anti-HBs generally persists for a lifetime in over 80% of patients and indicates immunity.

Acute HBV patients who maintain a constant serum HBsAg concentration, or whose serum HBeAg persists 8-10 weeks after symptoms have resolved, are likely to become carriers and at risk for developing chronic liver disease.

Clinical Presentation

There are 2 different clinical presentations of HBV, acute and chronic. In general, HBV has an incubation period of 8 – 12 weeks. When a person is first infected with HBV, this is called an “acute infection.” An acute illness generally displays influenza-like symptoms, however, more serious symptoms including jaundice and gastrointestinal symptoms may also appear.

The diagnosis of acute hepatitis B is based on the detection of HBsAg and anti-HBc (IgM). HBeAg and HBV DNA are also present, but not generally tested for. Acute HBV infection recovery is marked by a disappearance of detectable HBV DNA, the appearance of anti-HBe, anti-HBs, and anti-HBc (IgG) within 3 months of diagnosis.

Following acute HBV infection, the pattern of serologic markers depends on the outcome of the immune response. Most healthy adults (90%) who become infected with HBV will recover and develop antibodies against future infections. If the virus remains in the blood for more than six months, a diagnosis of chronic infection usually occurs.
The risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of HBeAg-positive mothers to 25%-30% in infants and children under 5 years of age and to less than 5% in adults. In addition immunosuppressed persons are more likely to develop chronic HBV infection after acute infection. Therefore, adults generally have acute infection with complete resolution as compared with vertical transmission which is associated with persistence of infection and development of chronic infection.

Chronic HBV presents with findings of fatigue or vague, right-upper quadrant discomfort. Some patients have systemic symptoms associated with deposition of circulating HBV antigen-antibody immune complexes such as arthritis, leukocytoclastic vasculitis, glomerulonephritis, cryoglobulinemia, and generalized vasculitis. Chronic HBV infection may result in long-term sequelae including cirrhosis, chronic hepatitis, and hepatocellular carcinoma.

Patients who develop chronic HBV infection have a serologic response in the acute phase of HBV infection that is similar to patients who subsequently resolve the HBV infection. With chronic HBV infection, HBSAg and anti-HBc (IgG antibodies) generally persist for life and HBV DNA is usually detectable. The presence of HBSAg for longer than 6 months after acute infection indicates chronic infection.

Laboratory assays can help distinguish between acute and chronic HBV (Table 1).

Table 1. Serological Markers in HBV Infection

<table>
<thead>
<tr>
<th>HBV Category</th>
<th>HBSAg</th>
<th>Anti-HBc</th>
<th>Anti-HBs</th>
<th>IgM anti-HBc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Not tested</td>
</tr>
<tr>
<td>Immune due to natural infection</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Not tested</td>
</tr>
<tr>
<td>Immune due to Hepatitis B vaccination</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Not tested</td>
</tr>
<tr>
<td>Acutely infected</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Chronically infected</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

There are several phases of chronic HBV where the HBeAg, antibody, and DNA vary in detectability (Table 2).

Table 2. Phases of Chronic HBV

<table>
<thead>
<tr>
<th>Phase</th>
<th>HBe Antigen</th>
<th>HBe Antibody</th>
<th>HBV DNA</th>
<th>Transaminases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune tolerance</td>
<td>Positive</td>
<td>Negative</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Immune active</td>
<td>Positive</td>
<td>Negative</td>
<td>Moderately high</td>
<td>Elevated</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td>Moderately high</td>
<td>Elevated</td>
</tr>
<tr>
<td>Inactive carriers</td>
<td>Negative</td>
<td>Positive</td>
<td>Absent or low</td>
<td>Normal</td>
</tr>
<tr>
<td>Reactivation</td>
<td>Negative or positive</td>
<td>Negative or positive</td>
<td>Moderately high</td>
<td>Elevated</td>
</tr>
</tbody>
</table>
**Laboratory Testing for Chronic HBV**

Individuals with chronic HBV (even those who are asymptomatic) will require long-term monitoring for the development of chronic hepatitis, cirrhosis, and cancer. The aim of monitoring is to assess the progression of liver disease and clarify the indication for treatment. There are several guidelines that suggest appropriate levels of HBV DNA and ALT that would trigger the initiation or change of treatment.

HBV DNA quantitative real-time PCR is useful as an aid to assessing viral response to treatment as measured by changes in HBV DNA levels and evaluated patients with chronic HBV infection. Monitoring in pregnancy should also occur to identify and treat HBV positive women, thereby reducing the chance of vertical transmission. Additionally, it may be useful to monitor patients with HBV DNA who were infected with HBV prior to liver transplantation.

In general, HBV chronic disease is measured every 3-6 months. HBV DNA is usually ordered with HBV surface antigen, HBV surface antibody, HBe antigen and HBe antibody. Most HBV DNA assays used in clinical practice are based on polymerase chain reaction (PCR) amplification. Early assays had lower limits of detection of 50-200 IU/mL (250 – 1,000 copies/mL), and a limited dynamic range, up to 4-5 log 10 IU/mL.

Recently, HBV DNA assays that utilize real-time PCR technology with improved sensitivity (5-10 IU/mL) and wider dynamic range (up to 8-9 log 10 IU/mL) have become available. The Abbott RealTime HBV assay has a lower limit of detection of 10 IU/mL and a linear dynamic range of 8 log 10 IU/mL. The Roche COBAS Taqman assay has a lower limit of detection of 20 IU/mL and a linear dynamic range with an upper limit of detection of $1.7 \times 10^8$ IU/mL.

Alanine transaminase (ALT) is also used in conjunction with HBV DNA levels for determining initiation or modification of treatment for HBV.

**CLINICAL EVIDENCE**

There have been many published consensus papers and/or guidelines for the management of chronically-infected HBV patients and most of them recommend an initial quantification of viral load and continuous measurements during follow-up. Monitoring is important for deciding on initiation of treatment or changes to the patient’s drug regimen. In addition, sensitive quantification methods are needed for detection of even low viremia in patients infected with strains bearing a high risk for development of hepatocellular carcinoma such as HBeAg negative strains.

The aims of treatment of chronic HBV are to achieve continual suppression of HBV replication and reduction of liver disease. The ultimate goal is the prevent cirrhosis, liver failure and cancer. Parameters used to assess treatment response include standardization of serum ALT, decrease in serum HBV DNA levels, loss of HBeAg with or without detection of anti-HBe, and improvement in liver histology.

**HBV DNA and Therapy Monitoring Applications**

Initiation of therapy depends on the phase of hepatitis and laboratory values. It is important that those patients with persistently active disease or high viral load be treated.
Patients with chronic hepatitis B may have a wide variety of HBV DNA levels that may fluctuate from undetectable to > 2 million IU/mL. It is important to have regular, serial monitoring of HBV DNA levels for determining prognosis and the need for treatment. Serial monitoring allows for early detection of treatment failure that may result from poor compliance or the emergence of viral resistance.

There are many categories of therapeutic response (Table 3). These categories are further defined by on-therapy, maintained (persist throughout therapy course), end-of-treatment, off-therapy, or sustained (SR-6, 6 months post-therapy; SR-12, 12 months post-therapy).

Table 3. Categories of Therapeutic Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical response</td>
<td>a decrease in serum ALT levels to values within normal range</td>
</tr>
<tr>
<td>Virologic response</td>
<td>a decrease in serum HBV DNA to undetectable levels on PCR assays and the loss of HBeAg in patients who were initially HBeAg – positive</td>
</tr>
<tr>
<td>Primary nonresponse</td>
<td>a decrease of less than 2 log 10 IU/mL in serum HBV DNA levels after at least 24 weeks of therapy</td>
</tr>
<tr>
<td>Virologic relapse</td>
<td>an increase of 1 log 10 IU/mL in serum HBV DNA levels after discontinuance of treatment in at least 2 determinations more than 4 weeks apart</td>
</tr>
<tr>
<td>Histologic response</td>
<td>a decrease of at least 2 points in the histology activity index and no worsening of the fibrosis score in comparison with pretreatment liver biopsy</td>
</tr>
<tr>
<td>Complete response</td>
<td>fulfillment of the criteria for biochemical and virologic response in conjunction with the loss of HBsAg</td>
</tr>
</tbody>
</table>

With currently approved therapies for HBeAg-positive patients, viral suppression can be sustained in 50-90% of patients if treatment is stopped after HBeAg seroconversion is achieved. However, for HBeAg-negative patients, relapse is frequent even when HBV DNA levels have been undetectable for greater than one year. Thus, the endpoint for stopping treatment in this group is unclear.

Viral rebound and the development of drug resistance is a major concern with long-term therapy. Viral rebound is defined as an increase in serum HBV DNA to > 20,000 IU/mL or above pretreatment level after achieving virologic response during continued treatment. The rate of anti-viral resistance is related to the pretreatment HBV DNA levels, the speed at which there is viral suppression, the length of treatment, and any prior exposure to certain drugs.

**HBV DNA and Disease Prognosis**

Treatment outcome has been shown to be correlated with HBV replication (HBV DNA levels). Reductions in HBV DNA levels are associated with higher rates of histologic response, increased rates of seroconversion in HBeAg-positive patients, and lower rates of liver disease complications.

Several studies have shown a link between high viral load and the risk of death, cirrhosis, or cancer. It is also recognized that lower HBV DNA levels (3-5 log 10 IU/mL) may be associated with progressive liver disease and may warrant treatment, particularly in those who are HBeAg-negative or have already developed cirrhosis.
The REVEAL (Risk Evaluation of Viraemia Elevation and Associated Liver Disease) HBV study followed a cohort of 3653 HBsAg-positive patients in Taiwan. A baseline high HBV-DNA level > 10,000 copies/mL was associated with a significant increased risk of cancer and with progression towards cirrhosis.18,19

Fattovich et al., evaluated a cohort of 70 Caucasian patients with HBeAg-positive chronic hepatitis at presentation.21 They showed that the risk of liver-related mortality in these patients with chronic hepatitis was strongly related to sustained disease activity and ongoing high levels of HBV replication, irrespective of HBeAg status.

A high level of HBV DNA has been demonstrated as an independent risk factor for development of cirrhosis and cancer. Kumar et al., in a large prospective study, showed that baseline ALT and DNA level are good predictors of histologically significant fibrosis.22

GUIDELINES AND RECOMMENDATIONS

There are several sets of guidelines for selecting patients requiring treatment that have been published by the major liver associations: American Association for the Study of Liver Diseases (AASLD), Asian Pacific Association for the Study of the Liver (APASL), and European Association for the Study of the Liver (EASL). These guidelines are basically in agreement, however, the ALT or HBV DNA cut-off levels for instituting treatment can differ (Table 2).5,10,17,18

Table 2. Cut-off levels for ALT and HBV-DNA levels used to determine need for treatment as recommended by international societies.81012

<table>
<thead>
<tr>
<th>Society</th>
<th>HBeAg-positive</th>
<th>HBeAg-negative</th>
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<tbody>
<tr>
<td></td>
<td>DNA (IU/mL)</td>
<td>ALT</td>
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<tr>
<td>EASL (2009)</td>
<td>&gt; 2,000</td>
<td>&gt; ULN</td>
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<tr>
<td>APASL (2008)</td>
<td>&gt; 20,000</td>
<td>&gt; 2 ULN</td>
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<tr>
<td>AASLD (2009)</td>
<td>&gt; 20,000</td>
<td>&gt; 2 ULN³</td>
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</table>

³ULN: men = 30, women = 19

World Gastroenterology Organization⁹

In evaluating the response to therapy, the frequency of monitoring and types of laboratory testing depend on phase, disease severity, and treatment protocol.⁹ According to the World Gastroenterology Organization Practice Guideline, for HBeAg positive hepatitis patients, as a general rule, those with persistent ALT > 2 x upper limit of normal and with HBV DNA > 10⁴ IU/mL or > 10⁵ c/mL should get treatment.⁹ In addition, for HBeAg negative hepatitis patients, those with persistent ALT > 2 x upper limit of normal and with HBV DNA > 10⁴ IU/mL or > 10⁵ c/mL should get treatment.⁹ Furthermore, during drug therapy, the viral load should be monitored frequently (i.e., every 3-6 months) during treatment.⁹
US FOOD AND DRUG ADMINISTRATION (US FDA)

There are several FDA approved nucleic acid based assays for the detection and monitoring of HBV. If a test is used that has not been cleared or approved by the FDA, the performing institution must determine the performance characteristics.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

For Medicare populations only, CMS often does not cover screening tests.

There are several CMS policies that apply to HBV Testing (Prognosis, including Monitoring). In some cases, CMS reimbursement is limited to FDA approved and “home-brew” tests only. Physicians should consult their state’s regulations.

APPLICABLE CODING

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<th>Description</th>
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<td>87517</td>
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REFERENCES


POLICY HISTORY/REVISION HISTORY

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