Chronic Hepatitis B Virus: What an Internist Needs to Know

Serologic Diagnosis, Treatment Options, and Hepatitis B Virus Reactivation

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KEYWORDS

• Hepatitis B • Epidemiology • Diagnosis • Treatment • Drug therapy • Reactivation

KEY POINTS

- Chronic hepatitis B infection remains a global public health burden associated with significant morbidity and mortality due to cirrhosis and hepatocellular carcinoma.
- Patients with chronic hepatitis B require regular laboratory monitoring and screening for liver cancer based on the assessment of individual risk.
- Antiviral therapy with oral nucleos(t)ide analogs or pegylated interferon is indicated in patients with immunoactive disease based on HBeAg status, hepatitis B virus (HBV) DNA, serum ALT, and stage of liver fibrosis.
- Current therapies are not associated with the virologic cure but are aimed at virologic suppression, which is associated with a decreased risk for cirrhosis, liver failure, hepatocellular carcinoma, and liver-related mortality.
- HBV reactivation may occur in hepatitis B surface antigen (HBsAg) positive or HBsAg negative/HBcAb positive individuals (with or without anti-HBsAb) in the context of immunosuppressive drug therapy and may be associated with hepatitis flare and liver failure.

INTRODUCTION

Hepatitis B virus (HBV) remains a challenge for primary care providers on a global scale. Current estimates place the worldwide prevalence of chronic HBV infection (CHB) approximately 292 million individuals.[1] Among those living with HBV, 15% to 40% may develop HBV-related complications including cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[2] (**Figs. 1** and **2**)

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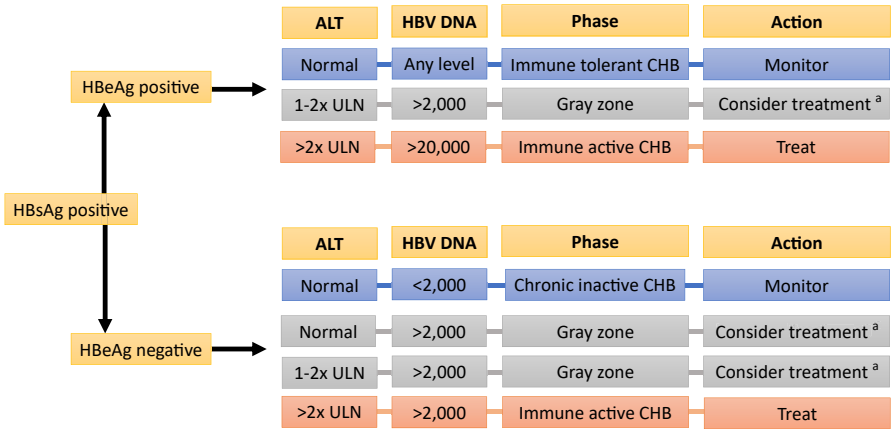

Fig. 1. Approach to treatment of chronic hepatitis B infection. Chronic infection is established by persistently positive HBsAg, then stratified by the presence or absence of HBeAg. The decision to start antiviral therapy is then determined by mainly by the ALT level, HBV DNA level, and degree of liver fibrosis. If patients fall within a "gray zone" for treatment, then other patient factors are weighed in the decision process. [a]Treat if advanced fibrosis or cirrhosis is present. Consider treatment if >40 years old, family history of HCC, or abnormal ALT without alternate cause.

Despite the availability of effective vaccines and antiviral therapies, an inadequate cascade of care has limited efforts by the health care community to detect, monitor, and treat those with HBV. In the United States, only 15% of the nearly 1 million individuals with CHB are aware of their infection, and only 4.5% are receiving antiviral

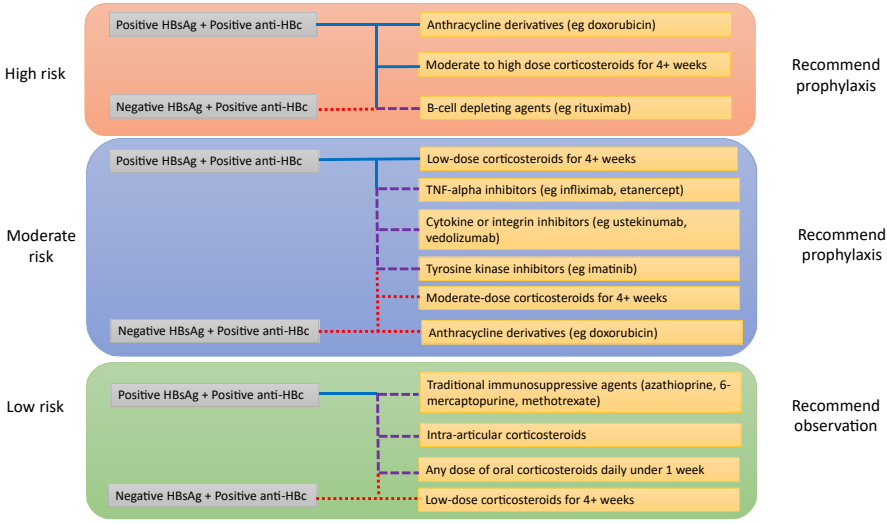

Fig. 2. Risk stratification to guide prevention management of HBV reactivation. Patients' risk of HBV reactivation is determined by their serology, namely HBsAg and anti-HBC, and the type of immunosuppression. Patients stratified into a moderate or high-risk group are recommended to receive antiviral prophylaxis. Low-risk patients can be observed with surveillance lab work to monitor for HBV reactivation.

therapy.[3] Gaps in care are attributable to both patient and provider factors. Patient-related barriers include a confluence of social, economic, cultural, and educational factors.[4–6] On the other hand, surveys of both primary care providers and subspecialty clinicians have consistently illustrated gaps in the knowledge and application of guideline recommendations for HBV management.[7–12]

This article provides a concise review of the fundamentals of CHB management with the purpose to serve as a touchstone for primary care clinicians overseeing the care of patients with CHB in their clinic.

DIAGNOSIS AND CLINICAL EVALUATION

Diagnosis of HBV infection is based on the interpretation of multiple viral antigens and antibodies. These markers can indicate the presence of acute, chronic, or past infection with or without protective immunity. Important HBV blood tests and interpretation of common serological patterns are outlined in **Tables 1** and **2**.

Chronic hepatitis B infection (CHB) is defined by the presence of Hepatitis B surface antigen (HBsAg) over 6 months. Loss of HBsAg with or without the development of antibodies against HBsAg (anti-HBs) is termed seroclearance and is considered a functional cure.[13–15] Protective immunity is regarded as anti-HBs levels >10 IU/mL.[16]

If CHB is established, a comprehensive assessment of the patients' history, exam, serological data, and radiographic imaging should be collated to determine the phase of HBV infection, degree of underlying liver fibrosis, and presence of co-existing causes of chronic liver disease. This includes assessing patients' alcohol use, the

Table 1
Overview of hepatitis B virus tests

HBV Tests	Clinical Relevance
HBsAg	Primary marker for infection. Positive HBsAg over 6 months defines chronic HBV
Anti-HBs	Defines immunity against HBV. Antibody levels above 10 IU/mL is protective
HBeAg	Marker of viral replication and infectivity in CHB
Anti-HBe	Loss of HBeAg and gain of anti-HBe is termed "seroconversion". Seroconversion after age 40 is associated with increased risk of HCC, whereas seroconversion before age 30 is a good prognostic sign
Anti-HBc IgM	Marker of acute infection. May be present before other viral markers are detected
Anti-HBc (total or IgG)	Indicates an active or past infection. Other viral markers (eg, HBsAg, anti-HBs, and HBV DNA) are needed to interpret anti-HBc IgG
HBV DNA	Important in determining phase of infection and carries prognostic value. Higher DNA levels are associated with a higher risk of developing cirrhosis or HCC
ALT	Used to determine the presence of hepatic necroinflammation in CHB. Elevations of ALT above ULN signify a proportionally elevated level of inflammation within the liver

Summary of clinically relevant blood tests for diagnosis, evaluation, prognostication, and management of hepatitis B.

Abbreviations: Anti-HBc, IgG or all antibodies against hepatitis B core antigen; anti-HBc IgM, IgM antibodies against hepatitis B core antigen; anti-HBe, antibody against HBeAg; anti-HBs, antibody against HBsAg; HBeAg, hepatitis e antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; ULN, upper limit of normal.

Table 2
Summary of hepatitis B virus serological patterns commonly encountered in screening for hepatitis B virus

HBsAg	Anti-HBc	Anti-HBs	Interpretation
–	+	–	Chronic hepatitis B
–	+	+	Past infection, now immune. Risk of reactivation if immunocompromised
–	+	–	Past infection, occult HBV infection, or false positive test. Risk of reactivation if immunocompromised
–	–	+	Immune from vaccination
–	–	–	Naïve to HBV (not immune, not exposed). Susceptible to infection

Abbreviations: anti-HBc, HBV core antibody; anti-HBs, HBV surface antibody; HBsAg, HBV surface antigen.

presence of metabolic risk factors (obesity, diabetes), and family history of HCC. Co-existing infections, including hepatitis A virus (HAV), human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis D virus (HDV) should be evaluated. Immunization for HAV should also be provided for patients who do not show immunity.

Notably, laboratory values at a single time point are unreliable in characterizing a patient's disease status given the inherently variable clinical course of CHB. Regular monitoring of HBV DNA and liver enzymes is therefore of paramount importance to determine a patients' phase of infection and guide the potential initiation of antiviral therapy. Determining the degree of underlying hepatic inflammation and liver fibrosis will also inform the decision to treat patients with anti-viral therapy, and requires either liver biopsy or noninvasive fibrosis testing.

ASSESSMENT OF FIBROSIS

Assessment of liver fibrosis is an important step in the evaluation of those with CHB. The gold standard diagnostic intervention to assess for fibrosis is liver biopsy.[17,18] However, its use in routine clinical practice is limited given the inherent invasiveness and potentially severe complications associated with the technique.[18] Noninvasive tools to assess liver fibrosis have become increasingly used within clinical practice. These tools include both novel imaging modalities and serum assays.

Imaging tests to assess fibrosis include transient elastography (TE), shear wave elastography (SWE), and magnetic resonance elastography (MRE). TE and SWE are ultrasound-based techniques in which a probe transmits a wave through the liver parenchyma to quantify liver stiffness in kPa units, termed "liver stiffness measurement (LSM)".[19] The LSM is used to determine the presence of severe fibrosis, cirrhosis, or normal liver parenchyma.[20] In those with CHB, an LSM of 11.0 kPa or above is the recommended cutoff to diagnose cirrhosis.[21] Perhaps the most common example is FibroScan, which is a commercially available type of transient elastography.[19]

Serum-based tools include the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), Fibrosis-4 test (FIB-4), as well as biochemical markers that predict the degree of hepatic fibrosis.[22] One of the most commonly used serum biomarker tests is the FibroTest.[22] Finally, some studies have suggested that using both elastography and serum biomarker tests in patients can improve the accuracy of fibrosis assessment, decreasing the potential need for liver biopsy.

NATURAL HISTORY OF INFECTION

The natural history of HBV infection reflects the dynamic interplay between host and viral factors, carrying clinical consequences in the management of CHB. Although those exposed to HBV in adulthood will often spontaneously eliminate the virus from serological detection, most infections occur perinatally and result in CHB.

In those with CHB, four phases of infection have been described and are defined with similar terms across the major hepatology professional societies.[13–15,23] Determining a patient's phase of infection sheds insight on the patient's disease status and guides treatment decisions.

The four phases of CHB include an immune tolerant phase, an immune active phase with positive HBeAg, an inactive carrier state, and an immune (re)activated phase with negative HBeAg.[23] Although typically sequential, the duration of each phase can vary between patients. Moreover, patients may not pass through all four phases during their course of infection. In turn, characterizing a patient's phase of infection requires serial monitoring of patients' virological markers and liver chemistries. These phases are outlined in **Table 3**.

SCREENING

Initial screening for HBV should include an assessment of HBsAg, anti-HBc, and anti-HBs. According to the US Preventive Services Task Force (USPSTF) 2020 guidelines, screening for HBV should include HBsAg testing in all high-risk populations. This includes all persons from endemic countries (HBsAg seroprevalence of 2% or greater), pregnant women, men who have sex with men, persons with a history of intravenous drug use, and those with end-stage renal disease.[24] However, the CDC published new draft guidance in April 2022 which recommends universal screening of all US adults age 18 or older with one-time serologic testing of HBsAg, anti-HBc, and anti-HBs, and is expected to be implemented in 2023.[25]

TREATMENT

In the United States, treatment of CHB includes two broad categories: nucleoside/nucleotide analogs (NAs) and interferon (IFN) therapy. NAs are well tolerated, effective, and carry an excellent safety profile.[26] IFN therapy has more side effects and is less well tolerated than NAs, but has the advantage of a time-limited treatment course. Guidelines are in general agreement that entecavir, tenofovir, or pegylated IFN should be used as initial therapy for CHB.[14,15,23]

CHB cannot be cured with currently available antiviral therapies. The viral template that establishes chronic infection, covalently closed circular DNA (cccDNA), can persist within hepatocytes irrespective of therapy, thereby posing a lifelong risk of HBV-related complications. Nevertheless, antiviral therapies are effective at suppressing viral replication to undetectable HBV DNA levels in greater than 90% of patients, which in turn is associated with a decreased risk of cirrhosis, hepatic decompensation, and hepatocellular carcinoma, and a decrease in liver-related mortality.[27]

Once therapy is started, regular monitoring of patients' HBV DNA, viral serology, and ALT should be performed to track the response to therapy. Although the overall side effect profile for NAs is excellent, rare side effects have been identified. All NAs carry an FDA black box warning of lactic acidosis, though this is a rare adverse event.[26] Tenofovir disoproxil fumarate (TDF) has also been associated with acute and chronic kidney injury, as well as reduced bone density, though the overall incidence of TDF-associated renal or bone dysfunction is low.[26] Moreover, renal and

Table 3
Phases of chronic hepatitis B virus infection

	Immune Tolerant	Immune Active–HBeAg Positive	Inactive	Immune Active–HBeAg Negative
HBsAg	High	High/intermediate	Low	
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	High (>106 IU/mL)	104 to 107 IU/mL)	<2000 IU/mL	<2000 IU/mL
ALT	Normal	Elevated	Normal	Elevated
Histology	Normal	Inflammation	Minimal inflammation	Moderate/severe inflammation
Clinical characteristics	Typically seen in children and young adults infected perinatally	ALT fluctuates, representing flares of immune-mediated inflammation	HBeAg seroconversion occurs in this phase. Seroconversion >40 years old is associated with higher HCC risk	Variable ALT and DNA. Older population and higher rate of cirrhosis

Serological patterns, typical histology on liver biopsy, and characteristic clinical features are highlighted.

bone side effects are rare with the newest formulation of tenofovir, and tenofovir alafenamide (TAF).[23]

INDICATIONS FOR TREATMENT

There are two main indications for the treatment of CHB. First, treatment is indicated for those with immuneactive CHB. This is defined as an ALT >2 ULN plus HBV DNA >20,000 IU/mL (HBeAg positive) or >2000 IU/mL (HBeAg negative). The second indication is in those with CHB and underlying cirrhosis. In patients with decompensated cirrhosis, antiviral therapy should be started irrespective of ALT level or HBV DNA level, as antiviral therapy has been shown to improve liver function and liver-related mortality.[28] In patients with compensated cirrhosis, all patients with detectable HBV DNA should be treated with antivirals, irrespective of ALT level.[23] IFN therapy is contraindicated in patients with decompensated cirrhosis due to the risk of hepatotoxicity and hepatic decompensation.[23] Thus, NAs are the agents of choice in patients with HBV-related cirrhosis.

INDICATIONS FOR OBSERVATION

In those with immune-tolerant CHB or chronic inactive CHB, observation is generally recommended over treatment. Immune-tolerant CHB is defined as normal ALT (<35 U/L in males, <25 U/L in females) with high HBV DNA levels (>10^6 IU/mL). Similarly, chronic inactive CHB is defined as normal ALT levels with low-level viremia (HBV DNA <2000 IU/mL) and negative HBeAg. This recommendation is based on prior studies which have not shown a reduction in liver-related complications in patients with immune-tolerant CHB treated with antivirals.[13] In turn, the potential harms of prolonged antiviral therapy (eg, side effects, cost, development of viral resistance) are considered to outweigh potential benefits by society guidelines.[13–15] Thus, regular monitoring of serum ALT and HBV DNA is recommended at 6-month intervals to monitor for transition to the immune active phase, at which time antiviral therapy would be indicated.[13]

GRAY AREAS FOR TREATMENT

Patients commonly are observed to have ALT and HBV DNA profiles that do not neatly fall within established phases of infection to determine treatment eligibility. This includes two common scenarios, such as the patient with borderline elevated HBV DNA (2000 to 20,000 IU/mL) and ALT (1 to 2x ULN but not 2x ULN, defined as <70 U/L for men, <50 U/L for women) and the patient with very high HBV DNA (>1,000,000 IU/mL) but persistently normal ALT (defined as <35 U/L for men, <25 U/L for women). In these cases, it is important to weigh other risk factors in determining whether to initiate treatment or actively monitor, including the presence of significant fibrosis (F2 fibrosis or greater on biopsy or noninvasive testing), older age (>40 years old), genotype C HBV, or family history of HCC.[13] The presence of any of one of these risk factors could strengthen consideration to initiate treatment. Indeed, the AASLD recommends that treatment be considered in older age individuals (>40 years old) with normal ALT, high HBV DNA levels (>1,000,000 IU/mL), and liver biopsy with moderate-to-severe necroinflammation or fibrosis.[23]

DURATION OF THERAPY

Treatment duration with NAs is typically considered “long-term,” as such medications do not eliminate cccDNA or viral DNA integrated into host genomes. Long-term NA therapy is generally well-tolerated given the excellent safety profile, high threshold

for drug resistance, and strong long-term efficacy in suppressing HBV DNA replication.[26] On the other hand, indefinite therapy is challenging for patients to sustain, exposes patients to rare side effects, may be associated with financial burden due to specialty prescription drugs, and uncommonly may result in drug resistance due to treatment interruptions and nonadherence.[13]

Cessation of therapy can therefore be considered in select patient populations without cirrhosis who achieve HBeAg seroconversion (among patients with HBeAg positive infection at baseline), which occurs in approximately 20% to 40% of patients within 5 years of NA therapy, and/or HBsAg loss, which occurs in fewer than 5% of patients within 5 years of NA therapy.[23] In those who may qualify for treatment cessation, the potential risks should be discussed frankly with the patient. These risks include virological reactivation, hepatic decompensation, and death. If discontinuation of anti-viral therapy is planned, then it is recommended that treatment be continued for an additional 6 to 12 months after the above criteria are met.[13] This period of "consolidation therapy" has been shown to decrease the likelihood of virological relapse once therapy is stopped.[29] Following consolidation therapy, patients' lab work (eg HBV DNA and ALT levels) should be monitored regularly during the first 12 months off therapy to assess for viral recurrence and hepatitis flares.[13]

COMPLICATIONS OF CHRONIC HEPATITIS B VIRUS INFECTION

The two major liver-related complications related to CHB are cirrhosis and HCC. The risk of developing these complications is influenced by viral, host, and environmental factors. The most important viral determinants for progression to cirrhosis are HBV DNA level, ALT, and HBeAg status. Similarly, viral and host factors most strongly associated with the onset of HBV-related HCC include the presence of cirrhosis, HBV DNA level, HBeAg status, genotype, HDV coinfection, and family history of HCC. Of note, unlike other etiologies of chronic liver disease, HBV-associated HCC can develop at any stage of liver fibrosis and does not require advanced fibrosis/cirrhosis.

HEPATOCELLULAR CARCINOMA MONITORING

CHB is a major cause of HCC, accounting for the majority of cases worldwide. The oncogenic nature of the virus is reflected in its ability to lead to HCC even in the absence of cirrhosis, although the presence of cirrhosis significantly raises the risk of HCC in those with CHB.[30] High levels of HBV DNA have also been linked to a higher likelihood of HCC.[31] Suppression of viral replication with antiviral therapy reduces but does not eliminate, the risk of HCC.[32]

For these reasons, surveillance for HCC with an abdominal ultrasound every 6 months is recommended in those with CHB and additional risk factors. Measurement of AFP alone is insufficient for HCC surveillance but can be used as an adjunct surveillance test with ultrasound. Screening should be done whether or not patients are receiving antiviral therapy.

All patients with CHB and cirrhosis should be screened for HCC every 6 months. In those without cirrhosis, high-risk groups in whom twice annual HCC surveillance should be performed: black men or women > age 20 years, Asian men > age 40 years, Asian women >50 years old, family history of HCC, or HDV coinfection.[23,33–36]

REACTIVATION OF HEPATITIS B VIRUS

HBV reactivation (HBVr) is defined as the re-emergence of infection in those with previously resolved HBV infection or chronically inactive CHB.[37] The key pathophysiological

factors are cccDNA and host immune suppression, where cccDNA serves as a reservoir for rapid viral propagation in an immunocompromised host.[38]

HBVr has three different clinical phenotypes.[38] In the first phenotypic presentation, HBVr can be a silent event in which HBV DNA rises without aberrations in liver tests. Alternatively, HBVr can manifest with acute hepatitis illustrated by abnormal liver tests. Finally, HBVr can present with fulminant liver failure, represented by elevated HBV DNA in the setting of acute encephalopathy and hepatic synthetic dysfunction.

Initiation of immunosuppressive or immunomodulatory therapy is the main risk factor for HBVr.[39] The type of immunosuppressive regimen and serological pattern of HBV both influence the risk of reactivation. Reactivation rates have been reported as high as 41% to 53% in patients receiving anti-neoplastic therapies with positive anti-HBc and positive HBsAg levels.[40] Reactivation also occurs in those with positive anti-HBc and negative HBsAg levels, though at lower rates of occurrence (8%–18%).[41]

Although historical data have shown the risk of HBVr with conventional chemotherapies and immunosuppressive medications (eg, B-cell depleting agents), emerging evidence indicates that varying degrees of risk are also present with newer classes of both immunosuppressive and immunomodulatory therapies. Whereas antiviral prophylaxis is not recommended for patients undergoing therapies associated with low HBVr risk (tyrosine kinase inhibitors, T-cell depleting agents, and immune checkpoint inhibitors), antiviral therapy may be considered for patients undergoing treatment associated with high (B-cell depleting therapies, Janus kinase inhibitors) or intermediate HBV risk (cytokine inhibitors, CAR-T cell immunotherapy, and calcineurin inhibitors).[42]

HBVr can be prevented by screening those about to receive immunosuppression, stratifying their risk of reactivation, and then tailoring management based on their risk. In terms of screening, HBsAg and anti-HBc levels should be obtained. If either test is positive, then HBV DNA should be measured to establish a baseline level. Guidelines vary on whether anti-HBs should be included in HBVr screening, as data are limited on its clinical utility in risk stratification of HBV.[14,15,23,37,43] Whether anti-HBs influence the clinical severity of viral reactivation or if quantitatively high levels of anti-HBs lower the risk of HBVr are two scenarios without evidence-based answers.[37] Importantly, HBVr can still occur in those with positive anti-HBs level, where reactivation occurs at an estimated rate of 4.3% in those with positive levels of anti-HBc and anti-HBs.[37] Thus, checking HBsAg and anti-HBc with or without anti-HBs are the consensus serological tests that should be obtained for HBVr screening purposes.

HBV testing is recommended before initiation of immunosuppressive therapy,[14,15] although clinical practice patterns to date suggest low rates of adherence.[38,39,44] If screening tests are positive, then patients should be stratified based on their serological HBV pattern and immunosuppressive regimen. The AGA HBVr guideline categorizes patients into three risk groups: high (>10%), moderate (1%–10%), and low risk (<1%) for HBVr.[37] Determining a patients' risk category will guide their HBV management plan while on immunosuppression.

If patients fall within the high-risk group, then they should receive antiviral prophylaxis.[37] Similarly, patients with moderate risk of HBVr are recommended to receive antiviral prophylaxis, although active monitoring off therapy is an alternative option if the patient prefers avoiding antiviral medications.[37] Low-risk patients do not typically need antiviral prophylaxis, but should be monitored with interval blood work with antiviral therapy available "on-demand" if HBVr is identified.[37] Tenofovir or entecavir are first-line agents for antiviral prophylaxis, as prior studies have shown that these

medications result in a decreased incidence of HBVr, hepatitis flares, and mortality in comparison to prophylaxis with lamivudine.[23]

Antiviral prophylaxis should be started before initiation of immunosuppressive therapy when possible, but chemotherapy should not be delayed. This treatment should be continued throughout the duration of immunosuppressive therapy and then continued for an additional 6 to 12 months after the immunosuppressive regimen is completed.[37] Routine blood work should be obtained to monitor for HBVr (HBV DNA, liver tests) in patients receiving immunosuppressive therapy, preferably every 1 to 3 months, and for an additional 12 months after cessation of immunosuppressive therapy.[23]

SUMMARY

Although HBV infection remains a public health challenge worldwide, there are effective tools available to the primary care provider to mitigate its impact. This includes an armory of serological and radiographic tools to screen, stage, and prognosticate infection. Oral medications that are well-tolerated and reduce the risk of HBV-related complications are also available for the treatment of chronic infection, as well as evidence-based guidelines that can provide insights into the nuanced management of CHB. However, effective and appropriate employment of these tools can be daunting, especially given the often silent, yet pernicious and complex, course of chronic infection. This review article has provided a concise overview of CHB management to serve as a resource for the primary care provider to guide decision-making through the complex care cascade faced by patients and providers.

CLINICS CARE POINTS

- Chronic hepatitis B infection remains a global public health burden associated with significant morbidity and mortality due to cirrhosis and hepatocellular carcinoma
- Chronic hepatitis B infection is defined by positive hepatitis B surface antigen (HBsAg) and/or positive hepatitis B virus (HBV) DNA of 6 months duration or longer
- Patients with chronic hepatitis B require regular laboratory monitoring and screening for liver cancer based on the assessment of individual risk
- Antiviral therapy with oral nucleos(t)ide analogs or pegylated interferon is indicated in patients with immunoactive disease based on HBeAg status, HBV DNA, serum ALT, and stage of liver fibrosis
- Current therapies are not associated with the virologic cure but are aimed at virologic suppression, which is associated with a decreased risk for cirrhosis, liver failure, hepatocellular carcinoma, and liver-related mortality
- HBV reactivation may occur in HBsAg positive or HBsAg negative/HBcAb positive individuals (with or without anti-HBsAb) in the context of immunosuppressive drug therapy, and may be associated with hepatitis flare and liver failure
- Antiviral prophylaxis may be indicated in patients identified as moderate or high risk of HBV reactivation based on HBsAg/HBcAb status and immunosuppressive drug class

DISCLOSURE

P.D. Block reports no disclosures. J.K. Lim reports research contracts (to institution) from: Allergan, Celgene, Eiger, Gilead, Intercept, Pfizer, Viking.

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