Evaluation of the Patient with Chronic Hepatitis B

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Recommended counseling for newly diagnosed chronic hepatitis B virus (HBV) patients (i.e., hepatitis B surface antigen [HBsAg]-positive for >6 months) includes education regarding measures to minimize the risk of inadvertent HBV transmission and promotion of healthy lifestyle habits.[1,2] In addition, a review of the patient's current and past medical history, HBV replication status, and liver disease severity allows one to better estimate the risk of developing progressive liver disease and hepatocellular carcinoma (HCC). These data also help the clinician determine the need and type of potential antiviral therapy and subsequent frequency and type of disease monitoring.

Recommended Testing for Patients with Chronic HBV

The physical examination in chronic HBV patients should include an assessment for spider angioma, gynecomastia, and splenomegaly, which are indicative of more advanced liver disease. An assessment of the route (vertical versus horizontal) and duration of infection, family history of cirrhosis and HCC, alcohol and smoking habits, and current medication and herbal product use should be undertaken (Table 1). Although prothrombin time and bilirubin are normal in most outpatients with chronic HBV, serial assessment of serum aminotransferase (i.e., aspartate aminotransferase and alanine aminotransferase [ALT]) levels can help determine the current status of infection. In addition, a complete blood count can help detect thrombocytopenia, which is an early marker of portal hypertension. Chronic HBV patients should be screened for concomitant hepatitis C virus, hepatitis D virus, and human immunodeficiency virus coinfection. Finally, a baseline serum alpha-fetoprotein level and liver ultrasound is recommended to screen for early stage HCC, radiographic stigmata of cirrhosis, and other causes of liver disease.[2]

HBV Replication Markers and Disease States

Laboratory markers of HBV replication include serum hepatitis B e antigen (HBeAg), anti-HBe, and quantitative HBV DNA levels. Most HBV DNA assays are based on polymerase chain reaction amplification with a lower limit of detection of 10 to 50 IU/mL and a 4 to 5 log 10 dynamic range, while assays using real-time polymerase chain reaction have improved sensitivity and have a greater dynamic range (8-9 $\log_{10}$). Quantification of HBV DNA at initial diagnosis and periodically thereafter in conjunction with serum ALT levels obtained on three or more occasions can help categorize disease stage and guide antiviral treatment decisions (Fig. 1). For example, immune tolerant patients that are HBeAg-positive with persistently high HBV DNA ($>10^6$ IU/mL) but normal ALT levels can defer antiviral therapy and be observed with serial laboratory measurements. In contrast, immune active HBeAg-positive patients with serum ALT levels persistently >2 times the upper limit of normal (ULN) and HBV DNA >20,000 IU/mL and HBeAg-negative patients with similar ALT elevations and HBV DNA >2,000 IU/mL should be considered for immediate antiviral therapy.[2] After spontaneous HBeAg seroconversion to anti-HBe positivity, most inactive carriers remain HBeAg-negative with low or undetectable HBV DNA and normal or near normal serum ALT levels. However, up to 30% of these patients may develop a spontaneous disease reactivation that requires antiviral therapy, highlighting the need for indefinite laboratory and clinical monitoring of all untreated chronic HBV patients.[3]

HBV Genotypes and Precore/Core Promoter Variants

There are eight HBV genotypes labeled A through H that differ in their nucleotide sequence throughout the HBV genome (Table 2).[4] In one multicenter study of 694 patients in

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, interferon; ULN, upper limit of normal.

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TABLE 1: Initial and Recommended Follow-up of Chronic HBV Patients

Initial evaluation
History and physical examination
Education to reduce transmission
Test/vaccinate household and sexual contacts
Minimize alcohol and smoking
Family history of HCC/cirrhosis
Assess body mass index
Laboratory tests
Serum AST/ALT, albumin, bilirubin, INR, complete blood count, platelet count
HBeAg, anti-HBe, quantitative HBV DNA level
Exclude HCV, HDV, HIV coinfection
Serum AFP and liver ultrasound
EGD if portal hypertension suspected to excluded varices
General recommendations
HAV vaccination
Minimize alcohol consumption
Stop smoking
Balanced diet and exercise to reduce insulin resistance/hepatic steatosis
Acetaminophen analgesics <4 g/day preferred over NSAIDs/aspirin
Use of steroids/immunosuppressants/chemotherapy requires prophylactic oral antiviral
Follow-up evaluation*
Immune tolerant (HBeAg-positive)
Normal ALT, HBV DNA $>10^6$ IU/mL
No immediate therapy
Untreated follow-up†
ALT every 3-6 months, then every 6 months
HBV DNA every 6 months
Immune active (HBeAg-positive)
Increased ALT, HBV DNA $>2 \times 10^4$ IU/mL
Antiviral recommended
Untreated follow-up†
ALT and HBV DNA every 3-4 months
Immune active (HBeAg-negative)
Increased ALT, HBV DNA $>2 \times 10^3$ IU/mL
Antiviral recommended
Untreated follow-up†
ALT and HBV DNA every 3-4 months
Inactive carrier (HBeAg-negative)
Normal or near normal ALT, HBV DNA low or undetectable
No immediate therapy
Untreated follow-up†
ALT and HBV DNA every 6-12 months
Treat if reactivation/disease flare detected

Abbreviations: AST, aspartate aminotransferase; EGD, esophagogastroduodenoscopy; HAV, hepatitis A virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; INR, international normalized ratio.

*Disease state categorization should be based on three or more determinations of serum ALT and HBV DNA levels over time.

†Obtain liver biopsy if uncertain, HCC surveillance per American Association for the Study of Liver Diseases guidelines.[2]

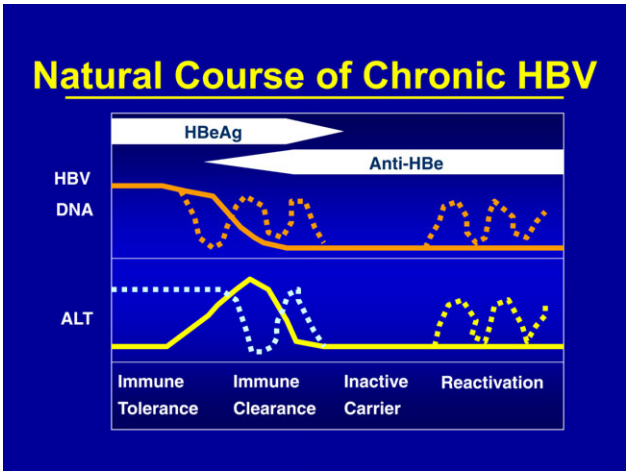

FIGURE 1. Subjects with vertically acquired HBV typically are HBeAg-positive with persistently high serum HBV DNA but normal serum ALT levels for several decades in the immune tolerant phase of infection. In young adulthood, the host immune response tries to clear infected hepatocytes, which typically results in a fluctuating serum ALT and HBV DNA level and HBeAg seroconversion at a rate of 5% to 15% per year. HBeAg-positive and HBeAg-negative subjects in the immune active phase of infection should be considered for antiviral therapy to control HBV replication and reduce the risk of ongoing liver injury. Most inactive carriers have a low to undetectable HBV DNA level and normal or near normal serum ALT level. However, up to 30% may spontaneously reactivate with or without HBeAg seroreversion and should be considered for treatment to prevent further liver injury.

the United States, a broad distribution of HBV genotypes was reported with genotypes A (35%) and D (10%), identified mostly in Caucasians and African Americans, whereas genotypes B (22%) and C (31%) predominated in Asian Americans.[5] HBV genotypes may play an important role in disease progression and potential response to interferon (IFN) therapy. For example, Asian patients with HBV genotype B have earlier spontaneous HBeAg seroconversion and a better response to IFN therapy compared with patients with genotype C.[6] In addition, the rate of disease progression and lifetime risk of HCC appears to be greater with untreated HBV genotype C > B.[7] Similarly, Caucasian HBV patients with genotype A are most responsive to IFN therapy, with a 40% to 50% likelihood of HBeAg seroconversion. However, HBV genotypes are not associated with the likelihood of response to oral antiviral agents. Therefore, most experts do not recommend testing for HBV genotype in routine clinical practice unless IFN therapy is being considered.

Patients with active and inactive HBeAg-negative liver disease frequently harbor viral variants that lead to reduced expression of HBeAg in the serum.[8] Precore variants that arise due to a point mutation at G1896A in the precore region and core promoter variants are frequently detected during spontaneous and treatment-induced HBeAg seroconversion. One large study suggested that the presence of core promoter and precore variants may increase the risk of HCC among untreated Taiwanese men with long-standing chronic HBV.[7] Although commercial assays are available, most experts do not recommend testing for precore and core promoter variants due to their dynamic status and uncertain clinical significance.

Quantitative HBsAg Levels

Quantitative HBsAg levels are being studied in relationship to the natural history of chronic HBV and response to antiviral therapy.[9] Serum quantitative HBsAg levels largely reflect the extent of host immune control over HBV replication. The dynamic range of available HBsAg assays vary from 0.1

TABLE 2: HBV Genotypes and Variants

HBV Genotype	Frequency of Variants		Location	Clinical Significance
	PC	BCP		
A	Low	High	North America, Europe, Central Africa	Highest response to IFN
B	High	Low	China, Japan, Korea, Asia	Earlier HBeAg seroconversion; increased IFN response compared with genotype C
C	Low	High	China, Japan, Korea, Asia	Delayed HBeAg seroconversion; increased risk of HCC
D	High	High	The Mediterranean, Middle East, South Asia	Most are HBeAg-negative
E	ND	ND	West Africa	
F	Low	ND	South and Central America	
G	High	ND	United States, France	
H	ND	ND	Mexico, South America	

Abbreviations: BCP, basal core promoter; ND, not described; PC, precore.

to 1,000 IU/mL with serial dilutions possible from high titer samples. Quantitative HBsAg levels correlate positively with quantitative HBV DNA levels, and the correlation appears to be more consistent in HBeAg-positive patients compared with HBeAg-negative patients and inactive carriers. Retrospective studies suggest that lower baseline HBsAg levels in untreated patients are associated with a higher rate of spontaneous HBsAg seroconversion and lower risk of HCC. Baseline and on-treatment changes in HBsAg levels also may prove to be a more reliable and sensitive predictor of sustained response to IFN and oral antiviral therapy. However, additional prospective studies that account for HBV genotype, HBV DNA level, and HBeAg status are needed to determine the role of HBsAg quantification in individualizing the type and duration of treatment for chronic HBV.

Liver Biopsy and Noninvasive Staging Methods

A liver biopsy in a patient with viral hepatitis provides important objective information on the severity of liver inflammation as well as the stage of fibrosis. A liver biopsy can also help identify concomitant disease processes such as hepatic steatosis or steatohepatitis, which may increase the risk of liver disease progression. Therefore, a liver biopsy may influence the decision to treat a patient if more disease is noted than suspected based on serum ALT and HBV DNA levels. In addition, because the risk of HCC and disease progression is markedly higher in patients with bridging fibrosis and cirrhosis, monitoring and surveillance strategies may be altered. However, it should be noted that most experts do not believe that a liver biopsy is required prior to initiating antiviral therapy unless there is clinical uncertainty regarding the severity of liver disease. In addition, the limitations of liver biopsy with regard to understaging hepatic fibrosis, sampling artifact, and the procedural risk need to be considered.

Panels of serum fibrosis markers that reflect the extent of hepatic fibrogenesis, fibrolysis, and liver apoptosis have been proposed to noninvasively assess disease stage in chronic HBV.[10] However, their specificity and reliability may be more limited in chronic HBV patients that frequently experience bursts of viral replication and liver necroinflammation that can lead to false positive test results. Liver elastography is a new noninvasive imaging modality wherein an external transducer is placed against the right costal margin and the speed of shear wave propagation reflects the extent of liver stiffness that is proportional to the extent of hepatic fibrosis.[11] Studies of liver elastography in chronic HBV patients have demonstrated a good positive predictive value for detection of cirrhosis, but the presence of high serum ALT can lead to false positive test results. In particular, chronic HBV patients with a spontaneous surge in viral replication (high HBV DNA) and liver necroinflammation (high serum ALT) may have transient increases in liver stiffness that reflect inflammation rather than fibrosis. Furthermore, measurement of liver elastography can be technically difficult and less accurate in overweight and obese patients. Magnetic resonance elastography is another promising modality that samples a larger volume of tissue but requires further study.

Conclusions

All newly diagnosed chronic HBV patients should undergo a complete history, physical assessment, and laboratory assessment in an effort to assess the severity of liver disease and potential need for antiviral therapy. Counseling to reduce transmission and maintaining a healthy lifestyle are recommended to minimize the influence of environmental cofactors associated with liver disease progression. Markers of HBV replication (HBeAg, HBV DNA) along with serum ALT levels should be obtained initially and periodically thereafter to assess the state of HBV infection. A liver ultrasound is recommended in all newly diagnosed chronic HBV patients to assess for unsuspected liver masses, splenomegaly, and a nodular liver suggestive of advanced fibrosis or portal hypertension, which would influence decisions regarding treatment and monitoring. In addition, serial serum alpha-fetoprotein and ultrasound imaging is recommended for chronic HBV patients at increased risk of developing HCC based upon their disease state, demographic features, and medical history. Newer

noninvasive modalities such as liver elastography may play a future role in assessing disease severity, but liver biopsy is currently recommended in cases of diagnostic uncertainty.

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