

Management of Hepatitis B: Our Practice and How It Relates to the Guidelines

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Seven drugs have been approved for the treatment of chronic hepatitis B. Antiviral treatment has been shown to be effective in suppressing hepatitis B virus replication, decreasing inflammation and fibrosis in the liver, and preventing progression of liver disease. However, current medications do not eradicate hepatitis B virus; therefore, a key question is which patients need to start treatment and which patients can be monitored. Professional societies have developed guidelines to assist physicians in recognition, diagnosis, and optimal management of patients with chronic hepatitis B. These guidelines suggest preferred approaches, and physicians are expected to exercise clinical judgment to determine the most appropriate management based on the circumstances of the individual patient. This article reviews recommendations in hepatitis B guidelines and the basis for those recommendations, and we discuss what we do in our practice to illustrate factors that may influence decisions regarding hepatitis B management.

Keywords: Chronic Hepatitis B; Management; Antiviral Therapy; Hepatitis B Guidelines.

The advent of sensitive assays for the detection of hepatitis B virus (HBV) and the availability of potent antiviral agents have improved the management of patients with chronic hepatitis B (CHB); however, current treatment cannot eradicate the virus. Because of the high cost and risk of adverse events, as well as drug resistance with long-term treatment, the most important question regarding the management of hepatitis B is which patients need to be treated now and which patients can be monitored and have treatment deferred. The American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), and Asian Pacific Association for the Study of the Liver (APASL) have developed clinical practice guidelines to assist physicians in recognition, diagnosis, and optimal management of patients with CHB.^{1–3} These guidelines suggest preferred approaches and physicians are expected to exercise clinical judgment to determine the most appropriate management based on the circumstances of the individual patient. Recommendations of the 3 guidelines vary slightly because of differences in timing when the guidelines were issued and also differences in available resources. This article reviews recommendations in hepatitis B guidelines and the basis for those recommendations and we discuss what we do in

our practice to illustrate factors that may influence the management of CHB.

Natural History of Chronic Hepatitis B Virus Infection

The natural course of chronic HBV infection consists of 4 phases; however, patients may not experience all phases (Figure 1).⁴

Host, viral, and environmental factors influence progression of HBV-related liver disease. Recent studies have focused on the importance of HBV replication as an independent predictor of cirrhosis, hepatocellular carcinoma (HCC), and liver-related deaths.^{5,6} However, other factors including sex, age, HBV genotype, co-infection with human immunodeficiency virus, hepatitis C virus, or hepatitis D virus, increased alanine aminotransferase (ALT) level, and alcohol and tobacco use also contribute to cirrhosis and HCC.

Indications for Treatment

Practice guidelines recommend that the treatment decision be made based on clinical status, serum HBV DNA and ALT levels, hepatitis B e antigen (HBeAg) status, and liver histology if available.^{1–3}

Who Should Be Treated?

All guidelines recommend starting treatment as soon as possible in patients with life-threatening liver disease: acute liver failure, decompensated cirrhosis, or severe exacerbation of CHB regardless of HBV DNA and ALT levels. Although data from randomized controlled trials

Abbreviations used in this paper: AASLD, American Association for the Study of Liver Diseases; AFP, α -fetoprotein; ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B e antibody; APASL, Asian Pacific Association for the Study of the Liver; CHB, chronic hepatitis B; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; IFN, interferon; NUC, nucleos(t)ide analogue; PEG-IFN, pegylated-interferon; ULN, upper limit of normal.

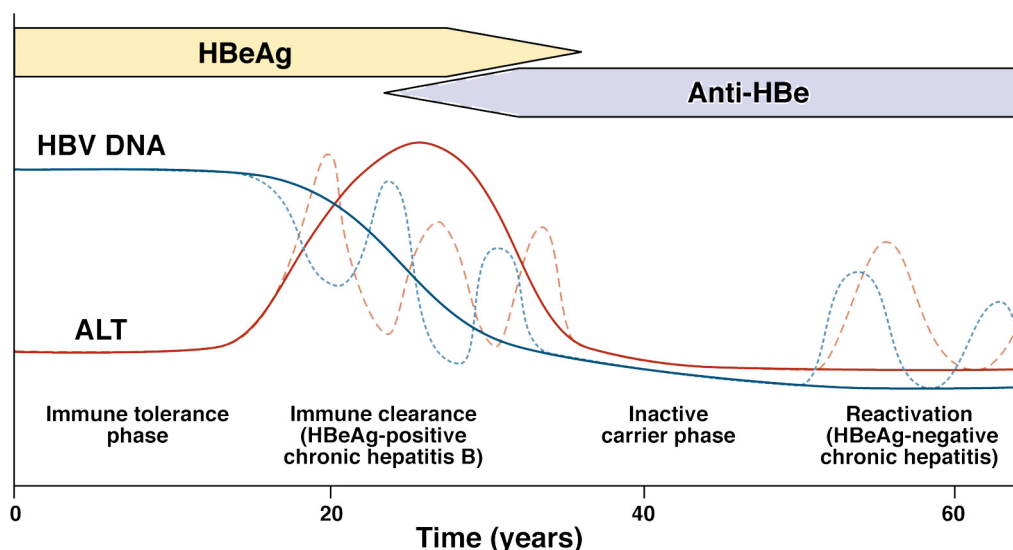


Figure 1. The natural course of chronic HBV infection consists of 4 phases. The immune tolerance phase is characterized by the presence of HBeAg, high HBV DNA levels, and persistently normal ALT levels, but no evidence of active liver disease. The immune clearance phase is characterized by the presence of HBeAg and high/fluctuating HBV DNA and ALT levels. An outcome of the immune clearance phase is HBeAg seroconversion. Most patients then enter the inactive HBV carrier phase, which is characterized by the absence of HBeAg and the presence of anti-HBe, low or undetectable HBV DNA levels (<2000 IU/mL), normal ALT levels, and no/minimal inflammation on liver biopsy. The reactivation phase is characterized by the absence of HBeAg, intermittent/persistently increased ALT and HBV DNA levels, and inflammation on liver biopsy. Reprinted with permission from Lok.⁴

in these settings are lacking, in case series antiviral treatment has been shown to be beneficial with little or no adverse effects. In addition, for patients requiring liver transplantation, viral suppression decreases the risk of HBV recurrence after transplant.⁷

The AASLD and APASL guidelines recommend antiviral therapy in patients with compensated cirrhosis and serum HBV DNA level greater than 2000 IU/mL regardless of ALT level.¹⁻³ For patients with increased ALT levels, the AASLD guidelines recommend treatment regardless of HBV DNA level.¹ The EASL guideline recommends treatment of patients with any detectable level of serum HBV DNA.² There is growing evidence that long-term treatment with nucleos(t)ide analogues (NUCs) not only prevents disease progression but also reverses fibrosis and cirrhosis. In a double-blind, randomized, placebo-controlled study of 651 patients with advanced fibrosis or cirrhosis, who were HBeAg-positive or had high levels of HBV DNA (>150,000 IU/mL), lamivudine therapy was shown to decrease progression of liver disease.⁸ A follow-up report of the phase 3 tenofovir vs adefovir trial including 348 patients who had paired biopsies at baseline and year 5 showed that 51% of patients had a decrease in fibrosis stage by 1 or more and 71 of 96 (74%) patients with cirrhosis on initial biopsy had regression of cirrhosis.⁹

All guidelines agree that treatment should be initiated in noncirrhotic patients with serum HBV DNA levels greater than 20,000 IU/mL and persistently increased ALT levels and/or histologic evidence of moderate/severe inflammation or fibrosis. However, cut-off values of HBV DNA and ALT levels and the need for liver biopsy in determining treatment indications vary slightly among

the guidelines (Table 1). The AASLD guideline suggests an arbitrary HBV DNA level of 20,000 IU/mL for initiating treatment.¹ The APASL guideline recommends an HBV DNA threshold of 20,000 IU/mL for HBeAg-positive patients and 2000 IU/mL for HBeAg-negative patients, whereas the EASL guideline recommends a cut-off value of 2000 IU/mL irrespective of HBeAg status.^{2,3} All guidelines agree that serial HBV DNA and ALT level is more important than a single value in making treatment decisions. For patients who fulfill the criteria for HBV DNA, the EASL recommends treating patients with ALT levels greater than the upper limit of normal (ULN) if the liver biopsy (or noninvasive markers validated in HBV-infected patients) shows moderate-severe inflammation and/or at least moderate fibrosis, whereas the APASL and AASLD recommend treatment for patients with an ALT level greater than 2 times the ULN. The AASLD guideline suggested lower values be used to define the ULN for an ALT level of 30 U/L for men and 19 U/L for women, and a liver biopsy should be performed in patients with mildly increased ALT levels, particularly in patients older than age 40.¹ Besides HBV replication status, ALT levels, and liver histology, all guidelines recommend that patient age, HBeAg status, family history of HCC, occupational requirements, family planning, and patient preference should be considered in making treatment decisions.

All guidelines recommend 3 to 6 months of observation in HBeAg-positive patients and treatment if there is no spontaneous HBeAg seroconversion, but a period of pretreatment observation is not necessary in HBeAg-negative patients who meet criteria for treatment. Recommendations for treatment of noncirrhotic HBeAg-

Table 1. Comparison of AASLD, APASL, and EASL Guideline Recommendations Regarding Treatment of Hepatitis B¹⁻³

	AASLD (2009)	APASL (2012)	EASL (2012)
HBV DNA cut-off level, IU/mL			
HBeAg-positive	20,000	20,000	2000
HBeAg-negative	2000–20,000	2000	2000
ALT cut-off level, U/L	30 for men, 19 for women	Traditional cut-off value of 40 U/L	Traditional cut-off value of 40 U/L
Recommendations for treatment and monitoring			
Noncirrhotic patients			
HBeAg-positive	HBV DNA >20,000 IU/mL, ALT >2× ULN Monitor for 3–6 mo Treat if no spontaneous HBeAg loss Liver biopsy before treatment is optional	HBV DNA >20,000 IU/mL, ALT >2× ULN Monitor for 3–6 mo Treat if no spontaneous HBeAg loss Liver biopsy before treatment is optional	HBV DNA >2000 IU/mL, ALT >ULN Monitor for 3–6 mo Liver biopsy (or noninvasive markers of fibrosis) is recommended Treat if no spontaneous HBeAg loss and biopsy shows moderate-severe inflammation and/or at least moderate fibrosis
HBeAg-negative patients	HBV DNA >20,000 IU/mL, ALT ≤2× ULN Monitor every 3–6 mo Consider biopsy in patients >40 y, ALT persistently 1–2× ULN, or with family history of HCC Treat if biopsy shows moderate/severe inflammation or significant fibrosis HBV DNA >20,000 IU/mL, ALT >2× ULN Treatment is clearly indicated, liver biopsy is optional HBV DNA 2000–20,000 IU/mL, ALT 1–2× ULN Consider liver biopsy Treat if liver biopsy shows moderate/severe inflammation or significant fibrosis	HBV DNA >20,000 IU/mL, ALT 1–2× ULN Monitor every 1–3 mo Consider biopsy in patients >40 y, ALT persistently 1–2× ULN, or with family history of HCC Treat if biopsy shows moderate/severe inflammation or fibrosis HBV DNA >2000 IU/mL, ALT >2× ULN Treatment is clearly indicated, liver biopsy is optional HBV DNA >2000 IU/mL, ALT 1–2× ULN Monitor ALT and HBV DNA every 1–3 mo Consider liver biopsy if patient is ≥40 y Treat if biopsy shows moderate/severe inflammation or fibrosis	HBV DNA >20,000 IU/mL, ALT <ULN Monitor every 3–6 mo Consider biopsy in patients >30 y, ALT persistently 1–2× ULN, or with family history of HCC Treat if biopsy shows moderate-severe inflammation or significant fibrosis HBV DNA >20,000 IU/mL, ALT >2× ULN Treatment is clearly indicated, liver biopsy is optional HBV DNA >2000 IU/mL, ALT >ULN Liver biopsy (or noninvasive markers of fibrosis) is recommended Treat if biopsy shows moderate-severe inflammation and/or at least moderate fibrosis
Cirrhosis			
Compensated	HBV DNA ≤2000 IU/mL, ALT ≤ULN Monitor HBV DNA >2000 IU/mL Treat regardless of ALT level HBV DNA <2000 IU/mL Consider treatment if ALT >ULN Regardless of HBV DNA or ALT level Treat and refer for liver transplantation	HBV DNA ≤2000 IU/mL, ALT ≤ULN Monitor HBV DNA >2000 IU/mL Treat regardless of ALT level HBV DNA <2000 IU/mL Consider treatment if ALT >ULN Regardless of HBV DNA or ALT level Treat and refer for liver transplantation	HBV DNA ≤2000 IU/mL, ALT ≤ULN Monitor HBV DNA detectable Treat regardless of ALT level
Decompensated	Regardless of HBV DNA or ALT level Treat and refer for liver transplantation	Regardless of HBV DNA or ALT level Treat and refer for liver transplantation	Regardless of HBV DNA and ALT level Treat and refer for liver transplantation
HCC surveillance	US every 6 months	US and AFP every 6 months	US every 6 months

US, ultrasound.

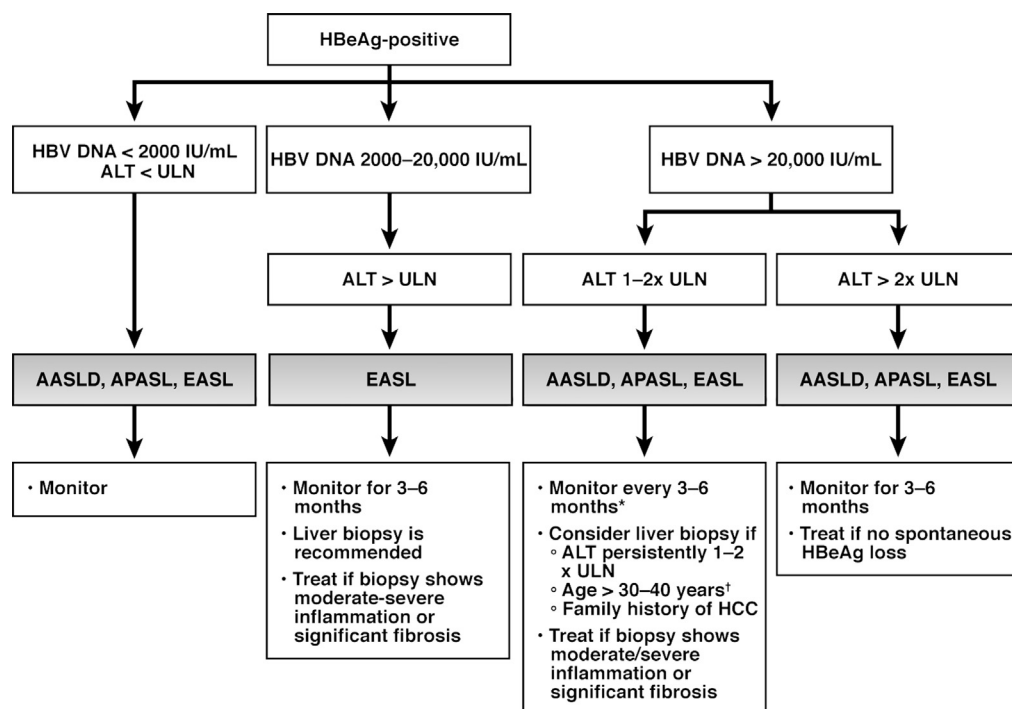


Figure 2. Algorithm showing guideline recommendations for the treatment of patients with HBeAg-positive CHB. *APASL recommends monitoring every 1 to 3 months. †EASL: age, >30 years; AASLD and APASL: age >40 years.

positive and HBeAg-negative patients are summarized in Figures 2 and 3.

Our Practice

In our practice, we initiate treatment as soon as we recognize that the patient has acute liver failure or severe acute hepatitis B (prolonged jaundice or coagulopathy), severe exacerbation of CHB, or decompensated cirrhosis, regardless of ALT or HBV DNA levels. For patients with compensated cirrhosis, we follow the AASLD guidelines, although increasingly we initiate treatment even in patients with HBV DNA levels less than 2000

IU/mL. We have become more liberal in treating patients with compensated cirrhosis because of the high barrier to resistance of the newer antiviral agents entecavir and tenofovir, the established safety of these drugs, and the difficulty in predicting which patient with cirrhosis will develop HCC. For patients without cirrhosis, we follow the AASLD guidelines and recommend treatment if HBV DNA level is greater than 20,000 IU/mL and ALT level is greater than 2 times the ULN. For both HBeAg-positive and HBeAg-negative patients in the gray zone, we recommend liver biopsy particularly if they are older than age 40. We inform the patients that a histologic finding of moderate/severe inflammation/fibrosis will

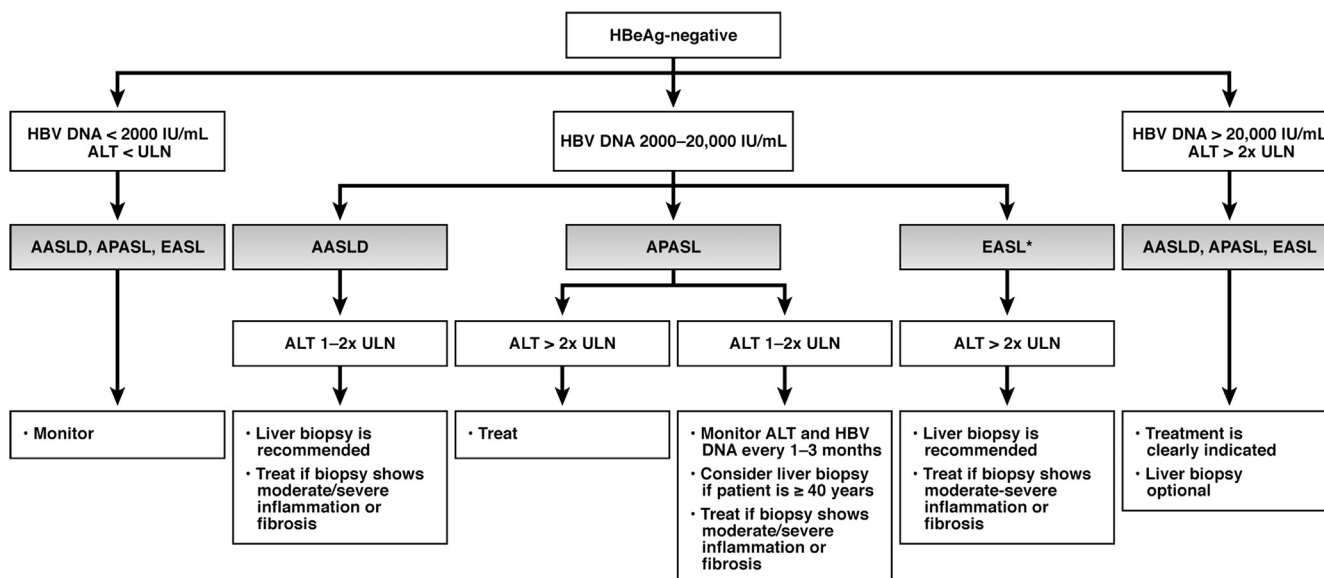


Figure 3. Algorithm showing guideline recommendations for the treatment of patients with HBeAg-negative CHB. *EASL indicates treatment may be initiated in patients with normal ALT level if the biopsy shows moderate-severe inflammation or fibrosis.

urge us to treat, but the absence of these findings does not rule out the risk of HCC. For patients who decline a liver biopsy, we rely on a combination of ultrasound and laboratory tests including the aspartate-aminotransferase-platelet-ratio index to assess stage of liver disease because liver stiffness measurement is not readily available in the United States.

Who Can Be Monitored?

All guidelines agree that treatment is not required in the immune tolerance phase because liver injury is mild and the likelihood of response (in particular HBeAg seroconversion) to available treatment is low.¹⁻³ Liver biopsy should be considered in patients with persistent borderline normal or slightly increased ALT levels, particularly those older than age 40 (age 30 according to the EASL guidelines), and treatment should be recommended if the biopsy shows moderate/severe inflammation and/or fibrosis. All guidelines recommend that patients in the inactive carrier phase do not require treatment.¹⁻³

Our Practice

We do not recommend treatment of patients in the immune tolerance phase except in the context of clinical trials or in patients older than the age of 40. The rationale for treating HBeAg-positive patients who remain in the immune tolerance phase after the age of 40 is because the population-based REVEAL study, in which 67% of patients enrolled were older than age 39, showed that persistently high serum HBV DNA levels are associated with increased risk of cirrhosis, HCC, and liver-related death.⁵ Other studies in Taiwan found that patients who remained HBeAg-positive after age 40 had an increased risk of HCC.⁶ We do not recommend treatment of patients who are confirmed to be in the inactive carrier phase after 3 or more evaluations showing persistently normal ALT level and low (<2000 IU/mL) or undetectable HBV DNA level.

Other Indications for Treatment

The EASL guideline recommends that in women of childbearing age, the immediacy of their plans to become pregnant should be discussed before deciding to initiate treatment.² Perinatal transmission of HBV has been reported to occur in 9% to 39% of newborns of highly viremic mothers (>7–8 log IU/mL).^{10,11} The EASL and APASL recommends prophylactic antiviral treatment in pregnant women with high levels of viremia. Lamivudine, telbivudine, or tenofovir may be considered.

Reactivation of HBV replication in patients receiving immunosuppressive therapy can lead to severe hepatitis, liver failure, and even death. The EASL and AASLD guidelines recommend testing for hepatitis B surface

antigen (HBsAg) and hepatitis B core antibody (anti-HBc) in patients who will be receiving chemotherapy or immunosuppressive therapy.^{1,2} The APASL guideline recommends screening for HBsAg only, and additional testing for anti-HBc in patients who will be receiving biologic treatment such as rituximab or anti-tumor necrosis factor- α .³ Prophylactic antiviral therapy has been shown to decrease the risk of HBV reactivation.¹² All 3 guidelines recommend initiating prophylactic antiviral therapy in HBsAg-positive patients who will be receiving cancer chemotherapy or immunosuppressive therapy and monitoring of HBsAg-negative, anti-HBc-positive patients and initiating antiviral therapy when serum HBV DNA level becomes detectable.¹⁻³ The EASL guideline recommends prophylactic antiviral therapy in patients who will receive rituximab or stem cell transplantation.²

Our Practice

We defer treatment in women who have plans to be pregnant unless they have active or advanced liver disease. We discuss the benefits and risks of prophylactic antiviral treatment with women who have serum HBV DNA level greater than 7 log IU/mL during the second trimester of pregnancy. We recommend starting antiviral treatment around week 30 if the patient agrees and prefer tenofovir in this setting. When the goal of treatment is to prevent perinatal transmission, we stop treatment immediately after delivery and emphasize the importance of monitoring for postpartum flares. We discuss the potential risk of exposing the infant to the antiviral medication if treatment is continued, but we do not advise against breastfeeding.

We recommend HBsAg and anti-HBc testing of all patients who will be receiving chemotherapy or immunosuppressive therapy and prophylactic antiviral therapy in patients at high risk of HBV reactivation: all HBsAg-positive patients and HBsAg-negative, anti-HBc-positive patients with hematologic malignancies or who will require rituximab or long-term high-dose steroid therapy.

Monitoring of Patients With Chronic Hepatitis B Virus Infection

All guidelines recommend that patients who are not deemed to be treatment candidates at presentation and those who decide to defer treatment should undergo monitoring. Guidelines recommend monitoring immune tolerant patients at 3-6 month intervals and more frequent monitoring if ALT levels become increased.¹⁻³ For HBeAg-negative patients with normal ALT and HBV DNA levels less than 2000 IU/mL, the AASLD guideline recommends testing for ALT level every 3 months during the first year to confirm that they are truly in the inactive carrier state.¹ Thereafter, patients should be monitored by ALT and HBV DNA levels every 6 to 12 months.¹⁻³ For

patients with persistently normal ALT and HBV DNA levels between 2000 and 20,000 IU/mL, the EASL guideline recommends monitoring ALT level every 3 months and HBV DNA level every 6 to 12 months for the first 3 years.²

Our Practice

We emphasize to all patients that HBV infection is a chronic condition and regular monitoring is critical. We follow up young (<30 y) patients in the immune tolerance phase every 6 to 12 months and older patients every 3 to 6 months. We monitor HBeAg-negative patients every 3 months over a 1-year period before determining they are truly in the inactive carrier phase, at which time we decrease monitoring to every 6 to 12 months. We ask patients to inform us if they have unexplained fatigue or if they are diagnosed with cancers or other medical conditions that require long-term steroid or other immunosuppressive therapy.

Hepatocellular Carcinoma Surveillance: Who and How?

The AASLD guideline recommends HCC surveillance for HBV carriers who are Asian men older than age 40 and Asian women older than age 50, persons with cirrhosis, persons with a family history of HCC, first-generation African Americans older than age 20, and any carrier older than age 40 with persistent or intermittent ALT increases and/or HBV DNA levels greater than 2000 IU/mL.¹ Surveillance with ultrasonography at 6-month intervals is recommended by the EASL and AASLD guidelines.^{1,13,14} The APASL recommends a combination of ultrasound and α -fetoprotein (AFP) testing every 6 months.¹⁵

Our Practice

We follow the AASLD guidelines regarding which patients should undergo HCC surveillance, but we rely on both AFP and ultrasound. Although AFP has limited sensitivity and specificity, the reliability of ultrasound in the surveillance of HCC is suboptimal and operator-dependent. Studies have shown that AFP and ultrasound are complementary. We evaluate absolute as well as delta AFP values.

First-Line Treatment

Approved medications for chronic HBV infection include interferon (IFN), either standard or pegylated IFN (PEG-IFN), and NUCs, lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir disoproxil fumarate. Rates of response and resistance to these medications are summarized in Table 2.¹⁶

Interferon/Pegylated-Interferon

IFN has both antiviral and immunomodulatory activity, which may lead to a higher rate of HBeAg and HBsAg loss and more durable viral suppression. Phase 3 clinical trials showed that 1-year treatment with pegylated-interferon (PEG-IFN) with or without lamivudine in HBeAg-positive patients resulted in 29% to 32% HBeAg seroconversion and 3% to 7% HBsAg loss 24 weeks after completion of treatment.^{17,18} In one study, follow-up evaluation of patients for 3.5 years after completion of treatment found that HBeAg loss was durable in 81% and HBsAg loss occurred in 30% (58% for genotype A and 11% for genotype non-A) of patients.¹⁹ Phase 3 clinical trials showed that 1-year treatment of PEG-IFN with or without lamivudine in HBeAg-negative patients resulted in a sustained response, defined as normalization of ALT level, suppression of HBV DNA levels to 10,000 IU/mL or less in approximately 25% of patients, and HBsAg loss in 9% at 3 years after completion of treatment.²⁰

IFN is administered parenterally and has many side effects. High serum ALT levels, low viral load, HBV genotype A and B, and high histologic activity index are pretreatment predictors of IFN/PEG-IFN response in HBeAg-positive patients.²¹ Predictive factors for response in HBeAg-negative patients have not been defined clearly. On-treatment ALT flares and HBsAg decreases and interleukin-28B polymorphisms also have been reported to be associated with IFN/PEG-IFN response.^{18,22-24}

Nucleos(t)ide Analogues

NUCs have become the mainstay of CHB treatment because they can be administered orally and have potent antiviral activity and very few side effects. A major drawback with earlier NUCs was the high rate of antiviral drug resistance; however, the new NUCs, entecavir and tenofovir, have high barriers to resistance, with rates of antiviral drug resistance reported to be 1.2% and 0% after 5 years of treatment, respectively, in phase 3 trials of NUC-naïve patients.^{9,20,25,26} The risk of entecavir resistance is much higher, 51% after 5 years of treatment, in patients with lamivudine-resistant HBV.²⁷ Continued treatment with entecavir or tenofovir for up to 5 years resulted in undetectable serum HBV DNA levels in 94% to 98% of patients, HBeAg seroconversion in 40% to 41% of HBeAg-positive patients, and HBsAg loss in 3% to 10%.^{26,28} Long-term viral suppression has been shown to reverse fibrosis and cirrhosis.^{9,28}

High pretreatment ALT level is the most important predictor of response to NUC treatment in HBeAg-positive patients.²⁹ Predictors of response to NUC have not been identified for HBeAg-negative patients. Contrary to IFN, HBV genotype is not predictive of response to NUC, and NUC treatment results in a minimal decrease in HBsAg levels.

Table 2. Response Rates and Genotypic Resistance Rates to Approved Therapies in HBeAg-Positive and HBeAg-Negative Patients¹⁸

Treatment response parameters	Approved therapies						
	Lamivudine	Adefovir dipivoxil	Entecavir	Telbivudine	Tenofovir disoproxil fumarate	PEG-IFN ^a	PEG-IFN plus lamivudine ^a
HBeAg-positive patients							
At week 48 or 52							
Undetectable HBV DNA level, %	36–44	13–21	67	60	76	25	69
HBeAg seroconversion, %	16–21	12–18	21	22	21	27	24
HBsAg loss, %	<1	0	2	0	3	3	3–7
Histologic improvement, % ^b	49–56	53	72	65	74	38	41
Genotypic resistance, %	27	0	0	4.4	0	0	4–11
During extended treatment ^c							
Undetectable HBV DNA level	39 (2)	39 (5)	94 (5)	79 (4)	97 (5)	19 (3.5) ^c	26 (3.0) ^c
HBeAg seroconversion	47 (3)	48 (5)	41 (5)	42 (4)	40 (5)	37 (3.5) ^c	25 (3.0) ^c
HBsAg loss	0–3 (2–3)	2 (5)	5 (2)	1.3 (2)	10 (5)	11 (3.5) ^c	15 (3.0) ^c
Genotypic resistance	65 (5)	42 (5)	1.2 (6)	21 (2)	0 (5)	0	NA
HBeAg-negative patients							
At week 48 or 52							
Undetectable HBV DNA level, %	60–73	51	90	88	93	63	87
HBsAg loss, %	<1	0	<1	<1	0	4	3
Histologic improvement, % ^b	60–66	64–69	70	67	72	48	38
Genotypic resistance, %	23	0	0.2	2.7	0	0	1
During extended treatment ^c							
Undetectable HBV DNA level, %	6 (4)	67 (5)	NA	84 (4)	99 (5)	18 (3) ^d	13 (3) ^d
HBsAg loss, %	<1 (4)	5 (5)	NA	<1 (2)	0.3 (5)	8 (3) ^d	8 (3) ^d
Genotypic resistance, %	70–80 (5)	29 (5)	NA	8.6 (2)	0 (5)	0	NA

^aLiver biopsy was performed at week 72 or 78, 24 weeks after stopping treatment.^bHistologic improvement was defined as a ≥ 2 -point decrease in necroinflammatory score and no worsening of fibrosis score.^cThe time point at which response was assessed in years from start of treatment is shown in parentheses.^dAssessment was performed while off treatment.

Resistance to lamivudine or telbivudine (M204V/I) increases the risk of resistance to entecavir, and resistance to adefovir (N236T) decreases susceptibility to tenofovir. To date, there has been no confirmed case of genotypic resistance to tenofovir in patients with HBV mono-infection. Combination of 2 NUCs with no cross-resistance have been proposed to prevent the development of drug resistance; however, the need for combination therapy is doubtful given the low rate of resistance to entecavir or tenofovir monotherapy. Furthermore, although combination of 2 NUCs can accelerate viral suppression in patients with high viremia,³⁰ there is no evidence that combination therapy will result in incremental clinical benefit.

Approved NUCs for HBV are generally safe. Mitochondrial toxicity is a potential side effect of NUCs but is very rare. Myopathy and neuropathy have been reported in patients treated with telbivudine,³¹ lactic acidosis has been reported in patients with severely impaired liver function treated with entecavir,³² and nephrotoxicity and renal tubular dysfunction have been reported in patients receiving adefovir or tenofovir.³³

Which Should Be the First-Line Treatment?

Selection of first-line treatment should be based on the safety and efficacy of the medication, risk of drug resistance, cost of treatment, and patient preference. The main advantages of IFN include a finite duration of treatment and a higher rate of HBeAg and HBsAg loss, particularly in HBeAg-positive patients with genotype A. NUCs are well tolerated but most patients require many years or lifelong treatment. Entecavir, telbivudine, and tenofovir have more potent antiviral activity, and entecavir and tenofovir have very low rates of drug resistance.

The AASLD, EASL, and APASL guidelines all recommend initial treatment with PEG-IFN, entecavir, or tenofovir as monotherapy.^{1–3} Because of cost concerns and the lack of access to tenofovir in some Asian countries, the APASL guideline recommends entecavir, adefovir, telbivudine, or lamivudine as first-line treatment in treatment-naïve patients.³ To avoid hepatic decompensation secondary to ALT flare, APASL recommends NUCs and not IFN in patients with an ALT level greater than

5 times the ULN.³ IFN is not recommended in patients with acute liver failure, decompensated cirrhosis, or severe exacerbations of CHB in all 3 guidelines. The EASL and APASL guidelines indicate PEG-IFN can be used with careful monitoring in patients with compensated cirrhosis because IFN has been shown to be safe in carefully selected patients with compensated cirrhosis in clinical trials.^{1,2} The AASLD guideline states that patients with compensated cirrhosis are best treated with NUCs because of the risk of hepatic decompensation associated with IFN-related hepatitis flares.¹ All guidelines recommend entecavir or tenofovir as the preferred treatment in patients with decompensated cirrhosis. Two randomized trials in patients with decompensated cirrhosis showed similar efficacy and safety after 1 to 2 years of treatment with tenofovir, emtricitabine/tenofovir, or entecavir in one study, and entecavir vs tenofovir in another study.^{34,35}

Our Practice

We follow the 3 guidelines and recommend PEG-IFN, entecavir, or tenofovir monotherapy as first-line treatment to patients with no cirrhosis. Despite our experience with PEG-IFN and our belief that PEG-IFN has a higher chance of HBeAg and HBsAg loss in patients, less than 10% of our patients opt for PEG-IFN. We are more enthusiastic in recommending PEG-IFN to young patients, particularly those who are hesitant to commit to a long duration of treatment and young women who are planning to start a family within the next 2 to 3 years. For NUC-naïve patients, we believe that entecavir and tenofovir are comparable. We prefer entecavir in patients who are at increased risk of renal impairment such as patients with decompensated cirrhosis, older patients, and patients with hypertension or diabetes. We prefer tenofovir in young women who might become pregnant during the course of treatment. During the past 5 to 6 years, we have not initiated treatment with lamivudine, telbivudine, or adefovir in any patient. In addition, we systematically have switched patients from adefovir to tenofovir because tenofovir is more potent. For patients taking lamivudine plus adefovir because of prior lamivudine resistance, we have switched them to tenofovir monotherapy if they have undetectable HBV DNA levels or to the combination pill Truvada (emtricitabine plus tenofovir; Gilead, Foster City, CA). We have switched most patients taking lamivudine monotherapy to tenofovir, except for a few who had been on lamivudine for many years with undetectable serum HBV DNA levels because the risk of antiviral drug resistance in these patients is very low.

Monitoring During Treatment and Deciding When to Stop Treatment

Guidelines recommend all patients should be monitored closely during treatment to evaluate response,

tolerability, and adherence. Patients receiving IFN require frequent clinical and laboratory monitoring. Guidelines recommend monitoring patients receiving IFN/PEG-IFN therapy with blood counts and a liver panel every 4 weeks initially and then every 4 to 12 weeks.¹⁻³ The AASLD and EASL also recommend thyroid-stimulating hormone testing every 12 weeks.^{1,2} The AASLD and APASL recommend monitoring HBV DNA levels every 12 weeks, and the EASL recommends HBV DNA testing at weeks 24 and 48.¹⁻³ The EASL guideline also recommends monitoring HBsAg levels at week 12.² For patients who initially were HBeAg positive, the AASLD and EASL recommend HBeAg and hepatitis B e antibody (anti-HBe) testing every 24 weeks during treatment, and the APASL recommends testing every 12 weeks.¹⁻³ After completion of IFN/PEG-IFN therapy, blood counts, liver panel, HBeAg, and anti-HBe if initially HBeAg-positive should be tested every 12 weeks during the first 24 weeks. In the post-treatment period, the APASL recommends monitoring ALT and HBV DNA levels monthly for the first 3 months and then every 3 months in the first year.³ The AASLD and EASL recommend HBsAg testing every 6 to 12 months in patients with HBeAg seroconversion and undetectable HBV DNA levels.^{1,2} Patients receiving NUC should have their renal function checked initially to ensure appropriate dosing. Patients who are at risk of impaired renal function should have their renal function monitored regularly, particularly if they are receiving adefovir or tenofovir because of the risk of nephrotoxicity. A phase 3 trial of tenofovir showed that only 1% of patients had an increase in serum creatinine level after 5 years treatment.⁹

All guidelines recommend administration of PEG-IFN for 48 to 52 weeks in both HBeAg-positive and HBeAg-negative patients.¹⁻³ There is some variation in recommendations regarding when NUC can be stopped. All guidelines recommend that in HBeAg-positive patients, NUC can be stopped when the patient has achieved HBeAg seroconversion and undetectable HBV DNA levels and completed 6 to 12 months of consolidation treatment.¹⁻³ Because of the high rate of relapse after withdrawal of NUC and the persistence of HBV replication in some patients despite HBeAg seroconversion, the EASL recommends continuing NUC until HBsAg loss in patients with severe fibrosis and cirrhosis.² Given the low rate of NUC-induced HBsAg loss, most of these patients will remain on treatment indefinitely.

In HBeAg-negative patients, the EASL and AASLD agree that NUC should be continued until the patient has achieved HBsAg clearance^{1,2}; however, the APASL recommends considering withdrawal of treatment in HBeAg-negative patients who have been treated for 2 years with undetectable HBV DNA levels documented on 3 separate measurements 6 months apart.³ The basis for the APASL recommendation is related mainly to cost.

All guidelines recommend lifelong NUC in patients with cirrhosis before treatment; however, discontinuation of treatment may be considered in patients who had

Table 3. AASLD and EASL Recommendations for Salvage Therapy in Patients With Antiviral Drug Resistance^{1,2}

Drug to which resistance has developed	AASLD (2009)	EASL (2012)
Lamivudine or telbivudine resistance	Add adefovir or tenofovir Stop lamivudine, switch to Truvada	Switch to tenofovir Add adefovir if tenofovir is not available
Adefovir resistance	Add lamivudine Stop adefovir, switch to Truvada Switch to or add entecavir	If nucleoside-naïve before adefovir then switch to entecavir or tenofovir If the patient has high viremia then switch to entecavir If there is prior lamivudine resistance then switch to tenofovir or add a nucleoside analogue
Entecavir resistance	Switch to tenofovir or Truvada	Switch to or add tenofovir Add adefovir if tenofovir is not available

compensated cirrhosis if they achieved HBsAg loss.¹⁻³ After withdrawal of treatment, patients need to be monitored closely for relapse so that treatment can be re-instituted promptly if needed.

Our Practice

We follow the guidelines regarding monitoring of patients on treatment. In patients receiving IFN, we continue treatment if there is an ALT flare unless the patient is symptomatic or bilirubin level is increased. In patients receiving NUC, we monitor serum HBV DNA levels less often now than in the past when we were using drugs with a lower barrier to resistance. We test serum HBV DNA levels every 3 months until it becomes undetectable and every 6 months thereafter. We check HBeAg and anti-HBe levels every 6 to 12 months in patients who are HBeAg positive, and we check HBsAg every year in patients who are HBeAg negative with undetectable serum HBV DNA levels.

For patients receiving NUC, we continue treatment indefinitely in those who had cirrhosis before treatment and in many older patients (>60 y) unless they lose HBsAg. For noncirrhotic HBeAg-positive patients, we discontinue treatment after 12 months of consolidation therapy because of reports of low durability of NUC-induced HBeAg seroconversion and the encouraging results of 12 months of consolidation therapy in one study.³⁶ For noncirrhotic HBeAg-negative patients, we discontinue treatment after confirmed HBsAg loss, but this has happened to only 1 patient in the past 5 years. We have, however, discontinued treatment in several patients who can no longer afford or are no longer willing to commit to long-term treatment if they have completed at least 5 years of treatment with undetectable HBV DNA levels in the past 3 years. Although all patients experienced virologic relapse after treatment was stopped, most patients continue to have low HBV DNA levels and normal ALT levels and have not required resumption of treatment, confirming the observations of Hadziyannis et al.³⁷

Management of Treatment Failure

Recent studies have suggested that a lack of or insufficient decrease in HBsAg level by week 12 of PEG-IFN is associated with a low chance of sustained response.^{38,39} The 2012 EASL guideline recommends discontinuation of PEG-IFN in HBeAg-positive patients who fail to achieve serum HBsAg levels of less than 20,000 IU/mL or who have no decrease in serum HBsAg levels by week 12 because these patients have a low probability of achieving HBeAg seroconversion.² For HBeAg-negative patients, particularly those with genotype D, discontinuation of PEG-IFN is recommended if they fail to achieve any decline in serum HBsAg levels and a 2 log₁₀ decrease or greater in HBV DNA levels by week 12.² Patients who failed to respond to IFN therapy can be treated with NUC with the expectation of a similar response as treatment-naïve patients.

Primary nonresponse is very rare with NUC therapy except for adefovir. An inadequate decrease in HBV DNA levels during the first 12 to 24 weeks of NUCs that have a low barrier to resistance is associated with a higher chance of subsequent antiviral resistance, prompting the roadmap approach that recommends the addition of a second NUC in patients with an inadequate initial response; however, these data do not apply to NUCs with a high barrier to resistance. Phase 3 trials and observations in clinical practice showed that patients with detectable HBV DNA levels after 48 weeks of entecavir or tenofovir have a very low rate of antiviral resistance even if they continue on the same treatment.^{26,40} Guidelines recommend counseling patients with a virologic breakthrough regarding medication adherence and confirmation of breakthrough by retesting HBV DNA levels after 1 to 3 months. Salvage therapy should be initiated immediately in patients who have decompensated liver disease or severe hepatitis flares, but in other patients it can be deferred until after breakthrough is confirmed to avoid unnecessary changes in medications. The choice of salvage therapy depends on the current and prior treatments and the pattern of drug

resistance mutations. The EASL and AASLD recommendations for salvage therapy are shown in Table 3.^{1,2}

Our Practice

Quantitative HBsAg assays are not available for clinical use in the United States. We recommend completion of the intended duration of PEG-IFN therapy unless the patient experiences serious adverse events or there is little or no decrease in serum HBV DNA level after 3 to 6 months treatment.

For NUC-naïve patients receiving entecavir or tenofovir, we have encountered only 1 patient (out of >200) with confirmed entecavir resistance and none with confirmed tenofovir resistance. We found that transient reappearance of serum HBV DNA at low levels, typically less than 100 IU/mL, occurs in some patients. Although many of these instances may be related to medication nonadherence, some, particularly those with levels below the limit of quantification, may represent false-positive results. In NUC-naïve patients receiving entecavir or tenofovir monotherapy with detectable HBV DNA levels after 1 year of treatment, we have not adapted treatment as long as the HBV DNA level is low (<10,000 IU/mL) and continues to decrease. We have added a second drug in a few patients on dialysis receiving weekly dosing of entecavir and 2 patients with high baseline HBV DNA levels receiving immunosuppressive therapy.

Conclusions

Guidelines provide an evidence-based framework for managing patients; however, management of individual patients must be flexible, taking into account the patient's preference and other medical or psychosocial conditions, evolution in knowledge over time, and the provider's experience.

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Conflicts of interest

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