

Indications for Therapy in Hepatitis B

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Increased treatment options that are more efficacious and safe and new knowledge on the natural history of chronic hepatitis B virus (HBV) infection have expanded the indications for therapy in hepatitis B. The question is no longer “Who should be treated?” but “When should treatment be initiated?” Treatment is clearly indicated in patients with life-threatening liver disease (acute liver failure, decompensated cirrhosis, or severe hepatitis flare) and in those with compensated cirrhosis and high levels of serum HBV DNA. For patients with precirrhotic liver disease, treatment indications should be based on clinical, biochemical, or histological evidence of liver disease, such as elevated alanine aminotransferase (ALT) levels, abnormal histology, and high levels of serum HBV DNA. The cutoff for ALT and HBV DNA values are constantly being revised and should be set at a lower level for older patients who may have been infected for a longer period of time. High serum HBV DNA levels persisting for a few decades are associated with increased risk of clinical outcomes, but there is insufficient data to support the initiation of treatment based on high serum HBV DNA alone, particularly in young patients, those with persistently normal ALT levels, and those with a single high HBV DNA level. The decision to initiate treatment at the time of assessment or to defer treatment should take into consideration other factors such as desire to start a family, occupational requirement, family history of hepatocellular carcinoma, access to care and insurance coverage, and commitment to long-term treatment and medication compliance. All patients who are not initiated on treatment should continue to be monitored so treatment can be started if and when the indication arises. (HEPATOLOGY 2009;49:S129-S137.)

Introduction

Substantial progress has been made in the treatment of hepatitis B in the last decade. Increased treatment options that are more efficacious and safe, together with new knowledge on the natural history of chronic hepatitis B virus (HBV) infection, have expanded the indications for therapy in hepatitis B. The question is no longer “Who should be treated?” but “When should treatment be initiated?” Every person with chronic HBV infection is a

potential candidate for treatment. The patient who is not a treatment candidate at the time of presentation may become one in the future because of the dynamic nature of chronic hepatitis B as shown by spontaneous changes in virus replication status and/or activity or stage of liver disease. When deciding whether to start or to defer treatment, one needs to have information on the activity and stage of liver disease at the time of assessment and the predicted risk for developing cirrhosis and hepatocellular carcinoma (HCC). Thus, treatment should be initiated in patients who have active or advanced liver disease at presentation or who are predicted to have a high risk of cirrhosis and HCC in the foreseeable future.¹ On the other hand, treatment can be deferred in patients who have quiescent, early stage liver disease, and who are predicted to have a low risk of cirrhosis and HCC. The latter patients should continue to be monitored, and treatment can be initiated if and when the indications arise.

Decisions regarding hepatitis B treatment are usually made based on clinical features, levels of serum alanine aminotransferase (ALT) and HBV DNA, and, when available, liver histology (Table 1). The decisions are further modified by patient age, hepatitis B e antigen (HBeAg) status, occupational requirements, patient preference, and, in women of reproductive age, plans for start-

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; RR, relative risk; ULN, upper limit of the normal range.

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Table 1. Factors to Consider When Deciding When Treatment Should Be Initiated

A. Factors that Play a Role in Disease Progression	
1. Age	
2. Duration of infection	
3. HBV replication: serum HBV DNA level, HBeAg status	
4. Hepatic necroinflammatory activity or serum ALT levels	
5. Hepatic fibrosis	
6. Coinfection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus	
7. Family history of HCC	
B. Factors Associated with Treatment Response	
1. HBV DNA replication: serum HBV DNA level, HBeAg status	
2. Activity of liver disease: serum ALT level, histological necroinflammatory activity	
3. HBV genotype (interferon treatment only)	
C. Patient-Related Factors	
1. Age	
2. Plans to start a family in women of reproductive age	
3. Occupational requirements	
4. Cost and health insurance coverage	
5. Patient preference: willingness to commit to long-term treatment	

ing a family. Because current HBV treatments suppress but do not eradicate the virus, most patients require long-term therapy and some may require life-long therapy, which raise the important issues of drug resistance, adverse events, and costs. For these reasons, the decision to initiate treatment should also take into account the anticipated duration of treatment and the likelihood of achieving sustained virus suppression after a finite course of treatment.

Life-Threatening HBV-Related Liver Disease

The indication to start treatment is obvious in patients who present with life-threatening HBV-related liver disease: acute liver failure or decompensated cirrhosis. Although randomized controlled trials have not been performed in these settings, case series support a beneficial role of antiviral treatment, and adverse events have not been reported in patients who received nucleoside analog

therapies. Furthermore, antiviral therapy will reduce the risk of HBV recurrence should these patients require liver transplantation.

Acute Liver Failure. In a prospective study of lamivudine therapy in 17 patients with severe acute or fulminant hepatitis B, therapy was associated with a lower rate of hepatic encephalopathy (18% versus 69%) as well as mortality or need for liver transplantation (18% versus 80%) compared to historical controls.² However, antiviral therapy is usually not necessary in patients with acute hepatitis B. Thus, in a randomized controlled trial of lamivudine versus placebo in 71 patients with acute hepatitis B and jaundice (serum bilirubin >5 mg/dL), serum HBV DNA levels decreased more rapidly in lamivudine-treated patients, but there was no difference in rate or rapidity of biochemical or clinical improvement compared to placebo. At 1 year, 94% of treated patients and 97% of the controls had cleared hepatitis B surface antigen (HBsAg).³

The American Association for the Study of Liver Diseases (AASLD) Practice Guidelines recommend that only patients with acute liver failure or protracted, severe acute hepatitis (prolonged prothrombin time and deep jaundice persisting for more than 4 weeks) be treated (Table 2).¹ This recommendation is empiric but is based on the potential for benefit and lack of evidence for harm.

Decompensated Cirrhosis. Several uncontrolled studies of patients with decompensated cirrhosis have shown that antiviral therapy results not only in biochemical improvement but also stabilization of liver disease, allowing these patients to undergo liver transplantation.⁴⁻⁶ In some cases, antiviral therapy led to the resolution of complications of cirrhosis, thus obviating the need for transplant.⁷

The AASLD Practice Guidelines recommend that antiviral therapy be initiated in patients with decompensated cirrhosis and detectable serum HBV DNA

Table 2. Treatment Recommendations for Patients with Life-Threatening or Advanced HBV-Related Liver Disease

	HBV-DNA	ALT	Recommendation
Acute Liver Failure	Detectable*	Any value	Start treatment for patients with acute liver failure or protracted, severe acute hepatitis
Decompensated Cirrhosis	Detectable	Any value	Start treatment as soon as possible, and coordinate treatment with transplant center
Severe Hepatitis Flare	Detectable*	Abrupt ALT increase, usually >10× ULN	Immediate treatment if associated coagulopathy and clinical jaundice
Compensated Cirrhosis	>2000 IU/mL	Any value	Start treatment
	<2000 IU/mL	Elevated	Start treatment

*Lack of data to support which cutoff HBV DNA level for initiating treatment.

ULN, upper limit of normal.

Adapted with permission from Lok and McMahon.¹

Table 3. Effect of Lamivudine and Antiviral Resistance on Treatment Outcomes in Patients with Advanced Fibrosis or Cirrhosis (Liaw et al.)¹⁵

Endpoints of Treatment Outcome	Type of Treatment				P Value†
	Lamivudine Group (n = 436)		Placebo Group (n = 215)		
	Total (n = 436)	Resistance (+)* (n = 209)	Resistance (-) (n = 221)	Total (n = 215)	
Overall disease progression	7.8%	11%	5%	17.7%	0.001
Increase in Child-Pugh score	3.4%	7%	0.4%	8.8%	0.002
Hepatocellular carcinoma	3.9%	4%	4%	7.45%	0.047
Renal insufficiency	0.5%			0	—
Bleeding varices	0.5%			1.4%	—
Spontaneous bacterial peritonitis	0	0	0	0	—
Liver-related death	0	0	0	0	—

All patients were HBeAg positive and/or had serum HBV DNA levels of greater than 700,000 genome equivalents/mL.

*Lamivudine resistance was defined as presence of YMDD mutation (rtM180V/I).

†P values for entire lamivudine group vs. placebo group.

NA, not available.

regardless of ALT level (Table 2).¹ Treatment should be initiated as soon as possible because clinical improvement usually requires 3-6 months.⁵

Severe Flares of Hepatitis. Flares or acute exacerbations of hepatitis are common during the course of chronic HBV infection. Some flares are a manifestation of immune clearance and precede clearance of HBeAg and subsequent remission in disease.⁸ Other flares are associated with only transient virus suppression without improvement in disease activity. Patients with mild flares of hepatitis may be observed in the hope that spontaneous HBeAg seroconversion will ensue; those with severe flares (accompanied by increases in serum bilirubin levels or prothrombin time) should receive antiviral therapy, because hepatic decompensation and deaths from liver failure have been reported.⁹ The benefit of antiviral therapy in patients with severe flares of hepatitis has not been evaluated in prospective, randomized controlled trials. However, several case series have reported biochemical and clinical improvement and increased survival compared to historical controls.^{10,11}

The AASLD Practice Guidelines recommend that antiviral therapy be initiated in patients with severe or icteric flares (Table 2).¹

Compensated Cirrhosis

Patients with compensated cirrhosis are at risk of developing liver failure and HCC. Some, but not all, long-term follow-up studies have reported that patients who received interferon therapy for chronic hepatitis B with or without cirrhosis had decreased progression to liver failure, HCC, and liver-related mortality. However, a meta-analysis of the studies identified marked heterogeneity in the results, particularly in HCC development, and re-

ported that benefit was observed mainly in patients who achieved sustained virus suppression.¹² The discrepancies in the study outcomes were largely related to the low rate of sustained virus suppression that is typical of interferon therapy and the lack of randomization in the studies which might have caused imbalances between the treated and untreated patients. A beneficial long-term effect of lamivudine therapy on clinical outcomes had also been reported,^{13,14} but most of these studies also were not randomized, and many had the same limitations as the studies of interferon therapy.

The benefit of antiviral therapy in improving clinical outcome in patients with high levels of HBV replication and advanced fibrosis or cirrhosis was convincingly demonstrated in a landmark prospective, double-blind, placebo-controlled randomized trial of lamivudine from China, Southeast Asia, and Australia. In this study, 651 patients who were HBeAg-positive and/or had high levels of serum HBV DNA (>700,000 genome equivalents/mL, ~200,000 IU/mL) with bridging fibrosis or cirrhosis (an Ishak fibrosis score of 4 or greater) on liver biopsy were randomized in a 2:1 ratio to receive lamivudine or placebo.¹⁵ After a median duration of 32 months (range: 0-42 months), 7.8% of treated patients compared to 17.7% of controls ($P = 0.001$) reached one of several predetermined clinically important endpoints (Table 3). Clinical benefit was observed mainly in patients who did not develop viral resistance to lamivudine. These findings provide firm support to the recommendation that patients with advanced liver disease and high levels of HBV DNA receive antiviral therapy. Uncertain is which antiviral agent should be used, for how long, and using what endpoints to gauge success or failure of therapy. Furthermore, the efficacy of antiviral therapy in preventing disease pro-

gression in patients with lower levels of HBV DNA has not been established.

The AASLD Practice Guidelines recommend that antiviral therapy be initiated in all patients with compensated cirrhosis and serum HBV DNA > 2000 IU/mL (Table 2).¹ This lower threshold HBV DNA level was chosen on the basis of recent evidence that high levels of HBV DNA (>10,000 copies/mL or ~2000 IU/mL) is a strong predictor of disease progression.¹⁶⁻¹⁹ However, the efficacy of antiviral therapy in preventing clinical outcomes in patients with compensated cirrhosis and serum HBV DNA between ~2000 and ~200,000 IU/mL (the higher levels being the cutoff used in the large lamivudine trial in patients with advanced fibrosis or cirrhosis) has not been established.

Compensated Precirrhotic Liver Disease

Treatment Indication Based on ALT and Histology. Traditionally, treatment indications for chronic hepatitis B are based on elevated ALT levels and/or inflammation or fibrosis on liver biopsy. A threshold ALT level of two times the upper limit of the normal range (ULN) has been recommended, based on the assumption that the ALT level is a reliable marker for necrosis and inflammation in the liver. More importantly, elevated ALT levels are a strong predictor of antiviral treatment-related response (HBeAg seroconversion). Pooled data from 805 adults who received lamivudine, interferon, the combination of lamivudine and interferon, or placebo showed that among patients with pretreatment ALT levels of greater than twice the ULN, all three treatment groups had a higher rate of HBeAg seroconversion compared to the control group.²⁰ By contrast, among patients with pretreatment ALT levels of one to two times ULN or less than the ULN, treatment did not result in a higher rate of HBeAg seroconversion than the control group. A strong correlation between pretreatment ALT levels and HBeAg seroconversion has also been observed in patients who received other nucleoside analogs or peginterferon (Fig. 1).²⁰⁻²⁴

Currently, antiviral therapy is recommended for patients with HBeAg-positive or HBeAg-negative chronic hepatitis B (i.e., HBeAg-positive patients in the immune-active or clearance phase and HBeAg-negative patients in the reactivation phase). Treatment is not recommended for HBeAg-positive patients in the immune-tolerant phase because these patients rarely have significant liver disease and have a low likelihood of treatment-related HBeAg seroconversion. Treatment is also not recommended for HBeAg-negative patients in the inactive carrier state because the prognosis of these patients is generally favorable and there is no evidence that further

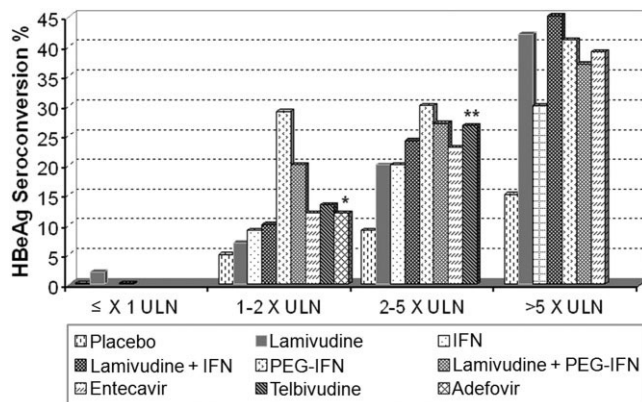


Fig. 1. HBeAg seroconversion rates in relation to pretreatment ALT level in patients who received placebo, lamivudine, interferon (IFN), lamivudine + IFN, pegylated IFN (PEG-IFN), lamivudine + PEG-IFN, entecavir, telbivudine, or adefovir. * >1.2 × upper limit of normal (ULN); ** ≥2 × ULN

suppression of low serum HBV DNA levels improves underlying liver histology or affects disease progression.

Should Treatment Indication Be Based Solely on Serum HBV DNA? Recently, several large population-based studies have suggested that indications for treatment of chronic hepatitis B should be based on HBV DNA levels alone, without major consideration of ALT levels or liver histology. These studies reported a close association of high levels of serum HBV DNA (and HBeAg) with increased risk of cirrhosis, HCC, and liver-related mortality even in patients with normal ALT levels.^{16-19,25} In a community-based prospective study, 2361 HBsAg-positive Taiwanese men, aged 30-65 years, were followed for an average of 8.5 years for clinical outcomes of hepatitis B. Among men who were HBeAg-positive at entry, there was a 6.2-fold increase in adjusted relative risk (RR) of HCC compared to those who were HBeAg-negative.²⁵ In a nested case-control analysis of the men who were HBeAg-negative, the odds ratio for HCC development was 2.3 for those with baseline HBV DNA of 2.5-13 pg/mL (~5-6 log₁₀ IU/mL) and 6.0 for those with HBV DNA of >13 pg/mL. A second larger, prospective study among both men and women from Taiwan (the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV [REVEAL-HBV] Study) provided long-term follow-up (mean = 11 years) on more than 3500 HBsAg carriers (85% HBeAg-negative), aged 30-65 years. In that study, the risk of development of cirrhosis (identified clinically or by ultrasound) increased with serum HBV DNA levels (taken at the start of the study) in a dose-dependent manner. The multivariate adjusted RR of cirrhosis started to increase at an entry HBV DNA level of 10,000 copies/mL (RR = 2.5; 95% confidence interval = 1.6-3.8) and went up to 6.5 (95% con-

fidence interval = 4.1-10.2) for carriers with entry HBV DNA levels above 1,000,000 copies/mL.¹⁷ In this same study, baseline serum HBV DNA levels of greater than 10,000 copies/mL was a strong predictor of HCC, independent of HBeAg status, ALT level, and presence of cirrhosis¹⁶; and death from HCC or other liver-related causes.¹⁹ Similar findings have been observed in studies conducted in Hong Kong, China, Greece, Italy, and Senegal.²⁶⁻²⁸

To date, most studies of predictors of clinical outcomes in HBsAg carriers has focused on baseline HBV DNA levels. In the REVEAL-HBV Study, when paired HBV DNA levels at entry and at last follow-up were considered, the risk of HCC was significantly increased only in individuals with serum HBV DNA levels exceeding 10,000 copies/mL in one sample and 100,000 copies/mL in the other sample but not in those with serum HBV DNA between 4-5 log₁₀ copies/mL in both.¹⁶ In another study of 240 Taiwanese adults with a mean age of 28 years who presented in the immune-tolerant phase, the rate of progression to cirrhosis increased markedly in those who had delayed HBeAg seroconversion: 28% versus 4.1% and 1.1% in patients who had HBeAg seroconversion after age 39, between 30-39, and prior to 30 years, respectively.²⁹ These findings indicate that persistently high levels of HBV DNA and continued presence of HBeAg is more predictive of poor outcome than a single high HBV DNA level or initial presence of HBeAg.

Most studies supporting the importance of serum HBV DNA levels in predicting outcome in chronic hepatitis B were conducted in Asian countries, where the majority of the patients were likely infected perinatally or in childhood. In these studies, the median age at enrollment was above the age of 40 years, indicating that those with high baseline HBV DNA levels may have had high levels of HBV replication for more than 4 decades. Whether results from these studies can be generalized to patients with adult-acquired HBV infection or patients with childhood-acquired HBV infection who are in their teens and twenties is unclear.

Is Treatment Indicated in Patients with Normal ALT Levels? The serum ALT is a marker of hepatic necrosis and inflammation, and patients with normal ALT levels are generally considered to have minimal liver injury with negligible risk of liver-related mortality. Therefore, treatment is not recommended for patients with normal ALT levels unless there is other clinical or histological evidence of active or advanced liver disease.

Recent studies have reported that up to half of HBV carriers with normal ALT levels may have histologically significant liver disease. However, most of these studies were small, and it was unclear whether the patient samples

were broadly representative. In these studies, patients were tested for ALT levels only once or only on a few occasions, and most patients who underwent evaluation had high levels of serum HBV DNA levels (>4-5 log₁₀ copies/mL). In one study, only patients with serum HBV DNA >4 log₁₀ copies/mL underwent liver biopsy,³⁰ and normal ALT levels were documented to be persistently normal, based upon testing on at least two occasions at least 6 months apart and with no ALT level being elevated at any time before the biopsy. Of the 59 patients who met these stringent requirements for having normal ALT levels, significant fibrosis (Metavir stage of 2 or more in a range of 0-4) was found in 18% and significant inflammation (Metavir grade of 2 or more in a range of 0-3) was found in 34% of patients. Age greater than 40 years was a predictor of significant liver disease. In a second study using stringent ALT criteria, 21% of HBeAg-negative patients with normal ALT levels and HBV DNA levels below 5 log₁₀ copies/mL had histologically active liver disease.³¹ However, only 29 of the 75 patients who met the ALT and HBV DNA criteria underwent liver biopsy. Furthermore, the conclusion that a fair proportion of "inactive carriers" had histologically significant liver disease was based on the findings of six patients who had a maximum fibrosis score of 1 (in a range of 0-4) and a maximum histology activity index of 5 (in a range of 0-18).

Studies that focused on patients in the immune-tolerant phase have shown that hepatic inflammation and fibrosis are negligible to mild in most patients. In a study of 40 patients (median age 29 years, median HBV DNA level 8.6×10^8 copies/mL), 20 had stage 0 fibrosis (Metavir), and the other 20 had stage 1.³² Nine patients had Metavir activity grades of 0, 29 had grade 1, and two had grade 2. In another study of 57 patients (median age 31 years, median HBV DNA 9.8 log₁₀ copies/mL), Ishak fibrosis scores (range 0-6) were 0 in 19 patients and 1 in 38 patients.³³ Follow-up biopsies after a mean of 5 years revealed no change in the fibrosis score in 42 of 48 patients who remained in the immune-tolerant phase.

These findings indicate that histologically significant liver disease can be found in HBV carriers with normal ALT levels, but the likelihood is low in those with persistently normal ALT levels, particularly if they are younger than 40 years or have serum HBV DNA levels below 10,000 copies/mL (~2000 IU/mL).

Two studies have reported that HBV carriers with ALT levels that are normal but between 0.5 and 1 times ULN ("high normal") had higher rates of liver-related deaths or liver-related complications than those with ALT levels <0.5 times ULN ("low normal"). In the first study, only two ALT values 2 years apart were analyzed, and the etiology of the liver disease was not determined.³⁴ In the

second study, all patients had chronic HBV infection but only one ALT value at presentation was analyzed, and corresponding HBV DNA level was not available.³⁵ Other studies found that patients in the inactive carrier state have negligible liver-related morbidity or mortality, particularly if the patients reach this phase early and stay in the inactive state indefinitely.³⁶⁻³⁸ These studies found that adverse outcome occurred mainly in patients who had sustained reactivation of HBV replication.^{37,38}

Treatment Recommendations for Precirrhotic Liver Disease. Increasing evidence support that high level HBV replication, particularly if persistent, is an important predictor of adverse outcome, and normal ALT levels, if not sustained, do not guarantee the absence of significant liver disease. Thus, while ALT levels were a key factor in the 2007 AASLD Practice Guidelines on indications for treatment of chronic hepatitis B, patient age, HBeAg status, serum HBV DNA level, liver histology, and family history of HCC were also considered. The guidelines did not recommend treatment based on serum HBV DNA alone, because high serum HBV DNA level on a single occasion has not been shown to be associated with increased risk of clinical outcomes even in persons who had been chronically infected for more than 4 decades.

HBeAg status can influence treatment decision in several ways. Treatment can be deferred at least temporarily in HBeAg-positive patients who have elevated ALT levels and compensated liver disease because some of these patients may achieve spontaneous HBeAg seroconversion in the next few months. Treatment can also be deferred in HBeAg-positive patients who have persistently normal ALT values (those in the immune-tolerant phase), because the likelihood of significant liver disease and of treatment-related HBeAg seroconversion is low.^{20,29,33} Treatment should not be deferred in patients with HBeAg-negative chronic hepatitis, because the likelihood of sustained spontaneous remission is low. However, the need for long-term, and often lifelong, treatment may

Management of HBeAg-Positive Precirrhotic Patients*

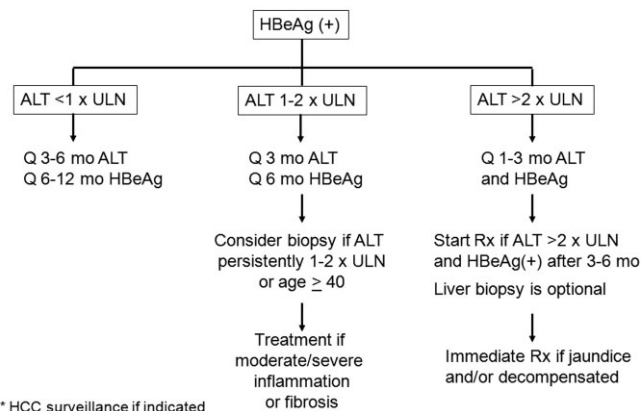


Fig. 2. Algorithm for management of HBeAg-positive patients with precirrhotic liver disease. ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; Rx, treatment; ULN, upper limit of the normal range. Adapted with permission from Lok and McMahon.¹

deter patients and physicians from initiating therapy, particularly in young patients who do not have advanced liver disease.

The AASLD Practice Guidelines recommended different approaches for patients who are HBeAg-positive and HBeAg-negative. Antiviral treatment should be initiated in HBeAg-positive patients who have ALT levels twice the ULN if they remain HBeAg-positive during 3-6 months of observation (Fig. 2).¹ Liver biopsy should be considered in patients with persistently borderline-normal or mildly elevated ALT levels (less than twice ULN), particularly if the patient is above the age of 40. Treatment should be considered if there is moderate or severe inflammation or fibrosis. For HBeAg-negative patients, the guidelines recommended that treatment be initiated in patients with serum HBV DNA above 20,000 IU/mL and ALT levels greater than twice ULN (Fig. 3).¹ Liver biopsy should be considered in patients with serum HBV DNA levels that are between 2000 and 20,000 IU/mL and borderline-normal or mildly elevated ALT levels (less

Management of HBeAg-Negative Precirrhotic Patients*

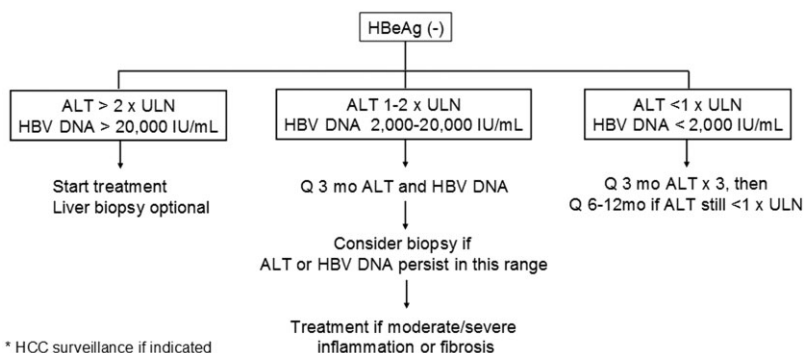


Fig. 3. Algorithm for management of HBeAg-negative patients with precirrhotic liver disease. ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; Rx, treatment; ULN, upper limit of the normal range. Adapted with permission from Lok and McMahon.¹

than twice ULN). Treatment should be considered if liver biopsy shows moderate or severe inflammation or fibrosis. Other patients should continue to be monitored so that treatment can be initiated when the indication arises.

A recent retrospective analysis of 369 HBsAg-positive patients followed for a mean of 7 years reported that using criteria for antiviral therapy as stated in current treatment guidelines, only 20%-60% of the patients who developed HCC and 27%-70% of patients who died of non-HCC liver-related deaths would have been recommended for antiviral therapy.³⁹ However, the mean age of the patients at recruitment was 48 years and the majority was presumed to be infected perinatally or during early childhood. Based on the 2007 AASLD Practice Guidelines, many of these patients would have been considered for treatment even if their HBV DNA or ALT levels were lower than the standard cutoffs recommended for patients who were precirrhotic. Furthermore, these guidelines recommended that patients who are not treated should be monitored and treatment initiated if and when indications arise. In the published study, the authors focused on laboratory test results at the first visit only and did not consider the option of treatment after an initial period of observation. As the authors indicated, mean ALT levels fluctuated during follow-up, and it is likely that many of these patients would have warranted therapy during the course of follow-up. Finally, the authors assumed that all cases of HCC and liver-related mortality would be prevented if antiviral treatment was administered at presentation, but clinical studies have shown that antiviral therapy is not effective in improving survival for patients with advanced liver failure,⁵ and antiviral therapy decreases but does not completely prevent the risk of HCC.^{4,15}

Other Considerations in Therapy

In addition to the clinical, biochemical, virological, and histological features discussed above, other factors may be important in individual decision to initiate or to defer treatment.

Women of Reproductive Age. Because of the need for long-term and perhaps lifelong treatment, the decision to initiate therapy in young patients must be made cautiously. Caution is particularly appropriate for young women who might be contemplating pregnancy. There is a paucity of data on safety of the approved HBV drugs during the first trimester of pregnancy. Although two of the approved HBV medications are listed as class B and there are increasing human data to support the safety of lamivudine in pregnancy,^{40,41} these medications are secreted in breast milk, and their effect on the development of exposed infants is unclear. Thus, treatment decisions

must balance the activity or severity of liver disease at presentation, the anticipated duration of treatment needed to achieve therapeutic endpoint, and the likelihood of adverse outcome in the next few years with the immediacy of the patient's desire to become pregnant. Patients who present with life-threatening liver disease and those with compensated cirrhosis and high levels of HBV DNA should be started on treatment. Patients with HBeAg-positive chronic hepatitis who are predicted to have a high likelihood of HBeAg seroconversion (e.g., pretreatment ALT above $5 \times$ ULN) and are not planning to start a family for another 2-3 years may be started on treatment because of the high likelihood of sustained viral suppression. Patients who are predicted to have a low likelihood of HBeAg seroconversion (and would remain on treatment for many years) and those with HBeAg-negative chronic hepatitis may defer treatment. These patients should be monitored and treatment initiated if their liver disease becomes more active, when they have completed their family, or subsequent data demonstrate the safety of HBV medications in pregnancy and newborns.

Health Care Workers. Health care workers who test positive for HBsAg, especially those who are HBeAg-positive and/or have high levels of serum HBV DNA, may be prohibited from working if they are engaged in exposure-prone procedures.^{42,43} It has been suggested that antiviral treatment should be initiated in such cases to allow these workers to return to work.⁴⁴ This practice has become common in some European countries where health care workers with serum HBV DNA levels below a certain threshold (varying from 3-5 log₁₀ copies/mL) are permitted to return to work provided that surveillance testing shows that HBV DNA levels remain suppressed.⁴³ However, health care workers opting to start treatment for occupational reasons should be aware that in most instances long-term or lifelong treatment would be necessary to maintain virus suppression, and permission to work might be relinquished if there is virologic relapse or breakthrough.

Family History of HCC. Several studies have reported familial clustering of HCC. Whether this is related to genetic factors, exposure to the same environmental carcinogens, or shared infection with a more virulent strain of HBV is unclear. Because HCC is often diagnosed late when curative treatments are not amenable, some experts have recommended that a family history of HCC should suffice as an indication for treatment. However, there is no data to support that initiating treatment in HBV carriers who otherwise do not meet treatment criteria will lower the risk of HCC.

Individual Preference. As in other asymptomatic medical conditions with variable outcomes, patient pref-

erence plays an important role in determining when treatment should be initiated. The participation of the patient in the decision-making process is critical given the lack of data to guide all treatment decisions, the need for long durations of treatment, and the importance of medication compliance. In addition to the issues discussed above, access to care and out-of-pocket expenses may influence the patient's decision to initiate or to defer treatment as well as the choice of therapy.

Summary

In summary, treatment of hepatitis B is clearly indicated in patients with life-threatening liver disease and in those with compensated cirrhosis and high levels of serum HBV DNA. For patients with precirrhotic liver disease, treatment indications should be based on clinical, biochemical, or histological evidence of liver disease, such as elevated ALT levels, abnormal histology, and high levels of serum HBV DNA. The cutoff for ALT and HBV DNA values for initiating treatment are being constantly revised as new data become available. These values should be set at a lower level for older patients who may have been infected for a longer period. The decision to treat now or to defer treatment should take into consideration other factors such as patient age, desire to start a family, occupational requirements, family history of HCC, access to care and insurance coverage, and commitment to long-term treatment and compliance with medications. All patients who are not initiated on treatment should continue to be monitored so treatment can be started if the indication arises.

Needs for Future Research

Although the indications for treatment are clear in certain patient populations such as those with decompensated cirrhosis, uncertainty remains for many patients with less advanced forms of chronic hepatitis B. Should patients with precirrhotic liver disease who have normal or minimally elevated ALT levels be started on treatment? Should treatment be limited to patients who remain HBeAg-positive after the age of 35 or 40, HBeAg-negative patients with high serum HBV DNA levels (>2000 IU/mL), or only those with significant liver disease on biopsy? (And what should be the cutoff for degree of inflammation and fibrosis?) Should treatment be recommended for all patients with compensated cirrhosis regardless of serum HBV DNA level? If not, what cutoff level should be used? What will be the impact of antiviral therapy on clinical outcomes in patients with low HBV DNA levels? Should treatment be recommended for occupational reasons only? Should a family history of HCC

dictate treatment in patients who otherwise do not meet criteria for treatment? Will antiviral treatment reduce the risk of HCC in patients who otherwise do not meet treatment criteria? For women planning to start a family, is current treatment safe when used during the first trimester of pregnancy? How long can treatment be deferred for those with active precirrhotic liver disease? When should treatment be considered for patients with acute hepatitis B? What are the criteria for protracted or severe course of acute hepatitis B?

Addressing these questions is important because empiric treatment for all patients will incur tremendous expenses given the need for long-term, if not lifelong, treatment for many patients. The best approach to determining which of these patients will benefit from antiviral treatment and the magnitude of the benefit would be through prospective, well-designed, randomized controlled clinical trials. In some cases such as patients with severe acute hepatitis, clinical trials may not be feasible because of the rarity of this problem. In other cases such as health care workers engaged in exposure-prone procedures, medicolegal and ethical constraints make it difficult for such individuals to be randomized. However, clinical trials should and can be conducted in patients with precirrhotic liver disease with normal or minimally elevated ALT levels, or in patients with compensated cirrhosis and low levels of serum HBV DNA. These trials will require multiple centers, a large number of patients, a long duration, and support from funding agencies that are not expecting immediate returns on their investment.

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