Hepatitis B virus: Case studies

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INTRODUCTION

The management of hepatitis B virus (HBV) infection is complex and depends upon multiple factors including clinical variables (eg, the presence or absence of liver inflammation and/or cirrhosis), the patient's immunologic response to infection (eg, hepatitis B e antigen status), virologic factors (eg, HBV DNA level and genotype), and risk factors for disease progression (eg, age >40 years, sex, family history of hepatocellular carcinoma, alcohol use, obesity, and diabetes).

The following topic will outline issues related to the management of hepatitis B through the use of cases studies that incorporate patient-specific clinical information and test results. Our approach to treatment is generally consistent with guidelines from the European Association for the Study of the Liver guidelines, Asian-Pacific Association for the Study of the Liver guidelines, and American Association for the Study of Liver Diseases Practice Guidelines and Guidance [1-5].

Additional topic reviews that address the diagnosis and management of HBV include:

- (See "Hepatitis B and pregnancy".)
- (See "Clinical manifestations and diagnosis of hepatitis B virus infection in children and adolescents" and "Management of hepatitis B virus infection in children and adolescents".)
- (See "Pegylated interferon for treatment of chronic hepatitis B virus infection".)
- (See "Entecavir in the treatment of chronic hepatitis B virus infection".)
- (See "Tenofovir and adefovir for the treatment of chronic HBV infection".)

YOUNG MAN WITH ACTIVE REPLICATION

The patient is a 25-year-old Asian man who is hepatitis B surface antigen (HBsAg) positive and hepatitis B e antigen (HBeAg) positive with serum HBV DNA of 140 million international units/mL. He has mild inflammation and stage 1 fibrosis on biopsy. His serum alanine transaminase (ALT) is 100 U/L (the upper limit of normal is considered 35 U/L for males).

This patient should be considered for therapy with entecavir, tenofovir (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]), or pegylated interferon alfa. However, a short period of observation (up to six months) is reasonable to see if this patient would undergo spontaneous HBeAg seroconversion, given his young age and mild inflammation and fibrosis.

The degree of elevation of the serum ALT is particularly important in influencing the decision to treat HBeAg-positive patients, since it has proven to be one of the most important predictors of HBeAg seroconversion. Treatment with any of the approved therapies is unlikely to be successful in achieving HBeAg seroconversion in those with normal or minimally elevated serum ALT. In one study on lamivudine, for example, the rates of HBeAg seroconversion for patients with pretreatment ALT levels within normal, one to two times normal, two to five times normal, and more than five times normal were 2, 9, 21, and 47 percent, respectively [6]. HBeAg-positive patients with high ALT are also more likely to undergo spontaneous HBeAg seroconversion. (See "Hepatitis B virus: Overview of management", section on 'Indications for antiviral therapy'.)

The degree of liver inflammation on liver biopsy is also useful in predicting treatment-related HBeAg seroconversion. In addition, data indicate that the presence of HBeAg and high serum HBV DNA lasting four decades or longer are associated with an increased risk of cirrhosis, hepatocellular carcinoma, and liver-related deaths. As a result, treatment may also be considered in patients who remain HBeAg positive after the age of 40 years, even if ALT is normal.

The pros and cons of various treatment options should be discussed with the patient. The main advantages of nucleos(t)ide analogs are their favorable side effect profile and ease of administration. Among the nucleos(t)ide analogs, entecavir, TDF, or TAF is preferred to minimize risk of drug resistance. However, given the young age of the patient, peginterferon should also be considered because of the finite duration of treatment, particularly if he has genotype A infection or if application of a 12-week futility stop rule is planned. Patients with HBV genotype A are more likely to achieve HBeAg as well as HBsAg seroconversion; however, genotype A is rare among Asians while genotypes B and C predominate. The disadvantages of interferon are

costs, side effects, and need for parenteral administration. (See "Hepatitis B virus: Overview of management", section on 'Choice of initial agent'.)

PRESUMED PRECORE VARIANT

The patient is a 20-year-old woman who is hepatitis B surface antigen (HBsAg) positive and hepatitis B e antigen (HBeAg) negative. Her HBV DNA is 250,000 international units/mL. She has mild portal inflammation and no fibrosis. Her serum alanine transaminase (ALT) is 60 U/L (the upper limit of normal is considered 25 U/L for females). This patient has the characteristics of HBeAg-negative chronic hepatitis and is likely to be infected with a precore variant. (See "Hepatitis B virus: Clinical manifestations and natural history", section on 'Immune-active, HBeAg-negative'.)

Because she is young and has only mild histologic changes on liver biopsy, I think it is reasonable to observe her for the time being. I would repeat liver chemistries every three to six months, and I would start treatment if the ALT is persistently elevated and the HBV DNA remains high after one year of observation. I would not have delayed treatment if the patient had moderate to severe inflammation, bridging fibrosis, or cirrhosis on liver biopsy. I would have also initiated treatment if the patient was older (eg, in her 60s) and had more than one elevated ALT.

If treatment is initiated, the patient should receive entecavir, tenofovir, or peginterferon. Treatment will need to be administered for many years or for life if the goal is to achieve HBsAg loss. Recent studies suggest that in patients with no cirrhosis pretreatment, discontinuation of nucleos(t)ide analogs may be considered after at least three years of treatment if the patient achieves an undetectable HBV DNA and agrees to close follow-up. Although there is no standard approach to discontinuing treatment within this time frame, my preference is four to five years treatment with at least three years of undetectable HBV DNA.

In some studies, withdrawal of treatment was associated with a higher rate of HBsAg loss compared with those who continued nucleos(t)ide analog therapy. However, there is a risk of severe flare and even hepatic decompensation when discontinuing therapy, particularly in older patients and those with advanced fibrosis or cirrhosis; in addition, the rate of HBsAg loss remains very low in Asian patients. The data on discontinuing therapy in HBeAg-negative patients are presented elsewhere. The strongest predictor of HBsAg loss after discontinuing nucleos(t)ide analog therapy is HBsAg level, and different cutoffs have been proposed for Asians versus White populations [7]. (See "Hepatitis B virus: Overview of management", section on 'Duration and treatment endpoints'.)

HBeAg-POSITIVE, HIGH HBV DNA, NORMAL ALT

The patient is a 22-year-old man who is hepatitis B surface antigen (HBsAg) positive, hepatitis B e antigen (HBeAg) positive, and anti-HBe negative. His HBV DNA is 14 million international units/mL and serum alanine transaminase (ALT) is persistently in the range of 20 to 30 U/L.

I would not treat this patient at this time although his HBV DNA level is high. He is very young, and has a serum ALT that is normal (which predicts low probability of HBeAg seroconversion to both peginterferon and nucleos[t]ide analogs).

Although antiviral therapy can decrease serum HBV DNA level in this patient, there is no evidence that treating this patient at this stage will improve the clinical outcome. Given the low rate of HBeAg seroconversion, this patient will need to receive treatment for many years and even decades to derive a clinical benefit. As an example, in a study of 126 HBeAg-positive individuals receiving tenofovir alone, or in combination with emtricitabine, HBeAg seroconversion only occurred in three patients (5 percent) after four years of treatment [8].

For such patients, the feasibility of achieving a clinical benefit must be balanced against the need for long-term antiviral therapy and its associated costs and risks (eg, adverse events and drug resistance). It is also possible that this patient may undergo spontaneous HBeAg seroconversion during the next few years. Thus, I would follow this patient and recheck the ALT every three to six months. If his ALT becomes more than two times normal, I would monitor him more frequently and recommend treatment if he does not spontaneously seroconvert after three to six months.

The management of this patient would be different if he was older. I would biopsy this patient if he was 45 years old with similarly high HBV DNA levels. Alternately, noninvasive measures of liver fibrosis, such as vibration-controlled transient elastography or magnetic resonance elastography, can be used to assess liver fibrosis. I would consider treatment if the HBV DNA level was persistently high or if there was moderate/severe inflammation and/or advanced fibrosis. The association of a high viral load with cirrhosis and hepatocellular carcinoma was examined in studies that enrolled patients in their 40s, and were most likely infected two decades longer than this patient who is in his 20s.

This patient is considered to be in the immune-tolerant phase, though some studies have found that immune response to HBV in patients in this phase is not substantially different from that in patients in immune-active phase. (See "Hepatitis B virus: Clinical manifestations and natural history".)

DENTAL STUDENT WITH ACTIVE REPLICATION

The patient is a 24-year-old who has recently been admitted to dental school. He is hepatitis B surface antigen (HBsAg) positive, hepatitis B e antigen (HBeAg) positive, and anti-HBe negative. His HBV DNA is 80 million international units/mL and serum alanine transaminase (ALT) is 45 U/L. The Dean of the dental school has denied his matriculation pending your advice.

Recommendations are periodically issued by the United States Centers for Disease Control and Prevention (CDC), the most recent of which were updated in 2012 [9]. The CDC recommends that chronic HBV infection in itself not preclude the practice or study of medicine, surgery, dentistry, or allied health professions provided that the following criteria are met:

- Health care providers and students who perform invasive exposure-prone procedures should have oversight from an expert panel. The expert panel should include one or more persons with expertise in the provider's specialty, infectious diseases and hospital epidemiology, liver disease, the infected provider's occupational health, student health or primary care clinicians, ethicists, human resource professionals, hospital or school administrators, and legal counsel.

- HBV-infected providers can conduct exposure-prone procedures if a low or undetectable HBV viral load (spontaneous or while on treatment) is documented by regular testing at least every six months. A threshold of 1000 international units/mL is appropriate. The assay used should have a detection capability as low as 10 to 20 international units/mL. Spontaneous fluctuations above this level may occur and should prompt the HBV-infected provider to abstain from performing exposure-prone procedures while awaiting subsequent retesting, changing drug therapy, or other reasonable steps.

- Standard precautions should be rigorously adhered to in all settings.

Based on the above, I would advise this patient to reconsider his plans to enter dental school. Because he has high HBV DNA and low ALT levels, the likelihood of him responding (HBeAg loss) to current treatment is low and the chance of him clearing HBsAg is even more remote. He will likely need long-term if not life-long treatment and be subjected to frequent monitoring throughout his career (see "Epidemiology, transmission, and prevention of hepatitis B virus infection"). The impact of chronic HBV infection with high level viremia on career paths of dental students is different from medical students who can choose career paths that do not involve performance of invasive procedures.

CHRONIC CARRIER, ADVANCED HISTOLOGIC FEATURES

The patient is a 50-year-old Asian man who is hepatitis B surface antigen (HBsAg) positive and hepatitis B e antigen (HBeAg) negative. His serum alanine transaminase (ALT) is 75 U/L. He has moderate hepatitis with bridging fibrosis on liver biopsy.

Although this patient has only a mildly elevated serum ALT, I would recommend treatment if his serum HBV DNA level is >2000 international units/mL, based upon the advanced histologic features on his liver biopsy. The threshold HBV DNA level for initiating treatment in HBeAg-negative patients is lower than HBeAg-positive patients. (See "Hepatitis B virus: Overview of management", section on 'HBeAg-negative chronic hepatitis'.)

This patient highlights the importance of liver biopsy in patients with normal or mildly elevated ALT, particularly older patients and those who have been infected for many years. An alternative approach is to perform a noninvasive assessment of liver fibrosis (eg, FibroScan). This type of noninvasive test is most reliable in the setting of a normal or minimally elevated ALT. Assuming he has no comorbid conditions or evidence of hepatic decompensation, entecavir, tenofovir, or peginterferon would be reasonable options. Interferon should **not** be used in patients with decompensated cirrhosis, but it may be used cautiously in patients who have bridging fibrosis and no evidence of clinical decompensation, normal hepatic synthetic function, and minimal or no evidence of portal hypertension. Because of the need for long-term treatment, entecavir or tenofovir is preferred if oral treatment is desired.

If biopsy or noninvasive assessment had indicated that this patient has cirrhosis, I would recommend treatment if serum HBV DNA was detected, even if the level is below 2000 international units/mL. (See "Hepatitis B virus: Overview of management", section on 'Compensated cirrhosis'.)

DECOMPENSATED CIRRHOSIS

The patient is a 75-year-old woman who is hepatitis B surface antigen (HBsAg) positive, hepatitis B e antigen (HBeAg) positive, and has a serum alanine transaminase (ALT) of 50 U/L. Her HBV DNA is 1600 international units/mL. She has ascites and known esophageal varices. She is not considered to be a candidate for liver transplantation.

Treatment with interferon is not an option for this patient because she has decompensated cirrhosis. I would treat this patient because there is little to lose and suppression of HBV DNA

and any accompanying inflammation may be of benefit in a patient with very little hepatic reserve.

An important question is whether these patients should receive de novo combination oral antiviral therapy. A trial comparing de novo entecavir monotherapy with a combination of entecavir and tenofovir found no difference in virologic and serologic responses overall, but combination therapy resulted in more rapid viral suppression and a higher percent with HBV DNA <50 international units/mL at week 96 among the subset of patients with baseline HBV DNA >10^8 international units/mL [10]. None of the patients had evidence of genotypic resistance up to week 96. These data indicate that de novo combination therapy is not necessary in most patients but may have a potential benefit in patients with high baseline HBV DNA, leading to more rapid viral suppression though the impact on clinical outcomes is unknown.

With these considerations in mind, entecavir or tenofovir is preferred. Entecavir may be a better choice because patients with decompensated cirrhosis are at risk of renal failure and because this patient is 75. Available data showed that entecavir and tenofovir are well tolerated in this patient population, although one case series reported the occurrence of lactic acidosis in patients with severe liver dysfunction receiving entecavir. If tenofovir is used, tenofovir alafenamide (TAF) with less adverse effects on kidneys and bone is preferred. (See "Entecavir in the treatment of chronic hepatitis B virus infection" and "Tenofovir and adefovir for the treatment of chronic HBV infection".)

Recommendations would be the same if this patient is a 44-year-old and is currently on the liver transplant waiting list. Suppressing HBV DNA to undetectable at the time of transplantation will reduce the risk of HBV recurrence post-transplant.

BREAKTHROUGH INFECTION WHILE ON LAMIVUDINE

The patient is a 56-year-old woman who is hepatitis B e antigen (HBeAg) positive and has early cirrhosis on liver biopsy. Treatment with lamivudine was associated with an initial decline in HBV DNA titers to undetectable levels and normalization of serum alanine transaminase (ALT). However, after 18 months of treatment, she developed a flare in ALT with increasing levels of HBV DNA. She remains HBeAg positive.

It is likely that this patient has developed breakthrough infection with a lamivudine-resistant HBV mutant. If possible, specific testing to confirm resistance should be performed, as breakthrough infection may also be due to medication noncompliance. It is important to differentiate hepatitis flares associated with HBeAg seroconversion (which is accompanied by

decrease in HBV DNA level) versus flares associated with emergence of drug resistance (which is accompanied by increase in HBV DNA level).

In this case, the patient was compliant with medication and had increasing HBV DNA level. Given that she has advanced histologic features, I would stop lamivudine and switch to tenofovir. Tenofovir is preferred to entecavir because mutations to lamivudine decrease susceptibility to entecavir and increase the risk of entecavir resistance. Studies have shown that tenofovir monotherapy is equally effective compared with the combination of tenofovir and emtricitabine in suppressing lamivudine-resistant HBV. (See "Hepatitis B virus: Overview of management", section on 'Persistent viremia/breakthrough infection' and "Tenofovir and adefovir for the treatment of chronic HBV infection".)

Given the high risk of lamivudine resistance during long-term treatment, I would switch the patient to tenofovir even if she does not have breakthrough infection, as a biochemical flare associated with lamivudine resistance can be fatal in patients with cirrhosis if not detected and managed promptly.

ACUTE INFECTION

The patient is a 68-year-old man who is hospitalized with low grade fever, abdominal pain, anorexia, and jaundice. Serologic evaluation reveals that he is hepatitis B surface antigen (HBsAg) positive, immunoglobulin (Ig)M anti-HBc positive, with serum HBV DNA level of 300,000 international units/mL. Serum alanine transaminase (ALT) is 2000 U/L, total bilirubin is 8.0 mg/dL, and international normalized ratio (INR) is 1.5. Other causes of liver disease are excluded. The patient is not known to be a carrier for HBV; however, he is bisexual and thus has potential risk factors for HBV infection. His aminotransferases, INR, and total bilirubin rise slightly during the first two days of hospitalization while awaiting the results of the above serology.

It would appear that this patient has acute HBV, although spontaneous exacerbation of chronic HBV infection is also possible. It can sometimes be difficult to distinguish acute HBV from exacerbation of chronic hepatitis B based upon serology alone (unless there are previous laboratory tests available). The diagnosis of acute hepatitis B is based upon the detection of HBsAg and IgM anti-HBc (table 1 and figure 1). However, IgM anti-HBc can also be seen during severe exacerbation of chronic HBV. This patient is more likely to have exacerbation of pre-existing chronic HBV if he has cirrhosis at diagnosis, a family history of HBV, or past history of liver disease. By contrast, acute infection is more likely in patients with a known recent exposure and no prior history of liver disease.

A question is whether the patient should be treated with antiviral therapy. The prognosis with acute infection is relatively worse in patients who are immunocompromised, have concomitant infection with hepatitis C virus, have pre-existing liver disease, or are older. Thus, the patient's advanced age is a risk factor for morbidity (and possibly mortality) from acute infection.

Few studies have addressed the benefits of antiviral therapy during acute infection. There are relatively more data with reactivation of infection in patients receiving immunosuppressive therapy. In this setting, prophylaxis with antiviral treatment can help prevent severe reactivation of hepatitis. (See "Hepatitis B virus: Clinical manifestations and natural history", section on 'Acute hepatitis' and "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

We do not believe that all patients with acute HBV require antiviral treatment since the likelihood of fulminant HBV is less than 1 percent, and in immunocompetent adults the likelihood of progression to chronic HBV infection is less than 5 percent [11]. As a general rule, we treat patients with a severe (such as those who develop a coagulopathy [INR >1.5]) or a protracted course (such as persistent symptoms or marked jaundice [bilirubin >10 mg/dL]) for more than four weeks after presentation. We also recommend treating patients with fulminant HBV to reduce the likelihood of reinfection post-liver transplant. These recommendations are consistent with the American Association for the Study of Liver Diseases guidelines and guidance [3,4].

Treatment would be reasonable given this patient's advanced age and coagulopathy. Interferon should be avoided because of the risk of infection and further increase in hepatic necroinflammation. Entecavir or tenofovir are preferred, particularly if there is any doubt that this patient may have a severe exacerbation of chronic HBV and not severe acute HBV. Treatment can be stopped after confirmation (2 consecutive tests 12 weeks apart) that the patient has cleared HBsAg.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Management of hepatitis B".)

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GRAPHICS

Diagnostic tests to determine phase of acute or chronic hepatitis B virus infection[1]

HBsAg	HBeAg	IgM anti-HBc	Total anti-HBc*	Anti-HBs	Anti-HBe	HBV DNA	ALT¶	Interpretati
Acute HBV infection								
+	+	+	±			+++	Elevated	Early phase
		+	±			+	Elevated	Window phase
			+	+	+	±	Normal	Recovery phas
Chronic HBV infection (HBsAg-positive for >6 months)								
+	+		+	-	-	+++ (Serum HBV typically >1 million international units/mL)	Normal or mildly elevated	Immune-tolera phase[Δ]
+	+		+	-	-	+++ (Serum HBV >20,000 international units/mL)	Persistently elevated	Immune-active HBeAg-positive
+	-		+	-	+	++ (Serum HBV >2000 international units/mL)	Elevated	Immune-active HBeAg-negativ
+	-		+		+	- to ++ (Serum HBV ≤2000 international units/mL)	Normal or mildly elevated	Inactive chroni HBV[§]
-	-		± (generally	±	±	+ in liver; - to + in serum	Normal	Occult HBV

			+)					

ALT: alanine aminotransferase; anti-HBc: antibody to hepatitis B core antigen; anti-HBe: antibody to hepatitis B e antigen; anti-HBs: antibody to hepatitis B surface antigen; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

* This test is typically ordered as total anti-HBc, which includes IgM and IgG.

¶ The upper limits of normal for ALT in healthy adults are reported to be 29 to 33 units/L for males and 19 to 25 units/L for females. For healthy children after infancy, the upper limits of normal are 25 to 38 units/L and 22 to 31 units/L for boys and girls, respectively.

Δ For patients with immune-tolerant chronic hepatitis B, liver biopsy or noninvasive tests show no fibrosis and minimal inflammation. This is the initial phase seen in patients with perinatally acquired HBV infection.

◇ For patients with immune active chronic hepatitis B, liver biopsy or noninvasive tests show chronic hepatitis with moderate or severe necroinflammation with or without fibrosis. For patients who are HBeAg positive, immune-active chronic hepatitis B (also known as the clearance phase) can last for 10 to 20 years, and may be associated with the loss of HBeAg. For patients who are HBeAg negative, immune-active chronic hepatitis B is associated with immune reactivation and is also referred to as HBeAg-negative chronic hepatitis B or HBeAg-negative replicative phase.

§ Patients with inactive chronic hepatitis B are HBeAg negative. In such patients, liver biopsy confirms the absence of significant necroinflammation, but biopsy or noninvasive testing show variable levels of fibrosis. This stage has also been referred to as the nonreplicative or carrier phase.

References:

1. *Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.*

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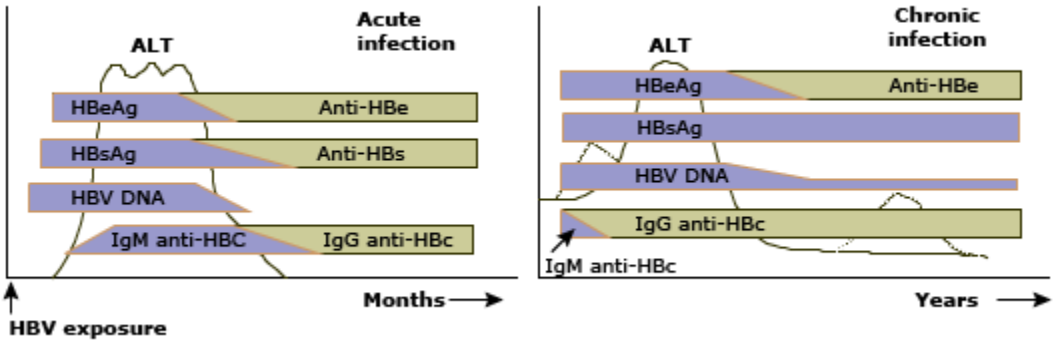
Serologic responses to hepatitis B virus infection



Schematic representation of the serologic responses to acute and chronic HBV infection in relation to the serum ALT concentration.

(Left panel) Acute infection is characterized initially by the presence of HBeAg, HBsAg, and HBV DNA beginning in the preclinical phase. IgM anti-HBc appears early in the clinical phase; the combination of this antibody and HBsAg makes the diagnosis of acute infection. Recovery is accompanied by normalization of the serum ALT, disappearance of HBV DNA, HBeAg to anti-HBe seroconversion, and subsequently HBsAg to anti-HBs seroconversion and switch from IgM to IgG anti-HBc. Thus, previous HBV infection is characterized by anti-HBs and IgG anti-HBc.

(Right panel) Chronic infection is characterized by persistence of HBeAg (for a variable period), HBsAg, and HBV DNA in the circulation; anti-HBs is not seen (in approximately 20% of patients, a non-neutralizing form of anti-HBs can be detected). Persistence of HBsAg for more than 6 months after acute infection is considered indicative of chronic infection.

HBV: hepatitis B virus; ALT: alanine aminotransferase; HBeAg: hepatitis B e-antigen; anti-HBe: antibody to hepatitis B e-antigen; HBsAg: hepatitis B surface antigen; anti-HBs: antibody to hepatitis B surface antigen; IgM: immunoglobulin M; anti-HBc: antibody to hepatitis B core antigen; IgG: immunoglobulin G.

Graphic 69344 Version 5.0

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