

Hepatitis B: Evaluation, Management, and Prevention

Case Study and Commentary, Robert J. Fontana, MD

INTRODUCTION

Hepatitis B is a prevalent infectious disease in the United States and throughout the world [1]. The clinical sequelae of hepatitis B virus (HBV) infection range from subclinical hepatitis to symptomatic, chronic hepatitis, which may evolve into cirrhosis and hepatocellular cancer. Each year approximately 5000 Americans die of hepatitis B-related liver disease [2]. In the United States, there are an estimated 1.2 million infectious carriers of HBV and more than 200,000 cases of acute HBV infection each year. The estimated lifetime risk of acquiring HBV in the United States is approximately 5% [3].

Identifying and treating patients with hepatitis B is an important public health issue. Treatment may slow the progression of liver disease and reduce morbidity and mortality in individuals with chronic infection [4]. Primary prevention via hepatitis B vaccination can not only reduce the prevalence of hepatitis B but also significantly reduce the development of hepatocellular cancer in highly endemic areas of the world [5]. However, until a comprehensive vaccine policy has been successfully implemented in low-prevalence areas like the United States, significant morbidity and mortality due to hepatitis B can be expected. The following case study highlights important considerations in the diagnosis, prevention, and management of HBV infection.

CASE STUDY

Initial Presentation



A 28-year-old man presents to his primary care physician with complaints of fatigue and abdominal pain.

History

The patient reports a 6-month history of fatigue and vague abdominal pain. His appetite and weight have been stable, and he denies fevers or chills. The epigastric pain is dull and intermittent and unrelated to meals or bowel habits. He has taken antacids on an intermittent basis with minimal relief. He denies insomnia, depression, or anxiety. He takes ibuprofen 3 to 4 times per week for headaches. He has no prior medical problems and has never had a blood transfusion, exposure to injection or illicit drugs, or a tattoo. At a routine physical examination 2 years ago, he was told that he had

abnormal liver biochemistries and "hepatitis," but he never sought further medical attention.

The patient's mother was born in Vietnam and immigrated to the United States at age 15 years. His father is of Northern European background. Both of his parents and an older brother are healthy. A maternal aunt in Vietnam apparently had "hepatitis" and died of liver cancer at age 40 years.

The patient is a social studies graduate student. He drinks 4 caffeinated beverages per day and consumes an average of 12 beers per week. He has been in a stable, heterosexual relationship for 2 years.

Physical Examination

The patient is a healthy-appearing man. Vital signs include a blood pressure of 100/60 mm Hg, pulse of 72 bpm, and temperature of 98.9°F. Head and neck examination reveals no scleral icterus, thyromegaly, or cervical lymphadenopathy. Lung and heart examinations are unremarkable. The liver edge is smooth and tender, extending 3 cm below the costal margin and percussing to 15 cm in height. There is slight fullness in the left upper quadrant, and there is mild tenderness to deep palpation in the epigastrium. Rectal examination reveals brown heme-negative stool. Examination of the extremities reveals no discernible jaundice, palmar erythema, or spider angiomas. Neurologic examination is unremarkable.

Laboratory Evaluation

The primary care physician orders screening laboratory tests to determine if a systemic illness such as an occult infection, anemia, or liver disease or an endocrine disorder (hypothyroidism) may be present. The results of testing are as follows:

	Result	Normal
Hemoglobin	15 g/dL	14–18 g/dL
White blood cell (WBC) count	3200/mL	4000–10,000/mL

Robert J. Fontana, MD, Assistant Professor of Medicine, Department of Internal Medicine, Division of Gastroenterology, University of Michigan Medical Center, Ann Arbor, MI.

	Result	Normal
Platelet count	120,000/mm ³	150,000–450,000/mm ³
Aspartate aminotransferase (AST)	150 U/L	5–35 U/L
Alanine aminotransferase (ALT)	220 U/L	5–45 U/L
Alkaline phosphatase (ALP)	100 U/L	30–130 U/L
Total bilirubin	0.9 mg/dL	0.1–1.1 mg/dL
Glucose	80 mg/dL	73–110 mg/dL
Cholesterol	180 mg/dL	120–240 mg/dL
Thyroid-stimulating hormone	2.0 µU/mL	0.3–6.5 µU/mL

The patient has hepatosplenomegaly, mild pancytopenia, and abnormal serum aminotransferase levels suggestive of liver disease. The physician advises the patient to discontinue ibuprofen, caffeinated beverages, and alcohol and prescribes ranitidine for symptomatic relief. He asks the patient to return in 2 weeks for a follow-up visit and repeat laboratory studies.


- What diagnoses should be considered in this patient?

Differential Diagnosis

The persistently elevated serum aminotransferase levels indicate the presence of a chronic hepatitis (elevated serum aminotransferase levels for more than 6 months). The reduced platelet and WBC counts may be due to splenic sequestration in the setting of chronic liver disease. Causes of chronic hepatitis to consider in this young patient include viral infection (hepatitis B or C), alcohol-related liver injury, drug-induced hepatitis (ibuprofen), and metabolic liver disease such as genetic hemochromatosis (iron overload), Wilson's disease (copper overload), and alpha₁-antitrypsin deficiency (accumulation of aberrant protein in the liver). Fatty infiltration of the liver also may be considered; however, this patient does not demonstrate any evidence of conditions frequently associated with fatty liver or nonalcoholic steatohepatitis such as obesity, hyperlipidemia, or occult diabetes [6]. The patient's Asian background and family history of "hepatitis" and liver cancer support the possibility of HBV infection.

Other less likely etiologies in a young man include autoimmune hepatitis (female predominance) or infiltrative disorders of the liver such as malignancy or granulomatous disease (typically present with cholestasis). The epigastric pain could be related to underlying liver disease or other common conditions such as gastroesophageal reflux disease, peptic ulcer disease, pancreatitis, biliary tract disease, or nonulcer dyspepsia.

Diagnostic Evaluation

 Two weeks after discontinuing alcohol, caffeine, and ibuprofen, the patient reports improvement in his abdominal pain but persistent fatigue. Testing shows that serum AST and ALT levels remain elevated at 300 U/L and 400 U/L, respectively. The physician orders further laboratory testing and an ultrasound scan to determine a cause of the patient's liver disease. Ultrasound reveals a mildly enlarged liver and spleen with no focal masses and normal bile ducts and gallbladder. Laboratory studies reveal the following:

	Result	Normal
Hepatitis B surface antigen (HBsAg)	positive	negative
Antibody to hepatitis B core antigen (anti-HBcAg)	positive	negative
Antibody to hepatitis B surface antigen (anti-HBsAg)	negative	negative
Hepatitis C antibody (anti-HCV)	negative	negative
Ceruloplasmin	28 mg/dL	20–42 mg/dL
Serum iron	50 µg/dL	33–150 µg/dL
Iron binding capacity	310 µg/dL	210–400 µg/dL
Serum ferritin	240 ng/mL	10–200 ng/mL
Antinuclear antibody (ANA)	negative	negative
Smooth muscle antibody	negative	negative
Serum protein electrophoresis (SPEP)	normal	

- What do these laboratory findings reveal about this patient's liver disease?

Diagnosis

The detectable levels of HBsAg and anti-HBcAg confirm that this patient has hepatitis B. A diagnosis of chronic hepatitis B would explain the fatigue, abdominal pain, hepatosplenomegaly, and abnormal liver chemistries observed in this patient. The remaining findings rule out other possible causes of liver disease. It is unlikely that the patient's liver disease is due to alcohol or ibuprofen use, since discontinuation of these potential hepatotoxins should have led to improvement in his aminotransferase levels. Furthermore, the pattern of serum AST and ALT elevations is not typical of alcoholic liver injury; in alcoholic liver injury, the AST/ALT ratio usually is greater than 2. The absence of detectable HCV antibody and parenteral risk factors (injection drug use, blood transfusion, tattoos) eliminates HCV infection as a possible etiology. Similarly, negative ANA and smooth muscle antibody tests exclude autoimmune

hepatitis. The normal serum ceruloplasmin level along with the unremarkable neurologic and ocular examinations (eg, no Kayser-Fleischer rings) exclude Wilson's disease. Adult men with genetic hemochromatosis typically present with an iron-to-iron binding capacity ratio of more than 55% and a fasting serum ferritin level of more than 300 $\mu\text{U}/\text{mL}$ [7]. Thus, the 40% iron saturation and minimally elevated ferritin level make genetic hemochromatosis an unlikely cause of chronic hepatitis in this patient. Fatty infiltration of the liver is a common cause of abnormal serum aminotransferase levels in middle-aged Americans [6], but the ultrasound findings do not demonstrate increased echogenicity suggestive of fatty liver. Finally, a normal SPEP makes a diagnosis of α_1 -antitrypsin deficiency unlikely.

• **How is HBV acquired?**

Epidemiology

HBV is acquired from direct contact with the highly infectious blood and body secretions of an individual positive for HBsAg. Groups at increased risk of acquiring HBV include homosexuals, health care workers, injection drug users, sexual and household contacts of chronic carriers, and infants and children born to an infected mother. However, as many as 30% to 40% of patients with chronic hepatitis B have no identifiable risk factor [8]. This patient may have acquired HBV "vertically" from his mother (at birth or during early childhood) or "horizontally" as an adolescent/adult through close or intimate contact with an HBsAg-positive individual. In areas of the world where hepatitis B is highly endemic (eg, Southeast Asia), vertical transmission is common. In highly endemic areas, as much as half of the population has been exposed, and 10% to 20% are chronic carriers of HBV [9]. In low-prevalence areas like the United States, the increasing incidence of hepatitis B following adolescence and the recognition of multiple sexual partners as a common risk factor in adults suggest that sexual transmission is a common means of acquiring HBV [3]. Therefore, horizontal transmission from the large silent pool of HBsAg-positive individuals in the general population should be considered in any newly diagnosed patient with acute or chronic hepatitis B.

- **What factors are associated with the development of chronic infection?**
- **How is acute hepatitis B distinguished from chronic hepatitis B?**

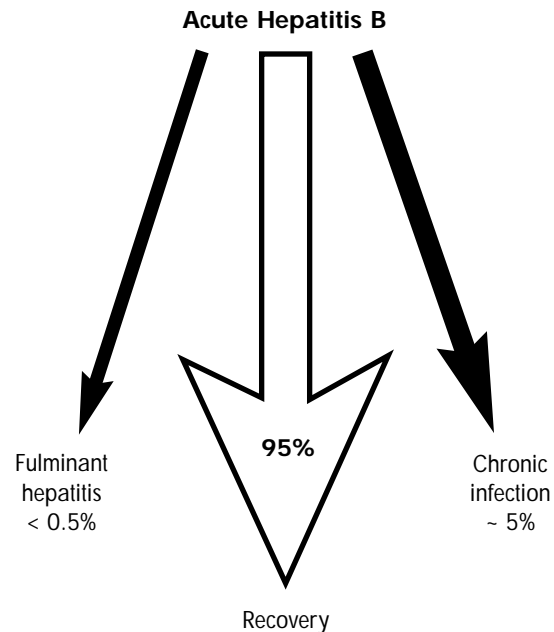


Figure 1. Clinical sequelae of acute hepatitis B infection in adults.

Acute versus Chronic Hepatitis B

The outcome of acute HBV infection largely depends upon the age and immune status of the exposed individual. In immunocompetent adults, acute HBV infection is usually self-limited, with 95% of exposed individuals developing long-lasting protective immunity (Figure 1) [10]. Hemodialysis patients, HIV-infected individuals, organ transplant recipients, and other immunosuppressed individuals are at increased risk of developing chronic infection. Approximately 90% of neonates with vertically acquired acute HBV infection develop chronic infection, and 20% to 40% of children exposed to HBV develop chronic infection due to an inadequate immune response.

The diagnosis and staging of HBV infection is based on serologic testing, serum aminotransferase levels, and liver biopsy (Table 1). HBV is a partially double-stranded DNA virus with an outer membrane consisting of HBsAg particles. Once HBV establishes infection in host hepatocytes, HBsAg and HBV e antigen (HBeAg) are produced in excess and secreted into the serum. The presence of detectable HBsAg, HBeAg, and HBV DNA in the serum implies active viral replication. Following exposure, the host attempts to control further spread of the virus by developing anti-HBsAg and antibodies to e antigen (anti-HBeAg). Anti-HBcAg is also generated, initially of the immunoglobulin (Ig)M subtype and then of the IgG subtype.

A diagnosis of acute HBV infection is established via detection of HBsAg and/or anti-HBcAg (IgM) in a patient

Table 1. Diagnosis and Staging of Hepatitis B Infection

	Acute Hepatitis B	Chronic Carrier	Chronic Active Hepatitis	Prior Exposure	Prior Vaccine
HBsAg	+	+	+	-	-
anti-HBcAg	+ (IgM)	+	+	+	-
anti-HBsAg	-	-	-	+	+
Serum ALT	+ to ++++	+/-	+ to ++++	-	-
HBV DNA*	+	+/-	+	-	-
HBeAg	+	+/-	+/-	-	-
anti-HBeAg	+/-	+/-	-	+/-	-
Inflammation and fibrosis on liver biopsy	+ to ++++	+/-	+ to ++++	-	-

*By non-polymerase chain reaction based assay.

with abnormal aminotransferase levels (Table 1). Most individuals with acute self-limited hepatitis B experience mild to moderate elevations in serum aminotransferase levels [10]. Only 30% of adults with acute hepatitis B have clinical symptoms (eg, fatigue, abdominal pain, jaundice). Rarely, massive hepatocellular necrosis with fulminant liver failure may develop [11]. Most individuals with an adequate immune response to HBV lose detectable HBsAg within 6 months of exposure and develop long-lasting anti-HBcAg (IgG) and protective anti-HBsAg.

A diagnosis of chronic hepatitis B is based upon the continual detection of HBsAg for more than 6 months after initial exposure. Individuals with chronic infection typically have anti-HBcAg of the IgG subtype and no detectable anti-HBsAg. With flares in disease activity, patients with chronic hepatitis B may intermittently have detectable anti-HBcAg of the IgM subtype.

- **What is the natural history of chronic hepatitis B?**
- **What is the role of liver biopsy in chronic hepatitis B?**

Natural History of Chronic HBV Infection


The natural history of chronic HBV infection is highly variable. Patients with chronic hepatitis B may develop an asymptomatic “carrier” state characterized by little or no detectable viral replication (HBeAg-negative/HBV DNA-negative) but the persistent presence of HBsAg [12]. Serum aminotransferase levels are usually normal or only minimally elevated in chronic carriers, and liver biopsy reveals minimal inflammation and fibrosis. However, chronic carriers of hepatitis B are at increased risk of developing hepatocellular cancer [13]. Other individuals may develop chronic “active” hepatitis characterized by detectable hepatitis B replication

(HBeAg-positive/HBV DNA-positive) and host-mediated immune destruction of infected hepatocytes. These patients typically have elevated serum aminotransferase levels and active liver disease on biopsy [13]. If left untreated, patients with chronic “active” hepatitis B can develop cirrhosis and subsequent liver failure or hepatocellular cancer in a relatively short time period [4,14]. Liver disease tends to progress more rapidly in men, those with active viral replication (high HBV DNA and ALT levels), and alcohol abusers [15–17]. In addition, patients with HCV and/or hepatitis D virus co-infection and those receiving immunosuppressive therapy tend to have more severe liver disease [18–20].

Role of Liver Biopsy

Patients with chronic hepatitis B may have nonspecific symptoms of fatigue, malaise, and abdominal pain or may be entirely asymptomatic. Chronic carriers can be distinguished from those with chronic active hepatitis B infection on the basis of serologic and laboratory testing. However, serum aminotransferase elevations do not reliably correlate with the severity of histologic liver damage, and patients with cirrhosis may have normal serum aminotransferase levels. Therefore, liver biopsy is the most useful means of establishing the stage and extent of liver damage in chronic hepatitis B. Furthermore, liver histology may influence treatment options and disease monitoring. For example, surveillance strategies may be altered following a liver biopsy because patients with cirrhosis are at greater risk of developing hepatocellular cancer than noncirrhotic patients [12,13].

Gastroenterology Referral

 The patient is referred to a local gastroenterologist with expertise in liver disease for further evaluation. Laboratory studies reveal detectable HBeAg and HBV DNA of 500 pg/mL by B-DNA assay indicative of active hepatitis B replication with no detectable anti-HBeAg. A liver biopsy

is done to determine the extent of inflammation and fibrosis. The liver biopsy demonstrates moderate lobular hepatitis and bridging fibrosis. The patient asks whether he should be treated and what would be the anticipated duration and side effects of treatment.

-
- **What are indications for treating chronic hepatitis B?**
 - **What pharmacologic therapies are available? What are their potential risks and benefits?**
-

Indications for Treatment

Patients with acute hepatitis B require general supportive care and need to be monitored for the development of complications (eg, dehydration, hypoglycemia). Since the majority of these individuals develop long-lasting protective immunity following a brief clinical illness, no further intervention is required. However, the rare patient with fulminant acute hepatitis B who develops encephalopathy and coagulopathy should be urgently referred to a liver transplant center for further evaluation and management. These patients may require emergency liver transplantation.

Indications for treatment of chronic hepatitis B include the presence of active hepatitis B replication (HBeAg-positive/HBV DNA-positive) with elevated serum aminotransferase levels and moderate to severe necroinflammation on liver biopsy. Untreated individuals are at significant risk of developing progressive liver disease and hepatocellular cancer [4]. However, some patients with chronic active hepatitis B spontaneously develop enhanced immunity with loss of replicative markers and development of anti-HBeAg. Chronic carriers with normal serum aminotransferase levels and no detectable viral replication do not benefit from antiviral therapy and should not be treated [21,22]. Due to the potential severity of treatment-related side effects, only carefully selected patients without known contraindications to immunomodulatory or antiviral therapy should be considered for treatment.

Pharmacologic Therapy

Interferon alpha-2b and lamivudine currently are the only approved treatments for chronic hepatitis B. The short-term goals of treatment are to suppress HBV replication (loss of HBeAg, HBV DNA) and to induce a remission in liver disease. The long-term goals of treatment are to prevent progression to cirrhosis and hepatocellular carcinoma, eliminate the virus, and improve patient survival.

Interferon

Interferons are proteins with immunomodulatory, antiprolif-

erative, and antiviral effects. Treatment response to interferon is defined as a loss of detectable HBV DNA and HBeAg and is assessed 12 months after initiation of therapy. A meta-analysis of 15 clinical trials of interferon in hepatitis B demonstrated an overall response rate of 33% in treated patients compared with 12% in untreated controls [23]. The loss of HBsAg was 8% in treated patients and 2% in untreated controls. During or immediately after therapy, responders to interferon may develop a flare in serum aminotransferase levels indicative of enhanced host immunity to infected hepatocytes. Because of this potential flare, a pretreatment liver biopsy should be performed and patients with established but compensated cirrhosis should be followed carefully.

Interferon treatment of hepatitis B consists of subcutaneous injections of 5 million U daily or 10 million U 3 times per week for 16 weeks with careful clinical and laboratory monitoring by an experienced physician. Unfortunately, high-dose interferon therapy is expensive and associated with many side effects including early flu-like symptoms, myelotoxicity, and neuropsychiatric toxicity (ie, depression and anxiety). As many as 40% of treated patients require dose reductions, and 5% to 10% discontinue treatment due to side effects. Contraindications to interferon therapy include decompensated liver disease, moderate to severe psychiatric illness, leukopenia, thrombocytopenia, autoimmune disorders, and major medical comorbidities.

Loss of HBeAg in interferon responders appears to be durable over many years of follow-up [24,25]. Several recent studies have suggested that individuals with HBeAg loss following interferon therapy have improved long-term outcomes compared with patients who do not lose HBeAg and untreated controls [25–27]. Despite the costs and toxicity associated with treatment, interferon treatment of chronic hepatitis B is cost-effective, with a mean improvement in life span of 3.1 years at a cost of \$6000 per quality adjusted life-year gained [28].

Lamivudine

Lamivudine, a nucleoside analogue, is a potent antiviral agent that inhibits HBV replication. Following oral administration and absorption, lamivudine is phosphorylated intracellularly to an active intermediate that acts as a chain terminator. Daily lamivudine therapy leads to a rapid suppression of detectable serum HBV DNA in more than 90% of patients followed by a decrease in serum ALT levels in 40% to 70% of treated patients [29]. The combined data from 3 large clinical trials demonstrate that 12 months of lamivudine therapy is associated with a loss of replicative markers (HBeAg and HBV DNA) and the development of anti-HBeAg in 18% of treated patients compared with 5% of untreated controls [30]. The majority of lamivudine-treated patients also demonstrate improved liver histology [31]. However, 15% to

Table 2. Treatment Options for Chronic Active Hepatitis B

Variable	Interferon	Lamivudine
Mechanism of action	Immunomodulatory	Antiviral
Treatment duration	4 mo	≥ 12 mo
Route of administration	Subcutaneous	Oral
Cost*	\$5000	\$1800/yr
Efficacy		
HBeAg loss	33%	30%
anti-HBeAg	20%	20%
HBV DNA loss	20%	20%
Normal ALT	50%	70%
HBsAg loss	5%–10%	< 5%
Common side effects	Flu-like symptoms (80%) Myelotoxicity (60%) Neuropsychiatric (40%)	~ Placebo [†]
Contraindications	Autoimmune disorder Psychiatric illness Decompensated cirrhosis Noncompliance	Noncompliance
Drug resistance	No	1 yr, 15%–30% 2 yr, 40%–50% 3 yr, 50%–60%

*Estimated outpatient medication costs.

[†]Rare side effects associated with lamivudine include lactic acidosis, pancreatitis, and hepatomegaly [30].

30% of patients receiving lamivudine for 12 months develop escape mutations in the active site of the HBV polymerase gene termed the YMDD locus. These mutations lead to a decreased sensitivity to lamivudine with reappearance of HBV DNA [32]. The emergence of YMDD mutants is frequently associated with an increase in serum ALT levels, but clinical decompensation is uncommon. However, a recent report demonstrated that up to 40% of patients may develop an acute exacerbation in liver disease following the emergence of a YMDD mutant and transient liver failure may occur [33]. Still, in light of the reduced replicative capacity of YMDD mutants compared with wild type strains of hepatitis B virus, patients with YMDD mutants should remain on lamivudine therapy if they are experiencing a clinical benefit [31]. Furthermore, as many as 25% of patients with YMDD mutants may go on to develop HBeAg seroconversion following 2 years of lamivudine treatment [33]. However, careful monitoring of patients with YMDD mutants is required because information on long-term observation of patients treated with lamivudine is limited.

Other Antiviral Agents

In addition to lamivudine, several other nucleoside and nucleotide analogues are being evaluated for use against

HBV. Famciclovir, a purine nucleoside analogue, has shown activity against hepatitis B both in vitro and in vivo [34]. However, famciclovir is much less potent than lamivudine, and drug-resistant mutants that appear to be cross-resistant to lamivudine emerge following long-term treatment [35]. Adefovir dipivoxil, the oral prodrug of adefovir, shows promise as a potent antiviral agent in chronic hepatitis B. Pilot studies demonstrate a rapid suppression in serum HBV DNA levels and loss of HBeAg in 27% of treated patients after 3 months of therapy [36,37]. Adefovir alone or in combination with other antivirals may prove useful in chronic active hepatitis B since lamivudine- and famciclovir-resistant mutants remain sensitive to adefovir both in vitro and in vivo [38,39].

- **Is there evidence to support the use of one therapy over another?**

Selecting a Therapy

The relative safety and efficacy of lamivudine compared with interferon in chronic hepatitis B has not been established. However, in a pilot study comparing lamivudine to lamivudine plus interferon in patients with interferon-refractory hepatitis B, the overall response rates were comparable. The lamivudine-treated patients had fewer and less severe adverse events than the combination therapy patients [40]. Furthermore, clinical trials demonstrate an incidence of adverse events in patients treated with lamivudine comparable to that seen in placebo patients [22]. Although lamivudine is clearly more convenient to administer than interferon, the relative cost-effectiveness of these 2 treatments has not been established. Therefore, the selection of an agent for the treatment of chronic hepatitis B needs to be tailored to the individual patient (Table 2).

Lamivudine may be preferred over interferon in certain patient populations. For example, HBeAg-negative/HBV DNA-positive patients with pre-core mutants that do not secrete HBeAg respond poorly to interferon therapy but have been shown to respond to lamivudine [41,42]. Other patient populations that may benefit from lamivudine include patients with decompensated cirrhosis, transplant recipients, and those with contraindications to interferon therapy. However, lamivudine is currently only approved for the treatment of immunocompetent patients with compensated hepatitis B; its use in other populations requires further study [30].

Initiation of Treatment




In light of the patient's active viral replication and liver disease, the gastroenterologist recommends

that they proceed with treatment. After reviewing the potential risks and benefits of interferon and lamivudine, the patient requests to be treated with lamivudine due to its favorable side-effect profile and ease of administration. The patient is placed on lamivudine 100 mg/day.

• **How should patients receiving lamivudine be monitored?**

Currently, there are no published guidelines for monitoring patients receiving lamivudine for chronic hepatitis B. Furthermore, the optimal duration of therapy is not known [30]. Periodic assessment of serum ALT levels during treatment helps identify patients who are responding. In addition, assessment of hepatitis B replicative markers helps to determine if the endpoints of treatment have been reached (Table 3). The currently recommended endpoints to achieve prior to discontinuing lamivudine are (1) undetectable HBV DNA by non-polymerase chain reaction assay; (2) absence of HBeAg; and (3) detection of anti-HBeAg on 2 or more occasions. Office visits every 3 to 4 months are recommended during treatment to assess patient compliance. If the patient does not achieve all 3 endpoints after 12 months of therapy but is experiencing a clinical benefit, continued treatment with laboratory monitoring is recommended. Breakthrough infection due to development of a YMDD mutant typically does not occur until after a minimum of 8 months of treatment. However, genotyping assays for the detection of YMDD mutants are not commercially available. Breakthrough infection can be diagnosed by detecting phenotypic resistance—the reappearance of HBV DNA in the serum after its initial suppression in a compliant patient on lamivudine.

Treatment Course

 The patient does not experience any adverse events. Serum HBV DNA becomes undetectable by month 3, and serum ALT levels normalize by month 12 (Figure 2). However, HBV DNA becomes detectable again at month 12, and serum ALT levels increase shortly thereafter consistent with phenotypic resistance resulting from emergence of a YMDD mutant. However, the HBV DNA level is lower than that seen before treatment. Both serum HBeAg and HBeAb remain undetectable. In light of his clinical response to lamivudine (reduced ALT, loss of HBeAg), the patient remains on lamivudine with ongoing clinical and laboratory monitoring.

Screening of Contacts

Serologic screening of household and sexual contacts of the patient is undertaken by the primary care physician [43]. The patient's older brother and father demonstrate detectable anti-HBcAg (IgG) and anti-HBsAg with no detectable

Table 3. Guidelines for Monitoring Lamivudine Treatment of Chronic Active Hepatitis B

Tests to Be Performed	Frequency
During treatment*	
Serum AST/ALT	Every month
HBV DNA [†]	Every 3 months
HBeAg/anti-HBeAg	Every 6 months
Office visit	Every 3 months
After treatment [‡]	
Serum AST/ALT	Every month for 6 months
HBV DNA [†]	Every 3 months for 6 months
HBeAg/anti-HBeAg	Every 3 months for 6 months

NOTE. Treatment candidates should have elevated serum ALT, be HBV DNA-positive, and have moderate to severe hepatitis on liver biopsy; HBeAg may or may not be detectable.

*The optimal duration of therapy is unknown. Patients with breakthrough infection who are experiencing a clinical benefit should remain on lamivudine; therapy should be stopped in patients with breakthrough infection who experience clinical deterioration.

[†]By non-polymerase chain reaction based assay.

[‡]Lamivudine should be reinstated if there is evidence of clinical deterioration after treatment is stopped.

HBsAg consistent with prior exposure. The patient's mother has detectable HBsAg and anti-HBcAg (IgG) with normal serum aminotransferase levels and no detectable anti-HBsAg; she is a chronic asymptomatic carrier. The physician advises her to have her serum aminotransferase levels measured every 6 months to monitor for the development of chronic active hepatitis. She is also advised to undergo periodic serologic (serum alpha-fetoprotein) and ultrasound surveillance in light of her increased risk of developing hepatocellular cancer [44].

HBsAg, anti-HBcAg, and anti-HBsAg are not detected in the patient's girlfriend. The physician advises her to undergo vaccination against hepatitis B to minimize the risk of acquiring hepatitis B via sexual and household contact [43]. Following the third injection at month 6, the physician also recommends that an anti-HBsAg titer be obtained to ensure that she has developed protective immunity (ie, anti-HBsAg > 10 µU/mL) [45]. He advises the couple to use barrier contraception to reduce the risk of sexual transmission.

• **Who should receive hepatitis B vaccination?**

Hepatitis B Vaccination

A highly immunogenic and safe recombinant vaccine for hepatitis B has been available in the United States for more than

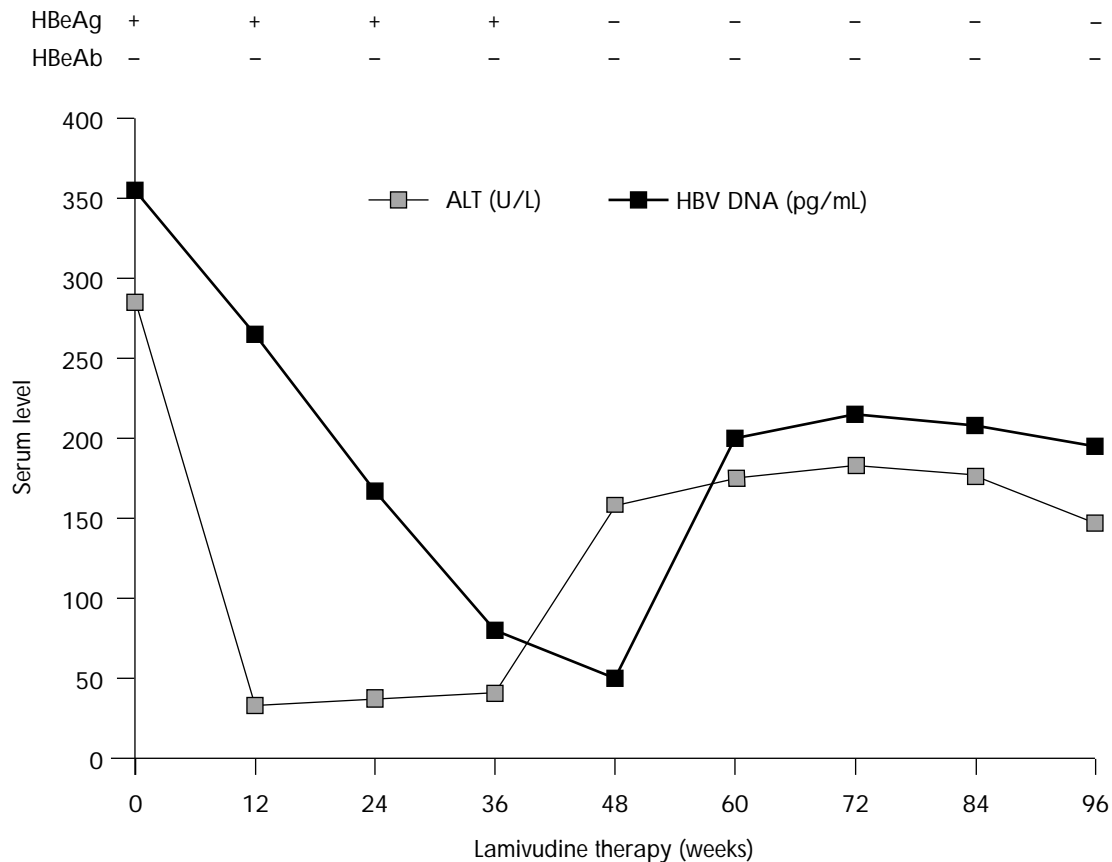


Figure 2. Biochemical and virologic response to lamivudine.

20 years [46]. However, the strategy of selective vaccination of high-risk subgroups has not resulted in a decline in the prevalence of HBV infection due to the difficulty in identifying and immunizing these individuals [3]. As a result, more widespread vaccination of the general population, including newborns and adolescents, is now recommended [43]. Vaccination of a larger proportion of the population has been shown to be cost-effective [47]. Current recommendations for hepatitis B vaccination include (1) routine infant vaccination; (2) catch-up vaccination of adolescents not previously vaccinated; (3) catch up vaccination of young children at high risk of infection; and (4) pre-exposure vaccination of adolescents and adults based on lifestyle or environmental factors. More widespread use of hepatitis B vaccination is expected to reduce the prevalence of infection in the United States in the next decade [45,46].

Summary

The outcome of acute hepatitis B infection largely depends upon the patient's age at infection and immune status as well as the level of hepatitis B replication. The diagnosis and staging of hepatitis B is based upon serum ALT levels, serologic

testing, and liver biopsy. Patients with chronic hepatitis B infection are at increased risk of developing progressive liver disease and hepatocellular cancer. Immunomodulatory (interferon) and antiviral (lamivudine) treatment of chronic hepatitis B can lead to a remission in liver disease in patients with active viral replication and elevated serum aminotransferase levels. The advantages of lamivudine over interferon include ease of administration and its side-effect profile. However, the long-term benefits of treatment are better established with high-dose interferon therapy compared with lamivudine treatment. Furthermore, 15% to 30% of patients treated with lamivudine for 12 months will develop breakthrough infection, and the long-term outcome with YMDD mutants is not established. With the development of newer antiviral agents like adefovir either alone or in combination with other drugs, more efficacious and safer treatment options for patients with chronic active hepatitis B may soon be available. In the interim, more widespread vaccination of the general population against hepatitis B is needed to prevent future morbidity and mortality from this highly infectious and prevalent disease.

Author address: 3912 Taubman Center, Box 0362, Ann Arbor, MI 48109-0362.

References

1. Purcell RH. The discovery of the hepatitis viruses. *Gastroenterology* 1993;104:955-63.
2. Alter MJ, Mast EE. The epidemiology of viral hepatitis in the United States. *Gastroenterol Clin North Am* 1994;23:437-55.
3. McQuillan GM, Coleman PJ, Kruszon-Moran D, Moyer LA, Lambert SB, Margolis HS. Prevalence of hepatitis B virus infection in the United States: the National Health and Nutrition Examination Surveys, 1976 through 1994. *Am J Public Health* 1999;89:14-8.
4. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer* 1988;61:1942-56.
5. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 1997;336:1855-9.
6. Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis. *Med Clin North Am* 1996;80:1147-66.
7. McLaren CE, McLachlan GJ, Halliday JW, Webb SI, Leggett BA, Jazwinska EC, et al. Distribution of transferrin saturation in an Australian population: relevance to the early diagnosis of hemochromatosis. *Gastroenterology* 1998;114:543-9.
8. Alter MJ, Hadler SC, Margolis HS, Alexander WJ, Hu PY, Judson RN, et al. The changing epidemiology of hepatitis B in the United States. Need for alternative vaccination strategies. *JAMA* 1990;263:1218-22.
9. Margolis HS, Alter MJ, Hadler SC. Hepatitis B: evolving epidemiology and implications for control. *Semin Liver Dis* 1991;11:84-92.
10. Tassopoulos NC, Papaevangelou GJ, Sjogren MH, Roumeliotou-Karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. *Gastroenterology* 1987;92:1844-50.
11. Pappas SC. Fulminant viral hepatitis. *Gastroenterol Clin North Am* 1995;24:161-73.
12. Hoofnagle JH, Shafritz DA, Popper H. Chronic type B hepatitis and the "healthy" HBsAg carrier state. *Hepatology* 1987;7:758-63.
13. Popper H, Shafritz DA, Hoofnagle JH. Relation of the hepatitis B virus carrier state to hepatocellular carcinoma. *Hepatology* 1987;7:764-72.
14. Di Marco V, Lo Iacono O, Camma C, Vaccaro A, Giunta M, Martorana G, et al. The long-term course of chronic hepatitis B. *Hepatology* 1999;30:257-64.
15. de Jongh FE, Janssen HL, de Man RA, Hop WC, Schalm SW, van Blankenstein M. Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. *Gastroenterology* 1992;103:1630-5.
16. Realdi G, Fattovich G, Hadziyannis S, Schalm SW, Almasio P, Sanchez-Tapias J, et al. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. The Investigators of the European Concerted Action on Viral Hepatitis (EUROHEP). *J Hepatol* 1994;21:656-66.
17. Donato F, Tagger A, Chiesa R, Ribero ML, Tomasoni V, Fasola M, et al. Hepatitis B and C virus infection, alcohol drinking, and hepatocellular carcinoma: a case-control study in Italy. Brescia HCC Study. *Hepatology* 1997;26:579-84.
18. Chan HL, Lok AS. Hepatitis B in adults: a clinical perspective. *Clin Liver Dis* 1999;3:291-307.
19. Lau JY, Bain VG, Smith HM, Alexander GJ, Williams R. Modulation of hepatitis B viral antigen expression by immunosuppressive drugs in primary hepatocyte culture. *Transplantation* 1992;53:894-8.
20. Tur-Kaspa R, Burk RD, Shaul Y, Shafritz DA. Hepatitis B virus DNA contains a glucocorticoid-responsive element. *Proc Natl Acad Sci U S A* 1986;83:1627-31.
21. Lai CL, Lok AS, Lin HJ, Wu PC, Yeoh EK, Yeung CY. Placebo-controlled trial of recombinant alpha 2-interferon in Chinese HBsAg-carrier children. *Lancet* 1987;2:877-80.
22. Lai CL, Ching CK, Tung AK, Li E, Young J, Hill A, et al. Lamivudine is effective in suppressing hepatitis B virus DNA in Chinese hepatitis B surface antigen carriers: a placebo-controlled trial. *Hepatology* 1997;25:241-4.
23. Wong DK, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. *Ann Intern Med* 1993;119:312-23.
24. Korenman J, Baker B, Waggoner J, Everhart JE, Di Bisceglie AM, Hoofnagle JH. Long-term remission of chronic hepatitis B after alpha-interferon therapy. *Ann Intern Med* 1991;114:629-34.
25. Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, Haussinger D. Long-term follow-up of HBeAg-positive patients treated with interferon alpha for chronic hepatitis B. *N Engl J Med* 1996;334:1422-7.
26. Lau DT, Everhart J, Kleiner DE, Park Y, Vergalla J, Schmid P, Hoofnagle JH. Long-term follow-up of patients with chronic hepatitis B treated with interferon alpha. *Gastroenterology* 1997;113:1660-7.
27. Fattovich G, Giustina G, Realdi G, Corrocher R, Schalm SW. Long-term outcome of hepatitis B e antigen-positive patients with compensated cirrhosis treated with interferon alpha. European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology* 1997;26:1338-42.
28. Wong JB, Koff RS, Tine F, Pauker SG. Cost-effectiveness of interferon-alpha 2b for hepatitis B e antigen-positive chronic hepatitis B. *Ann Intern Med* 1995;122:664-75.
29. Dienstag JL, Perrillo RP, Schiff ER, Bartholomew M, Vicary C, Rubin M. A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med* 1995;333:1657-61.
30. Lamivudine package insert. Research Triangle (NC): Glaxo-Wellcome, Inc.
31. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med* 1998;339:61-8.
32. Chayama K, Suzuki Y, Kobayashi M, Kobayashi M, Tsubota A, Hashimoto M, et al. Emergence and takeover of YMDD motif mutant hepatitis B virus during long-term lamivudine therapy and re-takeover by wild type after cessation of therapy. *Hepatology* 1998;27:1711-6.

33. Liaw YF, Chien RN, Yeh CT, Tsai SL, Chu CM. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology* 1999;30:567-72.
34. Luscombe CA, Locarnini SA. The mechanism of action of antiviral agents in chronic hepatitis B. *Viral Hepatitis Rev* 1996;2:1-35.
35. Bartholomeusz A, Groenen LC, Locarnini SA. Clinical experience with famciclovir against hepatitis B virus. *Intervirology* 1997;40:337-42.
36. Gilson RJ, Murray-Lyon IM, Nelson MR, Rice SJ, Tedder RS, Murray A, et al. Extended treatment with adefovir dipivoxil in patients with chronic hepatitis B virus infection [abstract]. *Hepatology* 1998;28:A1316.
37. Heathcote EJ, Jeffers L, Wright T, Sherman M, Perrillo R, Sacks S, et al. Loss of serum HBV-DNA and HBeAg and seroconversion following short-term (12 weeks) adefovir dipivoxil therapy in chronic hepatitis B: two placebo controlled phase II studies [abstract]. *Hepatology* 1998;28:A620.
38. Ono-Nita SK, Kato N, Shiratori Y, Lan KH, Yoshida H, Kato J, et al. Susceptibility of lamivudine resistant hepatitis B virus to other anti-virals: adefovir and lobucavir [abstract]. *Hepatology* 1998;28:A12.
39. Perrillo R, Schiff E, Magill A, Murray A. In vivo demonstration of sensitivity of YMDD variants to adefovir [abstract]. *Gastroenterology* 1999;116: L0356.
40. Schiff E, Karavalcin S, Frimm I, Perrillo R, Dienstag J, Husa P, et al. A placebo controlled study of lamivudine and interferon alpha 2b in patients with chronic hepatitis B who previously failed Interferon therapy [abstract]. *Hepatology* 1998;A901.
41. Hoofnagle JH, di Bisceglie AM. The treatment of chronic viral hepatitis. *N Engl J Med* 1997;336:347-56.
42. Tassopoulos NC, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, et al. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Lamivudine Precore Mutant Study Group. *Hepatology* 1999;29:889-96.
43. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Morb Mortal Wkly Rep* 1991;40(RR-13):1-25.
44. Liaw YF, Tai DI, Chu CM, Lin DY, Sheen IS, Chen TJ, Pao CC. Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis. A prospective study. *Gastroenterology* 1986;90:263-7.
45. Zimmerman RK, Ruben FL, Ahwesh ER. Hepatitis B virus infection, hepatitis B vaccine, and hepatitis B immune globulin [published erratum appears in *J Fam Pract* 1997;45:464]. *J Fam Pract* 1997;45:295-315.
46. Lemon SM, Thomas DL. Vaccines to prevent viral hepatitis. *N Engl J Med* 1997;336:196-204.
47. Bloom BS, Hillman AL, Fendrick AM, Schwartz JS. A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness analysis. *Ann Intern Med* 1993;118:298-306.

Copyright 1999 by Turner White Communications Inc., Wayne, PA. All rights reserved.