

**HESHAM M. ELGOUHARI, MD**

Assistant Professor of Medicine, University of South Dakota School of Medicine; Avera Center for Liver Disease/Transplant Institute, Sioux Falls, SD

**TAREK I. ABU-RAJAB TAMIMI, MD**

Department of Gastroenterology and Hepatology, Cleveland Clinic

**WILLIAM CAREY, MD**

Department of Gastroenterology and Hepatology, Cleveland Clinic

# Hepatitis B: A strategy for evaluation and management

## ABSTRACT

In hepatitis B virus (HBV) infection, a single approach to treatment cannot be applied to all patients. Acute, adult-acquired HBV infection rarely requires treatment, whereas treatment for chronic infection should be based on the patient's clinical situation and test results. The ideal agent for treating hepatitis B does not exist, and trade-offs are the essence of agent selection. In last month's *Journal* (Cleve Clin J Med 2008; 75:881–889), we outlined the natural history and diagnosis of chronic HBV infection; in this article we outline its management.

## KEY POINTS

Patients with HBV infection should be screened for hepatocellular carcinoma, especially if they have cirrhosis.

Nucleoside and nucleotide analogue reverse transcriptase inhibitors are easy to use and therefore are usually the first-line therapy. Problems with these agents are that the optimal treatment duration is not known, and that drug resistance can emerge.

Patients with advanced liver disease or hepatocellular carcinoma should be referred promptly for possible liver transplantation.

Candidates for immunosuppressant therapy or cytotoxic chemotherapy should be screened for HBV, as this therapy can cause a potentially fatal flare of HBV.

People at risk should be vaccinated; many have not been.

**H**EPATITIS B VIRUS (HBV) INFECTION is sometimes challenging to manage because the disease has several stages and many clinical scenarios. HBV-infected patients are a very heterogeneous group, and we cannot apply a single management approach to all.

An understanding of the natural history of HBV infection and its diagnosis, which we reviewed in last month's issue of this *Journal*<sup>1</sup> (available online at [www.ccjm.org/content/75/12/881](http://www.ccjm.org/content/75/12/881)), is critical to understanding how to manage HBV infection.

In this article, we will review the principles of HBV management in adults, including those on immunosuppressant therapy and pregnant women, and guidelines for HBV vaccination.

## WORKUP FOR HBV INFECTION

Once the diagnosis of HBV infection is made,<sup>1</sup> a full management strategy should be formulated, as outlined below.

### History

**When and how did the patient acquire HBV?** This information is important to know when making treatment decisions. For example, most acute, adult-onset cases (eg, acquired recently via sexual contact or parenteral drug abuse) resolve spontaneously within a few months, whereas most chronic cases (defined as being positive for HBV surface antigen for more than 6 months) were acquired at birth or in early childhood. Therefore, we should try to determine if the patient's mother, siblings, household contacts, and sexual partners are positive for HBV surface antigen or have risk factors for HBV infection<sup>1</sup>; those without infection or immunity to HBV should be vaccinated.

### People at risk of HBV infection include:

- Parenteral drug users
- People with multiple sexual partners
- Household contacts and sexual partners of people positive for HBV surface antigen
- Infants born to HBV-infected mothers
- Patients and staff in custodial institutions for the developmentally disabled
- Recipients of certain plasma-derived products (including patients with congenital coagulation defects)
- Hemodialysis patients
- Health and public-safety workers who have contact with blood
- People born in areas where HBV is endemic, and their children.<sup>1</sup>

**Does the patient have risk factors for other infections?** Especially look for risk factors for human immunodeficiency virus (HIV) infection (eg, intravenous drug users and men having sex with men) and hepatitis D virus (intravenous drug users and patients from countries where hepatitis D virus infection is common, particularly Eastern Europe, Mediterranean countries, and the Amazon basin).

**Does the patient have other modifiable risk factors for progressive liver disease,** particularly alcohol abuse and obesity?

**Does the patient have symptoms or signs of cirrhosis or hepatocellular carcinoma?** Symptoms and signs that involve multiple systems could be extrahepatic manifestations of HBV infection, such as polyarteritis nodosa, which causes abdominal pain, arthralgia, hypertension, and asymmetric polyneuropathy.

### Baseline laboratory evaluation

At baseline we should obtain a complete blood count, blood urea nitrogen level, serum creatinine level, liver profile, prothrombin time, urinalysis, and HBV serologic markers. In addition, HBV DNA can be detected in the serum at levels as low as 60 IU/mL, and it should be measured in the initial evaluation to establish a baseline before starting antiviral therapy in patients with chronic HBV infection and subsequently to monitor the response.

All patients with chronic HBV infection should also be tested for serologic markers of hepatitis A and hepatitis C; patients at risk of HIV and hepatitis D should also be tested for these diseases.

### Not all patients need liver biopsy

Liver biopsy is the most accurate tool for staging the degree of HBV-related hepatic fibrosis in patients who have no obvious clinical manifestations of cirrhosis.

Not all patients with HBV infection need a biopsy, however. In patients with acute HBV infection, liver biopsy has no benefit except if concomitant pathology (eg, iron overload, nonalcoholic steatohepatitis, or alcoholic steatohepatitis) is suspected. In patients with chronic hepatitis B, liver biopsy is helpful when the viral load alone does not provide sufficient guidance for treatment, eg, when the viral load is less than  $2 \times 10^4$  IU/mL in a patient positive for hepatitis e antigen or less than  $2 \times 10^3$  IU/mL in a patient negative for hepatitis e antigen. (The presence of e antigen is a marker of HBV replication and infectivity.<sup>1</sup>) Biopsy should also be considered in those who have been infected a long time (eg, more than 10 years), because they may have occult cirrhosis, and if they do they may need to undergo antiviral treatment, endoscopy to look for varices, and surveillance for liver cancer.

In some situations it is easy to decide whether antiviral therapy is indicated without resorting to liver biopsy.

#### We would treat:

- A patient positive for HBV e antigen for more than 6 months, whose HBV DNA level is higher than  $2 \times 10^4$  IU/mL and whose alanine aminotransferase (ALT) level is high
- A patient with HBV for more than 6 months who is negative for e antigen and who has an HBV DNA level higher than  $2 \times 10^3$  IU/mL and elevated ALT
- A patient with compensated HBV cirrhosis and an HBV DNA level higher than  $2 \times 10^3$  IU/mL
- A patient with HBV cirrhosis with decompensation and any detectable HBV DNA.

#### We would not treat:

- An HBV carrier with a normal ALT level and an HBV DNA level that is lower than  $2 \times 10^4$  IU/mL or undetectable.

If a patient does not fit into one of these categories but has HBV DNA, a liver biopsy showing significant necroinflammation or fibrosis would be an indication for treatment.

**In HBV, we cannot apply a single management approach to all**

TABLE 1

### Common indications for antiviral therapy in patients with chronic hepatitis B virus (HBV) infection

CATEGORY	INDICATIONS FOR THERAPY
<b>HBV e antigen positivity</b>	Persistent alanine aminotransferase (ALT) elevation with HBV DNA $> 2 \times 10^4$ IU/mL, or Significant liver injury (necroinflammation or fibrosis) on liver biopsy, or Icteric ALT flare, or Recurrent hepatitis flares with failed seroconversion
<b>HBV e antigen negativity</b>	Persistent ALT elevation with HBV DNA $> 2 \times 10^3$ IU/mL, or Significant liver injury (necroinflammation or fibrosis) on liver biopsy
<b>Compensated cirrhosis</b>	HBV DNA level $> 2 \times 10^3$ IU/mL Consider therapy even with lower HBV DNA levels if ALT is elevated
<b>Decompensated cirrhosis</b>	Any detectable HBV DNA; refer to a liver transplantation center

#### ■ ANTIVIRAL THERAPY

Below, we summarize the main principles of anti-HBV therapy, emphasizing whether to treat and with which agent. Treatment of HBV infection in patients who are also infected with HIV or hepatitis C virus and in those with resistant or refractory hepatitis B is not within the scope of this article.

#### Acute infection rarely needs treatment

Acute, adult-acquired HBV infection is self-limited in most cases,<sup>1</sup> and antiviral therapy is not routinely indicated.

In the rare cases of acute liver failure related to acute HBV infection, use of a nucleoside or nucleotide analogue reverse transcriptase inhibitor (nucleoside/nucleotide analogues) has been recommended, although no properly designed studies have been done.<sup>2,3</sup> This recommendation is based on anecdotal experience, the relative safety of the antiviral agents, the serious nature of acute liver failure, and the possible need for emergency liver transplantation that requires prophylaxis against recurrence.

The nucleoside/nucleotide analogues that have been recommended in acute liver failure are lamivudine (Epivir), telbivudine (Tyzeka), and entecavir (Baraclude)—but not adefovir (Hepsera), which has a slow action and potential nephrotoxicity. Interferon drugs are contraindicated because they frequently cause side effects and can worsen hepatitis.<sup>4</sup>

Patients with acute liver failure should be referred promptly to a liver transplant center, and other management measures should also be started in a timely fashion.

#### In chronic HBV infection, treatment decisions are individualized

In chronic hepatitis B (ie, lasting  $> 6$  months), treatment decisions should be based on the patient's clinical situation and test results. The route and duration of infection (if known), history of previous hepatitis flares, ALT levels, current and previous HBV serologic test results and DNA levels, findings on liver biopsy (if previously done), and clinically suspected cirrhosis are all important to consider when deciding whether antiviral therapy is needed.

Because the HBV DNA level has a major impact on the risk of cirrhosis and hepatocellular carcinoma, it is increasingly the main variable used for treatment decisions. These levels, however, differ according to the clinical stage of chronic HBV infection.<sup>4,5</sup> TABLE 1 summarizes the common indications for antiviral therapy in chronic HBV infection.

For many patients with chronic HBV infection, observation without antiviral therapy is warranted, eg:

- Young patients ( $< 30$  years old) who acquired HBV at birth and who have persistently normal ALT levels with no evidence of advanced liver disease, regardless of their HBV DNA level (immune tolerance phase)

See the review of the natural history of HBV in the December 2008 issue of CCJM

**TABLE 2**

**Approved agents for treating hepatitis B virus infection**

	INTERFERONS		NUCLEOSIDE/NUCLEOTIDE ANALOGUES				
	INF ALFA-2B (INTRON-A)	PEG IFN ALFA-2A (PEGASYS)	TENOFOVIR (VIREAD)	ENTECAVIR (BARACLUDE)	ADEFOVIR (HEPSERA)	TELBIVUDINE (TYZEKA)	LAMIVUDINE (EPIVIR-HBV)
<b>Dose</b>	5 MU/day or 10 MU 3 times weekly	180 µg/week	300 mg/day	0.5 mg/day <sup>a</sup>	10 mg/day	600 mg/day	100 mg/day
<b>Renal dose adjustment<sup>b</sup></b>	None <sup>c</sup>	None <sup>c</sup>	Yes	Yes	Yes	Yes	Yes
<b>Route</b>	Subcutaneous	Subcutaneous	Oral	Oral	Oral	Oral	Oral
<b>Duration in chronic hepatitis</b>							
e antigen-positive	4–6 months	1 year	> 1 year	≥ 1 year <sup>d</sup>	≥ 1 year <sup>d</sup>	≥ 1 year <sup>d</sup>	≥ 1 year <sup>d</sup>
e antigen-negative	1 year	1 year	> 1 year	> 1 year	> 1 year	> 1 year	> 1 year
<b>Black-box warnings</b>	No	No	Yes <sup>e,f</sup>	Yes <sup>e,f,g</sup>	Yes <sup>e,f,g</sup>	Yes <sup>e,f</sup>	Yes <sup>e,f,g</sup>
<b>Drug resistance</b>	None	None	None at 96 weeks	< 1% up to 2 years	None at 1 year; 29% at 5 years	~ 25% up to 2 years	~ 20% at 1 year; ~ 70% at 5 years
<b>Pregnancy risk category</b>	C <sup>h</sup>	C <sup>h</sup>	B <sup>i</sup>	C <sup>h</sup>	C <sup>h</sup>	B <sup>i</sup>	B <sup>i</sup>
<b>Cost<sup>j</sup></b>	High	High	Low	High	Intermediate	Intermediate	Low

<sup>a</sup> Entecavir dose for lamivudine-refractory or resistant patients is 1.0 mg daily

<sup>b</sup> When indicated, doses are adjusted for patients with estimated creatinine clearance < 50 mL/minute (see TABLE 3 for the detailed doses)

<sup>c</sup> There are only very limited data about interferon-based therapy in HBV-infected patients with renal impairment

<sup>d</sup> Treatment for at least 12 months continuing for at least 6 months after e antigen seroconversion

<sup>e</sup> Severe lactic acidosis, sometimes fatal, may occur with nucleoside/nucleotide analogues

<sup>f</sup> Hepatitis B exacerbations may occur upon discontinuation of therapy

<sup>g</sup> Offer HIV counseling and testing prior to use; higher dose may be indicated if HIV infection is present

<sup>h</sup> Animal studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

<sup>i</sup> Animal studies show no risk to the fetus and there are no adequate and well-controlled studies in pregnant women; or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women show no risk to the fetus in any trimester

<sup>j</sup> Based on treatment duration of 1 year

INF alfa-2B = interferon alfa-2B, PEG INF alfa-2A = pegylated interferon alfa 2A

ADAPTED FROM LOK AS, MCMAHON BJ. CHRONIC HEPATITIS B. HEPATOLOGY 2007; 45:507–539, WITH PERMISSION.

- Chronic inactive carriers who have no e antigen, persistently normal ALT levels, and very low or undetectable levels of HBV DNA without evidence of significant liver injury. These patients can be managed by internists by close monitoring for hepatitis flares with serial ALT measurements along with other general management measures.

**Antiviral agents for chronic HBV infection**

An ideal agent for treating hepatitis B does not exist. Trade-offs are the essence of agent selection.

**Interferons**, the first drugs shown to be effective against HBV, can in some respects be considered the best available initial choice, especially in patients positive for hepatitis e antigen. Interferons have numerous side effects but, unlike all the other options, they have a well-defined duration of treatment (4–6 months in patients positive for e antigen). The principal goal of this therapy is disappearance of e antigen.

Interferon-based therapy is not recommended in patients with cirrhosis, however, because of the risk of hepatic decompensation

TABLE 3

## Doses of nucleoside analogues according to creatinine clearance

DRUG	CREATININE CLEARANCE (ML/MINUTE)	RECOMMENDED DOSE
<b>Tenofovir</b> (Viread)	≥ 50	300 mg daily
	30–49	300 mg every 48 hours
	10–29	300 mg every 72–96 hours
	< 10	Not defined
	Hemodialysis	300 mg every 7 days
<b>Entecavir</b> <sup>a</sup> (Baraclude), in patients who have never taken nucleoside analogues	≥ 50	0.5 mg daily
	30–49	0.25 mg daily
	10–29	0.15 mg daily
	< 10 or hemodialysis <sup>b</sup> or CAPD <sup>c</sup>	0.05 mg/day or 0.5 mg/week
<b>Entecavir</b> , in patients resistant to lamivudine	≥ 50	1 mg daily
	30–49	0.5 mg daily
	10–29	0.3 mg daily
	< 10 or hemodialysis <sup>b</sup> or CAPD	0.1 mg daily
<b>Adefovir</b> (Hepsera)	≥ 50	10 mg daily
	20–49	10 mg every other day
	10–19	10 mg every third day
	Hemodialysis	10 mg weekly, given after dialysis
<b>Telbivudine</b> (Tyzeka)	≥ 50	600 mg daily
	30–49	600 mg every 48 hours
	< 30 (not requiring dialysis)	600 mg every 72 hours
	End-stage renal disease	600 mg every 96 hours (after dialysis)
<b>Lamivudine</b> (Epivir)	≥ 50	100 mg daily
	30–49	100 mg 1st dose, then 50 mg daily
	15–29	35 mg 1st dose, then 25 mg daily
	5–14	35 mg 1st dose, then 15 mg daily
	< 5	35 mg 1st dose, then 10 mg daily

<sup>a</sup> Available in tablet form (0.5 mg and 1.0 mg) and liquid form (0.05 mg/mL)

<sup>b</sup> To be given after hemodialysis

<sup>c</sup> Continuous ambulatory peritoneal dialysis

ADAPTED FROM LOK AS, MCMAHON BJ. CHRONIC HEPATITIS B. HEPATOLOGY 2007; 45:507–539, WITH PERMISSION.

**Test all patients with chronic HBV for hepatitis A, hepatitis C, and possibly HIV and hepatitis D**

associated with interferon-related flares of hepatitis.<sup>4</sup>

**Nucleoside/nucleotide analogues** are easy to use and therefore are usually the first-line therapy. Problems with these agents are that the optimal treatment duration is not known, and that drug resistance can emerge (TABLE 2, TABLE 3).

Of the analogues now available, we recommend tenofovir (Viread) or entecavir. These agents are less likely to result in emergence of resistant strains than the prototypical agent, lamivudine. Three other agents, clevudine, adefovir, and tenofovir with emtricitabine (Truvada), are also available or in late stages

of clinical trials.

Although single-agent antiviral therapy may someday be replaced by a multidrug regimen, the data so far are not sufficiently robust to recommend multidrug regimens except possibly in cases of established drug resistance.

### Adjunctive management

**Vaccinations.** All patients with chronic hepatitis B should be vaccinated against hepatitis A if serologic testing indicates they have no immunity to it. Influenza and pneumococcal vaccines are recommended for all patients with chronic liver disease.<sup>6</sup>

TABLE 4

Findings of prognostic value in hepatitis B virus (HBV) infection

	DISEASE ACTIVITY	INFECTIVITY	DISEASE PROGRESSION	CIRRHOSIS	HEPATOCELLULAR CARCINOMA
HBV surface antigen	0	+	0	0	0
HBV DNA level	+	++	++	++	++
Alanine aminotransferase	+	0	0	0	0
HBV e antigen	+	++	++	0	0
Hypersplenism	0	0	++	++	0
Liver imaging	0	0	++	+	++
Liver biopsy	+++	0	+++	+++	0

0 not valuable, + valuable, ++ very valuable, +++ extremely valuable

An ideal agent for treating HBV does not exist

**Alcohol rehabilitation.** Patients who abuse alcohol should be counseled, and many need consultation with a psychosocial care provider for alcohol rehabilitation.

**Smoking cessation.** Cigarette smoking is linked to a higher risk of hepatocellular carcinoma in patients with chronic liver disease, including chronic HBV infection.<sup>7</sup> Therefore, smokers should be counseled to quit.

**Surveillance for hepatocellular carcinoma.** Hepatocellular carcinoma can occur in patients with chronic hepatitis B, in most cases on top of cirrhosis, although important exceptions exist. The American Association for the Study of Liver Diseases recommends surveillance for hepatocellular carcinoma in all HBV carriers with cirrhosis and in the following groups regardless of whether they have cirrhosis<sup>8</sup>:

- Asian men age 40 and older
- Asian women age 50 and older
- African patients age 20 and older
- Patients with a family history of hepatocellular carcinoma
- Possibly, those with high HBV DNA levels and ongoing inflammatory activity.

In the United States, liver ultrasonography and alpha fetoprotein measurement every 6 to 12 months is a reasonable strategy.

If there is evidence of cirrhosis, esophagogastroduodenoscopy is recommended to screen for esophageal and gastric varices.

Laboratory, radiologic, and histologic findings of prognostic value in HBV-infected patients are outlined in TABLE 4.

■ SCREEN BEFORE CHEMOTHERAPY OR IMMUNOSUPPRESSIVE THERAPY

When patients who are positive for HBV surface antigen undergo immunosuppressive therapy or cancer chemotherapy, from 20% to 50% develop reactivated HBV infection with high HBV viral loads. Even patients who have resolved hepatitis B (ie, negative for HBV surface antigen and positive for surface antibody) may experience hepatitis B reactivation, with serious consequences. Hepatic decompensation and death have been reported during and after chemotherapy, especially in patients with cirrhosis.<sup>9</sup> Therefore, patients at risk of HBV infection should be screened for it before starting these therapies.<sup>4</sup> Furthermore, perhaps all patients about to undergo anticancer therapies that include anti-B-cell or anti-T-cell therapies or hematopoietic stem cell transplantation should be screened.<sup>9</sup>

Recent data indicate that many oncologists have not been screening for HBV.<sup>10</sup> Hence, more effort is needed to make this important testing routine in this setting.

The initial tests in these patients should be liver chemistry tests, HBV surface antigen, HBV surface antibody, and HBV core antibody. In those who test positive for surface antigen, one should test for e antigen, e antibody, and HBV DNA.

Patients with indications for anti-HBV therapy (TABLE 1) should receive antiviral therapy. Otherwise, those positive for surface anti-

**TABLE 5**  
**Child-Turcotte-Pugh scoring system**

POINTS	1	2	3
Encephalopathy	None	Grade 1–2	Grade 3–4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2–3	> 3
In primary biliary cirrhosis	1–4	4–10	> 10
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (seconds over control) or	< 4	4–6	> 6
Prothrombin time (international normalized ratio)	< 1.7	1.7–2.3	> 2.3

**The HBV DNA level has a major impact on the risk of cirrhosis and hepatocellular carcinoma**

gen should start taking anti-HBV medication at the start of chemotherapy or immunosuppressive therapy and should continue taking it until 6 months after the chemotherapy or immunosuppressive therapy is finished.<sup>4</sup> Some experts also recommend starting anti-HBV therapy 7 days before the chemotherapy or immunosuppressive therapy and continuing it for 1 year afterward.<sup>10</sup> Those with HBV DNA levels higher than  $2 \times 10^3$  IU/mL should continue HBV therapy until they reach the same treatment end points as for immunocompetent patients as outlined above.<sup>4</sup>

Because we have little information on patients who are negative for surface antigen and who have antibodies against surface antigen and core antigen, we cannot make an unequivocal recommendation for anti-HBV therapy in this group.<sup>11</sup> Rather, these patients should be monitored during immunosuppressive treatment, preferably with liver chemistry tests and HBV DNA titers, and antiviral drugs should be given as a deferred therapy upon evidence of HBV reactivation.<sup>9</sup> Few cases of fatal hepatic failure in patients with this serologic pattern receiving rituximab (Rituxan) have been reported.<sup>12–14</sup>

With their small risk of drug resistance and rapid onset of action, entecavir or tenofovir may be the preferred anti-HBV therapy in patients undergoing immunosuppression or chemotherapy, especially in those requiring prolonged immunosuppressive therapy (longer than 12 months). In those requiring shorter courses, lamivudine or telbivudine is a possible alternative.<sup>4</sup>

**OUTCOMES OF LIVER TRANSPLANTATION HAVE IMPROVED IN HBV PATIENTS**

The early results of liver transplantation for HBV were discouraging because many patients developed rapidly progressive recurrent disease (fibrosing cholestatic hepatitis) and died within 12 to 18 months after the operation.<sup>15</sup> However, patients with HBV are now treated perioperatively with lamivudine or adefovir combined with prolonged administration of hepatitis B immune globulin, and their survival now exceeds that of patients who receive transplants for many other conditions.<sup>16</sup>

Like patients with cirrhosis due to other causes, those with HBV-related cirrhosis who have any of the following should be referred for liver transplantation evaluation<sup>16</sup>:

- A Model for End-Stage Liver Disease (MELD) score of 10 or higher (calculated from the serum creatinine level, total bilirubin level, and international normalized ratio of the prothrombin time; see [www.unos.org/resources/MeldPeldCalculator.asp?index=98](http://www.unos.org/resources/MeldPeldCalculator.asp?index=98)).
- A Child-Turcotte-Pugh score of 7 or higher (TABLE 5).
- A major complication of cirrhosis such as ascites, variceal bleeding, hepatocellular carcinoma, or hepatic encephalopathy.

**PREVENTING VERTICAL TRANSMISSION**

The major problem in young women with chronic HBV infection is the risk of vertical (mother-to-infant) transmission at

TABLE 6

**Which adults should receive hepatitis B vaccination?****People at risk for infection by sexual exposure**

Sex partners of HBV surface antigen-positive persons  
 Sexually active people who are not in a long-term, mutually monogamous relationship (eg, people with more than one sex partner during the previous 6 months)  
 Patients seeking evaluation or treatment for a sexually transmitted disease  
 Men who have sex with men

**People at risk of infection by percutaneous or mucosal exposure to blood**

Current or recent injection-drug users  
 Household contacts of HBV surface antigen-positive persons  
 Residents and staff of facilities for developmentally disabled persons  
 Health care and public safety workers with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids  
 Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients

**Others**

International travelers to regions with high or intermediate levels (HBV surface antigen prevalence of 2% or higher) of endemic HBV infection  
 People with chronic liver disease  
 People with HIV infection  
 All other people seeking protection from HBV infection

FROM MAST EE, WEINBAUM CM, FIORE AE, ET AL. A COMPREHENSIVE IMMUNIZATION STRATEGY TO ELIMINATE TRANSMISSION OF HEPATITIS B VIRUS INFECTION IN THE UNITED STATES: RECOMMENDATIONS OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP) PART II: IMMUNIZATION OF ADULTS. MMWR RECOMM REP 2006 DEC 8;55(RR-16):1-33.

delivery. The risk varies, depending on the viral load and e antigen status of the mother at the time of delivery; if she is positive for e antigen, the risk of HBV infection in the newborn is 70% to 90% by the age of 6 months if the newborn does not receive postexposure immunoprophylaxis; if the mother is positive for surface antigen but negative for e antigen, the risk of chronic infection is less than 10%, even without postexposure immunoprophylaxis.<sup>17</sup>

All women should be tested for HBV surface antigen early in pregnancy each time they become pregnant. If a patient tests negative early in pregnancy but continues behaviors that put her at risk of HBV infection (eg, having multiple sexual partners, having had a sex partner positive for surface antigen, using injection drugs, or contracting any sexually transmitted disease), she should be retested at the time of admission to the hospital for delivery.<sup>17</sup> This also includes women who were not screened prenatally and those with clinical hepatitis.

**Vaccine and immune globulin for the infant**

If the mother is positive for HBV surface antigen, the infant should receive single-antigen HBV vaccine and hepatitis B immune globulin within 12 hours of birth, given at different injection sites.<sup>17</sup> The second dose of vaccine should be given at age 1 to 2 months and the third at age 6 months (but not before age 24 weeks). The response to vaccination should be ascertained by testing for surface antigen and surface antibody after completion of the vaccine series, at age 9 to 18 months.

Maternal HBV infection does not contraindicate breastfeeding, as studies suggest that breastfeeding by a mother positive for surface antigen does not increase the infant's risk of acquiring HBV infection.<sup>18</sup>

**Which HBV therapy for a pregnant woman?**

Some evidence supports antiviral therapy with nucleoside/nucleotide analogues in pregnant women who have viral loads of  $10^6$  IU/mL or higher. Lamivudine is safe in pregnancy and, together with immunization

**All pregnant women should be tested for HBV early in pregnancy**



TABLE 7

Adult dosing schedule for hepatitis B virus vaccines

RECIPIENTS	RECOMBIVAX HB DOSE	ENGERIX-B DOSE	TWINRIX DOSE	SCHEDULE
Adults (≥18 years)	Not applicable	Not applicable	20 µg (1.0 mL)	At 0,1, and 6 months
Adults (≥ 20 years)	10 µg (1.0 mL)	20 µg (1.0 mL)	20 µg (1.0 mL)	At 0,1, and 6 months <sup>a</sup>
Adults on dialysis and other immuno-compromised patients aged ≥ 20 years	40 µg (1.0 mL) <sup>b</sup>	40 µg (2.0 mL) <sup>c</sup>	Not applicable	Formulation-specific schedule

<sup>a</sup> Other schedules applicable only for Recombivax HB and Engerix-B are 0, 1, 4 months and 0, 2, 4 months

<sup>b</sup> A special 40-µg dose in a 1-mL volume is given in a three-dose schedule at 0,1, and 6 months

<sup>c</sup> Two 20-µg standard doses are administered at one site in a four-dose schedule at 0, 1, 2, and 6 months

All infants should be vaccinated against HBV at birth, 1 month, and 6 months

of the infant, reduces HBV transmission. Interferon-based therapy is contraindicated in pregnant women (and in women who may want to become pregnant) because of interferon’s antiproliferative effects. Nucleoside/nucleotide analogues classified as category B (eg, lamivudine, telbivudine, and tenofovir) could be used when the benefit of treating the pregnant mother outweighs the risk to the mother or fetus,<sup>2</sup> although the possible effects of tenofovir on bone density argue against its use during pregnancy or breastfeeding.<sup>19</sup>

■ VACCINATION HAS REDUCED THE INCIDENCE OF ACUTE HEPATITIS B

HBV vaccination, a major achievement in HBV management, has played a big role in reducing the incidence of acute HBV infection, especially in children and adolescents.<sup>20</sup>

The currently available vaccines in the United States contain HBV surface antigen derived through recombinant DNA technology from yeast.<sup>21</sup> Two single-antigen vaccines are available in the United States, under the brand names Recombivax HB and Engerix B. Of the three licensed combination vaccines, one (Twinrix) is used in adults, and two (Comvax and Pediarix) are used in infants and young children. Twinrix contains recombinant HBV surface antigens and inactivated hepatitis A virus and it is recommended for people age 18 years and older and at risk of both HBV and hepatitis A infections.<sup>20</sup>

Vaccinate all infants

All infants should be vaccinated against HBV as part of the recommended childhood immunization schedule. The vaccine is given on a three-dose schedule at birth and again at 1 month and 6 months of age.<sup>16</sup> All children and adolescents under age 19 who have not previously received HBV vaccine should be vaccinated at any age with an appropriate dose and schedule.<sup>16</sup>

Vaccinate adults at risk—or who ask for it

Hepatitis B vaccination is recommended for all unvaccinated adults at risk of HBV infection and for all adults who ask for it (TABLE 6).<sup>20</sup>

TABLE 7 summarizes the adult dosing schedule for HBV vaccines.<sup>20</sup> The vaccines should be given intramuscularly in the deltoid with a 1- to 2-inch needle, depending on the patient’s sex and weight.<sup>20</sup> If doses are missed, the series should be resumed as soon as possible; there is no need to restart the series if the time between doses is longer than recommended.

Vaccination is less effective in older people

The three-dose vaccine series given intramuscularly initially, then again at 1 month and 6 months, produces a protective antibody response in approximately 30% to 55% of healthy adults under age 40 after the first dose, 75% after the second dose, and more than 90% after the third dose.<sup>21,22</sup> After age 40, however, the proportion of persons who have a protective antibody response after three doses declines to less than 90%, and by age 60, protective levels of antibody develop in only 75%.<sup>23</sup>

Other factors that lower the response to vaccination are smoking, obesity, genetic factors, and immune suppression.<sup>20</sup>

Postvaccination serologic testing for immunity is not necessary after routine vaccination of adults, but it is recommended for patients whose subsequent clinical management depends on knowledge of their immune status, such as health care workers who have contact with patients or blood and are at ongoing risk of injuries with sharp instruments or needlesticks; chronic hemodialysis patients and people infected with HIV or otherwise immunocompromised; and sex partners or needle-sharing partners of people positive for HBV surface antigen.<sup>20</sup> A protective concentration of HBV surface antibody measured 1 to 2 months after completion of the vaccine series is defined as 10 mIU/mL. Further periodic testing to document persistence of protective levels of surface antibody is not indicated.

### If the first series does not 'take'

Patients who do not respond to the primary

vaccine series should complete a second three-dose series, with doses at 0, 1, and 6 months. Serologic testing is done 1 to 2 months after finishing the second series.

Patients who do not have protective levels of HBV surface antibody after revaccination by the appropriate schedule in the deltoid muscle (< 5% of those receiving six doses of hepatitis B vaccine) either are primary nonresponders or are infected with HBV.<sup>20</sup> Therefore, they should be tested for HBV surface antigen. If this test is negative, then they should be considered susceptible to HBV infection and should be counseled accordingly.

### Contraindications and precautions

HBV vaccination is contraindicated in people with a history of hypersensitivity to baker's yeast or to a previous dose of HBV vaccine.<sup>20</sup> Patients with moderate or severe acute illness at the time the shot is scheduled should wait until they recover before getting HBV vaccine. Pregnancy is not a contraindication.<sup>20</sup> ■

## REFERENCES

1. Elgouhari HM, Abu-Rajab Tamimi T, Carey WD. Hepatitis B virus infection: understanding its epidemiology, course, and diagnosis. *Cleve Clin J Med* 2008; 75:881-889.
2. Stravitz RT, Kramer AH, Davern T, et al. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. *Crit Care Med* 2007; 35:2498-2508.
3. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology* 2007; 45:1056-1075.
4. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007; 45:507-539.
5. Keefe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States. *Clin Gastroenterol Hepatol* 2004; 2:87-106.
6. Jacobs RJ, Meyerhoff AS, Saab S. Immunization needs of chronic liver disease patients seen in primary care versus specialist settings. *Dig Dis Sci* 2005; 50:1525-1531.
7. Wang LY, You SL, Lu SN, et al. Risk of hepatocellular carcinoma and habits of alcohol drinking, betel quid chewing and cigarette smoking: a cohort of 2416 HBsAg-seropositive and 9421 HBsAg-seronegative male residents in Taiwan. *Cancer Causes Control* 2003; 14:241-250.
8. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005; 42:1208-1236.
9. Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology* 2006; 43:209-220.
10. Tran T, Oh M, Poordad F, Martin P. Screening for hepatitis B in chemotherapy patients: survey of current oncology practices [abstract]. *Hepatology* 2007; 46:978A.
11. Kohrt HE, Ouyang DL, Keefe EB. Antiviral prophylaxis for chemotherapy-induced reactivation of chronic hepatitis B virus infection. *Clin Liver Dis* 2007; 11:965-991.
12. Westhoff TH, Jochimsen F, Schmittl A, et al. Fatal hepatitis B virus reactivation by an escape mutant following rituximab therapy. *Blood* 2003; 102:1930.
13. Sarrecchia C, Cappelli A, Aiello P. HBV reactivation with fatal fulminating hepatitis during rituximab treatment in a subject negative for HBsAg and positive for HBsAb and HbcAb. *J Infect Chemother* 2005; 11:189-191.
14. Law JK, Ho JK, Hoskins PJ, Erb SR, Steinbrecher UP, Yoshida FM. Fatal reactivation of hepatitis B post-chemotherapy for lymphoma in a hepatitis B surface antigen-negative, hepatitis B core antibody-positive patient: potential implications for future prophylaxis recommendations. *Leuk Lymphoma* 2005; 46:1085-1089.
15. Todo S, Demetris AJ, Van Thiel D, Teperman L, Fung JJ, Starzl TE. Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease. *Hepatology* 1991; 13:619-626.
16. Murray KF, Carithers RL Jr, AASLD. AASLD practice guidelines: Evaluation of the patient for liver transplantation. *Hepatology* 2005; 41:1407-1432.
17. Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep* 2005; 54:1-31.
18. Beasley RP, Stevens CE, Shiao IS, Meng HC. Evidence against breast-feeding as a mechanism for vertical transmission of hepatitis B. *Lancet* 1975; 2:740-741.
19. Parsonage MJ, Wilkins EG, Snowden N, Issa BG, Savage MW. The development of hypophosphataemic osteomalacia with myopathy in two patients with HIV infection receiving tenofovir therapy. *HIV Med* 2005; 6:341-346.
20. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep* 2006; 55:1-33.
21. Andre FE. Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine. *Am J Med* 1989; 87:145-205.
22. Zajac BA, West DJ, McAleer WJ, Scolnick EM. Overview of clinical studies with hepatitis B vaccine made by recombinant DNA. *J Infect* 1986; 13(suppl A):39-45.
23. Averbhoff F, Mahoney F, Coleman P, Schatz G, Hurwitz E, Margolis H. Immunogenicity of hepatitis B vaccines: implications for persons at occupational risk for hepatitis B virus infection. *Am J Prev Med* 1998; 15:1-8.

ADDRESS: William D. Carey, MD, Division of Gastroenterology and Hepatology, A30, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail careyw@ccf.org.