



## Viral hepatitis in the 1990s, part II: hepatitis B and delta virus

WILLIAM D. CAREY, MD AND GIRISH PATEL, MD

■ Parenterally shared blood and sexual transmission are the main routes of spread of hepatitis B in the United States. Most cases resolve spontaneously without specific treatment. Passive immunization provides temporary protection in certain postexposure settings. Active immunization achieves high protection rates. Duration of protection and the need for booster doses are not well defined. Many cases of fulminant B hepatitis, severe chronic active hepatitis, and end-stage cirrhosis secondary to hepatitis B are due to hepatitis delta virus infection. The delta virus requires the presence of hepatitis B for expression of disease. Hepatitis B prophylaxis should help eliminate delta hepatitis.

□ INDEX TERMS: HEPATITIS, VIRAL, HUMAN; HEPATITIS B; DELTA INFECTION □ CLEVE CLIN J MED 1992; 59:393-401

**T**HE 1 MILLION CARRIERS of hepatitis B in the United States, although only 0.5% of the world's estimated 200 million carriers, nevertheless constitute a substantial health risk for the public and for health care workers. Effective vaccines are available and high-risk groups have been identified, yet effective, widespread prevention of hepatitis B infection remains an elusive goal. Universal immunization of children holds promise as a way of severely curtailing hepatitis B.

Important issues surrounding hepatitis B viral infection need to be resolved: What are the mechanisms by which it is transmitted? Are men more susceptible to hepatitis B infection than women? How can viral transmission from mother to offspring be prevented? What are the short-term and long-term risks to health care professionals?

From the Department of Gastroenterology, The Cleveland Clinic Foundation.

Address reprint requests to W.D.C., Department of Gastroenterology, S40, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

In a previous article<sup>1</sup> we reviewed the causes, clinical features, and management of viral hepatitis in general and hepatitis A in particular. In this article, we focus on risk, treatment, and prevention of hepatitis B and delta virus infection, while addressing the important issues facing clinicians and researchers.

### BACKGROUND

Hepatitis B is a 42-nm, double-shelled DNA virus comprised of a lipoprotein outer coat, a protein core, a circular strand of DNA, and a DNA polymerase.<sup>2-4</sup> It is termed a "hepadnavirus," indicating the hepatotropic nature of this DNA virus. It replicates by reverse transcription. The incubation period for hepatitis B may be as short as 15 days and as long as 180 days, longer than that for hepatitis A. The period of clinical illness also tends to be longer than that for hepatitis A, averaging several weeks.<sup>5</sup>

Several well-defined antigen-antibody systems are associated with hepatitis B virus (HBV) infection. For everyday clinical use, relatively few serologic markers

**TABLE 1**  
**SEROLOGIC MARKERS OF HEPATITIS B**

Abbreviation	Identification	Serologic significance
HBsAg	Surface antigens on the coat of HBV. There are several subtypes	Indicates infection present, either in replicative phase or integration of viral genetic material into hepatocyte genome
HBeAg	Antigen of HBV of uncertain function	Soluble; correlates with HBV replication, high HBV titer in serum, and infectivity
HBcAg	Central (core) portion of HBV	Present only transiently in serum, no commercial test available
Anti-HBs	Antibody to HBsAg	Indicates past HBV infection and immunity to HBV, passive antibody from hepatitis B immune globulin, or immune response to HB vaccine
Anti-HBe	Antibody to HBeAg	Correlates with disappearance of HBeAg and decreased viral replication and infectivity
Anti-HBc	Antibody to core antigen	Indicates prior infection with HBV at an undefined time
IgM anti-HBcAg	IgM antibody to HBcAg	Indicates recent infection with HBV; may be detectable up to 12 months after infection
DNA polymerase	Enzyme present in HBV	Implies ongoing viral replication (a research tool)
HBV-DNA	HBV genetic material	The most certain indicator of hepatitis B infection; indicates active viral replication; appears with DNA polymerase soon after HBsAg is detectable and before the onset of symptoms

HBV = hepatitis B virus

are identified in the "hepatitis profile" generated by most laboratories. *Table 1* lists some of the important serologic markers and indicates their clinical significance. *Table 2* presents the interpretation of typical serologic findings due to exposure to hepatitis B.

#### EPIDEMIOLOGY

The number of hepatitis B carriers in the world is close to 200 million,<sup>6</sup> with about 1 million in the United States alone.<sup>7</sup> Spread of hepatitis B by oral ingestion of virus requires a much higher inoculum than that required to spread hepatitis A.<sup>8</sup> This fits quite well with clinical observations that schoolyard and household epidemics of hepatitis B are uncommon. On the other hand, hepatitis B is extremely contagious via parenteral routes.<sup>8</sup>

Blood, serum, secretions, and other body fluids containing hepatitis B surface antigen (HBsAg) may infect individuals when transmitted parenterally via blood transfusions, needle stick accidents, or intravenous drug use. Parenterally shared blood is the main route of spread of hepatitis B in the United States. Hepatitis B is also spread through sexual activity and perinatal transmission from mother to offspring ("vertical transmission"). In endemic regions such as Africa and Southeast Asia, and in the world at large, vertical transmission is the most common way

hepatitis B moves through a community.

Although the exact mode of spread is still unknown, sexual partners of individuals secreting HBsAg are considered at high risk for hepatitis B. In households in which there is an adult with HBsAg, the spouse is at higher risk than all other household members.<sup>9</sup> HBsAg has been found in saliva, semen, vaginal secretions, and tears. Minor abrasions which occur during sexual activity may allow inoculation of the virus, but this has not been proved. Hepatitis B is widespread among male homosexuals but is not so common

among prostitutes. The reason for this discrepancy in susceptibility to hepatitis B in men and women has not been clarified. The acquired immunodeficiency state in male homosexuals only partially explains this male susceptibility.<sup>10</sup>

Vertical transmission may occur when a woman is a chronic carrier or develops acute viral hepatitis B in the last trimester of pregnancy. Presence of hepatitis B e antigen (HBeAg) in the mother's blood and secretions greatly increases the likelihood for transmitting infection.<sup>11</sup> Infants born to HBeAg-positive mothers stand a 95% to 100% chance of developing hepatitis and a nearly 85% chance of becoming chronic carriers. Cord blood is usually HBsAg-negative, so contagion in utero is not very common. However, 5% to 10% of cases of mother-to-offspring transmission of hepatitis B do seem to occur as a result of intrauterine transplacental leakage of HBeAg-positive maternal blood.<sup>12</sup>

In the United States, where the prevalence of hepatitis B is quite low, testing to identify mothers with HBsAg was formerly given only to those in high-risk groups, such as prostitutes and intravenous drug users. This selective approach missed many women whose infants were at risk.<sup>13</sup> New recommendations from the Centers for Disease Control (CDC) advise that all pregnant women be screened for HBsAg. This strategy is estimated to cost \$12,000 to \$20,700 for each newborn infant protected from becoming a chronic HBV

carrier.<sup>14</sup> Considering the morbidity and shortened life of those infected, these are dollars well spent. Attempts to prevent vertical transmission by caesarian section and by avoiding breast feeding have failed. In infants, passive immunization with hyperimmune B immune globulin (HBIG) combined with active immunization with hepatitis B vaccine was more than 90% effective at preventing hepatitis B in offspring in England and Wales,<sup>15</sup> but was only 81% effective in Korea. A recent report suggests that combining caesarian section with passive and active immunization eliminates vertical transmission of hepatitis B.<sup>16</sup> More studies on this matter will be necessary before this approach can be recommended.

**Risks for health care workers**

Hepatitis B is an occupational risk factor for health care workers who are in contact with HBV-infected patients and their bodily fluids. The likelihood of having serologic markers of hepatitis B increases with age and length of service in the health profession. It is particularly high for pathologists, surgeons, emergency room nurses, laboratory technicians, and dentists. Immunization of health care workers could eliminate more than 95% of this risk. Strict adherence to CDC universal precautions<sup>17</sup> should further minimize the risk of hepatitis B, although scientific demonstration of this is lacking. A study of oral surgeons revealed that the likelihood of serologic evidence of hepatitis B was not affected by the reported use of gloves, eye shields, or face masks.<sup>18</sup> While CDC guidelines should be adhered to as a matter of common sense (and to prevent other disease), we do not believe they are a suitable substitute for immunization of health care workers against hepatitis B.

Health care workers with hepatitis B seem to pose little risk to their patients. There are exceptions: for example, when three patients of a gynecologist who was a carrier of hepatitis B developed acute hepatitis B, his other patients were surveyed.<sup>19</sup> Nine percent of the patients treated during the preceding 16 months had evidence of HBV exposure. Patients who had hysterectomy or caesarian section were at the highest risk (19%) of infection.<sup>19</sup>

Health risks to patients and economic and social risks to the health care worker add force to the recommendation that adequate immunization of health care workers be mandatory. No limitation of working with patients is required for HBsAg-positive health care workers unless there is substantiated evidence that patients are affected.

TABLE 2  
SEROLOGIC PROFILES OF HEPATITIS B

HBsAg	Anti-HBc IgM	Anti-HBc IgG	Anti-HBs	Anti-HDV IgM	Interpretation
+	-	-	-	-	Early acute HBV infection
+	+	-	-	-	Acute HBV within past 12 months; occasionally seen in chronic infection
-	-	+	+	-	Recovery from HBV infection (past exposure)
+	-	+	-	-	Chronic HBV infection
+	+	-	-	+	Acute coinfection with HBV and HDV
+	-	+	-	+	Acute HDV superinfection on chronic carriage of HBV
-	-	-	-	-	No hepatitis B exposure

+, present in serum; -, not present in serum  
HBV, hepatitis B virus; HDV, hepatitis delta virus

CLINICAL COURSE OF HEPATITIS B INFECTION

The clinical and biochemical course of hepatitis B tends to be more insidious and prolonged than in hepatitis A. Initial symptoms develop less rapidly, and the prodrome is usually longer. Abdominal pain or discomfort also tends to last longer.

Arthralgia is common. Arthritis with redness, swelling, or effusion seems to occur only with hepatitis B and may cause a diagnostic dilemma.<sup>20,21</sup> It usually appears early in the prodrome and tends to clear over days or weeks, often before the onset of jaundice. Up to 20% of hepatitis B patients may experience dermatitis or arthritis as a prodrome of acute viral hepatitis B.<sup>22</sup> Many of these extra-hepatic manifestations are immune-complex mediated.<sup>22</sup> The syndrome has been likened to serum sickness. The skin eruption may be an erythematous macular or maculopapular eruption, an intensely pruritic urticaria, or may resemble erythema multiforme. Skin rashes without arthritis may occur. In patients with a syndrome resembling serum sickness, cryoprecipitates consisting of immunoglobulin G (IgG) and immunoglobulin M (IgM) can be seen in the serum and HBsAg in synovial fluid.<sup>22</sup> Chronic destructive joint disease does not occur as a sequela of

acute viral hepatitis. Glomerulonephritis, polyarteritis, mixed cryoglobulinemia, and chronic relapsing demyelinating polyneuropathy<sup>23</sup> have all been associated with chronic HBsAg states but are not ordinarily seen in the setting of acute hepatitis. Approximately 1% to 2% of patients with acute viral hepatitis B develop massive or submassive hepatic necrosis, which is usually fatal.

Unlike hepatitis A, which is self-limited, hepatitis B may progress to chronic hepatitis and cirrhosis, with persistence of HBsAg in serum. Up to 5% of patients with acute viral hepatitis B become chronic carriers of the virus. Chronic B carriers often have impaired cell-mediated immunity to the virus.<sup>24</sup> They are clinically well and may have normal or near-normal serum liver tests. Chronic B carriers may have viral antigen in one of two states. First, the viral DNA material may be incorporated into the human hepatocyte genome; in this case, no virus is being replicated, although recent evidence using highly sensitive polymerase chain reaction techniques suggests there is low-level viral replication. Second, carriers may have ongoing viral replication; these individuals are clearly infective for others. The presence of DNA polymerase, HBV-DNA, or immunohistochemical staining of liver biopsy material for hepatitis B c antigen all denote viral replicating activity ("replicative phase"); their absence suggests the noninfectious "integrative phase" of hepatitis B. Since most of the direct tests for the replicative phase are generally unavailable, testing for HBeAg has been employed as a surrogate test. Testing positive for HBeAg denotes a high degree of infectivity; patients without HBeAg but with anti-HBe antibodies are less infective.

Longstanding hepatitis B infection is an important cause of hepatocellular carcinoma in adults and children.<sup>24-26</sup> Hepatocellular carcinoma is the eighth most frequent cancer in the world, accounting for approximately 260,000 new cases each year.<sup>27</sup> There is a strong geographic association between endemic HBV infection and high incidence of hepatocellular carcinoma (eg, in China and Southeast Asia, where 10% to 15% of population may be HBV carriers).<sup>6</sup> Areas with low HBV carrier rates (eg, United States with 0.5%) have a low incidence of hepatocellular carcinoma.<sup>28-30</sup>

---

#### TREATMENT OPTIONS FOR HEPATITIS B

---

##### Antivirals

Most cases of hepatitis B resolve spontaneously and require no specific treatment. Antiviral therapy for

chronic hepatitis B can result in clearance of replicating virus from liver in some patients.<sup>31-36</sup> Adenosine arabinoside monophosphate, a potent inhibitor of HBV replication, is of limited usefulness because it causes significant neuromuscular toxicity. Trials of pretreatment with prednisone followed by adenosine arabinoside or adenine arabinoside monophosphate have shown high seroconversion, but toxicity remains the limiting factor. Acyclovir alone is relatively nontoxic but is clinically ineffective in eliminating HBV from the liver.<sup>31</sup>

##### Interferon

Recently, enthusiasm has arisen concerning immunoregulatory therapy, especially the use of interferons, in treating chronic hepatitis B. Interferons are elaborated in the normal host response to viral and other infections, including viral hepatitis. Interferon alpha is made by monocytes and transformed B lymphocytes; interferon beta comes from fibroblasts, and interferon gamma from helper/inducer T lymphocytes.

Studies suggest that between 30% and 40% of interferon-treated patients lose evidence of viral replication. It is too early to know whether any preparation is to be preferred, or what the optimal dose and duration of therapy may be. Therapy is usually given for 4 to 6 months, and side effects are frequent.<sup>37,38</sup> Another concern is whether the promising short-term benefits of interferon will be sustained long after treatment is stopped.

A recently published multicenter randomized controlled trial showed 40% HBeAg seroconversion and a sustained loss of HBV-DNA in nearly 50% of patients with clinically stable chronic hepatitis B after 5 million units of recombinant interferon alfa-2b daily for 16 weeks. Up to 50% response rate was reported in patients with low HBV-DNA levels (<100 pg/mL) with the same dose of interferon. Response rate was lower in patients with higher levels of viral replication (HBV DNA levels >200 pg/mL).<sup>39</sup> Pretreatment with a short course of prednisone (decreasing daily doses of 60 mg, 40 mg, and 20 mg each over 2 weeks), followed by a 2-week rest period and then 16 weeks of interferon alfa-2b added benefit only in patients with low alanine aminotransferase levels (<100 U/L).

During treatment with interferon,<sup>32</sup> clinical hepatitis may flare up, either as increased transaminase levels or increased clinical symptoms. This flare up often precedes clearance of viral replication.<sup>33</sup> For the most part, it may be considered a normal effect of treatment. There is concern that such a flare up in

patients with advanced cirrhosis could have serious deleterious consequences. Accordingly, interferon treatment should probably be withheld from patients with decompensated cirrhosis until its safety in this setting is known.

Only a minority of patients with chronic hepatitis B will benefit from interferon therapy. Most likely to respond are patients who: (1) are female; (2) are HIV-negative; (3) are heterosexual; (4) acquired hepatitis B in adult life; (5) have low levels of viral replication; (6) have high initial aminotransferase values; (7) are non-Chinese; and (8) have active liver disease.<sup>32-36,40-42</sup> Chinese patients achieved only a 15% sustained clearance of HBeAg after 24 weeks of interferon therapy. Poor results were attributed to the likelihood that many of these patients were long-term carriers, possibly from infancy.<sup>43</sup> Similar poor results in Chinese children indicate the likelihood that interferons currently available are useless in this setting.<sup>44</sup>

The value of interferon in treating extrahepatic manifestations of hepatitis B is unclear, although there are case reports of hepatitis B glomerulonephritis responding to interferon.<sup>45</sup> Systematic studies are needed.

Side effects from interferon are frequent, but most are not serious and are reversible with cessation of therapy. Most patients develop flu-like symptoms including muscle and joint aches, fatigue, nausea, and malaise. These side effects are usually tolerable at doses of 5 million units daily<sup>34</sup> and usually abate after a week or two. Unrecognized leukopenia can be serious if bacterial superinfection occurs, but this is rarely seen with the dosages used in treating hepatitis. Mental depression may be severe and is most likely to be troublesome in patients with a history of depression.

In summary, recombinant alpha interferons appear to be promising in single-agent therapy for many patients with chronic HBV infection, providing up to 50% HBeAg seroconversion (eliminating evidence of viral replication) in patients who acquired infection after the neonatal period. Higher conversion rates may be obtained with prednisone pretreatment in patients with low alanine aminotransferase levels. The response rate is low in patients with high levels of viral replication; thus, other approaches to the medical management of this condition are needed.<sup>39</sup>

### Liver transplantation

Liver transplantation in patients with cirrhosis due to HBV is controversial because the recurrence of viral infection cannot be prevented. However, many of

these patients have benefited from transplantation; therefore, it is difficult to make the HBsAg carrier state an absolute contraindication.<sup>46</sup> Removing the diseased liver reduces the titer of hepatitis B in the blood,<sup>47,48</sup> but with rare exceptions the graft becomes infected despite passive immunoprophylaxis.<sup>48</sup> Viral immunity has been demonstrated in patients with fulminant hepatitis,<sup>48</sup> but in most patients with chronic hepatitis, recurrence of the disease in the graft jeopardizes recovery<sup>47,48</sup> and reduces long-term survival.

In HBsAg-positive patients receiving a liver graft, efforts to treat perioperatively with hyperimmune globulin or interferon alfa have so far failed to prevent infection of the graft.<sup>48,49</sup> A human monoclonal antibody directed against hepatitis B has been produced (Sandoz Pharmaceuticals Corporation, East Hanover, New Jersey) by fusing peripheral blood lymphocytes from an immune human with cells of mouse × human myeloma-cell line.<sup>50</sup> The resulting human monoclonal hyperimmune globulin is 50,000 times more potent than commercially available hyperimmune globulin prepared from the blood of immune donors. This has been given to a few patients after liver transplantation,<sup>51</sup> with inconclusive results. Further trials have been slowed by a shortage of the antibody.<sup>52</sup>

---

### PREVENTION OF HEPATITIS B INFECTION

---

#### Passive techniques

Two options are available for prophylaxis against hepatitis B. Passive immunization involves administering plasma components containing a high titer of anti-HBs antibodies. This provides temporary, passive protection and is indicated only in certain postexposure settings. The titer of anti-HBs in standard immune globulin (IG) is too low to provide reliable protection against hepatitis B.<sup>53</sup> IG preparations of known high anti-HBs titer, called HBIG, are prepared from serum pooled from donors who are highly likely to have antibody against hepatitis B—eg, multiple-transfusion patients, such as hemophiliacs.

In the US, HBIG has an anti-HBs titer greater than 100,000 by radioimmunoassay. Human plasma from which HBIG is prepared is screened for antibodies to HIV; in addition, the Cohn fractionation process used to prepare this product inactivates and eliminates HIV from the final product. HIV cannot be transmitted by HBIG.<sup>7,54</sup>

The major indication for administering HBIG is a single acute exposure to hepatitis B virus. Recommendations for HBIG administration from the CDC Im-

**TABLE 3**  
POSTEXPOSURE IMMUNOPROPHYLAXIS FOR HEPATITIS B VIRUS

Type of exposure	Treatment
Perinatal	Hepatitis B immune globulin and vaccine
Sexual contact, source has acute infection	Hepatitis B immune globulin with or without vaccine
Sexual contact with a chronic carrier	Vaccine
Household contact with a chronic carrier	Vaccine
Household contact but no known exposure to source with acute infection	None
Household contact and known exposure to source with acute infection	Hepatitis B immune globulin and vaccine
Household exposure of an infant (< 12 months old) to a primary care giver with an acute infection	Hepatitis B immune globulin and vaccine
Inadvertent percutaneous or permucosal transmission	Vaccine with or without hepatitis B immune globulin

Dosage of hepatitis B immune globulin: for neonates, 0.5 mL intramuscularly, given within 12 hours of birth; for adults, 0.06 mL/kg intramuscularly.  
Modified from Centers for Disease Control, reference 55

**TABLE 4**  
RECOMMENDED DOSES OF CURRENTLY LICENSED HEPATITIS B VACCINES

Group	Dose (mL)*		
	Heptavax-B† 20 g/mL	Recombivax HB 10 g/mL	EngerixB‡ 20 g/mL
Infants of hepatitis B virus carrier mothers	0.5	0.5	0.5
Other infants and children under age 11	0.5	0.25	0.5
Children and adolescents ages 11 to 19	1.0	0.5	1.0
Patients over age 19	1.0	1.0	1.0
Dialysis patients and other immunocompromised persons	2.0	1.0§	2.0

\*Usual schedule for all three vaccines: one dose at 0, 1, 6, months

†Available only for hemodialysis and other immunocompromised patients and for persons with known allergy to yeast

‡Alternative schedule: one dose at 0, 1, 2, 12 months

§40 g/mL, special formulation for dialysis patients

|| Recommended schedule one dose at 0, 1, 2, 6 months

Modified from Centers for Disease Control, references 7 and 55

munization Practices Advisory Committee are given in *Table 3*.<sup>53</sup> The decision to use HBIG should be made rapidly, as there is evidence that maximal protection is afforded by giving HBIG within 48 hours of exposure.

**Active immunization**

Two types of hepatitis B vaccines are currently licensed in the United States. Plasma-derived hepatitis B vaccine is no longer being produced in the United States, and its use is now limited to hemodialysis patients, other immunocompromised hosts, and persons with known allergy to yeasts. The other type of vaccine available in the United States is derived from recombinant DNA technology.

Protection rates of 96% have been reported with the recommended series of three intramuscular injections (given at 0, 1, and 6 months).<sup>56</sup> The deltoid is the recommended site for vaccination of adults and children; immunogenicity of vaccine for adults is substantially lower when injections are given in the buttock.<sup>57</sup> One vaccine offers an alternative schedule of four doses (given at 0, 1, 2, and 12 months) for postexposure prophylaxis or for more rapid induction of immunity. However, there is no clear evidence that this regimen provides greater protection than the standard three-dose series.<sup>7</sup> The incidence of side effects is very low (less than 3%); the incidence of local arm soreness was higher in patients given the active compound compared to volunteers given a placebo injection. *Table 4* shows the dosage of currently licensed hepatitis B vaccines, and *Table 5* lists pre-exposure indications for their use.

Theoretically, if hepatitis B vaccine (containing

HBsAg) were given to patients carrying anti-HBs, immune-complex-mediated tissue injury analogous to serum sickness might develop. If this were so, testing for anti-HBs prior to administration of the vaccine would be required for each individual. However, evidence indicates that administering hepatitis B vaccine to patients with anti-HBs is safe. However, vaccination provides no benefit to individuals who have already been infected.<sup>58</sup> Therefore, the decision to test potential vaccine recipients for prior infection is primarily an issue of cost-effectiveness and should be based on whether the cost of testing is less than the cost of the vaccine that would be saved.

If pre-immunization testing is undertaken, only one

antibody test is necessary (either anti-HBc or anti-HBs). Anti-HBc identifies all previously infected persons, whether carriers or not, but does not differentiate members of the two groups. Anti-HBs identifies persons previously infected, except for carriers. Neither test has any particular advantage for groups with expected carrier rates of less than 2%, such as health care workers. For groups with higher carrier rates, anti-HBc may be preferred to avoid unnecessary vaccination of carriers.<sup>59</sup>

In some patients, active immunization is ineffective. The incidence of failure may be quite high in immunocompromised patients such as those on hemodialysis or on immunosuppressive drugs. Recent evidence suggests that the response to immunization is T-cell-dependent. For example, alcoholic patients who did not respond to hepatitis B vaccination had lower levels of helper/inducer (T4) cells and lower T4/T8 ratios compared to non-alcoholic controls.<sup>60</sup> Alcoholic patients with pre-existing cirrhosis were much less likely to respond to immunization than were either normal patients or alcoholic patients without liver disease.<sup>60</sup> Homosexual men, particularly those who are HIV-positive, frequently do not respond to vaccination.<sup>61</sup>

In a recent study, liver transplant recipients showed a hepatitis B vaccination response rate of only 20%. Immunosuppression from underlying disease and medications has been implicated in these poor response rates.<sup>62</sup> Also, in a mass hepatitis vaccination program in Taiwan for infants born to mothers with both HBsAg and HBeAg, administration of a series of hepatitis B vaccine (plus a single dose of HBIG within 24 hours of birth) failed to protect 15% of the infants.<sup>63</sup>

Even among apparently healthy patients, 4.2% fail to develop adequate titers of anti-HBsAg on vaccination.<sup>64</sup> Genetic factors may play a role. Revaccination of non-responding patients, using the same dose of human-derived vaccine as used initially, will result in success in over half.<sup>65</sup> Revaccination with human-derived vaccine may have a higher success rate than revaccination using yeast-derived vaccine. In a study using the latter preparation for revaccination of non-responding patients, out of 25 apparently healthy adults only 1 (4%) had a significant antibody level 12 months later. For patients who do not respond to a primary vaccine series given in the buttock, data suggest that revaccination in the arm induces adequate antibody in more than 75%.<sup>59</sup>

The duration of protection and the need for booster doses are not yet fully defined. Of patients who develop adequate antibody levels after three doses of vaccine,

**TABLE 5**  
GUIDELINES FOR PRE-EXPOSURE ADMINISTRATION  
OF ACTIVE HEPATITIS B VACCINE  
IN SELECTED HIGH-RISK GROUPS

*Vaccination is recommended for:*

- All newborns, to protect them before they get involved in high-risk practices (eg, intravenous drug use, homosexual activity)
- Persons with occupational risk; eg, health care workers and public safety workers (especially if tasks involve contact with blood or blood-contaminated body fluids)
- Patients and staff in institutions for the developmentally disabled
- Hemodialysis patients
- Sexually active homosexual men
- Users of illicit injectable drugs
- Recipients of certain blood products (eg, factor VIII, IX concentrates)
- Household and sexual contact of HBV carriers
- Adoptees from countries of high HBV incidence
- Populations with high rates of HBV infection (eg, Alaskan Eskimos, immigrants from eastern Asia)

*Vaccination is indicated in most cases for:*

- Inmates of long-term correctional facilities
- Heterosexually active persons with multiple partners, eg, prostitutes recently diagnosed with other sexually transmitted diseases
- Travellers planning to reside for more than 6 months in hyperendemic areas and likely to have close contact with local population

Modified from Centers for Disease Control, reference 55

between 30% and 50% will lose detectable antibody within 7 years. However, protection against infection and clinical disease appears to persist. Patients with low circulating antibody levels years after vaccination may have anamnestic responses to reinfection. Until more data are available, no confident recommendations are possible.<sup>66</sup> Recent recommendations from the CDC call for mandatory immunization of preschool children in the United States as a way of eradicating this disease (Table 5).<sup>55</sup>

#### HEPATITIS DELTA VIRUS

Hepatitis delta virus (HDV) is an unusual RNA virus which requires the presence of hepatitis B for expression of disease. It is a 35- to 37-nm viral particle, consisting of single-stranded RNA and an internal protein antigen (delta antigen [HDAG]), coated with HBsAg as the surface protein. It is defective in that it requires the presence of another virus for perpetuation<sup>67</sup>; therefore, it should be suspected only in patients who are HBsAg-positive. It may be present during an initial infection with hepatitis B (co-infection), or it may infect an individual with pre-existing chronic hepatitis B (superinfection). Risk factors for the two diseases are similar.

HDV infection results in a more virulent clinical course of disease. Many cases of hepatitis B that lead to fulminant hepatitis, severe chronic active hepatitis, and end-stage cirrhosis are due to the delta virus.<sup>68,69</sup> HDV infection may be diagnosed by detecting HDAg in serum during early infection and by the appearance of total or IgM-specific delta antibody (anti-HDV) during or after infection. A test for detecting total anti-HDV is commercially available. Other tests (for detecting HDAg or IgM anti-HDV) are available only in research laboratories. IgM anti-HDV tends to persist in high titers in patients with unremitting or progressive liver disease, while it declines or disappears before

the homologous IgG antibody in patients whose disease improves or resolves.<sup>70</sup> Therefore, testing for IgM anti-HDV permits HBsAg carriers with underlying HDV-related inflammatory liver disease to be distinguished from those with past HDV infection. Moreover, a persistently positive test may reflect an ominous prognosis, while a declining antibody titer may herald clinical improvement.<sup>70</sup>

The value of interferon therapy in delta hepatitis is unproven, although transient improvement in patients given interferon has been noted by some.<sup>71</sup> Prevention of hepatitis B by immunization and by not sharing intravenous needles should help eliminate delta hepatitis.

## REFERENCES

- Carey WD, Patel G. Viral hepatitis in the 1990s. Part I. *Cleve Clin J Med* 1992; 59:317-325.
- Robinson W, Clayton D, Greenman R. DNA of human hepatitis B virus candidate. *J Virol* 1974; 14:384-391.
- Dane DS, Cameron CH, Briggs M. Virus-like particles in serum of patients with Australia antigen-associated hepatitis. *Lancet* 1970; 1:695-698.
- Kaplan P, Greenman R, Gerin J, Purcell R, Robinson W. DNA polymerase associated with human hepatitis B antigen. *J Virol* 1973; 12:995-1005.
- Stewart JS, Farrow LJ, Clifford RE, et al. A three-year survey of viral hepatitis in West London. *Q J Med* 1978; 47:365-384.
- Szmuness W. Hepatocellular carcinoma and the hepatitis B virus. Evidence for a causal association. *Prog Med Virol* 1978; 24:40.
- Centers for Disease Control. Protection against viral hepatitis: recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1990; 39:(No. RR-2).
- Krugman S, Diles JP, Hammond J. Infectious hepatitis: evidence for two distinctive clinical, epidemiological and immunological types of infection. *JAMA* 1967; 200:365-373.
- Koff RS, Slavin MM, Connelly LJD. The contagiousness of acute hepatitis B: secondary attack rates in household contacts. *Gastroenterology* 1975; 69:838.
- Durack DT. Opportunistic infections and Kaposi's sarcoma in homosexual men. *N Engl J Med* 1981; 305:1465-1467.
- Beasley TP, Stevens CE. Vertical transmission of HBV and interruption with globulin. In: Vyas GW, Cohen SN, Schmidt R, eds. *Viral hepatitis*. Philadelphia: Franklin Institute Press, 1978:333-345.
- Lin HH, Lee TY, Chen DS, et al. Transplacental leakage of HBe Ag positive maternal blood as the most likely route in causing infection with hepatitis B virus. *J Pediatr* 1987; 111:877-881.
- Kumar ML, Dawson NV, McCullough AJ, et al. Should all pregnant women be screened for hepatitis B? *Ann Int Med* 1987; 107:273-277.
- Centers for Disease Control. Prevention of perinatal transmission of hepatitis B virus: prenatal screening of all pregnant women for hepatitis B surface antigen. *MMWR* 1988; 37:341-346.
- Polakoff S, Vandervelde EM. Immunization of neonates at high risk of hepatitis B in England and Wales: a national surveillance. *Br Med J* 1988; 297:249-253.
- Lee SH, Tsai YT, Wu TC, et al. Role of caesarian section in prevention of mother-infant transmission of hepatitis B virus. *Lancet* 1988; 2:833-834.
- Centers for Disease Control. Update: Universal precautions of transmission of human immunodeficiency virus, hepatitis virus, and other bloodborne pathogens on health care settings. *MMWR* 1988; 37:387-388.
- Reingold AL, Kane MA, Hightower AW. Failure of gloves and other protective devices to prevent transmission of hepatitis B virus to oral surgeons. *JAMA* 1988; 259:1558-2560.
- Welch J, Webster M, Tilzey AJ, Noah ND, Banatvala JE. Hepatitis B infections after gynecologic surgery. *Lancet* 1989; 1:205-207.
- Alpert E, Isselbacher KJ, Schur PH. The pathogenesis of arthritis associated with viral hepatitis. *N Engl J Med* 1971; 285:185-189.
- Onion DK, Crumpacker CS, Gilliland BC. Arthritis of hepatitis associated with Australia antigen. *Ann Int Med* 1971; 75:29-33.
- Gocke DJ. Immune complex phenomenon associated with hepatitis. In: Vyas GW, Choen SN, Schmidt R, eds. *Viral hepatitis*. Philadelphia: Franklin Institute Press, 1978:333-345.
- Inoue A, Tsukada N, Koh CS, Yanagisawa N. Chronic relapsing demyelinating neuropathy associated with hepatitis B infection. *Neurology* 1987; 37:1663-1666.
- Villa E, Baldini M, Pasquinelli C, et al. Risk factors for hepatocellular carcinoma in Italy. *Cancer* 1988; 62:611-615.
- Nomura A, Stemmermann GN, Wasnich RD. Presence of hepatitis B surface antigen before primary hepatocellular carcinoma. *JAMA* 1982; 247:2247-2250.
- Leuschner I, Harms D, Schmidt D. The association of hepatocellular carcinoma in childhood with hepatitis B infection. *Cancer* 1988; 62:2363-2369.
- Parkin DM, Stjernsward J, Muir CS. Cancer Control. Estimates of the world-wide frequency of 12 major cancers. *World Health Organization Bulletin* 1984; 62:163.
- Waterhouse J, Muir C, Correa P, et al. Cancer incidence in five continents. World Health Organization, Lyon, 1977.
- Higginson J. The geographical pathology of primary liver cancer. *Cancer Res* 1963; 23:1624.
- Dunham LJ, Bailor JC. World maps of cancer mortality rates and frequency rates. *J Natl Cancer Inst* 1968; 41:155.
- Jacyna MR, Thomas HC. Antiviral therapy: hepatitis B. *Br Med Bull* 1990; 46:368-382.
- Hoofnagle JH, Peters M, Mullen KD, et al. Randomized controlled trial of recombinant human alpha interferon in patients with chronic hepatitis. *Gastroenterology* 1988; 95:1318-1325.
- Alewander GJM, Brahm J, Fagan EA, et al. Loss of HBsAg with interferon therapy in chronic hepatitis B virus infection. *Lancet* 1987; 34:66-68.
- Perillo RP, Regenstein FG, Peters MG, et al. Prednisone withdrawal followed by recombinant alpha interferon in the treatment of chronic type B hepatitis. A randomized, controlled trial. *Ann Intern Med* 1988; 109:95-100.
- Scullard GH, Pollard RB, Smith JL, et al. Antiviral treatment of chronic hepatitis B virus infection. Changes in viral markers with interferon combined with adenine arabinoside. *J Infect Dis* 1981; 143:772-783.
- Dusheiko G, Di Bisceglie A, Bowyer S, et al. Recombinant leukocyte interferon treatment of chronic hepatitis B. *Hepatology* 1985; 5:556-560.



37. Perrillo RP. Interferon therapy for chronic type B hepatitis: The promise comes of age. *Gastroenterology* 1989; **96**:532-535.
38. Mazella G, Saracco G, Rizzetto M, et al. Human lymphoblastoid interferon for the treatment of chronic B hepatitis. A randomized controlled trial. *Am J of Med* 1988; **85**:141-142.
39. Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of Interferon Alpha-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. *N Engl J Med* 1990; **323**:295-301.
40. Lok ASF, Lai CL, Wu PC. Interferon therapy of chronic hepatitis B virus infection in Chinese. *J Hepatol* 1986; **3** (Suppl 2):S209-S215.
41. McDonald JA, Caruso L, Karayiannis P, et al. Diminished responsiveness of male homosexual chronic hepatitis B virus carriers with HTLV-III antibodies to recombinant alpha-interferon. *Hepatology* 1987; **7**:719-723.
42. Novick DM, Lok ASF, Thomas HC. Diminished responsiveness of homosexual men to antiviral therapy for HBsAg-positive chronic liver disease. *J Hepatol* 1984; **1**:29-35.
43. Lok ASF, Wu PC, Lai CL, Leung EKY. Long-term follow-up in a randomized controlled trial of recombinant alpha-2 interferon in Chinese patients with chronic hepatitis B infection. *Lancet* 1988; **2**:298-302.
44. 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**:877-880.
45. Mizushima N, Kanai K, Matsuda H, et al. Improvement of proteinuria in a case of hepatitis B associated glomerulonephritis after treatment with interferon. *Gastroenterology* 1987; **92**:524-526.
46. Starzl TE, Demetris AJ, Van Thiel D. Liver transplantation. *N Engl J Med* 321; **15**:1014-1021.
47. Corman JL, Putman CW, Iwatsuki S, et al. Liver allograft: its use in chronic active hepatitis with macronodular cirrhosis, hepatitis B surface antigen. *Arch Surg* 1979; **114**:75-78.
48. Demetris AJ, Jaffe R, Sheaghan DG, et al. Recurrent hepatitis B in liver allograft recipients: differentiation between viral hepatitis B and rejection. *Am J Pathol* 1986; **125**:161-172.
49. Portmann B, O'Grady J, Williams R. Disease recurrence following orthopic liver transplantation. *Transplant Proc* 1986; **18** Suppl 4:136-141.
50. Ostberg L, Pursch E. Human x (mouse x human) hybridomas stably producing human antibodies. *Hybridoma* 1983; **2**:361-367.
51. Starzl TE, Todo S, et al. Liver transplantation: an unfinished product. *Transplant Proc* 1989; **21**:2197-2200.
52. Starzl TE, Demetris AJ, Van Thiel D. Liver transplantation (second of two parts). *N Engl J Med* 321; **16**:1092-1099.
53. Centers for Disease Control. Immune globulins for protection against viral hepatitis. *Ann Intern Med* 1982; **96**:193-197.
54. Centers for Disease Control. Safety of therapeutic immune globulin preparations with respect to transmission of human T-lymphotropic virus type III/lymphadenopathy associated virus infection. *MMWR* 1986; **35**:231-233.
55. Centers for Disease Control. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the immunization practices advisory committee. *MMWR* 1991; **40**:1-25.
56. Szmuness W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. *N Engl J Med* 1980; **303**:833-841.
57. Centers for Disease Control. Suboptimal response to hepatitis B vaccine given by injection into the buttock. *MMWR* 1985; **34**:105-113.
58. Dienstag JL, Stevens CE, Bhan AK, Szmuness W. Hepatitis B vaccine administered to chronic carriers of hepatitis B surface antigen. *Ann Int Med* 1982; **96**:575-579.
59. Centers for Disease Control. Prevacination serologic testing for susceptibility. Protection against viral hepatitis: recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1990; **39** (No. RR2):13.
60. Mendenhall C, Roselle GA, Lybecker LA, et al. Hepatitis B vaccination. Response of alcoholic with and without liver injury. *Dig Dis Sci* 1988; **33**:263-269.
61. Collier AC, Corey L, Murphy VL, Handsfield HH. Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. *Ann Int Med* 1988; **109**:101-105.
62. Carey W, Pimentel R, Westveer MK, et al. Failure of hepatitis B immunization in liver transplant recipients: results of a prospective trial. *Am J Gastroenterol* 1990; **85**:1590-1592.
63. Hsu HM, Chen DS, Chuang CH, et al. Efficacy of a mass hepatitis B vaccination program in Taiwan. *JAMA* 1988; **260**:2231-2235.
64. Fattovich G, Boscard S, Noventa F, et al. Influence of hepatitis delta virus infection on progression to cirrhosis in chronic hepatitis type B. *J Infect Dis* 1987; **155**:931-935.
65. Craven DE, Awdeh ZL, Kunches LM, et al. Non-responsiveness to hepatitis B vaccine in health care workers. *Ann Int Med* 1986; **105**:356-360.
66. Hadler S. Are booster doses on hepatitis B vaccine necessary? *Ann Int Med* 1988; **108**:457-458.
67. Rizeetto M. The delta agent. *Hepatology* 1983; **3**:729-737.
68. Fattovich G, Boscard S, Noventa F, et al. Influence of hepatitis delta virus infection on progression to cirrhosis in chronic hepatitis type B. *J Infect Dis* 1987; **155**:931-935.
69. Lettau LA, McCarthy JG, Smith MH, et al. Outbreak of severe hepatitis due to delta and hepatitis B virus in parenteral drug users and their contacts. *N Engl J Med* 1987; **317**:1256-1262.
70. Patrizia F, Gerin JL, et al. Diagnostic and prognostic significance of the IgM antibody to the hepatitis delta virus. *JAMA* 1986; **255**:1443-1446.
71. Hoofnagle JH. Type D (delta) hepatitis. *JAMA* 1989; **261**:1321-1325.