Prevention of Hepatitis B with the Hepatitis B Vaccine

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 25-year-old registered nurse comes for a visit to initiate prenatal care after receiving a positive result on a pregnancy test. On review of her vaccination status, she reports that she declined hepatitis B vaccination when it was offered by her current employer, since she does not draw blood and thus does not consider herself at risk for infection. Should she receive the vaccine? What are the current recommendations for hepatitis B vaccination?

HEPATITIS B VIRUS AND INFECTION

The hepatitis B virus (HBV) is an enveloped, double-stranded DNA virus. It is the smallest DNA virus known to infect humans. The virus is very infectious in nonimmune persons. The incubation period for acute infection is 45 to 160 days, with a mean incubation period of 90 days. The primary reservoir is chronically infected people. There are no known animal reservoirs and no clear evidence that insects are responsible for transmission of HBV.

Acute HBV infection can be symptomatic or asymptomatic. The acute phase is followed by either a clearance of the infection or a chronic, indolent infection that can lead to cirrhosis, liver failure, hepatocellular carcinoma, and death. The risk of the development of the chronic carrier state is inversely related to the age at the time of infection. The risk of chronic carriage in infected neonates is as high as 90 percent. Prospective studies of infection in Taiwan demonstrate that 25 percent of persons who have a persistent HBV infection in infancy or early childhood ultimately die from either hepatocellular carcinoma or cirrhosis. The death rate declines to 15 percent for persistent infection that develops in adolescents and young adults.

EPIDEMIOLOGY

HBV infection occurs throughout the world and is endemic in Africa, Eastern Europe, the Middle East, Central Asia, China, Southeast Asia, the Pacific Islands, and the Amazon basin of South America. In these areas, most persons become infected as infants or young children, and up to 70 percent of the adult population tests positive for prior infection. Among those populations, 8 to 15 percent have chronic HBV infection. Globally, this translates into more than 2 billion people with evidence of previous HBV infection and more than 350 million chronic carriers of the virus, with an estimated 1 million deaths each year due to cirrhosis and hepatocellular carcinoma. Widespread immunization programs against HBV, which have been implemented in more than 100 countries, have dramatically reduced the occurrence of chronic HBV infection and hepatocellular carcinoma, and the vaccine can thus be considered the first anticancer vaccine.
United States, screening of blood and blood products with serologic tests to detect HBV, hepatitis C virus, human immunodeficiency virus, and human T-cell lymphotropic virus have dramatically reduced the transmission of these viruses through transfusions. Improved disposal of needles and other sharp objects and new devices designed to reduce the risk of inadvertent needle sticks have diminished exposures in medical settings. Furthermore, successful vaccination efforts have resulted in high proportions of vaccination and prenatal screening. As a result, reports of acute HBV infection have continued to decrease over the past decade in the United States. In 2002, the last year for which figures are available, the reported incidence of acute HBV infection in the United States was 8064 cases, but the incidence has continued to be higher among men than among women (by a ratio of 1.7 to 1).3

**Sources of Infection and Transmission**

HBV infection results from percutaneous or mucosal exposure to the blood or bodily fluids of infected persons. Infected persons need not be symptomatic to transmit the virus. Blood contains the highest concentrations of virus. Common sources of exposure include sexual contact, contaminated needles, contaminated blood or blood products, and perinatal exposure to an infected mother. In as many as one third of cases of acute HBV infection, the source of exposure is unknown. Nonsexual transmission has been documented in cases of long-term exposure in household settings. Although the mechanism has not been elucidated, it appears that horizontal transmission of HBV can occur among infants, children, and elementary school students who live with an infected household member. HBV is not transmitted by the fecal–oral route. Young adults (18 to 39 years of age) are at increased risk for HBV infection; this increase is attributed to the greater likelihood of multiple sex partners (defined as four or more sex partners during one’s lifetime), illicit injection of drugs, and other high-risk behaviors in this age group than in others.4

In countries where HBV is endemic, most infections result from vertical transmission from mother to child in the peripartum period or from infection in early childhood. There is no evidence of viral transmission through breast milk.5 In countries where the rate of endemic disease is low, transmission is primarily a result of multiple sexual contacts or the illicit injection of drugs. Chronically infected refugees from countries where the disease is endemic also represent sources of possible infection.

**Strategies and Evidence**

Effective strategies to prevent HBV infection include the avoidance of high-risk behaviors, the prevention of exposure to blood and bodily fluids, the screening of women in late pregnancy for the presence of HBV, active immunization with the hepatitis B vaccine, and passive immunization with hepatitis B immune globulin before or after exposure. Optimal protection is achieved with a completed series of hepatitis B vaccine before exposure occurs.

**Hepatitis B Vaccine**

Hepatitis B vaccines have been available in the United States since 1981. Multiple formulations (Recombinax HB and Convivax, Merck; Engerix-B, Pedvaxitrix, and Twinrix, GlaxoSmithKline) are now licensed in the United States (Table 1); all are produced with the use of yeast (Saccharomyces cerevisiae) and recombinant techniques to generate the hepatitis B surface antigen (HBsAg) protein.

In 1991, the Advisory Committee on Immunization Practices (ACIP) recommended a comprehensive strategy to eliminate HBV transmission in the United States, which included universal vaccination of infants. In 1995, routine immunization of adolescents was added. In 1999, the strategy was further modified to include immunization of all persons up to 18 years of age. This strategy has reduced the overall annual incidence of acute HBV infections in the United States (from 8.5 cases per 100,000 persons in 1990 to 2.8 per 100,000 in 2002, a decrease of 67 percent).

On the basis of data indicating a decrease in the burden of acute (and hence chronic) HBV infection as a result of immunization programs for infants, children, and adolescents,6 the World Health Organization (WHO) has recommended that all countries provide universal HBV immunization programs for infants and adolescents.7 As of 2003, 79 percent of the 192 WHO member states had adopted policies of universal childhood immunization against HBV.8,9 One compelling example of the associated benefit is the dramatic decline in the incidence of neonatal HBV infections and subsequent sequelae in Taiwan after the introduction and widespread use of hepatitis B vaccine.10-12

Since 1991, the Occupational Safety and Health Administration has mandated that health care workers be educated about the vaccine and that employers offer it free of charge. Except for pregnant women, routine screening for HBsAg or for antibodies to HBsAg (anti-HBs antibodies) is not routinely re-
ommended; whether or not to screen is a clinical decision that should be based on the likelihood of previous exposure to HBV or hepatitis B vaccine. Table 2 lists persons who are at high risk for HBV infection and who should therefore receive the vaccine.

**Administration of Vaccine**

All currently licensed hepatitis B vaccines are given intramuscularly, in the thigh (for neonates and infants) or the deltoid muscle (for children, adolescents, and adults). The needle should be long enough to achieve deep intramuscular penetration. For many people, a standard 12.7-cm (5/8-in.) needle is insufficient to penetrate the deltoid fat pad and result in intramuscular deposition of vaccine. The required needle length increases with increased body weight (Table 1).

Some researchers have advocated the use of split, smaller doses, to be delivered as repeated intradermal immunization in patients in whom a response has not occurred (i.e., the anti-HBs antibody level is less than 10 mIU per milliliter after the third dose of vaccine). This option is not recommended, because lower immunogenicity may result. Further-
more, the vaccine is not licensed for use in this manner.

The vaccine is generally administered in three doses, with the second dose given one month after the first dose and the third dose given six months after the first dose (Table 1). Vaccines from the two U.S. manufacturers can be used interchangeably, and it is not necessary to restart the series if there have been prolonged intervals between doses. Twinrix combines the vaccines for hepatitis A and B and is licensed for use in persons 18 years of age or older for whom both vaccines are indicated.21

VACCINE IMMUNOGENTICITY

The antibody response declines with increasing age. Patients older than 30 years have an increased risk of nonresponse to HBV vaccine, as compared with younger persons.22 Thus, immunization during childhood or adolescence offers the greatest potential for protection22 and provides lifelong immunity.

Ninety percent of healthy adults and 95 percent of infants, children, and adolescents have protective serum anti-HBs antibody concentrations after the vaccine series has been completed.23 Among immunocompetent persons in whom antibody levels of at least 10 mIU per milliliter develop, the efficacy of the vaccine is nearly 100 percent.

LACK OF RESPONSE

Ideally, the antibody response (the anti-HBs antibody level) is determined within one to three months after the last dose of vaccine in persons with risk factors for a lack of response (including an age greater than 30 years, obesity, or immunodeficiency) or those at high risk for exposure to blood or bodily fluids. Unfortunately, the antibody response is frequently tested years after completion of the vaccination series, in which case a true nonresponse (an antibody level of less than 10 mIU per milliliter after the appropriate vaccine series) must be distinguished from “waning” antibody levels (those that are initially protective but that become undetectable over time). Administration of a single dose of vaccine, followed by measurement of the anti-HBs antibody response 4 to 12 weeks later, will differentiate persons with no response (indicating an absence of protection against disease) from those with waning antibody levels (in whom an anamnestic response will occur, with anti-HBs antibody levels of at least 10 mIU per milliliter). For persons who remain seronegative after this booster dose, a second series, which involves two additional doses of vaccine (i.e., for a total of three doses), will result in seroconversion in 50 to 60 percent of recipients. For those with risk factors for nonresponse, the 40-µg dose should be used. A clinical algorithm for immunizing those in whom a response does not occur has been published.24

Several studies of vaccination in very-high-risk subjects have shown that in a small number of persons (1 to 9 percent) who initially had a protective antibody level after vaccination, this response was lost over time and markers of HBV infection (specifically, antibodies to hepatitis B core antigen [HBc]) developed.25-30 Generally, such infections were asymptomatic, and anti-HBc antibodies were identified by regular blood monitoring. Rare cases of chronic infection have been identified in such persons, generally those who are not immunocompetent.

SAFETY

Both the currently licensed vaccines and the previous plasma-derived vaccine have been demonstrated to

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Table 2. Groups for Whom Hepatitis B Vaccine Is Recommended.6

<table>
<thead>
<tr>
<th>Category</th>
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<tbody>
<tr>
<td>All infants</td>
</tr>
<tr>
<td>All persons 18 years of age and younger</td>
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<tr>
<td>Persons at occupational risk, including health care workers and public-safety workers who are exposed to blood</td>
</tr>
<tr>
<td>Clients and staff of institutions for the developmentally disabled</td>
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<tr>
<td>Patients on hemodialysis</td>
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<tr>
<td>Recipients of certain blood products, such as clotting-factor concentrates</td>
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<tr>
<td>Household members and sexual partners of HBV carriers</td>
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<tr>
<td>Adoptees from countries where HBV infection is endemic</td>
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<tr>
<td>Travelers who plan to spend more than six months in areas with high rates of HBV infection and who will have close contact with the local population</td>
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<tr>
<td>Short-term travelers who are likely to have contact with blood (e.g., in a medical setting) or sexual contact with residents of areas with high or intermediate levels of endemic disease</td>
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<tr>
<td>People who have more than one sexual partner in six months</td>
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<tr>
<td>Men who have sex with other men</td>
</tr>
<tr>
<td>People who illicitly inject drugs</td>
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<tr>
<td>Inmates of long-term correctional facilities</td>
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6 Recommendations are from the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention.33
be safe. Concerns about potential disease risks (including vaccine-induced autoimmune diseases, diabetes, chronic fatigue syndrome, demyelinating disorders, optic neuritis, and other syndromes\textsuperscript{7,31,32}) have not been supported by scientific data. Multiple studies have found no evidence of the initiation, relapse, or exacerbation of demyelinating disorders in association with hepatitis B vaccination.\textsuperscript{9,31-34}

Concerns regarding thimerosal and aluminum in vaccines have likewise not been supported by well-conducted studies.\textsuperscript{7,35} The Institute of Medicine, the WHO’s Global Advisory Committee on Vaccine Safety, and a number of independent scientific bodies have not found evidence to support these concerns and have concluded that hepatitis B vaccine is both safe and effective.\textsuperscript{7,0,31-36}

**Hepatitis B immune globulin**

Hepatitis B immune globulin is used to prevent hepatitis B infection in persons without demonstrated immunity to HBV who have been exposed to the virus perinatally (i.e., infants born to HBsAg-positive mothers), by cutaneous or mucosal contact with HBsAg-positive blood or bodily fluids or by sexual contact with a person who is positive for HBsAg, or in the case of infants younger than 12 months, by exposure to a primary caregiver in whom acute hepatitis B infection has been diagnosed.\textsuperscript{33} Generally, one dose of hepatitis B immune globulin is administered as soon as possible after exposure (within 24 hours after birth for perinatal exposure, within 7 days after needle-stick exposure, and within 14 days after sexual exposure), along with the first dose of the hepatitis B vaccine series (followed by additional doses of vaccine on the usual schedule). The reported efficacy of this approach is 85 to 95 percent for the prevention of newborn infection and approximately 75 percent for the prevention of infection after needle-stick or sexual exposure.\textsuperscript{33}

**Maternal screening for hepatitis B**

To prevent vertical transmission, women should be screened for HBsAg during the first prenatal visit and, if seronegative but at high risk, screened again in late pregnancy.\textsuperscript{37} Since the administration of hepatitis B vaccine is safe during any stage of pregnancy, nonimmune, uninfected pregnant women with risk factors can be immunized. The recommended management strategies for infants born to HBsAg-positive mothers are summarized in Table 1. All such infants should then undergo testing for anti-HBs antibodies and HBsAg at 9 to 15 months of life.

**Areas of uncertainty and concern**

Although some authors have recommended a 5-year or 10-year booster dose, data are lacking to support these recommendations, and neither the ACIP nor any official U.S. or European professional society currently recommends routine booster doses. Nonetheless, it is uncertain whether protective antibody levels are still present three or more decades after immunization, since the vaccine has not been routinely used for that long. Questions remain about the relevance of potential differences in immunogenicity among currently available vaccine formulations\textsuperscript{38} and about the effects of different dosing regimens and intervals.

The incidence of acute HBV infection actually increased from 1990 to 2002 among men 20 to 39 years of age and among men and women 40 years and older.\textsuperscript{3} This may indicate the need for a national program of HBV immunization in adults.

An area of particular concern is the identification of HBV “escape mutants,” for which immunity that is induced by the current vaccines may not be protective.\textsuperscript{39} Although the incidence of these mutants is uncertain, they have only rarely been recognized (and in persons who are from areas in which HBV is endemic or who have received antiviral therapy), are generally confined to one genetic region of the virus, and have led only in rare cases to breakthrough HBV infection (despite apparently protective levels of anti-HBs antibodies). To date, there is no evidence that these viruses are disrupting efforts to control HBV through immunization programs.

The role of new HBV vaccines that are in development remains unclear. So-called mixed-particle vaccines (which contain pre-S1, pre-S2, and S antigens) have been studied and have not been found to be superior to S subunit vaccines that are given in higher doses (40 µg) in persons who do not have a response to a standard series of three doses of 10 or 20 µg.\textsuperscript{40} Two doses of a novel recombinant vaccine containing pre-S2 and S subunits combined with an MF59 adjuvant resulted in a seroprotection rate of 89 percent and significantly higher antibody titers than after three doses of licensed vaccine.\textsuperscript{41} DNA vaccines for HBV have also been tested and, in one study, found to elicit antibody responses in persons in whom long-lasting responses did not occur after a standard vaccine series.\textsuperscript{42} These new candidates for vaccine are not currently approved by the Food and Drug Administration.
Guidelines for the administration of hepatitis vaccine are provided by the ACIP (www.cdc.gov/nip/publications/acip-list.htm) and endorsed by the Centers for Disease Control and Prevention; a list of indications appears in Table 2. Currently, all of the physician-based professional societies endorse the routine use of HBV vaccine in persons 18 years of age and younger and in those at high risk for infection.13

SUMMARY AND RECOMMENDATIONS

The use of HBV vaccine has been associated with a dramatic decrease in the incidence of HBV infections, as well as of hepatocellular carcinoma, in countries where it is widely used. Because of the serious nature of HBV infection, clinicians should be vigorous in their attempts to achieve universal vaccination of infants and children through the age of 18 years and to identify and vaccinate persons at risk for infection. For pregnant women, such as the woman described in the vignette, testing for HBsAg is warranted, to reduce the risk of vertical transmission. If the result is positive, the baby will need hepatitis B immune globulin and vaccination at birth; investigation is warranted to determine whether the infant’s father (and, potentially, other sexual partners of the mother) could be the source of infection. If she is not at high risk (Table 1), this patient should be tested again in her last trimester of pregnancy. Given the potential for work-related exposure, even if she does not draw blood, we would recommend immunization, since HBV vaccine is not contraindicated during pregnancy.

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REFERENCES


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