Hepatitis B in Children

Adam R. Davis and Philip Rosenthal

Pediatr. Rev. 2008;29;111-120
DOI: 10.1542/pir.29-4-111

Hepatitis B in Children

Adam R. Davis, MD,*
Philip Rosenthal, MD†

Author Disclosure
Drs Davis and Rosenthal did not disclose any financial relationships relevant to this article.

Objectives

After completing this article, readers should be able to:

1. Describe the structure of the hepatitis B virus and the function of its proteins.
2. Delineate the mode of transmission of the virus and identify at-risk populations.
3. Interpret the results of screening laboratory tests for hepatitis B.
4. Describe the various disease presentations and the natural history and complications of chronic hepatitis B infection.
5. List the currently approved therapies for hepatitis B and identify when patients are most likely to benefit from intervention.
6. List the current recommendations for immunoprophylaxis in infants, children, and adolescents.

Background

One third of the world's population has been infected by the hepatitis B virus (HBV), causing an enormous worldwide burden of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Although the virus can infect people of any age, those who are infected perinatally or as children are at greatest risk for developing the potentially fatal complications of the infection. Approval of the hepatitis B vaccine in 1982 has been the most important development in the clinical approach to this virus, changing the major goal from treatment to prevention. In this article, we review the nature of the virus, its epidemiology, serologic markers of disease, clinical manifestations of infection, the prevention of transmission, and current treatments.

The Virus

HBV is a member of the hepadnavirus family, which is named for its hepatotropic nature and its double DNA genome. It is the only member of the family that causes disease in humans. The virion has two forms: an empty envelope that does not have the potential to infect or replicate and a complete virion. The complete virion is comprised of an envelope containing the capsid, a DNA polymerase, and the viral DNA (Figure). The DNA is 3.2 kilobases long and circular. Hepadnaviruses are unique among DNA viruses in that they are partially double-stranded and partially single-stranded. The DNA contains four genes in overlapping reading frames. The P region gene codes for the DNA's polymerase, which also acts as a reverse transcriptase. The X region gene codes for the hepatitis X gene, which acts as a transcriptional transactivator. The S region gene codes for the hepatitis B surface antigen (HB*s*Ag). The C region gene codes for the hepatitis B core antigen (HB*c*Ag) and the hepatitis B *e* antigen (HB*e*Ag). The HB*c*Ag is the protein that forms the nucleocapsid that encloses the viral DNA. The HB*e*Ag is a secreted soluble antigen that is believed to induce tolerance and is a marker of high viral replication.

Interestingly, the HBV polymerase lacks a proofreading function, which has led to a high degree of sequence heterogeneity. The nucleotide substitution rate per generation is 10,000 times that of human DNA. This substitution has resulted in the development of multiple HBV genotypes. The genotypes are defined as forms of the virus that are stable over time and are replication-competent, having at least 8% variation in their sequence and at least 4% variation in the sequence of the S gene. These genotypes have been labeled

*Clinical Fellow, Division of Pediatric Gastroenterology, Hepatology and Nutrition, University of California, San Francisco, Calif.
†Professor of Pediatrics and Surgery; Medical Director, Pediatric Liver Transplant Program; Director, Pediatric Hepatology, University of California, San Francisco, Calif.

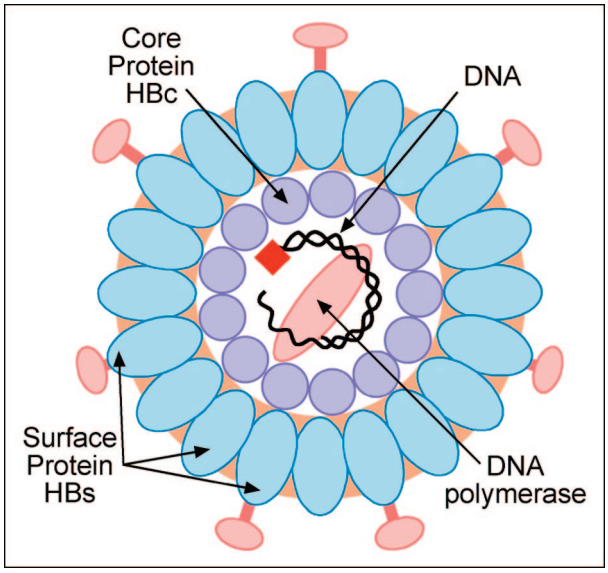

Figure. The complete hepatitis B virion.

A through H. Each genotype shows a distinct geographic distribution. The United States population carries a variety of genotypes, which is consistent with the heterogeneity of its populace. There is a strong correlation between the ethnicity of the carrier and his or her genotype. (1) Evidence regarding the clinical significance of the various genotypes is being gathered, but is still in its infancy. It appears that viral genotype is associated with both clinical outcome and response to treatment.

Epidemiology

As noted previously, nearly one third of the world's population, 2 billion people, has been infected by HBV. An estimated 350 million people are chronic carriers of the virus, and the complications of HBV infection are responsible for 1 million deaths each year worldwide. The rates of infection vary substantially by geographic region. Within endemic areas such as Africa, Eastern Europe, the Middle East, Southeast and Central Asia, the Pacific Islands, and the Amazon Basin of South America, up to 70% of the adult population shows serologic evidence of previous infection. In these areas, most people are infected either perinatally or during early childhood, and 8% to 15% of people are infected chronically.

The burden of HBV infection is considerably less in the United States, but still substantial. Before the vaccine was administered routinely to infants, an estimated 300,000 new infections occurred annually, including 24,000 in infants and children. According to the Third National Health and Nutrition Examination Survey conducted between 1988 and 1994, the lifetime prevalence rate of HBV infection among all people in the United States was estimated to be 4.9% and was 1.9% among children 6 to 19 years of age. According to this survey, 4 of every 1,000 people in the United States are chronically infected, and 4,000 to 5,000 deaths every year can be attributed to complications of HBV. In the United States, the rates of exposure to HBV vary significantly by ethnicity and country of origin. African Americans, Asian Americans, and Alaskan natives suffer disproportionately from HBV. In fact, prior to the universal vaccination program, nearly 50% of all children younger than 10 years of age who were exposed to HBV in the United States were Asian American. (2)

HBV is present to some degree in most body fluids, but the highest concentration is in the serum. Infection occurs when a person receives percutaneous or mucosal exposure to the body fluids of an infected person. Humans are the only reservoir of HBV. The most common routes of transmission are through percutaneous injection of body fluids, sexual contact, and perinatal vertical transmission. Percutaneous exposure generally occurs through three mechanisms: needle sharing, occupational exposure, and in the prescreening era, blood transfusions. The risk of acquiring HBV today from a blood transfusion is estimated to be 1 in 60,000 to 1 in 200,000. (3) This minimal risk continues because of donors who have acquired the virus recently and have yet to develop serologic markers. Less common forms of transmission include household and close contacts of highly infective people and in utero vertical transmission. Household and close contact infections are believed to be related to scrapes and cuts that break the protective barriers. Vertical transmission occurs when the pregnant mother has hepatitis B. The risk of transmission is higher if the mother is HB*e*Ag-positive because this antigen is a marker of high circulating virus concentrations. In utero transmission is rare, accounting for fewer than 2% of all vertical transmissions, but it is not preventable with postnatal immunoprophylaxis. Ninety-eight percent of vertical transmission occurs during delivery and can be prevented by postnatal immunoprophylaxis. Breastfeeding has not been demonstrated to be a mode of transmission of the virus. Some 20% to 30% of all patients infected with HBV have no identifiable risk factor for infection. HBV is not spread by the fecal-oral route.

The epidemiology of the HBV is changing rapidly, as vaccination programs become the standard of care. These recent changes are addressed in the immunoprophylaxis section of this article.

Table 1. **Significance of Serum HBV Markers**

HBV Antigen or Antibody	Interpretation
Hepatitis B surface antigen (HB*s*Ag)	Indicates acutely or chronically infected person
Antibody to HB*s*Ag (HB*s*Ab)	Indicates resolution of HBV infection or development of immunity after immunization
Hepatitis B *e* antigen (HB*e*Ag)	Indicates high viral replication and increased infectivity
Antibody to HB*e*Ag (HB*e*Ab)	Indicates decreased viral reproduction and decreased infectivity
Antibody to hepatitis B core antigen (HB*c*Ab)	Indicates acute, chronic, or resolved infection

Serum Markers

Understanding the meaning of the serologic markers of hepatitis B is critical to understanding the physiology and course of the disease. Antigens, antibodies, and the virus itself can be measured in the serum. Commonly, HB*s*Ag and HB*e*Ag are the two antigens and HB*s*Ab, HB*c*Ab, and HB*e*Ab are the antibodies that are measured. Table 1 summarizes the significance of these serum markers, and Table 2 summarizes the interpretation of the most common results of screening tests for hepatitis B. Notably, the vaccine's major component is a recombinant HB*s*Ag. Therefore, if screening is performed within 14 days of vaccine administration, HB*s*Ag may be present in the blood from the vaccine itself.

The Disease

Although HBV is named for its effect on the liver, it is a systemic infection that has the potential to affect many organ systems. Rare extrahepatic manifestations of HBV infection include polyarteritis nodosa, membranous proliferative glomerulonephritis, and leukocytoclastic vasculitis. More commonly, patients infected with acute hepatitis B may have arthralgias or even frank arthritis. An erythematous or urticarial rash may precede the hepatic manifestations of acute infection. All of these disorders are immune complex-mediated, and all respond to treatment with the same therapy used to treat the hepatic manifestations of HBV infection.

The virus itself generally is not cytopathic; rather, it is the host's immune response to the presence of the virus that leads to cell death and most of the clinical signs and symptoms of infection. It is also the virus' interaction with the host's immune system that determines whether an infection leads to an acute illness or a chronic carrier state.

The hepatic manifestations of the disease are not uniform in their presentation or course. HBV can present as acute self-limited hepatitis, acute fulminant hepatitis, chronic hepatitis, cirrhosis, or rarely, hepatocellular carcinoma. The infection has an incubation period of 2 to 6 months, making it an exceedingly rare cause of neonatal cholestasis. Generally, the earliest an infant becomes symptomatic from HBV infection is at 2 months of age. Thus, it is important to widen the diagnostic evaluation of neonatal cholestasis, even if the patient is known to have been infected maternally with HBV.

Acute self-limited hepatitis is marked by an increase in serum transaminases and resolution of the infection

Table 2. **Interpretation of the Serologic Markers of Hepatitis B in Common Situations**

Serologic Marker				
HB*s*Ag	Total HB*c*Ab	IgM HB*c*Ab	HB*s*Ab	Interpretation
-	-	-	-	No prior infection, not immune
-	-	-	+	Immune after hepatitis B vaccination (if concentration ≥10 mIU/mL or passive immunization from HBIG administration)
-	+	-	+	Immune after recovery from HBV infection
+	+	+	-	Acute HBV infection
+	+	-	-	Chronic HBV infection

HB*s*Ag=hepatitis B surface antigen, HB*c*Ab=antibody to hepatitis B core antigen, HB*s*Ab=antibody to hepatitis B surface antigen, HBIG=hepatitis B immune globulin

within 6 months, as indicated by hepatitis B surface antibody (HB*s*Ab) seroconversion. Children and adults generally are symptomatic when they have acute hepatitis. A small proportion remains asymptomatic and anicteric throughout the period in which they are infected. Acute hepatitis can present with any combination of nausea, fever, abdominal pain, jaundice, fatigue, and general malaise. Often, the clinical picture is nonspecific and the diagnosis is missed. Rarely do patients who have acute hepatitis B suffer any long-term sequelae.

Fulminant hepatitis is defined as acute hepatitis associated with a change in mental status brought on by hepatic encephalopathy. Fulminant hepatitis is a rare but potentially fatal presentation of hepatitis B infection, associated with a mortality rate of 55% to 70% without transplantation and 30% to 50% with transplantation. Those who survive generally recover without long-term sequelae. Most pediatric patients who suffer from fulminant hepatitis do so during infancy. However, infants generally are much less likely to suffer an acute course of disease. In fact, the likelihood of developing acute disease is inversely proportional to the age at which the person acquires infection. Perinatally acquired infection almost always is asymptomatic, children in the age range of 1 to 5 years have a 5% to 15% probability of presenting with acute hepatitis, and 33% to 50% of children older than 5 years and adults suffer from acute hepatitis after infection. (4)

Chronic HBV infection is defined as the presence of HB*s*Ag in the serum for at least 6 months or the presence of HB*s*Ag in a patient who concurrently is negative for the immunoglobulin M class of HB*c*Ab. The younger the person is exposed to HBV, the more likely he or she is to become chronically infected. Ninety percent of infants exposed become chronically infected compared with 25% to 50% of 1- to 5-year-olds and only 6% to 10% of those older than 5 years of age. The younger immune system is more tolerant of HBV than the more mature one. The more tolerant immune system permits chronic infection, whereas a more robust response in a mature immune system leads more often to acute hepatitis and clearance of the virus.

Chronic hepatitis generally is asymptomatic in childhood, having minimal or no effect on growth and development. Serum transaminase values usually are normal, although they can flare at any time, in most cases, without accompanying jaundice. Previous authors have called the condition of chronic infection without symptoms or abnormalities in serum tests a carrier state. We do not use that term because such patients can continue to have damage to their livers and can require histologic evidence of hepatitis.

Chronic hepatitis B generally proceeds through three phases: immune tolerance, immune clearance, and residual. The initial phase, immune tolerance, as the name implies, is marked by tolerance to the virus. The liver generally is not inflamed, and the serum aminotransferase values are normal during this stage. The hepatitis B viral counts are very high, and HB*e*Ag is present.

Gradually, the body develops an immune response to the virus, marking entrance into the immune clearance phase. This stage is characterized by a developing hepatitis with concurrent decrease in circulating viral counts. During this phase, liver inflammation fluctuates. Inflammatory damage to the liver occurs at this stage, and whether long-term sequelae such as cirrhosis occur is determined partly by how long a patient stays in this phase.

A sustained immune response can lead to spontaneous HB*e*Ab seroconversion, which signifies transition to the residual phase. A substantial elevation of the serum aminotransferase concentration predicts that seroconversion of HB*e*Ab is likely in the next 1 to 3 years. Once the person develops HB*e*Ab, HB*e*Ag becomes undetectable in the blood, and circulating HBV counts decrease substantially, possibly becoming undetectable. Generally, the serum aminotransferase values normalize, and active inflammation no longer is apparent on liver histology. However, disease recurrence is still possible during this stage, and flares may continue to occur.

Last, HB*s*Ab may develop in a small minority of patients. When HB*s*Ag is cleared from the blood, the patient has acquired immunity from the virus, and disease progression is unlikely unless the patient becomes immunosuppressed. This transition is uncommon, occurring in fewer than 1% of patients per year.

Up to 25% of children who have chronic HBV infection eventually develop cirrhosis or hepatocellular carcinoma. Factors that contribute to determining which infected patients develop these sequelae include race, genotype of the virus, alcohol consumption, coinfection with hepatitis C or D, coinfection with human immunodeficiency virus (HIV), and infection with hepatitis A.

Treatment

Currently available therapies do not eradicate the virus. The goal of therapy is long-term remission, defined as loss of detectable HBV in the serum or as loss of HB*e*Ag. The induction of remission in adults leads to decreased mortality from cirrhosis and hepatocellular carcinoma.

Two classes of medicine are used to treat HBV infec-

tions: interferon and nucleotide or nucleoside antivirals. Interferon is available as interferon or pegylated interferon. Pegylation of the interferon molecule allows for once-weekly dosing; regular interferon must be dosed three times a week. Only interferon alfa-2b has been approved by the United States Food and Drug Administration (FDA) for treatment of children who have chronic HBV. Four antiviral nucleotides or nucleosides are used to treat HBV infections: lamivudine, adefovir, entecavir, and emtricitabine, of which only lamivudine is FDA-approved for use in children.

Interferon therapy stimulates the immune system to maximize its own antiviral effect and is most effective when the patient already is having an immune response to the virus. Interferon should be reserved for children who have elevated serum aminotransferase concentrations that are sustained at twice the upper limits of normal. When interferon is administered under these conditions, loss of HB*e*Ag occurs 20% to 40% more in treated individuals than in those taking a placebo. Therapy generally is undertaken for 6 months, but may be extended to 1 year, depending on response to therapy and genotype. The disadvantages of therapy include three-times-a-week subcutaneous injections, cost, initial flulike illness, and occasional behavioral adverse effects.

Lamivudine is a nucleoside analog that interferes with the reverse transcriptase of HBV. It is extremely effective in lowering viral counts but less effective in inducing remission. The drug has been shown to be most effective when serum aminotransferase values are elevated and the viral DNA count is low. Discontinuation of therapy usually results in a return to pretherapeutic viral concentrations. In a large pediatric trial, 1 year of therapy induced remission in 23% of patients versus 13% of controls. An extension of therapy to 3 years showed continued effectiveness but increased development of resistant strains (YMDD mutants). Lamivudine is administered orally daily and generally is tolerated well by children.

Because both the approved therapies work best in those who have elevated serum aminotransferase concentrations, therapy generally is reserved for those who have evidence of chronic HBV infection (HB*s*Ag positivity for at least 6 mo) and have had serum alanine aminotransferase values greater than twice normal for at least 3 months.

Table 3. Hepatitis B Vaccine Schedules for Infants by Maternal Hepatitis B Surface Antigen (HB*s*Ag) Status[1,2]

Maternal HB*s*Ag Status	Single-antigen Vaccine		Single-antigen+Combination	
	Dose	Age	Dose	Age
Positive	1[3]	Birth (≤12 h)	1[3]	Birth (≤12 h)
	HBIG[4]	Birth (≤12 h)	HBIG[4]	Birth (≤12 h)
	2	1 to 2 mo	2	2 mo
	3[5]	6 mo	3[5]	4 mo
			4[5]	6 mo (Pediarix) or 12 to 15 mo (Comvax)
Unknown[6]	1[3]	Birth (≤12 h)	1[3]	Birth (≤12 h)
	2	1 to 2 mo	2	2 mo
	3[5]	6 mo	3[5]	4 mo
			4[5]	6 mo (Pediarix) or 12 to 15 mo (Comvax)
Negative	1[3,7]	Birth (before discharge)	1[3,7]	Birth (before discharge)
	2	1 to 2 mo	2	2 mo
	3[5]	6 mo	3[5]	4 mo
			4[5]	6 mo (Pediarix) or 12 to 15 mo (Comvax)

[1]Centers for Disease Control and Prevention. 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(RR-16):1–23.
[2]See Table 5 for vaccine schedules for preterm infants weighing <2,000 g.
[3]Recombivax HB or Engerix-B should be used for the birth dose. Comvax and Pediarix cannot be administered at birth or before 6 wk of age.
[4]Hepatitis B immune globulin (0.5 mL) administered intramuscularly at a separate site from the vaccine.
[5]The final dose of the vaccine series should not be administered before 24 wk (164 d) of age.
[6]Mothers should have blood drawn and tested for HB*s*Ag as soon as possible after admission for delivery; if the mother is found to be HB*s*Ag-positive, the infant should receive HBIG as soon as possible but no later than 7 d of age.
[7]On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs ≥2,000 g and whose mother is HB*s*Ag-negative, but only if a physician's order to withhold the birth dose and a copy of the mother's original HB*s*Ag-negative laboratory report are documented in the infant's medical record.

Adefovir is undergoing a clinical trial with children who have chronic HBV. In adults, the addition of adefovir has been used for patients who have lamivudine-resistant strains. Combination therapy with pegylated interferon and lamivudine had no better results than pegylated interferon alone in adults who had chronic HBV. Whether a combination therapy is more effective in pediatric patients who have chronic HBV remains to be demonstrated.

Because most pediatric patients do not have elevated serum aminotransferase concentrations, the current available therapies are unlikely to benefit them. It is hoped that medications will be developed to help patients who remain tolerant to the virus. The goal would be to clear the virus before inflammatory changes occur.

Patients who have chronic hepatitis B infection should be immunized against the hepatitis A virus. A screening program for hepatocellular carcinoma should be initiated. Serum aminotransferase concentrations, serum alpha-fetoprotein concentrations, and ultrasonographic imaging of the liver should be monitored. The appropriate interval for screening has not been determined, but very young children who have hepatocellular carcinoma caused by hepatitis B have been reported. At our institution, patients undergo yearly ultrasonography and have alpha-fetoprotein concentrations measured every 6 months.

Immunoprophylaxis

Two types of therapies are available for immunoprophylaxis: hepatitis B immune globulin (HBIG) and HBV vaccine.

HBIG is derived from the plasma of "hyperimmunized" donors. Standard immune globulin may not be effective in the prevention of HBV transmission because the concentration of HB*s*Ab may be too low. Thus, HBIG that has a high titer of HB*s*Ab is used.

The available hepatitis B vaccines in the United States are recombinant HB*s*Ag vaccines. Some other countries still use plasma-derived vaccines. The recombinant vaccines contain 10 to 40 mcg of HB*s*Ag per milliliter. The pediatric formulations in the United States are thimerosal-free. Although the manufacturers recommend completion of the immunization series with the same brand of vaccine, it is acceptable to interchange the brand of vaccine within a patient's immunization series if necessary. The vaccine is administered intramuscularly. Efficacy is estimated to be 90% to 95% in preventing HBV infection and has been shown to last more than 15 years. (3) Booster doses and postimmunization serologic testing are not recommended for patients who have standard risks for HBV infection.

Adverse reactions are uncommon, the most common being local pain at the site of injection. Fever, with a temperature above 99.9°F (37.7°C), is reported by 1% to 6% of those receiving inoculations. Anaphylaxis is a rare serious adverse event, occurring in an estimated 1 in 600,000 recipients.

With the approval of the hepatitis B vaccine in 1982, the ability to prevent HBV transmission and the goal of eradicating HBV became a reality. Taiwan was the first country to begin a universal immunization program and has demonstrated markedly decreased rates of infection and decreased rates of hepatocellular carcinoma in children. This success made the hepatitis B vaccine the first vaccine demonstrated to be efficacious in preventing cancer.

The Centers for Disease Control and Prevention (CDC) has set a goal of eliminating transmission of

Table 4. Hepatitis B Vaccine Schedules for Children, Adolescents, and Adults[1,2]

Age	Schedule
Children (1 to 10 y)	0, 1, and 6 mo[3] 0, 2, and 4 mo[3] 0, 1, 2, and 12 mo[3,4]
Adolescents (11 to 19 y)	0, 1, and 6 mo[3] 0, 1, and 4 mo[3] 0, 2, and 4 mo[3] 0, 12, and 24 mo[3] 0 and 4 to 6 mo[5,6] 0, 1, 2, and 12 mo[5,6]
Adults (≥20 y)	0, 1, and 6 mo[6,7] 0, 1, and 4 mo[6] 0, 2, and 4 mo[6] 0, 1, 2, and 12 mo[5,6]

[1]Centers for Disease Control and Prevention. 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(RR-16):1–23.
[2]Children, adolescents, and adults may be vaccinated according to any of the schedules indicated, except as noted. Selection of a schedule should consider the need to optimize compliance with vaccination.
[3]Pediatric/adolescent formulation.
[4]A 4-dose schedule of Engerix B is licensed for all age groups.
[5]A 2-dose schedule of Recombivax-HB adult formulation (10 mcg) is licensed for adolescents ages 11 to 15 y. When scheduled to receive the second dose, adolescents who are >15 y should be switched to a 3-dose series, with doses 2 and 3 consisting of the pediatric formulation administered on an appropriate schedule.
[6]Adult formulation.
[7]Twinrix may be administered to persons ages ≥18 y at 0, 1, and 6 mo.

Table 5. Hepatitis B Immunoprophylaxis Scheme by Infant Birthweight[1,2]

Maternal Status	Infant >2,000 g	Infant <2,000 g
HBsAg-positive	• Hepatitis B vaccine + HBIG (within 12 h of birth) • Continue vaccine series beginning at 1 to 2 mo of age according to recommended schedule for infants born to HBsAg-positive mothers • Check HBsAb and HBsAg after completion of the vaccine series[3] • HBsAg-negative infants with HBsAb concentrations ≥10 mIU/mL are protected and need no further medical management • HBsAg-negative infants with HBsAb concentrations <10 mIU/mL should be reimmunized with 3 doses at 2-mo intervals and retested • Infants who are HBsAg-positive should receive appropriate follow-up, including medical evaluation for chronic liver disease	• Hepatitis B vaccine + HBIG (within 12 h of birth) • Continue vaccine series beginning at 1 to 2 mo of age according to recommended schedule for infants born to HBsAg-positive mothers • Immunize with 4 vaccine doses; do not count birth dose as part of vaccine series • Check HBsAb and HBsAg after completion of the vaccine series[3] • HBsAg-negative infants with HBsAb concentrations ≥10 mIU/mL are protected and need no further medical management • HBsAg-negative infants with HBsAb concentrations <10 mIU/mL should be reimmunized with 3 doses at 2-mo intervals and retested • Infants who are HBsAg-positive should receive appropriate follow-up, including medical evaluation for chronic liver disease
HBsAg status unknown	• Test mother for HBsAg immediately after delivery • Administer hepatitis B vaccine (by 12 h) • Administer HBIG (within 7 d) if mother tests HBsAg-positive • Continue vaccine series beginning at 1 to 2 mo of age according to recommended schedule based on HBsAg result	• Test mother for HBsAg immediately after delivery • Administer hepatitis B vaccine (by 12 h) • Administer HBIG if mother tests HBsAg-positive or if mother's HBsAg result is not available within 12 h of birth • Continue vaccine series beginning at 1 to 2 mo of age according to recommended schedule based on mother's HBsAg result • Immunize with 4 vaccine doses; do not count birth dose as part of vaccine series
HBsAg-negative	• Administer hepatitis B vaccine at birth[4] • Continue vaccine series beginning at 1 to 2 mo of age • Follow-up HBsAb and HBsAg testing not needed	• Administer hepatitis B vaccine dose 1 to 30 d of chronological age if medically stable or at hospital discharge if before 30 days of chronological age • Continue vaccine series beginning at 1 to 2 mo of age • Follow-up HBsAb and HBsAg testing not needed

HB*s* Ag=hepatitis B surface antigen, HBIG=hepatitis B immune globulin, HB*s*Ab=antibody to hepatitis B surface antigen.
[1]Reprinted with permission from the American Academy of Pediatrics. *Red Book: 2006 Report of the Committee on Infectious Diseases.* 27th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2006.
[2]Extremes of gestational age and birthweight no longer are considerations for timing of hepatitis B vaccine doses.
[3]Test at 9 to 18 mo of age, generally at the next health supervision visit after completion of the primary series. Use testing methods that allow determination of a protective concentration of HB*s*Ab (≥10 mIU/mL).
[4]The first dose may be delayed until after hospital discharge for an infant who weighs ≥2,000 g and whose mother is HB*s*Ag-negative but only if a physician's order to withhold the birth dose and a copy of the mother's original HB*s*Ag-negative laboratory report are documented in the infant's medical record.

hepatitis B in the United States. To this end, it has identified four components of a comprehensive immunization program: 1) universal immunization of infants beginning at birth, 2) prevention of perinatal HBV transmission through routine screening of all pregnant women and appropriate immunoprophylaxis in infants born to HBsAg-positive women and those of unknown status, 3) routine immunization of children and adolescents who have not been immunized, and 4) immunization of previously unimmunized adults at increased risk of infection. (5)

Universal immunization of all infants against HBV is recommended to begin during the initial hospitalization after birth. To achieve high levels of compliance, delivery

Table 6. Guide to Postexposure Immunoprophylaxis of Unimmunized People to Prevent Hepatitis B Virus Infection[1]

Type of Exposure	Immunoprophylaxis[2]
Household contact of HBsAg-positive person	Administer hepatitis B vaccine series
Discrete exposure to an HBsAg-positive source • Percutaneous (eg, bite, needlestick) or mucosal exposure to HBsAg-positive blood or bodily fluids that contain blood • Sexual contact or needle sharing with an HBsAg-positive person • Victim of sexual assault/abuse by a perpetrator who is HBsAg-positive	Administer hepatitis B vaccine + HBIG; complete vaccine series
Discrete exposure to a source whose HBsAg status is unknown • Percutaneous (eg, bite, needlestick) or mucosal exposure to blood or bodily fluids that contain blood in which HBsAg status is unknown • Victim of sexual assault/abuse by a perpetrator whose HBsAg status is unknown	Administer hepatitis B vaccine series

HBsAg=hepatitis B surface antigen, HBIG=hepatitis B immune globulin
[1]Used with permission of the American Academy of Pediatrics. *Red Book: 2006 Report of the Committee on Infectious Diseases.* 27th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2006.
[2]Immunoprophylaxis should be administered as soon as possible, preferably within 24 h after exposure. Studies are limited on the maximum interval after exposure during which prophylaxis is effective, but the interval is unlikely to exceed 7 d for percutaneous and 14 d for sexual exposures.

hospitals should create policies that include hepatitis B vaccination as part of their care for all medically stable infants weighing more than 2,000 g, unless a physician orders deferment of the vaccination and a negative HBsAg is documented in the mother's medical record. Infants may complete their vaccination series with two to three additional doses over the next 4 to 12 months, as detailed in Table 3. Children and adolescents who have not been immunized should begin an immunization series at the first opportunity. Multiple schedules are recommended based on age, and all are considered equivalent (Table 4).

Infants born to mothers who are HBsAg-positive should receive the initial vaccination within the first 12 hours of birth and should be given HBIG concurrently at a different site. Even prior to hepatitis B vaccination programs, there were no reports of HBV transmission by breastfeeding, and two large studies did not demonstrate increased rates of transmission in breastfed infants. Therefore, the CDC recommends initiating breastfeeding without delay. Immunoprophylaxis does not need to be completed prior to initiation of such feeding.

Infants weighing 2,000 g or more who are born to mothers whose HBsAg status is unknown should receive the first vaccination within the first 12 hours of birth, and the mother's serum should be tested for HBsAg. If results of the mother's testing are not available by the seventh day after birth, HBIG should be administered. Many institutions administer HBIG sooner than 7 days when the mother's status remains unknown. We wait only 48 hours in our hospital. Infants whose birthweights are less than 2,000 g and who are born to HBsAg-negative mothers should receive the first dose of the hepatitis B vaccine within their first 30 days after birth but before discharge from the hospital. If an infant weighs less than 2,000 g and has a mother who is HBsAg-positive, both HBIG and the hepatitis B vaccine should be administered to the infant within 12 hours. HBIG should be administered to the infant within 12 hours if results remain unavailable, and the initial vaccine dose should not count toward completion of the HBV vaccine series (Table 5).

Performing serologic testing after completion of the vaccination series is indicated in high-risk groups, including: 1) people who have HIV infection, 2) people at occupational risk of exposure (such as health-care workers or prostitutes), 3) immunocompromised patients at risk of exposure to HBV, 4) hemodialysis patients, 5) regular sexual contacts of HBsAg-positive people, and 6) infants born to HBsAg-positive mothers. HBsAb concentrations of 10 mIU/mL or greater are considered an appropriate response. Partial responders (HBsAb <10 mIU/mL but >5 mIU/mL) should receive a booster dose of the vaccine and have antibodies remeasured 1 month later. Nonresponders should be treated with a second three-dose series. If no response occurs, using a different manufacturer for the series might be considered to obtain a response. Patients who do not respond to the second series are unlikely to respond to additional doses. (3)

Other special situations and high-risk groups such as

institutional residents, prison inmates, and international travelers are outside the scope of this review. Please refer to the CDC (5)(6) and American Academy of Pediatrics *Red Book* (3) recommendations.

Unimmunized patients are at risk of acquiring HBV infection if they are exposed to body fluids containing HBV. Postexposure immunoprophylaxis has been demonstrated to decrease the probability of seroconversion and disease acquisition. Table 6 summarizes the recommendations for postexposure immunoprophylaxis in the unimmunized patient. Ideally, the patient should receive the therapy within the first 24 hours after exposure, but immunoprophylaxis is believed to maintain some effectiveness up to 7 days after needle exposure or 14 days after sexual exposure. Previously immunized patients who have demonstrated an appropriate immunologic response (≥10 mIU/mL of HB*s*Ab) do not require postexposure therapy.

The risk of acquiring hepatitis B through casual contact is low enough that the CDC has recommended full integration of children who have this infection into schools and other activities. In this era of universal vaccination, the risk has become nearly negligible. Unimmunized students who are exposed to body fluids of another student who has hepatitis B should receive postexposure prophylaxis, as detailed in Table 6. Because most students are immunized, very few of these rare body fluid exposures require additional intervention.

Vaccination programs have been successful around the world, with the prevalence of chronic infection in children declining 90% since the institution of universal vaccination. In the United States, the results are most dramatic in Alaskan natives. Prior to the initiation of a routine vaccination program in Bristol Bay, Alaska, 7.6% of children by 9 years of age had evidence of resolved infection, and 3.2% had chronic HBV infection. Ten years after the initiation of the vaccination program, no children younger than 10 years of age had chronic infection, and only 1.5% evidenced previous infection. Overall in the United States, the incidence of HBV infection decreased by 94% in children younger than 20 years of age between 1990 and 2004. (7).

Risk groups still suffer disproportionately from HBV, such as injection drug users and immigrants from endemic countries. Programs that reach out to these communities for immunizations are needed.

Summary

- HBV is a circular DNA virus that can cause acute or chronic liver disease
- Liver damage caused by HBV is immune-mediated
- Infants and children are more likely to become chronically infected than are adults if exposed to HBV
- Chronic HBV infection can lead to cirrhosis and hepatocellular carcinoma in up to 25% of those infected as infants
- Interferon or lamivudine may be used with moderate effectiveness by clinicians experienced in their use to induce remission in children who have chronic infection and elevated serum transaminase values
- Universal vaccination has been effective in lowering the burden of hepatitis B in the United States and abroad

References

1. Kramvis A, Kew M, Francois G. Hepatitis B virus genotypes. *Vaccine*. 2005;23:2409–2423

2. Shepard CW, Finelli L, Fiore AE, Bell BP. Epidemiology of hepatitis B and hepatitis B virus infection in United States children. *Pediatr Infect Dis J*. 2005;24:755–760

3. American Academy of Pediatrics. Hepatitis B. In: Pickering L, Baker CJ, Long SS, McMillan JA, eds. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2006:335–355

4. Chang M-H. Postnatal infections: viral hepatitis B. In: Walker WA, ed. *Pediatric Gastrointestinal Disease*. 4th ed. Hamilton, Ontario, Canada: BC Decker Inc; 2004:1146–1155

5. 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(RR-16):1–31

6. 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(RR-16):1–33

7. Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. *Epidemiol Rev*. 2006;28:112–125

PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. Mother-infant transmission of hepatitis B is *most* likely to occur:

   A. During delivery.
   B. In utero.
   C. Through breastfeeding.
   D. Through salivary transmission.
   E. Via the fecal-oral route.

2. Postnatal immunoprophylaxis is *most* effective against hepatitis B acquired:

   A. During delivery.
   B. In utero.
   C. Through breastfeeding.
   D. Through salivary transmission.
   E. Via the fecal-oral route.

   Match the serum HBV serologic marker with its correct interpretation.

3. HBeAb

4. HBeAg

5. HBsAb with negative HBcAb

   A. Acute infection.
   B. High viral replication rate.
   C. Immunity after immunization.
   D. Immunity after recovery from infection.
   E. Low viral replication rate.

Clarification

In the article on varicella-zoster infections in the January issue (*Pediatr Rev.* 2008;29:5-11), the oral dose of acyclovir for children is given as 20 mg/kg qid. To clarify, the dose is 20 mg/kg per dose qid. The dose recommended in the article for adolescents is 4,000 mg/day and is based on the treatment for adults who have zoster. The American Academy of Pediatrics *Red Book* (27th ed. 2006:785) cites a dose of 800 mg qid (3,200 mg/day) for adolescents, and the author of the article in the January issue recommends using that dose, although there should be no significant clinical difference between the two regimens. Acyclovir is available in 800-mg tablets. Patients at serious risk for or who have severe or potentially severe infections should be treated with intravenous acyclovir.

Hepatitis B in Children

Adam R. Davis and Philip Rosenthal

Pediatr. Rev. 2008;29;111-120
DOI: 10.1542/pir.29-4-111