Hepatitis B Virus Infection, Hepatitis B Vaccine, and Hepatitis B Immune Globulin

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AUDIENCE
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OBJECTIVES
At the end of this session, every learner should be able to accomplish the following core set of objectives: (1) given a patient with jaundice, identify possible diagnoses and interpret hepatitis B serological tests; (2) predict the likely source of transmission, given the patient's behavioral, occupational, and environmental background; (3) explain the rationale for routine hepatitis B vaccination; (4) given a patient scenario, recommend vaccination based upon appropriate indications, such as occupation, international travel, and infection with the human immunodeficiency virus (HIV); (5) given an office setting, select procedures to (a) improve identification of persons needing vaccination, and (b) increase timely compliance with the second and third doses; and (6) recall contact tracing needs for an infected person, including appropriate screening tests.

Hepatitis B virus (HBV) infection is a major health problem in the United States; in 1995, approximately 128,000 cases occurred. Transmission of HBV occurs primarily by blood exchange (eg, by shared needles during injection drug use) and by sexual contact. Persons infected early in life are much more likely to become chronically infected than those infected during adulthood: as many as 90% of infants infected perinatally develop chronic infection and up to 25% will die of HBV-related chronic liver disease as adults. Clinical signs of acute hepatitis occur in about 50% of infected adults but in only 5% of infected preschool-aged children.

In the United States, hepatitis B vaccine is currently made by recombinant DNA technology using baker's yeast. Preexposure vaccination results in protective antibody levels in almost all infants and children (>95%) and healthy adults younger than 40 years of age (>90%). The most common adverse event following administration of hepatitis B vaccine is pain at the injection site, which occurs in 13% to 29% of adults and 3% to 9% of children. A comprehensive hepatitis B vaccination policy is now recommended that includes (1) routine infant vaccination; (2) catch-up vaccination of 11- to 12-year-olds who were not previously vaccinated; (3) catch-up vaccination of young children at high risk for infection; (4) vaccination of adolescents and adults based on lifestyle or environmental, medical, and occupational situations that place them at risk; and (5) prevention of perinatal HBV infection.

KEY WORDS. Hepatitis B virus; hepatitis B vaccines; immunization; public health; preventive services; sexually transmitted diseases; liver diseases; physicians, family. *(J Fam Pract 1997; 45:295-318)*

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Hepatitis B virus (HBV) infection (Table 1) is a major health problem in the United States; in 1995, approximately 128,000 cases occurred. 128,000 to 320,000 persons are infected annually (CDC, unpublished data). Approximately 6000 persons die annually of HBV-related complications of liver disease in the United States. Most of these deaths are in persons chronically infected with HBV, ie, persons who test positive for hepatitis B surface antigen (HBsAg) for 6 months or more. Complications of chronic HBV infection include cirrhosis and primary hepatocellular carcinoma. About 150 persons in the United States die of fulminant hepatitis following acute infection (Figure 1). Infection is not uncommon, as seen by the 5% lifetime risk for acquiring hepatitis B virus.[1,2] The number of persons chronically infected with HBV in the United States, each of whom is potentially infectious, is estimated at 1.25 million.[1]

TABLE 1

Hepatitis Nomenclature and Other Terminology

HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis B e antigen
HBcAg	Hepatitis B core antigen
Anti-HBs	Antibody to HBsAg
Anti-HBe	Antibody to HBeAg
Anti-HBc	Antibody to HBcAg
IgM anti-HBc	IgM class antibody to HBcAg
IgG anti-HBc	IgG class antibody to HBcAg
HBIG	Hepatitis B immune globulin

Other terminology

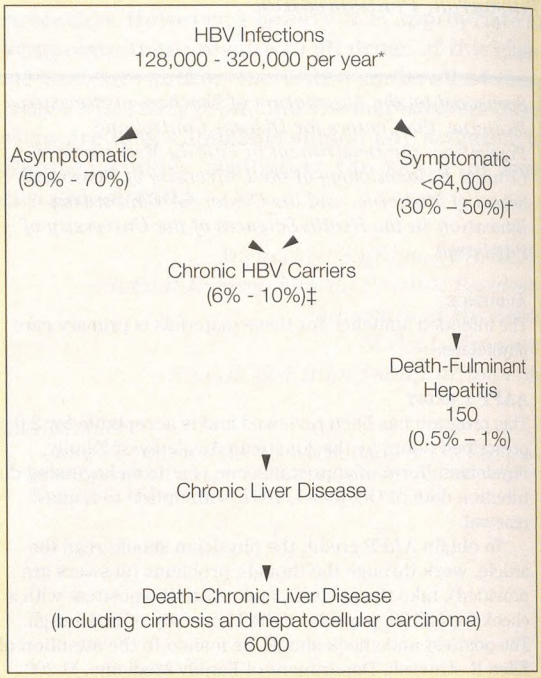
Commercial sex worker . . . *used interchangeably with the word prostitute.*

Injection drug user . . . . . *refers to persons who illegally use injectable drugs (previously called intravenous drug abusers).*

High rates of HBV infection are found in northern Canada, Alaska, the Amazon basin in South America, the Pacific Islands, Southeast Asia, China, parts of the Middle East, and Africa. HBV infection, which can lead to hepatocellular carcinoma, is the second known leading cause of cancer worldwide.[3]

FIGURE 1

Disease burden of acute and chronic HBV infections. Average annual incidence in all age groups, United States, 1984 -1995 estimates. Source: Centers for Disease Control and Prevention; unpublished data.



***Adjusted for underreporting and asymptomatic infections. †Symptomatic (jaundice): <5 years of age, <10%; ≥5 years of age, 30% to 50%. ‡Chronic infection: < 5 years of age, 30% to 50%; ≥5 years of age, 2% to 10%.**

Hepatitis B Virus Transmission and Communicability

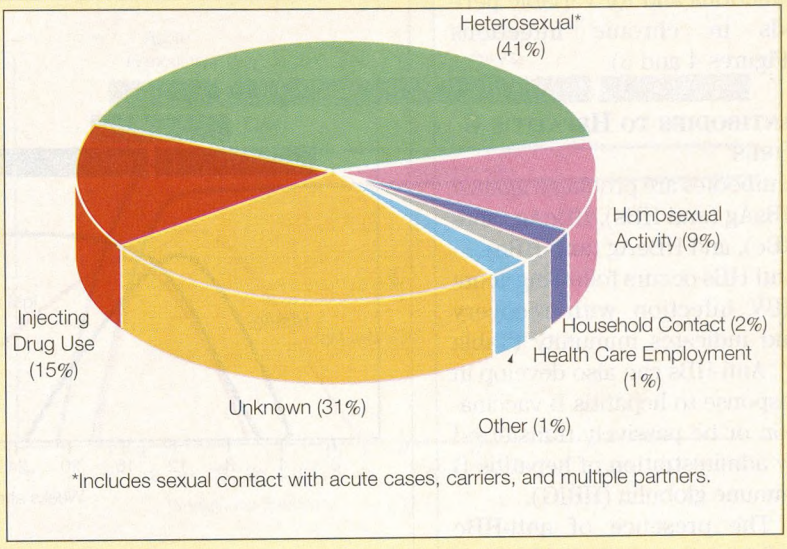
HBV can be contracted either from persons acutely or chronically infected with HBV. Transmission of HBV occurs primarily by blood exchange (eg, by shared needles during injection drug use) and by sexual contact. Perinatal transmission from infected mothers during delivery is common when postexposure prophylactic measures are not used. The source of infection is not identified for 30% to 40% of hepatitis B cases (Figure 2).[4] These cases may result from (1) underreporting of injection drug use and sexual activity, and (2) inapparent contamination of skin lesions or mucosal surfaces, since HBsAg is found in, for example, impetigo lesions and saliva of persons chronically infected with HBV, and on toothbrush racks and coffee cups in their homes.[5]

Epidemiological studies show that HBV can be transmitted between preschool-aged children.[6-9] HBV does not appear to be transmitted by fecal-oral or airborne routes.

Measures to prevent spread of hepatitis B include vaccination, which will be discussed later, and universal precautions.[10] Universal precautions include the use of barriers such as gloves, gowns, and masks, and should be implemented when handling any potentially infectious secretions, fluids, or tissues.

FIGURE 2

Risk factors for acute hepatitis B — United States, 1992-1993. Source: CDC Sentinel Counties Study of Viral Hepatitis.

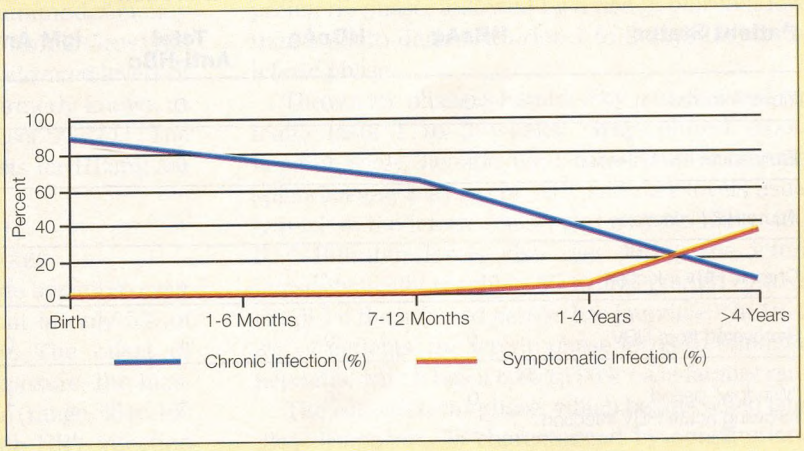


Importance of Age at HBV Infection on Development of Chronic Infection

Persons infected early in life are much more likely to become chronically infected than those infected during adulthood (Figure 3). Chronic HBV infection develops in 90% of those infected as infants, 30% to 60% of those infected before the age of 4 years, and 5% to 10% of those infected as adults.[1,2] Up to 25% of infected infants will die of HBV-related chronic liver disease as adults.[1] Although most acute infections in the United States occur in adulthood because of high-risk behaviors, 36% of all persons chronically infected in the United States contract HBV during early childhood.[11]

FIGURE 3

Outcome of hepatitis B virus infection by age at infection. Source: Centers for Disease Control and Prevention.



Hepatitis B Virus and Antigens

HBV is a DNA virus of the class *Hepadnaviridae*. The outer viral coat contains HBsAg, which is a marker of current infection and is present in both acute and chronic infections. HBsAg becomes detectable in serum from 1 to 12 weeks (mean, 30 to 60 days) after exposure to HBV (Figure 4). Persons can transmit HBV as long as HBsAg is present in their serum. The inner core contains hepatitis B core antigen (HBcAg), DNA, and hepatitis B e antigen (HBeAg).

HBcAg is found in liver tissue during acute or chronic infection. It is not detectable in serum by common laboratory techniques.[2]

HBeAg is present during HBV replication and is a marker for high levels of infectivity. HBeAg is present early in acute infections and for variable periods in chronic infections (Figures 4 and 5).

Antibodies to Hepatitis B Virus

Antibodies are produced against HBsAg (anti-HBs), HBcAg (anti-HBc), and HBeAg (anti-HBe). Anti-HBs occurs following acute HBV infection with recovery and indicates immunity (Table 2). Anti-HBs can also develop in response to hepatitis B vaccination or be passively transferred by administration of hepatitis B immune globulin (HBIG).

The presence of anti-HBc indicates that the individual has been infected with HBV at some

FIGURE 4

Acute hepatitis B virus infection with recovery: typical serologic course. Source: Centers for Disease Control and Prevention.

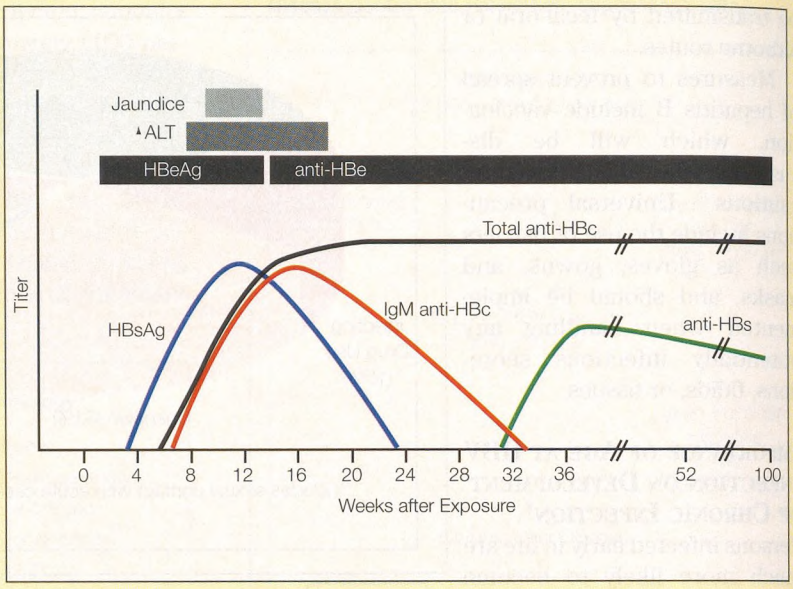


TABLE 2

Interpretation of Laboratory Tests to Detect HBV Infection

Patient Status	HBsAg	HBeAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	Infectivity
Never infected	0	0	0	0	0	0
Early acute HBV infection	+	0	0	0	0	+
Acute HBV infection	+	+	+	+	0	+
Chronic HBV infection	+	+/0	+	0	0	+
Recovered from HBV	0	0	+	0	+	0
"Window" period following acute HBV infection	0	0	+	+	0	0
Vaccinated	0	0	0	0	+	0

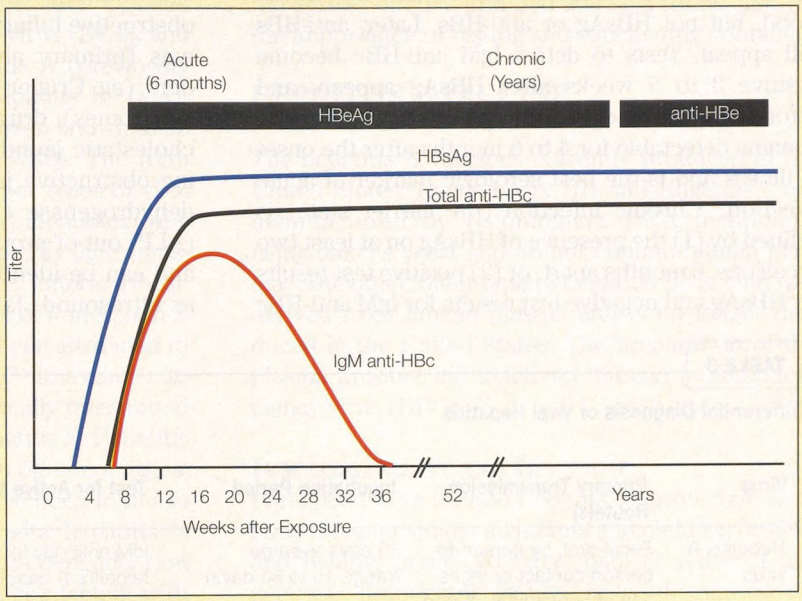
NOTE: HBV = hepatitis B virus; "0" = absent; "+"= present; "+/0"= variable presence.
Modified from Table 1 in Moyer LA, Mast EE. Hepatitis B: virology, epidemiology, disease, and prevention, and an overview of viral hepatitis. Am J Prev Med 1994; 10(suppl):45-55.

time; anti-HBc persists indefinitely in both persons who have recovered from the infection and in those who are chronically infected. Anti-HBc does not develop following vaccination, so testing for anti-HBc is the best way to determine susceptibility in an unvaccinated person. The presence of IgM anti-HBc indicates acute or recent infection; IgM anti-HBc develops approximately 8 weeks after exposure to HBV (Figure 4 and Table 2).

Anti-HBe develops when HBsAg and HBeAg disappear and indicates that infectivity has diminished.

FIGURE 5

Progression to chronic hepatitis B virus infection: typical serologic course. Source: Centers for Disease Control and Prevention.



Blood Product Screening for Hepatitis B Virus

Currently, only one in 63,000 persons in the United States develops posttransfusion hepatitis B; this level of safety is achieved by screening.[12] Blood is screened for HBsAg, anti-HBc, antibody to hepatitis C virus, syphilis, antibody to human immunodeficiency virus, antibodies to human T-lymphotropic virus type I and type II (HTLV-1, HTLV-2), and elevated levels of alanine aminotransferase (ALT), formerly known as serum glutamic-pyruvic transaminase(SGPT).[13] The sensitivity and specificity of the tests for HBsAg are greater than 98%.[14]

Clinical Description and Phases

Clinical signs and symptoms of acute hepatitis occur in about 50% of infected adults but in only 5% of infected preschool-aged children. The onset of symptoms occurs months after exposure; the incubation period is 120 days on average (range, 45 to 160 days).[3] The clinical course of acute HBV infection has three phases: preicteric, icteric, and convalescent.

The *preicteric* phase occurs from onset of initial symptoms until the start of jaundice and typically lasts 3 to 10 days. Hepatic symptoms include anorexia, nausea, vomiting, and right upper quadrant abdominal pain. Extrahepatic symptoms such as fever, malaise, rash, myalgia, and arthralgia may occur. Levels of ALT (SGPT) and aspartate aminotransferase (AST), formerly known as serum glutamic-oxaloacetic transaminase (SGOT), rise during the preicteric phase, followed by a rise in bilirubin level that leads to darkened urine 1 to 2 days before the icteric phase.

The *icteric* phase is heralded by jaundice and typically lasts 1 to 3 weeks. Gray-colored stools, hepatomegaly, hepatic tenderness, and sometimes splenomegaly may occur. ALT and AST levels usually peak in the icteric phase, and may be 400 to 4000 IU.[15] Bilirubin levels also rise during the icteric phase, typically reaching 85 to 340 µmol/L (5 to 20 mg/dL) if the infected person has jaundice.[15] In 1% to 2% of patients, the icteric phase leads to fulminant hepatitis, which has a 63% to 93% case-fatality rate.[2]

The *convalescent* phase, which begins when jaundice disappears, is characterized by constitutional symptoms, such as malaise and fatigue, and may last for several months.

Diagnosis and Differential Diagnosis

The diagnosis of HBV infection is made by serological testing. In acute infection, a test for HBsAg becomes positive between 1 and 12 weeks (mean, 30 to 60 days) after exposure and remains positive for 3

months on average.[2] When tests to detect HBsAg become negative, the patient is said to have entered the "window" period, during which IgM anti-HBc, IgG anti-HBc, and anti-HBe can be detected in the blood, but not HBsAg or anti-HBs. Later, anti-HBs will appear. Tests to detect IgM anti-HBc become positive 3 to 5 weeks after HBsAg appears and before the onset of clinical symptoms[16]; IgM anti-HBc remains detectable for 4 to 6 months after the onset of illness and is the best serologic marker of acute infection.[2] Chronic infection (the carrier state) is defined by (1) the presence of HBsAg on at least two occasions, 6 months apart, or (2) positive test results for HBsAg and negative test results for IgM anti-HBc on a single specimen (Figure 5 and Table 2).[2]

Differential diagnosis for jaundice includes cirrhosis, toxic hepatitis (including hepatitis caused by ethanol), viral hepatitis, neonatal jaundice, obstructive biliary or pancreatic diseases, carcinomas (primary and metastatic), congenital disorders, (eg, Crigler-Najjar, Dubin-Johnson, and Rotor syndromes), drug toxicity, hemolytic disease, and cholestatic jaundice of pregnancy. Diseases causing obstructive jaundice generally elevate lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) out of proportion to the other liver enzymes and can be identified by imaging techniques such as ultrasound. Jaundice due to alcoholic hepatitis

TABLE 3

Differential Diagnosis of Viral Hepatitis

Virus	Primary Transmission Route(s)	Incubation Period	Test for Active Infection	Epidemiology and Risk Factors
Hepatitis A virus	Fecal-oral, by person-to-person contact or ingestion of contaminated food	30 days average (range 15 to 50 days)	IgM antibody to hepatitis A capsid proteins	Household or sexual contact with an infected person, day care centers, and common-source outbreaks from contaminated food.
Hepatitis B virus	Sexual, blood and other body fluids	120 days average (range 45 to 160 days)	HBsAg*	Sexual promiscuity, male-to-male sexual practices, injection drug use, birth to an infected mother
Hepatitis C virus	Blood	Commonly 6 to 9 weeks (range 2 weeks to 6 months)	ELISA is the initial test to show if ever infected; it should be confirmed by another test, such as PCR	Injection drug use, occupational exposure to blood, hemodialysis, transfusion, possibly sexual transmission
Delta hepatitis virus	Blood, sexual and other body fluids	2 to 8 weeks (from animal studies)	Total antibody to delta hepatitis shows if ever infected; IgM test is in research labs	Requires active infection with HBV. Injection drug users and persons receiving clotting factor concentrates are at highest risk of infection.
Hepatitis E virus	Fecal-oral	26 to 42 days average (range 15 to 64 days)	Research laboratories	No known cases originated in the United States. International travelers are the only high-risk group to date.
Epstein-Barr virus (EBV)	Oropharyngeal via saliva	4 to 6 weeks	IgM antibody to EBV viral capsid	Seroconversion by age 5 years in 50% of persons in United States. Children with an acutely infected sibling are at greater risk.
Cytomegalo virus (CMV-human herpes virus 5)	Intimate contact with infected fluids: sexual, perinatal, blood transfusion, and infected breast milk	About 3 to 8 weeks for transfusion-acquired CMV	Culture, monoclonal antibody to early antigen	Household sexual contact with an infected person, male-to-male sexual practices, daycare centers, perinatal transmission

* The best test for acute or recent infection is IgM antibody to HBcAg.
ELISA denotes enzyme-linked immunosorbent assay; PCR, polymerase chain reaction.

generally results in the level of AST being twice the level of ALT.

The differential diagnosis of viral hepatitis includes hepatitis A, hepatitis B, hepatitis C, delta hepatitis, hepatitis E, Epstein-Barr virus (EBV), and cytomegalovirus (Table 3). Hepatitis A (previously called infectious hepatitis) and hepatitis B (previously called serum hepatitis) have been known to be different diseases since the early 1940s. The term non-A, non-B hepatitis refers to other types of viral hepatitis and encompasses two epidemiologically distinct types that may be categorized by their transmission routes: bloodborne versus enteric (fecal-oral). Most of the bloodborne cases of non-A, non-B hepatitis in the United States have been attributed to hepatitis C virus; tests for hepatitis C virus came into widespread use in the 1990s. Enterically transmitted non-A, non-B hepatitis is called hepatitis E. Hepatitis E has been reported in outbreaks in other countries; to date, no cases of hepatitis E have been found to originate in the United States. Delta hepatitis is another type of viral hepatitis that is dependent on HBV infection and occurs either as coinfection with HBV or superinfection of persons chronically infected with HBV.

Management of HBV Infection

Acute HBV infection is treated symptomatically. Certain contacts of infected persons should receive HBIG and hepatitis B vaccine (see section on Postexposure Prophylaxis).

Persons with chronic infection can be screened periodically for evidence of chronic liver disease and hepatocellular carcinoma. Some authorities believe screening for chronic liver disease is important because therapy with alpha-2b-interferon stops viral replication in approximately 40% of cases and results in disappearance of HBsAg from the serum in 10% to 20% of treated persons.[2,17,18] New treatments, including the nucleoside analogue lamivudine, are under investigation.[19] Some experts recommend monitoring serum alpha-fetoprotein (AFP) levels every 6 to 12 months to allow early diagnosis, and thus resection of tumors, since elevated AFP levels occur in most cases of hepatocellular carcinoma.[20,21] However, screening is somewhat controversial.[22,23]

Persons with either acute or chronic infection should be counseled on (1) mechanisms of HBV transmission, (2) the need to inform contacts, (3) the importance of not donating blood, other body fluids, or tissues, (4) the importance of not sharing household articles that could be contaminated with blood, (5) the need to cover skin lesions in order to prevent the spread of HBV in blood and secretions, and (6) the importance of testing and vaccinating contacts.

HEPATITIS B VACCINE

The hepatitis B vaccines currently produced in the United States, Recombivax HB and Engerix-B, are manufactured by recombinant DNA technology using baker's yeast and do not contain human plasma.[1] The other, older type of hepatitis B vaccine was derived from human plasma and is no longer produced in the United States. The preparation of the plasma product did inactivate human immunodeficiency virus (HIV).

Immunogenicity and Efficacy

Preexposure vaccination results in protective antibody levels in almost all infants and children (>95%) and healthy adults younger than 40 years of age (>90%).[1] Important issues in a discussion of immunogenicity include factors that affect immunogenicity, response differences by vaccine manufacturer, efficacy, and duration of immunity.

Factors Affecting Immunogenicity. Factors that affect immunogenicity include the number of doses administered, the interval between the second and third doses, age, underlying medical conditions, and genetics. Immunogenicity differs according to the number of doses received. After the third dose of hepatitis B vaccine, more than 95% of children seroconvert, ie, develop ≥10 mIU/mL of anti-HBs. The third dose is required for optimal protection; furthermore, geometric mean titers improve with longer intervals between the second and third doses. The dose of hepatitis B vaccine required for seroprotection differs by age; infants require smaller doses than adults (Table 4). Most (>90%) healthy adults younger than 40 years of age seroconvert after being vaccinated.[1] However, immunogenicity declines with age thereafter, dropping to 75% for recipients 60 years of age. Underlying medical conditions associated with lower likelihood of seroconversion include prematurity with low birth weight, immunosuppression, renal failure, obesity, and tobacco use. In comparison to full-term infants, premature infants with a birth weight less than 2 kg have lower seroconversion rates; the rates drop fur-

TABLE 4

Hepatitis B Vaccine Dose by Patient Age and immune Status and Vaccine Type

Patient Status	Each Dose: Recombivax HB µg	Each Dose: Engerix-B µg	Administration Site
Infant of HBsAg-positive mother	5	10	Anterolateral Thigh
Infant of HBsAg-negative mother	2.5	10	
Child <11 years old	2.5	10	Deltoid Muscle
Adolescent — 11 to 19 years old	5	10	
Adult — 20 years of age or older	10	20	
Dialysis patients or immunocompromised	40*	Total 40†	

*Special formulation of 40 µg in 1.0 mL.
†Four-dose schedule at 0,1, 2, and 6 months using two 1.0-mL doses (for a total of 40 µg) at one site.
Modified from Centers for Disease Control and Prevention. Hepatitis B virus infection: a comprehensive immunization strategy to eliminate transmission in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) [draft]. MMWR 1997. In press

ther if the birth weight is less than 1 kg.[1] Therefore, hepatitis B vaccination should be delayed in preterm infants weighing less than 2 kg unless the infant is born to an HBsAg-positive mother (see next section, Schedule and Administration).[1] Another factor that affects immunogenicity is genetics; in one study, many of those who did not respond to hepatitis B vaccination (anti-HBs titer <10 mIU/mL) appeared to lack a dominant immune response gene in the major histocompatibility complex.[24]

All hepatitis B vaccines manufactured in the United States have similarly high seroconversion rates for all age groups. In preexposure infant vaccination, no differences exist in seroconversion rates after the third dose between the vaccines produced by the two different US manufacturers.[25] Furthermore, the modest differences in response between the two different vaccines prior to the third dose have no practical significance.[1] A prospective study found no differences in immunogenicity by manufacturer for adults younger than 40 years of age.[26] For adults 40 years of age and older, seroconversion rates were 86% for Engerix-B and 80% for Recombivax HB (P =.02).[26] However, decision analysis showed no public health significance for this difference and it does not warrant preferential use of one manufacturer's vaccine over the other.[1]

Vaccine Efficacy. Efficacy, ie, protection against HBV infection, is high (80% to 95%) for hepatitis B vaccines licensed in the United States when given to susceptible infants, children, and adults.[1] Protection against clinical illness occurs when the level of anti-HBs is at least 10 mIU/mL.

Duration of Immunity. The duration of immunity in healthy persons is based on immunological memory. Although antibody levels may slowly diminish with time following vaccination, most persons remain protected by the immunological memory in B lymphocytes. The immunologic memory and long incubation period of hepatitis B infection allow most immunized persons who have low titers to mount an anamnestic immune response if challenged by HBV. A few persons who adequately responded to hepatitis B vaccine have developed HBV infection following exposure years after vaccination. However, none of those so infected in the United States has become chronically infected or developed serious complications such as chronic liver disease. The issue of waning antibody levels in some healthy persons needs further study, but current data indicate excellent long-term efficacy in preventing serious HBV infection in both infants and adults. Although some experts speculate that booster doses might be needed, they are not currently recommended. Of note, the duration of immunity in hemodialysis patients, in contrast to healthy persons, appears to persist only as long as the level of anti-HBs is ≥10 mIU/mL.

TABLE 5

Hepatitis B Vaccine Schedule

Hepatitis B Vaccine Dose	Vaccination of Infants Born to HBsAg-positive Mothers,* Catch-up Vaccination of Children and Adolescents	Routine Vaccination of Infants Born to HBsAg-negative Mothers (Age)	Alternative Schedule for Catch-up Vaccination of Children and Adolescents (1 to 19 years old)
Dose 1	Start (or within 12 hours of birth if newborn)	Birth to 2 months	Start
HBIG	Within 12 hours of birth if born to HBsAg-positive mother	NA†	NA
Dose 2	1 month later	1 to 4 months of age ‡	2 months later §
Dose 3	6 months from first dose	6 to 18 months of age	4 months from first dose

*Infants born to mothers who were not screened for HBsAg should receive hepatitis B vaccine within 12 hours of birth at the dose for infants born to HBsAg-positive mothers. Their subsequent management depends on their mother's HBsAg status.

†NA = not applicable.

‡The second dose should be administered at least 1 month after the first dose.

§For adolescents 11 to 19 years old, the second dose may be given 1 or 2 months after the first.

Based in part on Centers for Disease Control and Prevention. Recommended childhood immunization schedule--United States, 1997. MMWR 1997; 46(2):35-40 and Centers for Disease Control and Prevention. Hepatitis B virus infection: a comprehensive immunization strategy to eliminate transmission in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) [draft]. *MMWR* 1997. In press.

Schedule and Administration

The vaccine schedule depends on the recipient's age and indication for vaccination (Table 5). Hepatitis B vaccine should be delayed in premature infants weighing less than 2 kg born to HBsAg-negative women until the infant weighs 2 kg or more.[1] However, if the infant is born to a mother whose HBsAg status is positive or unknown, postexposure prophylaxis, including both HBIG and hepatitis B vaccine, should be initiated within 12 hours of birth, regardless of gestational age. Hepatitis B vaccine can be started at or before the time of hospital discharge for other newborns.

If the hepatitis B vaccine schedule is interrupted, it should be continued. If the schedule is interrupted after the first dose, the second dose should be given as soon as possible; the third dose can be given 2 months after the second dose and at least 4 months after the first dose.

In infants and children 2 years of age or younger, hepatitis B vaccine should be administered in the anterolateral thigh with a 5/8- to 1-in. needle. In older children and adults, hepatitis B vaccine should be administered in the deltoid muscle using a 1- to 1 1/2 -in. needle to ensure that vaccine is administered intramuscularly. In adults, the vaccine is less immunogenic when administered in the buttock than in the deltoid. Intradermal administration is not recommended due to decreased immunogenicity in infants, inconsistent antibody responses in older persons, and lack of data on the duration of immunity.[1] Hepatitis B vaccines from different manufacturers can be used interchangeably.

Hepatitis B vaccine should be refrigerated at 2 °C (35.6 °F) to 4 °C (39.2 °F). It should not be frozen, since freezing can decrease immunogenicity.

Adverse Events

The most common adverse event after administration of hepatitis B vaccine is pain at the injection site, which occurs in 13% to 29% of adults and 3% to 9% of children.[2] Mild, transient systemic adverse events such as fatigue and headache have been reported in 11% to 17% of adults and 8% to 18% of children. Temperature greater than 37.7 °C has been reported in 1% to 6% of vaccinees.

Although a rare epidemiological association was suggested between administration of plasma-derived hepatitis B vaccine and Guillain-Barré syndrome, the

study's authors stated that the data were not conclusive.[27] Furthermore, the Institute of Medicine reviewed the safety of hepatitis B vaccine and concluded that the evidence was inadequate to support such an association.[28] Among the estimated 2.5 million adults who received it from 1986 to 1990, recombinant hepatitis B vaccine has not been associated with Guillain-Barré syndrome (unpublished data, CDC).

Thimerosal, the preservative added to hepatitis B vaccine, or yeast proteins may be the cause of the rare cases of anaphylaxis reported following vaccination.[28] Therefore, hepatitis B vaccine is contraindicated in persons who have experienced anaphylaxis after a previous dose. Providers should contact the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 to report suspected adverse events resulting from vaccination. Since hepatitis B vaccine does not contain live virus and therefore is not infectious, it is safe for pregnant and lactating women.

Rationale for Comprehensive Vaccination

A comprehensive hepatitis B vaccination policy includes (1) routine infant vaccination, (2) catch-up vaccination of adolescents not previously vaccinated, (3) catch-up vaccination of young children at high risk for infection, (4) preexposure vaccination of adolescents and adults based on lifestyle or environmental, medical, and occupational situations that place them at risk, and (5) prevention of perinatal HBV infection.[1]

The rationale for a comprehensive hepatitis B vaccine policy follows: **1.** HBV causes considerable morbidity and mortality in the United States from sequelae such as cirrhosis, fulminant hepatitis, and hepatocellular carcinoma. **2.** HBV causes more deaths each year in the United States than most vaccine-preventable diseases of childhood, even at their peak fatality rate, as is seen in Table 6. **3.** Infants and preschool-aged children, if infected, have a much higher likelihood than adults of becoming chronically infected and developing subsequent complications. **4.** Transmission from child to child, although relatively infrequent, has been reported in schools, day care centers, and families, and between playmates.[6] **5.** The previous strategies of immunizing high-risk persons have had little impact. **6.** No risk factor can be identified in at least 30% of persons infected with HBV.[4,29-32] Hence, these cases are not preventable by immunizing only high-risk persons. **7.** Many high-risk persons become infected early during the course of their high-risk behaviors. **8.** High-risk persons, such as injection drug users, frequently are not compliant with the needed three-dose regimen. **9.** Routine infant hepatitis B vaccination is as cost-effective as other commonly used preventive

TABLE 6

Cases of Hepatitis B and Other Diseases of Children in the Years Before Vaccines Were Routinely Used

Disease	Year*	Cases per 100,000	No. of Cases	No. of Deaths
Hepatitis B	1989	54	132,000	5,820†
Haemophilus influenzae type b				
Invasive disease	1986	5	13,014	531
Meningitis		3	8,676	354
Poliomyelitis				
All types	1954	35	56,784	—
Paralytic		11	18,308	—
Measles	1964	240	458,083	380
Rubella	1970	29	57,686	—
Congenital rubella	1970	0.04	77	—

*The year preceding widespread use of specified vaccine.
†Includes an estimated 320 deaths from acute HBV infection and an estimated 5,500 deaths from chronic HBV infection.
Adapted from West DJ, Margolis HS. Prevention of hepatiits B virus infection in the United States: a pediatric perspective. *Pediatr Infect Dis J* 1992;11:886-74. In: Mahoney FJ, Burkholder BT, Matson CC. Prevention of hepatitis B virus infection. *Am Fam Physician* 1993; 47:867.

measures (eg, oat bran for hypercholesterolemia and pneumococcal vaccine for the elderly).[33]

Hepatitis B vaccine is recommended, for all infants and unvaccinated adolescents at ages 11 to 12 years, by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).[34]

Routine Infant Vaccination. Routine infant vaccination in the United States was recommended by the ACIP in 1991. The dosage and schedule are listed in Tables 4 and 5.

The major concerns about routine infant hepatitis B vaccination are cost, duration of immunity, interactions with other vaccines, and number of injections. Because the dose for infants is one quarter to one half that of adults, the cost is lower when the vaccine is administered during infancy and the cost is similar to that of other infant vaccines. Based on direct medical expenses, the estimated cost per year of life saved is $1522 for routine infant vaccination, but from a societal perspective, routine infant vaccination is cost saving.[35] The duration of immunity following vaccination of infants is not fully known, but current data indicate that long-term protection persists as a result of immunologic memory even if antibody titers decline. Breakthrough HBV infections are rare among persons in the United States who seroconverted following vaccination, and those infections that have occurred have been mild and none has become chronic. Simultaneous vaccination with multiple vaccines is generally safe and generally does not interfere with immunogenicity. Furthermore, although addition of hepatitis B vaccine to the childhood schedule increases the number of antigens administered in one visit, combined Hib conjugate and hepatitis B (recombinant) vaccine (COMVAX) for infants has been licensed in the United States that would decrease the number of injections, and others are being tested.[36]

Adolescent Catch-up Vaccination. All adolescents 11 to 12 years of age who have not previously received hepatitis B vaccine should receive the three-dose series, as recommended by the ACIP, AAFP, AAP, and American Medical Association.[34,37] Adolescent vaccination against hepatitis B is cost-effective at $3,730 per year of life saved.[35]

Catch-up Vaccination of High-Risk Children. Unvaccinated children younger than 11 years of age should be vaccinated if they live in a household with persons of Pacific Islander ethnicity or the household of first-generation immigrants from countries where intermediate or high HBV is endemic.[1]

Preexposure Vaccination of High-Risk Persons. Persons are at increased risk of contracting HBV due to exposure to potentially infectious blood or body fluids by needlesticks, sexual transmission, or environmental exposure should be vaccinated. Persons at risk due to exposure to blood or body fluids include those undergoing hemodialysis, recipients of factor concentrate, injection drug users, health care workers, morticians, public safety workers who have contact with blood or body fluids, and trainees in one of the health care fields (Table 7).[1] The risk of becoming infected with HBV from a needlestick contaminated by blood from a person with acute or chronic HBV infection is approximately 6% to 30% (30% represents HBeAg-positive patients). Persons at risk from sexual transmission include sexually active homosexual men, heterosexual persons with more than one partner in the past 6 months, sexual contacts of persons chronically infected with HBV, and international travelers to countries where high or intermediate HBV is endemic who will have close or sexual contact with citizens of those countries (Table 7).[1] Persons at potential exposure due to environmental situations include clients and staff of institutions for the developmentally disabled, household contacts of persons chronically infected with HBV, and families of foreign adoptees who are chronically infected with HBV. Although the high risk of HBV infection among clients of institutions for the developmentally disabled has declined substantially, they still should be considered at risk and routinely vaccinated.[1] Hepatitis B vaccination of high-risk groups has been found to be cost-effective.[33]

Postexposure Prophylaxis. Postexposure prophylaxis is recommended for (1) perinatal exposure, (2) household contacts in certain situations, (3) sexual exposure to an HBV-infected person, and (4) accidental percutaneous or permucosal exposure to infectious blood (Table 8).

Prevention of Perinatal Hepatitis B Virus Infection. According to the ACIP, the American College of Obstetricians and Gynecologists, the AAP, and the US Preventive Services Task Force, all pregnant women should be screened for HBsAg, optimally at an early prenatal visit.[1,38] Some (<10% to 85%) infants born to mothers who are chronically

infected with HBV will become infected themselves unless they are vaccinated and given postexposure prophylaxis.[1,11,39] These infants have a 90% risk of chronic infection and up to 25% of those infected perinatally eventually will die of chronic liver disease as adults.[1,40] Infants born to HBsAg-positive women should receive both the first dose of hepatitis B vaccine and HBIG within 12 hours of birth.[2] The combination of hepatitis B vaccine and 0.5 mL of HBIG given within 12 hours of birth is 75% to 95% efficacious in preventing chronic HBV infection and is generally more effective than vaccination alone.[1,40-42] For children born to HBsAg-positive women, the 5-µg dose of Recombivax HB or the 10-µg dose of Engerix-B should be used at birth, 1 month, and 6 months. Vaccinated offspring of per-

TABLE 7

Hepatitis B Vaccine Recommendations for High-Risk Persons

Persons with High-Risk Indication	Recommendations for Vaccine Administration
Family members of adoptees from foreign countries who are HBsAg-positive	Administer to all family members
Health care workers (dentist, DO, MD, RN, and trainees in health care fields	Administer
Hemodialysis patients or patients with early renal failure	Administer (see Table 4 for dosage)
Household or sexual contacts of persons chronically infected with hepatitis B	Administer
Immigrants from Africa or Southeast Asia	Recommended for children <11 years old and all susceptible household contacts of persons chronically infected with hepatitis B
Injection drug users	Administer
Inmates of long-term correctional facilities	Administer
Clients and staff of institutions for developmentally disabled	Recommended*
International travelers to countries of high or intermediate HBV endemicity	Administer if close or sexual contact with the local population anticipated or residing in these areas for >6 months
Laboratory workers	Administer if working around blood or other human tissues
Public safety workers (police, fire fighters, etc.)	Administer if contact with blood or blood-contaminated body fluids is anticipated
Recipients of clotting factors	Use fine needle (≤ 23 gauge) and firm pressure at injection site for ≥ 2 minutes (see MMWR 1994;43[RR-1] for details)
Persons with a sexually transmitted disease or multiple sexual partners in previous 6 months, commercial sex workers (prostitutes), homosexual or bisexual men	Administer

*Clients in nonresidential day-care programs should be vaccinated if an HBsAg-positive classmate behaves aggressively or has special medical problems that increase the risk of exposure to blood. Staff in nonresidential day-care programs should be vaccinated if a client is HBsAg-positive.

TABLE 8

Recommended Prophylaxis After Sexual or Household Exposure to Hepatitis B Virus

Type of Exposure	Type of Infection in Contact	Type of Prophylaxis
Perinatal	Acute or chronic	Vaccination + HBIG
Sexual	Acute	HBIG + vaccination
	Chronic	Vaccination
Household contact	Chronic	Vaccination
	Acute	
	No blood or sexual exposure	Consider vaccination (not required)
	Known exposure	HBIG ± vaccination—See Table 9
	Infant <12 months	Vaccination and, if no previous vaccination, HGIG

Modified from Centers for Disease Control and Prevention. Hepatitis B virus infection: a comprehensive immunization strategy to eliminate transmission in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) [draft]. *MMWR* 1997. In press.

sons chronically infected with HBV should be tested for HBsAg and anti-HBs at 9 to 15 months of age to determine the success of vaccination. According to published calculations, screening all pregnant women in the United States would result in detection of about 22,000 HBsAg-positive women each year and prevent chronic HBV infection in 6,000 neonates annually.[43] Women whose initial HBsAg test result is negative but who are at high risk (eg, injection drug users, persons with a recently diagnosed sexually transmitted disease, persons with multiple sexual partners or hepatitis during pregnancy) should be tested again for HBsAg late in pregnancy.

If a woman has not been tested for HBsAg prior to delivery, a blood sample should be drawn at delivery and the first dose of hepatitis B vaccine should be administered to her newborn within 12 hours of birth. The dose appropriate for HBsAg-positive mothers should be used until the HBsAg status of the mother is known. If her HBsAg test result is positive, then HBIG should be administered as soon as possible to her newborn. If HBsAg testing cannot be performed either prenatally or at delivery, hepatitis B vaccine should be administered within 12 hours of birth.

Prevention of HBV Infection of Household Contacts. Unvaccinated infants whose primary caregiver has acute HBV infection should receive 0.5 mL of HBIG and the three-dose series of hepatitis B vaccine. Other household contacts of a person acutely infected with HBV should be considered for vaccination but it is not required unless there is blood exposure (eg, on shared razors) or sexual contact. Household contacts of a person chronically infected with HBV should be vaccinated.[1]

Prevention of HBV Infection After Sexual Exposure. Susceptible *sexual* contacts of persons with acute HBV infection should receive HBIG and begin the hepatitis B vaccine series within 14 days of exposure. If the last sexual contact is greater than 14 days ago, postexposure prophylaxis is still recommended, although the efficacy may be lower. The period after sexual exposure during which HBIG is effective is unknown, but it is unlikely to exceed 14 days. Testing sexual contacts for susceptibility can be conducted it treatment would not be delayed beyond 14 days after the last exposure. Susceptible sexual contacts of persons chronically infected with HBV should receive hepatitis B vaccine but not HBIG.

Prevention of HBV Infection After Accidental Exposure to Blood Products. The prophylaxis protocol following *blood* exposure should be instituted as soon as possible (Table 9). The adult dose of HBIG is 0.06 mL/kg administered intramuscularly (IM) within 24 hours of exposure, if possible.[2]

Hepatitis B Immune Globulin. HBIG is indicated for post-exposure prophylaxis as has been discussed. HBIG is extracted from the plasma of donors who have high titers of anti-HBs. The plasma is screened for HBsAg antibodies to HIV and hepatitis

TABLE 9

Recommendations for Hepatitis B Prophylaxis for Percutaneous or Permucosal Exposure

Exposed Person	Treatment when source is: HBsAg-positive	HBsAg-negative	Source Not Tested or Unknown
Unvaccinated	HBIG × 1* and initiate hepatitis B vaccine	Initiate hepatitis B vaccine	Initiate hepatitis B vaccine
Previously vaccinated			
Known responder	No treatment	No treatment	No treatment
Known nonresponder	HBIG × 2 or HBIG × 1 and initiate revaccination	No treatment	If high-risk source, treat as if HBsAg-positive
Response unknown	Test exposed for anti-HBs 1. If inadequate, HBIG × 1† and vaccine booster 2. If adequate, no treatment	No treatment	Test exposed for anti-HBs 1. If inadequate, initiate revaccination 2. If adequate, no treatment

*HBIG dose, 0.06 mL/kg IM, within 24 hours of exposure.
†Adequate anti-HBs is 10 mIU/mL by radioimmunoassay or positive by enzyme immunoassay.
Modified from Centers for Disease Control and Prevention. Hepatitis B virus infection: a comprehensive immunization strategy to eliminate transmission in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) [draft]. *MMWR* 1997. In press.

C virus. HIV cannot be transmitted by HBIG because the preparation process removes HIV. For post-exposure prophylaxis, HBIG should be used instead of immune (gamma) globulin because the titers of anti-HBs are high in HBIG but low in gamma globulin. HBIG should be administered IM at a dose of 0.06 mL/kg for children and adults and 0.5 mL for infants.

Prevaccination and Postvaccination Serologic Testing. Serologic testing for susceptibility is not recommended unless HBV markers are present in sufficient numbers to make testing cost-effective. Groups in which testing is cost-effective generally have chronic HBV infection rates greater than 20% or overall infection rates greater than 30% (Table 10).[2] When testing before vaccination, the preferable test is anti-HBc.

Postvaccination testing for anti-HBs is recommended only when the results will affect the individual's subsequent medical care. Such persons include dialysis patients, infants born to HBsAg-positive mothers, sexual contacts of persons chronically infected with HBV, and health-care workers at high risk of percutaneous or permucosal exposure to body fluids (Table 10). Testing should be performed 1 to 2 months after completion of the vaccine series, with the exception of infants born to HBsAg-positive mothers, who should be tested at 9 to 15 months of age. An adequate antibody response to vaccination is 10 mIU/mL. Testing is not indicated after routine vaccination of infants, children, adolescents, or persons at low risk of exposure, eg, public safety workers and health-care workers who do not have contact with patients or their body fluids.

Revaccination is recommended for persons whose postvaccination level of anti-HBs is less than 10 mIU/mL. Such persons should receive three doses on a 0-, 1-, and 6-month schedule. Antibody testing should be conducted again 1 to 2 months after revaccination. Persons who do not respond after two series (six doses) of hepatitis B vaccine should be counseled about universal precautions and the need for HBIG if they are exposed. Also, testing such persons for HBsAg should be considered, since some may already be chronically infected. Hemodialysis and immunocompromised patients should have serological tests annually and should be given a booster dose when antibody levels decline to less than 10 mIU/mL.

OFFICE PROCEDURES TO IMPROVE VACCINATION COMPLIANCE

The most important procedures to improve vaccination rates are (1) assessment of the practice's vaccination rates, (2) incorporation of hepatitis B vaccination into the routine childhood vaccination schedule, (3) identification of adolescent and adult

TABLE 10

Groups for Whom Serologic Testing is Recommmended Before or After Hepatitis B Vaccination

Groups	Prevaccination	Postvaccination
Infants and children for routine vaccination	No	No
Sexually active heterosexuals	Yes	No
Homosexual men and bisexual men	Yes	No
Sexual contacts of HBsAg-positive persons	Yes	Yes
Household, nonsexual contacts of HBsAg-positive persons	No	No
Injection drug users	Yes	No
Health care workers and others with occupational indication for vaccination:		
At high risk of percutaneous/permucosal exposure	No	Yes
At low risk of percutaneous/permucosal exposure	No	No
In institutions for developmentally disabled:		
New admissions	No	No
Long-term clients	Yes	No
Hemodialysis/renal failure patients		
Previous dialysis	Yes	Yes
No previous dialysis	No	Yes
Recipients of clotting factor concentrates		
New patient	No	Yes
Previous infusion	Yes	Yes
Inmates of long-term correctional facilities	Consider	No
Persons from countries with intermediate or high endemicity of infection	Yes	No
Postexposure vaccination		
Infant of HBsAg-positive mother	No	Yes
Sex partners of persons with acute HBV infection	Yes	No

Modified from Centers for Disease Control and Prevention. Hepatitis B virus infection: a comprehensive immunization strategy to eliminate transmission in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) [draft]. *MMWR* 1997. In press.

patients needing hepatitis B vaccination, (4) establishment of a goal (ie, percentage of target population to be vaccinated), (5) development of a plan, and (6) provision of ongoing feedback to the physician about vaccination rates. The impact of assessment of vaccination rates and feedback to physicians cannot be overestimated—they are among the most important changes that a practice can make to improve vaccination rates.[44]

Once the process of assessment and feedback has been established, several other office procedures can be considered to enhance vaccination compliance. Some of these procedural enhancements are: **1.** Ask office staff to routinely evaluate the vaccination status of patients prior to the physician seeing the patient. This can be done at the time of registration (perhaps with the aid of a computer) or by nursing personnel when they obtain vital signs. Colored stickers, checklists, or inked rubber stamps are practical ways to communicate about needed vaccinations. **2.** Send reminder postcards to encourage follow-up with the second and third doses of hepatitis B vaccine. **3.** Write standing orders to allow nurses to administer vaccinations without needing to obtain a new order each time. **4.** Have nurses, not physicians, administer vaccines so that physicians have time to evaluate other preventive measures. **5.** Provide information pamphlets about hepatitis B. The pamphlet should state that the vaccine itself cannot cause hepatitis or HIV infection and that the incidence of adverse events is low.

THE TEACHING IMMUNIZATION FOR MEDICAL EDUCATION (TIME) PROJECT

This article, including the thought problems that follow this section, was written as a component of the Teaching Immunization for Medical Education (TIME) Project, a multiyear project guided by a national advisory committee of experts in the fields of immunization and medical education. The project is a collaborative effort of the Centers for Disease Control and Prevention, the Association of Teachers of Preventive Medicine (ATPM), and the University of Pittsburgh School of Medicine.[45] The goal of the project is to enhance the educational preparation of physicians through an innovative curriculum on immunization and vaccine-preventable diseases, thereby influencing the immunization practices of physicians to increase vaccination levels. Information about continuing medical education (CME) modules on other vaccine-preventable diseases and case-based materials designed for medical students and residents may be obtained by directly contacting ATPM, Suite 204, 1511 South Ritchie Highway, Arnold, MD 21012; telephone 800-789-6737, fax 800-678-7102. Some CME modules are available at the ATPM World Wide Web site http://www.atpm.org/cme/cme.htm.

THOUGHT PROBLEMS

Scenario 1

Mr Banks is a 41-year-old man who complains of fatigue, gray-colored stools, and cough. He has a 3-week history of gray-colored stools and a 3- to 7-day history of dark-colored urine. He complains of persistent nausea and vomiting after meals. His sclera are icteric. His liver is tender and palpable 4 fingerbreadths below the right costal margin. Laboratory values are as follows: total bilirubin, 5.8 mg/dL; direct bilirubin, 4.5 mg/dL; AST (SGOT), 1420 U/L; ALT (SGPT), 2668 U/L; LDH, 867 mg/dL; alkaline phosphatase, 1132 IU/L; total protein, 7.3 g/dL; and al bumin, 3.4 g/dL. IgM antibody to hepatitis A virus was negative but IgG was positive. Hepatitis B surface antigen (HBsAg) was present, as was IgM antibody to hepatitis B core antigen (anti-HBc). Hepatitis C enzyme-linked immunosorbent assay (ELISA) was nonreactive. Abdominal ultrasound revealed only hepatomegaly.

Thought Problems

1. What are the possible differential diagnoses for his chief complaint (before serological tests results are available)?
2. What do the liver function test results suggest?
3. How do you interpret his hepatitis test results? What is the pattern for a person chronically infected with HBV? What is the pattern for a person who has recovered?
4. Which hepatitis tests should have been ordered?
5. How likely is he to become chronically infected?

Scenario 2

Ms Davis recently noticed her skin turning yellow and appeared jaundiced on examination. Her test result is positive for hepatitis B surface antigen (HBsAg) and IgM antibody to hepatitis B core antigen (IgM anti-HBc). She has a 3-year history of injection drug use (IDU), including sharing of needles. Her HIV test result was negative. Her last IDU was 2 months ago. After receiving multiple stab wounds 1 year ago, she was hospitalized and received a transfusion during a laparotomy procedure. She is sexually active with her boyfriend; they last had intercourse 1 week ago.

Thought Problems

6. What was the most likely source of hepatitis?
7. What are the contact tracing needs? Does her case need to be reported?
8. What is the risk to Ms Davis' boyfriend? What should be done for him?
9. What is the risk for those with whom Ms Davis has shared needles? Given that she is willing to identify them if their names will be treated confidentially, what should be done for them?
10. Ms Davis was hospitalized approximately 1 year ago for treatment of stab wounds. Should she have received hepatitis B vaccine then?

Scenario 3

A nurse who started an IV on a jaundiced patient accidentally stuck herself with a needle contaminated by the patient's blood. Testing revealed that the patient was infected with HBV. The nurse is frightened by the possibility of hepatitis. However, she is even more frightened by

hepatitis B vaccine. She has heard that it is manufactured from the plasma of persons who have been infected with HBV and is concerned that she might get HIV from the vaccine.

Thought Problems

11. If the patient has acute or chronic HBV infection, what is the nurse's risk of contracting HBV infection from the needlestick?
12. How is hepatitis B vaccine currently produced?
13. Can hepatitis B vaccine transmit HIV? What are the vaccine's adverse events?
14. What should be done for the nurse?
15. What office procedures can be followed to help the nurse complete the hepatitis B vaccine series, since more than one dose will be needed?

Scenario 4

Ms Vang is the sex contact of a person who is acutely infected with HBV. She is asymptomatic, but her hepatitis B surface antigen test and total anti-HBc test results are positive. Old medical records indicate that Ms Vang tested positive 13 years ago, when she immigrated to the United States from Southeast Asia. She is pregnant and babysits for two infants. Dr Thomas, the physician to whom she plans to take her child for well-child care, does not have privileges at the hospital where the infant will be born.

Thought Problems

16. Where was Ms Vang most likely to have become infected with HBV?
17. What are the serious complications of her disease?
18. What is her child's risk for becoming infected with HBV at the time of delivery?
19. What should be done for her child following delivery? How soon should it be done? What doses are needed? Where should the treatment be administered?
20. How likely is it that the records about the newborn's need for hepatitis B vaccine will to be sent to the physician doing well-child care? How could this be facilitated?
21. What should be done for the two infants for whom she babysits?

Scenario 5

Dr Smith, a primary care physician, recently read a journal article that discussed the amount of suffering from hepatitis B in the United States. The article recommended routine hepatitis B vaccination of infants. Dr Smith's practice is in a suburban area. Dr Smith wonders if routine hepatitis B vaccination of infants is justified in a suburban practice.

Thought Problems

22. Is routine vaccination of infants against hepatitis B justified? Why or why not? List reasons.

Scenario 6

Dr Ruffa has become aware of the amount of suffering from hepatitis B in the United States and would like to increase use of hepatitis B vaccine in his office. However, Dr Ruffa's practice consists almost entirely of adults; furthermore, Dr Ruffa does not provide prenatal or obstetrical care.

Thought Problems

23. Which of Dr Ruffa's patients should receive hepatitis B vaccine? (List)
24. How can Dr Ruffa systematically identify which patients need hepatitis B vaccine?
25. How should hepatitis B vaccine be administered to adults?
26. What can Dr Ruffa do to encourage compliance with the second and third doses of hepatitis B vaccine?
27. When should the second and third doses of hepatitis B vaccine be given if the schedule is interrupted?

ANSWERS TO THOUGHT PROBLEMS

Scenario 1

1. Prior to laboratory test results, the differential diagnosis includes hepatitis (eg, viral, toxic, ethanol, autoimmune) and biliary obstruction.
2. His liver function test results suggest nonalcoholic hepatitis. In alcoholic hepatitis, the level of AST is generally twice that of the ALT level. In obstructive liver diseases, LDH and alkaline phosphatase are elevated out of proportion to other liver function tests.
3. He has acute HBV infection. A person chronically infected with HBV usually has HBsAg and IgG anti-HBc (rarely will a person have only the IgG anti-HBc and yet be chronically infected at a low level). A person who has had HBV infection and recovered has IgG anti-HBc and usually anti-HBs.
4. IgM antibody to hepatitis A virus, HBsAg, and IgM anti-HBc are the most important tests; many physicians would add IgG (or total) anti-HBc and a test for hepatitis C virus.

5. He has a 5% to 10% risk of becoming chronically infected with HBV.

Scenario 2

6. Ms Davis most likely contracted hepatitis through IDU. Transfusion is very unlikely as the source of her infection because (1) the incubation period for hepatitis B is 45 to 160 days (average, 120 days), whereas Ms Davis received her transfusion 1 year ago, and (2) the risk from transfusion is now very small.
7. The persons needing contact tracing include sex partners, persons with whom needles have been shared, and persons exposed as household contacts (eg, persons exposed by sharing toothbrushes). If the person becomes chronically infected, then all household members should be vaccinated. Her case should be reported to health authorities.
8. Ms Davis' boyfriend is at considerable risk of infection through sexual transmission, which is the most common form of HBV transmission in the United States. All susceptible persons whose sex partners have acute hepatitis B virus infection should receive a single dose of HBIG (0.06 mL/kg) and should begin the hepatitis B vaccination series within 14 days of last exposure. Administering the vaccine with HBIG may improve the efficacy of postexposure treatment. The vaccine has the added advantage of conferring long-lasting protection. If the last sexual contact is greater than 14 days ago, postexposure prophylaxis is still recommended, although the efficacy may be lower and HBIG is unlikely to be effective. Testing sexual contacts for susceptibility can be conducted if treatment would not be delayed beyond 14 days after the last exposure.
9. The persons with whom Ms Davis shared needles may be at risk; in fact, after 5 years of injection drug use, greater than 80% are infected.[1] Their risk of HBV infection depends on whether she has used injection drugs during the last 2 months and when Ms Davis became infected with HBV. Prevaccination testing for susceptibility using total anti-HBc is likely to be cost-effective in this situation. However, compliance may be improved by simultaneously administering the first dose of the hepatitis B vaccine series when conducting prevaccination testings.
10. Ms Davis could have received hepatitis B vaccine before discharge from the hospital 1 year ago. Many authorities would consider this a missed opportunity for vaccination.

Scenario 3

11. The nurse is at risk for HBV infection if the patient is acutely or chronically infected. The magnitude of the risk depends on the infectiousness of the patient and the amount of blood transferred. If the patient is HBeAg positive, the risk increases. The risk of becoming infected with HBV from the needlestick is approximately 6% to 30% (30% represents HBeAg-positive patients).
12. In the United States, hepatitis B vaccine is produced totally by recombinant DNA technology.
13. Neither the current recombinant vaccine nor the older plasma-derived vaccine has been associated with transmission of HIV; the plasma-derived vaccine underwent sufficient chemical processes to inactivate HIV. The adverse events are pain at the injection site (3% to 29%) and temperature >37.7 °C (1% to 6%); however, they do not occur more frequently than adverse events from placebo injection. Current data from reporting systems for adverse events do not indicate an association between receipt of recombinant vaccine and Guillain-Barré syndrome. Possible reasons that some people are not vaccinated include fear of adverse events, cost, and belief that they are unlikely to be exposed.
14. All health care personnel and persons who have occupations that expose them to blood should be vaccinated; the fact that this nurse is unvaccinated is considered a missed opportunity. The nurse should receive HBIG within 24 hours of the needlestick and begin the hepatitis B vaccine series. Medical personnel at high risk of percutaneous or permucosal exposure to contaminated fluids should be tested for response to hepatitis B vaccine after three doses so that they can be treated appropriately if they are exposed. If they have developed protective antibody titers, there is no need for further hepatitis B vaccination, even if exposed. Postvaccination testing should be done 1 to 2 months after completion of the vaccination series.
15. Reminders by telephone or postcard help inform patients of needed vaccinations. Employee health offices should consider using tracking systems to generate reminders for vaccination.

Scenario 4

16. Most likely, Ms Vang was infected with HBV at birth from her mother or during early childhood when she was in Southeast Asia. Approximately 70% of immigrants from Southeast Asia have been infected with

HBV and approximately 10% to 20% are chronically infected.

17. The serious complications of chronic HBV infection are cirrhosis and hepatocellular carcinoma. Persons chronically infected may also be at risk for hepatitis delta virus (HDV) superinfection. See the current ACIP recommendations for additional discussion of complications.
18. The child's risk of infection at time of delivery ranges from <10% to 85%, depending on the mother's hepatitis B e antigen status; HBeAg is a marker of increased infectivity. Infected infants have a 90% risk of chronic infection.
19. The child should receive hepatitis B vaccine and 0.5 mL of HBIG within 12 hours of birth. Hepatitis B vaccine is administered IM in the anterolateral thigh in infants. If Recombivax HB is used, a higher dose (5 µg) is used than is used for routine infant vaccination (2.5 µg). The dose for Engerix-B (10 µg) is the same as is used for routine infant vaccination.
20. It is unlikely that the vaccination records will be sent; therefore, special effort is needed to communicate to Dr Thomas the information about the HBsAg-positive status of the mother and the treatment the child received. The child needs additional doses of vaccine at 1 and 6 months of age. This is the recommended schedule for infants born to HBsAg-positive mothers. In this situation, the child should receive postvaccination testing for HBsAg between 9 and 15 months of age. The more permissive schedule for routine infant vaccination against hepatitis B should not be used.
21. It is prudent to treat the infants as household contacts; they should be vaccinated if they have not been previously vaccinated.

Scenario 5

22. Rationale for the recommended routine vaccination of infants against hepatitis B:
    a. About 128,000 cases of hepatitis B virus infection occur per year in the United States (in a population of 260 million, this is approximately 1 in 1000).
    b. An estimated 1.25 million persons are chronically infected with HBV, all of whom are potentially infectious (about 1 in 250 persons in the United States). These persons are at risk for cirrhosis, delta hepatitis, and hepatocellular carcinoma.
    c. Of reported hepatitis B cases, 30% have no known source of infection.
    d. Previous strategies to identify and vaccinate high-risk persons have been unsuccessful. Vaccination of injection drug users and commercial sex workers (prostitutes) with a three-dose schedule is problematic because such persons may not complete the second and third doses. However, effort should be made to vaccinate such persons.
    e. A person is at a higher risk for chronic HBV infection if he or she became infected early in life. Child-to-child transmission has been documented within families and in school settings.
    f. Comprehensive hepatitis B vaccination has been successful in Alaska. After successful implementation of a comprehensive program to vaccinate susceptible Alaskan Natives, including all newborns, the incidence of acute symptomatic HBV infection fell by over 90% (Lancet 1987;2:1134-1136).
    g. There is a higher rate of death from hepatitis B virus infection in the United States than from any other disease for which there is a routine childhood vaccination recommendation.
    h. The vaccine costs less than many other preventive measures. In some cases, the vaccine is even cost-saving.
    i. On the basis of studies conducted to date, long-term protection appears to last for at least 13 years after hepatitis B vaccination. In persons who initially respond to vaccination, anti-HBs titers may decline over time; however, loss of anti-HBs after vaccination does not imply loss of protection. In vitro studies have demonstrated intact immunologic memory in B lymphocytes obtained from vaccine responders who had low or undetectable anti-HBs levels 7 to 8 years after vaccination. Moreover, natural exposure to HBV long after primary vaccination results in an anamnestic increase in anti-HBs that protects against both clinically significant acute and chronic HBV infection. Routine booster doses of hepatitis B vaccine are therefore not currently recommended.
    j. Generally, simultaneous vaccination with other vaccines is believed to be safe.

Scenario 6

23. The ACIP recommends vaccination of all 11- to 12-year-old children who have not previously received hepatitis B vaccine. Persons with occupational

indications include health care workers, students in health care fields, public safety workers, and staff of institutions for the developmentally disabled. Persons with indications according to place of residence include clients of institutions for the developmentally disabled and household contacts of persons chronically infected with HBV. Persons who have medical indications include those who receive clotting factor concentrates, those with a recent diagnosis of a sexually transmitted disease (STD), and hemodialysis patients. Persons with lifestyle indications include injection drug users, sexually active homosexual and bisexual men, commercial sex workers (prostitutes), heterosexuals with more than one sex partner in the preceding 6 months, and inmates of long-term correctional institutions. In addition, international travelers who plan to spend more than 6 months in close contact with the local population in endemic areas should be vaccinated.

24. To complete the patient history, Dr Ruffa should question each patient about occupation, sexual history (including sexual orientation and STDs), and drug history. Dr Ruffa should revisit these issues during each periodic history and physical. These areas of the patient chart should be updated periodically, and charts of vaccine indications can be prominently displayed. The office computer can search diagnoses (eg, STDs) to identify patients with medical indications.
25. For adults, hepatitis B vaccine is given by the intramuscular route in the deltoid muscle.
26. Methods to encourage compliance include the following:
    a. Reminding patients by postcard or telephone.
    b. Educating patients about disease severity, the vaccination schedule, and the importance of the second and third doses.
    c. Having office staff ask vaccination status at registration or while taking vital signs. Colored stickers, checklists, or inked rubber stamps can communicate the information.
    d. Having the computer generate "tickler" reminders that determine and track any needed vaccinations.
27. If the vaccination series is interrupted after the first dose, the second dose should be administered as soon as possible. The second and third doses should be separated by an interval of at least 2 months. The third dose should be administered at least 4 months after the first dose. If only the third dose is delayed, it should be administered when convenient.

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