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Acute Viral Hepatitis: Immunization and Hepatitis Vaccines

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Goals. The goals of this lesson are to discuss the hepatitis vaccines and recommendations for their use in prevention of acute viral hepatitis.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. list the goals of immunization with hepatitis vaccines;
2. identify the hepatitis vaccines and state their indications, usefulness, efficacy, safety profile, and recommendations for use; and
3. choose from a list important points to convey to hepatitis vaccine recipients and their caregivers.

Acute viral hepatitis is a systemic infection that has high affinity (i.e., is hepatotropic) for the liver. The World Health Organization estimates that more than 500 million people (i.e., approximately one-sixth of the population) worldwide are infected with hepatitis B or C. This



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includes nearly five million people in the United States.

This lesson provides a brief review of acute viral hepatitis infection and discusses experiences with hepatitis A and B vaccines that have resulted in a substantial reduction in the incidence of HAV- and HBV-related infection and disease. It describes the vaccines' immunogenicity and benefits.

Acute Viral Hepatitis: Epidemiology and Pathogenesis

Most clinical cases of hepatitis are caused by one of five viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated hepatitis D virus (HDV), and hepatitis E virus (HEV). Other hepatitis viruses have been identified, but do not cause clinical hepatitis. Hepatitis A, B, and C are the most important types in the U.S.

Hepatitis A. HAV is highly contagious and causes human infection worldwide, particularly in developing countries. Transmission is achieved primarily through the fecal-oral route. Geographic areas include the Caribbean, Middle East, Eastern Europe, Southeast Asia, Central and South America, and Mexico. Areas in the United States with poor sanitation facilities have high HAV infection rates. The

course of HAV is variable; most infections in children are asymptomatic, whereas most adult infections are symptomatic. Approximately 100 people in the United States die each year as a result of HAV infection.

Hepatitis B. HBV is part of a family of genetically related DNA viruses (in contrast to all other known hepatitis viruses which are RNA viruses). The highest concentrations of infectious HBV are found in blood. Other fluids, including semen, vaginal secretions, and saliva, are also infectious. HBV can remain contagious in the environment for at least seven days. Approximately 50,000 new cases of HBV infection are reported in the United States each year; the number of unreported cases may be 10 times higher.

Transmission is accomplished via contact with contaminated body secretions, percutaneously (usually through accidental needlesticks or by sharing needles and/or syringes with infected people), or by maternal-neonatal transfer. Transmission of HBV can also occur during close contact with an infected person. Persons at risk of HBV infection include spouses of acutely infected persons and sexually promiscuous individuals (especially promiscuous men who have sex with men). Health care workers exposed to blood, persons who require repeated transfusions especially with pooled blood product concentrates, residents and staff of custodial institutions for the developmentally handicapped, prisoners, and family members of chronically infected patients are also at risk. Infection via HBV blood transfusion is now rare in the United States due to

routine screening of blood donors and their donated blood.

Hepatitis C. The most common chronic bloodborne infection in the United States, which accounts for an estimated 8000 to 10,000 deaths annually, is caused by HCV. Approximately four million persons in the United States have been infected; three million have chronic HCV infection. Hepatitis C is a progressing disease that may advance gradually over two to four decades.

Individuals who encounter infected blood or instruments or needles, such as users of illicit injection drugs, health care workers or public safety workers, are at risk of acquiring the virus. Intranasal cocaine use, tattooing and body piercing are other potential risks. People who live with HCV-infected individuals should not share personal items such as razors, toothbrushes, and nail clippers to reduce the risk of exposure to infected blood. Approximately 5 percent of infants born to HCV-infected females may be infected.

Hepatitis D. HDV has a worldwide distribution. In nonendemic areas such as the United States, HDV infection is confined to persons exposed frequently to blood and blood products such as users of illicit injection drugs and hemophiliacs. Globally, HDV infection is on the decline.

Pathogenesis. The hepatitis viruses are not directly cytopathic to hepatocytes. The clinical manifestations following acute hepatic damage associated with viral hepatitis are determined by the immunologic response of the host. Persons with defective cellular immune competence are more likely to remain chronically infected rather than to clear the virus from the body.

Immunization with Hepatitis Vaccines

Primer on Terminology. The terms vaccination and immunization are often used interchangeably even though they have distinctly

different meanings. *Vaccination* denotes only the administration of a vaccine to achieve immunity.

Immunization describes the process of inducing or providing immunity by any means, whether active or passive. Thus, vaccination does not assure immunization. *Active immunization* refers to the initiation of immune defenses (e.g., antibodies) by the administration of an appropriate antigen. *Passive immunization* provides temporary protection to a disease state by the administration of exogenously produced substances (e.g., immune globulin). A *vaccine* is a product of attenuated live, or killed, microorganisms that contains the antigenic portion(s) of these agents used to induce immunity and prevent disease in a host recipient. An *immune globulin* is the protein fraction of an antibody derived from human plasma that is used primarily to maintain the immunity status of persons with immunodeficiency disorders or for passive immunization when active immunization is unpredictable or not possible.

The adage: *an ounce of prevention is worth a pound of cure* is relevant for the hepatitis viruses. Although antiviral therapy is approved in the United States for treatment of HBV and HCV infections, the drugs are effective in only a portion of patients. The drugs are also associated with considerable adverse effects, drug interactions, and high cost. Moreover, there is no approved treatment for HAV infection. Emphasis, therefore, is on prevention of viral hepatitis through immunization.

Efforts to describe, delineate, prevent, and control hepatitis A and B have resulted in enormous challenges to the health care delivery system. A major advancement was achieved when the epidemiologic features of "infectious" hepatitis (hepatitis A) and "serum" hepatitis (hepatitis B) were delineated in the 1940s. This achievement was further advanced with provision of serologic tests in the

1970s to more clearly delineate each virus.

Hepatitis Vaccines

Hepatitis B. The first HBV vaccine was derived from human plasma and licensed in the United States in 1982. It is no longer available in this country. A recombinant HBV vaccine produced in the yeast *Saccharomyces cerevisiae* was licensed in the United States in 1986 (Engerix-B), followed closely by another vaccine in 1989 (Recombivax HB).

Following harvesting and purification of the antigenic component, it is adsorbed onto an aluminum salt. The vaccine contains >95 percent antigenic protein and <5 percent yeast-derived protein. No yeast DNA is detectable in the vaccine. Recombivax HB formulations and pediatric/adolescent and adult formulations of Engerix-B are preservative free.

Hepatitis A. The first HAV vaccine was licensed in the United States in 1995 (Havrix), followed by approval of a second vaccine in 1996 (Vaqta). Both vaccines are inactivated whole-virus vaccines that have demonstrated safety and efficacy in preventing HAV infection.

Antibodies that develop in response to HAV infection confer lifelong immunity. Hepatitis A vaccines are produced from a cell-culture-adapted virus that is grown in human fibroblasts, purified, inactivated with formalin, and adsorbed onto an aluminum salt. Vaqta is preservative free. Havrix contains 2-phenoxyethanol as a preservative.

Combined HAV/HBV. A combined HAV/HBV vaccine (Twinrix) was approved for use in the United States in 2001. The bivalent vaccine is intended for use in persons ≥ 18 years of age to provide protection against both HAV and HBV. It is administered on a 0-, 1-, and 6-month schedule. The hepatitis A

Table 1
Recommendations for Hepatitis A and B Vaccines

Vaccine	Age (Years)	Dose [†]	Volume (mL)	Dosing Schedule (month)*
Hepatitis A				
Havrix ^â	1-18	720 El.U.	0.5	0, 6-12
	>18	1440 El.U.	1.0	0, 6-12
Vaqta ^â	1-18	~25 U	0.5	0, 6-18
	>18	~50 U	1.0	0, 6-18
Hepatitis B				
Engerix-B ^â	<11 [±]	10 µg	0.5	0, 1, 6
	11-19	10 µg	0.5	0, 1, 6
	≥20	20 µg	1.0	0, 1, 6
	dialysis [‡]	40 µg	2.0	0, 1, 2, 6
Recombivax HB ^â	<11 [±]	5 µg	0.5	0, 1, 6
	11-19	5 µg	0.5	0, 1, 6
	≥20	10 µg	1.0	0, 1, 6
	predialysis/ dialysis [§]	40 µg	1.0	0, 1, 6

[†]El.U. = ELISA (enzyme-linked immunosorbent assay) Units; U = Units; µg = microgram

*0 represents timing of the initial dose; subsequent numbers represent months after the initial dose.

^âGlaxoSmithKline, Research Triangle Park, NC

^âMerck & Co., Inc., Whitehouse Station, NJ

[±]Infants whose mothers are hepatitis B surface antigen-positive should also receive hepatitis B immune globulin at birth.

[‡]Two 1.0 mL doses given at one site

[§]Special formulation for patients on dialysis

vaccine component is equivalent to the pediatric dose of Havrix; the hepatitis B vaccine component is equivalent to the adult dose of Engerix-B.

Hepatitis D and C. There is no vaccine to prevent HDV specifically. Hepatitis D infection can be effectively prevented by vaccinating susceptible persons with hepatitis B vaccine. Likewise, there is no vaccine to immunize against HCV. Prevention of infection is best achieved by screening donor blood, excluding blood donors in high-risk situations, and use of highly sensitive serologic screening tests for HCV infection.

Vaccine Immunogenicity and Efficacy

Hepatitis B. Protection conferred with hepatitis B vaccine correlates

with the number of doses received in the recommended schedule. Among infants, antibody response ranges from 16 to 40 percent following the first dose, 80 to 95 percent following the second dose, and 98 to 100 percent following the third dose. Reported ranges in antibody response for teenagers and adults are 20 to 30 percent following the first dose, 75 to 80 percent following the second dose, and 90 to 95 percent after the third dose. Factors that may lower the response include age >40 years, male gender, obesity, immune deficiency, and smoking. In general, efficacy to hepatitis B vaccine is typically 95 percent with a range in efficacy of 80 to 100 percent among individuals who receive all recommended doses. Chronic infection is rare among persons who demonstrate an

immunologic response to the vaccine.

Hepatitis A. Hepatitis A vaccines are highly immunogenic and provide protection against hepatitis A infection in persons who receive all recommended doses. Antibody titers are higher following a single dose of vaccine than those produced by immune globulin, but lower than levels produced following natural infection. Within one month of the first dose, >97 percent of children and adolescents, and >95 percent of adults will have developed protective levels of antibodies. Within one month of the second dose, essentially 100 percent of recipients will have responded to form protective antibody levels. Mathematical models show that antibodies formed in response to a second dose of vaccine administered six to 12

months after the initial dose should persist for 24 to 47 years.

Combined HAV/HBV. Among healthy individuals, immunogenicity for each component of the bivalent vaccine is at least as effective as that for each single-antigen vaccine administered separately. Combination vaccines provide for fewer injections while maintaining immunogenicity and safety comparable to separately administered vaccines. The Advisory Committee on Immunization Practices (the committee that advises the CDC on vaccines), American Academy of Pediatrics, and American Academy of Family Physicians recommend that combination vaccines be used when any single component of the vaccine is indicated and there are no contraindications to the other component(s).

Vaccine Safety

All hepatitis vaccines are safe. The most common adverse reaction is irritation at the injection site, reported in less than 10 percent of injections. Systemic reactions include fatigue, weakness, headache, nausea and vomiting, and fever. Health care professionals who administer hepatitis vaccines are advised to keep epinephrine injection and other appropriate agents readily available to control immediate allergic reactions should an anaphylactic reaction occur.

Vaccine Dosage and Administration

Table 1 summarizes dosage recommendations for hepatitis A and B vaccines. Alternate dosing schedules may benefit specific populations. Product Information Leaflets should be reviewed prior to use.

All hepatitis vaccines are injected intramuscularly into the deltoid muscle (adults) or anterolateral thigh (infants and small children), not into the gluteal region (buttocks) due to suboptimal re-

sponse from this site. Intravenous, intradermal and subcutaneous injection should be avoided. In persons with clotting factor disorders who are at risk for hemorrhage (e.g., hemophiliacs) subcutaneous injection is indicated for hepatitis B vaccines. The benefit versus risk of intramuscular injection of hepatitis A vaccines in these individuals must be carefully considered when contemplating immunization. If the decision is made to administer hepatitis A vaccine intramuscularly, it should be given with steps taken to avoid the risk of hematoma following injection.

Patient Advice

Despite the significant decline in HAV- and HBV-related morbidity that has occurred as a result of widespread use of HAV and HBV vaccines, significant morbidity still occurs that could be prevented with proper use of the vaccines. Individuals at risk and those who plan to travel to areas where the viruses are found are, therefore, urged to speak with their physician about immunization to protect against hepatitis. Persons who engaged in high-risk endeavors in the past, including illicit injectable drug use or promiscuous sexual activity, should be urged to be tested for HCV.

Health care professionals should inform patients, parents or guardians of potential benefits and risks of the vaccine. The vaccine recipient, parent or guardian should be questioned concerning appearance of signs and/or symptoms of an adverse reaction following a previous dose of hepatitis vaccine, advised of the potential for adverse reactions that have been associated with the vaccine, and told to report severe or unusual adverse events to the physician or clinic where the vaccine was administered. The patient, parent or guardian should be given a copy of the current Vaccine Information Statement (VIS) prior to immunization. Vaccine Information Statements can

be downloaded for printing from the CDC website (www.cdc.gov/nip).

Overview and Summary

Approximately one-sixth of the world's population is believed to be infected with hepatitis B or C virus. This demonstrates the clinical importance of having safe and effective vaccines to protect non-infected individuals. Vaccines for hepatitis A and B, but not C, are available and recommended. Their use has had a substantial impact on reducing the incidence of HAV and HBV infections and their related morbidity and mortality.

It is important that immunization with the vaccines start early in life, especially for individuals at high risk for acquiring hepatitis A or B. The time of exposure to these viruses is unpredictable; therefore, early vaccination improves the chance for successful immunization. Moreover, immunity conferred by each of these vaccines may continue for many years, if not a lifetime.