AMERICAN ACADEMY OF PEDIATRICS

Prevention of Hepatitis A Infections: Guidelines for Use of Hepatitis A Vaccine and Immune Globulin

Committee on Infectious Diseases

ABSTRACT. The licensing of two inactivated hepatitis A vaccines for persons 2 years or older necessitates development of recommendations for pediatric use, as well as a review of the current indications for immune globulin (IG) in hepatitis A prophylaxis. Both vaccines are immunogenic and protective in children and adults. A single dose of vaccine induced antibody in 88% to 96% of subjects by 2 weeks and 97% to 100% by 1 month, and protected against subsequent hepatitis A virus (HAV) disease occurring 21 days after receipt of the dose in a community with endemic hepatitis A infection. However, completion of the full vaccine schedule is recommended to assure high antibody titers and likely long-term protection. The major pediatric indications for vaccine are: (1) travelers to areas with intermediate to high rates of endemic hepatitis A, (2) children living in defined and circumscribed communities with high endemic rates or periodic outbreaks of HAV infection, and (3) patients with chronic liver disease. Immune globulin is recommended for postexposure prophylaxis, as vaccine has not yet been demonstrated to be protective for this purpose. Except for travelers, recommendations for IG use are not changed from those in the current edition of the Red Book, and include contacts of cases in the home, child care centers, and other selected sites.

ABBREVIATIONS. HAV, hepatitis A virus; CDC, Centers for Disease Control and Prevention; CCC, child care center; HIV, human immunodeficiency virus; IG, immune globulin; IVIG, intravenous immune globulin; FDA, Food and Drug Administration; SKB, SmithKline Beecham, Inc; EL.U., enzyme-linked immunosorbent assay units; IgG, immunoglobulin G; IgM, immunoglobulin M.

Epidemiology of Hepatitis A Infections

Hepatitis A virus (HAV) is a 27-nm RNA picornavirus (enterovirus) with only one serotype. Humans are by far the most important reservoir, but rarely, nonhuman primates may serve this role. Spread is usually by the fecal-oral route through personal contact, but common-source outbreaks from fecally contaminated food or water have been reported. Fecal-oral transmission also may occur between sexual partners, and seroprevalence surveys indicate higher rates among homosexual men than among heterosexual men. Nosocomial infections have been reported, particularly in newborn intensive care units. Blood transmission during the viremic phase rarely occurs.

After exposure to HAV, the incubation period is 15 to 50 days, with a mean of 28 days. Maximal infectivity occurs during the latter half of the incubation period and continues for a few days after the onset of jaundice. Most clinical cases are noninfectious after the first week of jaundice.

The major source of infection for clinical cases reported to the Centers for Disease Control and Prevention (CDC) from 1990 to 1992 is personal contact, but the source is unknown for close to half of the cases (Table 1). Personal contact is considered to have occurred for anyone who has frequently slept or eaten in the same dwelling with the index case, is a sexual contact, or shares food or drink with the HAV-infected person.

Most HAV infections in the United States occur during prolonged community-wide outbreaks characterized by extended, person-to-person transmission, especially from children to adults. Most HAV infections in young children are asymptomatic. In outbreaks in child care centers (CCCs), spread frequently has occurred by the time the first clinical (index) case is recognized. The index case is usually a child-care provider, a parent, or other adult household contact. The incidence of HAV disease for unprotected international travelers, including those staying in luxury hotels, is estimated to be 3 per 1000 travelers per month of stay in a developing country. Travelers eating and drinking in inadequate hygienic conditions have an HAV infection rate of 20 per 1000 per month. Although the source of infection in users of injection drugs is unknown, it is likely related to fecal-oral spread because of inadequate hygienic conditions or to contaminated blood from shared needles and syringes. In cases in which the source is unknown, HAV is likely to be spread by individuals with asymptomatic infections, particularly young children.

Prevalence of HAV antibody in the United States is approximately 25% to 35% in individuals 20 to 35 years, 35% to 70% in those 35 to 50 years, and greater than 80% in those older than 50 years. Prevalence is generally higher among Native Americans and Mexican-Americans.

Certain populations in the United States have high endemic rates of HAV infection, particularly Native Americans, Alaskan natives, and Latinos and Ha-
sidic Jews in selected communities. Within these communities, epidemics occur every 3 to 10 years as the population of susceptible hosts increases.

CLINICAL DISEASE

Since 1989, the highest rates of symptomatic HAV infections have occurred in children aged 5 to 14 years and the lowest rates in persons younger than 5 or older than 40 years (Fig 1). Clinical hepatitis occurs in fewer than 10% of infected children younger than 6 years, 40% to 50% of those from 6 to 14 years, and 70% to 80% of those older than 14 years.13

The usual duration of illness is 2 to 4 weeks, but a prolonged course or relapse occurs in 10% to 20%.13,14 Morbidity in adults can be appreciable. In a study in Washington State, HAV infection resulted in hospitalization in 11% of adult cases with a mean of 27 days work lost per case (C. Shapiro, CDC, written communication, July 1995). Mortality is rare, especially in children. The case-fatality rate has been estimated as 3 per 1000 clinical cases in the United States and .15 per 1000 cases during a large outbreak associated with contaminated shellfish in Shanghai in 1988.15 Fulminant hepatitis with mortality occurs mostly in people with underlying conditions, such as chronic liver disease, and in older age groups. Seventy percent of deaths occur in persons older than 50 years.13

ECONOMIC IMPACT

During recent years in the United States, 23,000 to 36,000 clinical cases of HAV infection have been reported annually to the CDC. Because of the frequent occurrence of subclinical infections, the actual number of HAV infections occurring each year probably is far higher than the number reported. Direct and indirect costs have been estimated to approximate $1000 per clinical case for persons 18 years or younger, and $2100 per case for persons older than 18 years, resulting in a projected cost in the United States of over $200 million annually (C. Shapiro, CDC, written communication, July 1995).

PREVENTION

General Measures

The major method for prevention of HAV infections is improved sanitation and personal hygiene (e.g., handwashing after diaper changes, especially in CCCs). Travelers to endemic areas should avoid consumption of foods likely to be contaminated, including uncooked shellfish and vegetables, fruit they do not clean and peel themselves, ice, and tap water.

Immune Globulin (IG)

IG for intramuscular injection produced in the United States for short-term hepatitis A prophylaxis is sterile and has not been a documented source of transmission of hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or any other infectious agent. To ensure inclusion of a broad spectrum of antibodies, IG is derived from the pooled plasma of at least 1000 donors per lot of final product. The HAV antibody content varies in proportion to the infectious experience of the population from which it was prepared. Blood donor screening programs do not test routinely for HAV antibody, but examination of sera obtained from blood donors indicates lower HAV antibody titers in more recent than in earlier lots of IG. However, protective efficacy against HAV disease still occurs.10 The presence of


<table>
<thead>
<tr>
<th>Source</th>
<th>Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal contact</td>
<td>24</td>
</tr>
<tr>
<td>Child care center</td>
<td>15</td>
</tr>
<tr>
<td>International travel</td>
<td>6</td>
</tr>
<tr>
<td>Food or water outbreak</td>
<td>4</td>
</tr>
<tr>
<td>Male homosexual contact</td>
<td>4</td>
</tr>
<tr>
<td>Use of injection drugs</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>44</td>
</tr>
</tbody>
</table>

TABLE 2. Recommendations for Pre-exposure Prophylaxis for Hepatitis A Infection for Travelers*

<table>
<thead>
<tr>
<th>Age of Patient</th>
<th>Likely Exposure</th>
<th>Recommended Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 y</td>
<td>&lt;3 mo</td>
<td>IG 0.02 mL/kg†</td>
</tr>
<tr>
<td>3-5 mo</td>
<td>Long-term</td>
<td>IG 0.06 mL/kg†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IG 0.06 mL/kg at departure and every 5 mo thereafter</td>
</tr>
<tr>
<td>&gt;2 y</td>
<td>&lt;3 mo</td>
<td>HAV vaccine‡</td>
</tr>
<tr>
<td>3-5 mo</td>
<td></td>
<td>or IG 0.02 mL/kg†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or HAV vaccine‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or IG 0.06 mL/kg†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-term HAV vaccine‡</td>
</tr>
</tbody>
</table>

*IG, immune globulin; HAV, hepatitis A virus. For travelers 2 years and older, vaccine is preferable, but IG is an acceptable alternative. IG is protective right after receipt of the dose. The time required for protection after the first dose of vaccine is not known currently, but this may occur within a few days. (See “Foreign Travel,” p 1211.) However, an interval of 2 weeks before travel is recommended in the package insert from both vaccine manufacturers and an interval of 1 month by the ACIP. To insure immediate protection, another option is to administer IG with the first dose of vaccine. (See “Effect of IG on Vaccine Immunogenicity,” p 1210.) To ensure long-term protection, administration of the booster vaccine dose is important.

† IG should be administered deep into a large muscle mass. Ordinarily no more than 5 mL should be administered in one site in an adult or large child; lesser amounts (maximum, 3 mL) should be given to small children and infants.

‡ Dose and schedule of HAV vaccine as recommended according to age in Table 4.

Fig 1. Reported cases of hepatitis A virus infection according to age in the United States, 1983 through 1993.
TABLE 3. Recommendations for Postexposure Prophylaxis for Hepatitis A Infection

<table>
<thead>
<tr>
<th>Time Since Exposure</th>
<th>Future Exposure Likely</th>
<th>Age of Patient</th>
<th>Recommended Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 wk</td>
<td>No</td>
<td>All ages</td>
<td>IG (0.02 mL/kg)*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>z=2 y</td>
<td>IG (0.02 mL/kg)* and HAV vaccine†</td>
</tr>
<tr>
<td>&gt;2 wk</td>
<td>No</td>
<td>All ages</td>
<td>No prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>z=2 y</td>
<td>HAV vaccine†</td>
</tr>
</tbody>
</table>

* Immune globulin (IG) should be administered deep into a large muscle mass. Ordinarily no more than 5 mL should be administered in one site in an adult or large child; lesser amounts (1 to 3 mL) should be given to small children and infants.
† Dose and schedule of hepatitis A virus (HAV) vaccine as recommended according to age in Table 4. HAV vaccine alone has not yet been shown to be effective postexposure prophylaxis in community settings. See “HAV Vaccine for Postexposure Prophylaxis,” p 1211. Seroconversion may have occurred from exposure. HAV vaccine may be withheld until antibody levels are measured at 4 weeks or more after exposure. However, HAV vaccine may be administered regardless of immune status.

antibody to HAV is not a contraindication to blood donation.

Tables 2 and 3 show the recommended pre-exposure and postexposure IG doses and duration of protection.16,17 Peak serum concentrations usually are achieved 48 to 72 hours after intramuscular injection. When given within 2 weeks after exposure, IG is 80% to 90% effective in preventing clinical HAV disease.16 The most common problem encountered with the use of IG is discomfort and pain at the site of administration. Immune globulin seems to cause less pain when administered at room temperature. Less common reactions include flushing, headache, chills, and nausea. Serious reactions are unusual and include chest pain or constriction, dyspnea, or rarely, anaphylaxis and systemic collapse.

The potential protective efficacy of intravenous immune globulin (IVIG) for prophylaxis against HAV infection is unknown, and IVIG is not approved by the Food and Drug Administration (FDA) for this indication. Although IVIG is likely to be protective, data concerning the appropriate dose and duration of protection are not available. Extrapolation from data about the protective efficacy of IG and from anti-HAV titers in IG and IVIG suggests that an IVIG dose of 400 mg/kg would be protective for at least 6 months. HAV antibody titers, however, may be variable in lots of IVIG because of different manufacturing processes and the characteristics and exposure of donors from which the lots were derived.

Vaccine

Manufacture and Handling

Inactivated HAV vaccines have been developed by SmithKline Beecham (SKB) and Merck & Co.16-27 The FDA licensed the SKB vaccine Havrix in February 1995, and the Merck vaccine Vaqta in April 1996. Both vaccines contain viral antigens purified from HAV-infected human diploid fibroblast cell cultures. Havrix is purified and concentrated by ultrafiltration and exclusion gel chromatography, formalin-inactivated, and adsorbed to an aluminum hydroxide adjuvant with 2-phenoxyethanol as the preservative.28 Final antigen content is determined by reactivity in a quantitative immunoassay for HAV antigen. Vaccine potency per dose is expressed as enzyme-linked immunosorbent assay units (EL.U.) for Havrix and as units (U, with each U equivalent to a nanogram of virus protein) for Vaqta.28 HAV vaccine should be stored and shipped between 2 and 8°C and not frozen.

Administration, Dosage, and Schedule

Both vaccines are approved for children 2 through 18 years and for adults. Havrix for children comes as two formulations, each in .5-mL volumes – 360 EL.U. for a three-dose series (licensed February 1995) and 720 EL.U. for a two-dose series (licensed April 1996). Vaqta for children contains 25 U in .5 mL for a two-dose series. The vaccines should be given by intramuscular injection in the anterolateral aspect of the thigh or the deltoid muscle according to the schedules indicated in Table 4.20,21 The adult formulations of the licensed vaccines contain 1440 EL.U. (Havrix) and 50 U (Vaqta). Both are recommended as a two-dose series (Table 4).22

HAV Antibody Assays

Serologic tests for total HAV (both immunoglobulin G [IgG] and immunoglobulin M [IgM]) and IgM-specific HAV antibodies to the capsid proteins are available commercially. The presence of IgM HAV antibodies usually indicates recent infection. IgM antibodies are present at the onset of illness and usually disappear within 3 months, but may persist for 6 months or longer.17 IgG HAV antibodies develop shortly after IgM HAV antibodies, persist for the lifetime of the individual, and are associated with enduring protection against disease. Children who have received the HAV vaccine, however, rarely have detectable anti-HAV IgM antibody titers.21,27

The commercially available antibody assays are

TABLE 4. Recommended Doses and Schedules for Hepatitis A Virus (HAV) Inactivated Vaccines*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Vaccine and Manufacturer</th>
<th>Dose</th>
<th>Volume per Dose</th>
<th>Number of Doses</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 through 18</td>
<td>Havrix SKB</td>
<td>360 EL.U.†</td>
<td>0.5mL</td>
<td>3</td>
<td>Initial, 1, and 6–12 mo later</td>
</tr>
<tr>
<td></td>
<td>Havrix SKB</td>
<td>720 EL.U.†</td>
<td>0.5mL</td>
<td>2</td>
<td>Initial, 6–12 mo later</td>
</tr>
<tr>
<td>19 and older</td>
<td>Vaqta Merck</td>
<td>25 U</td>
<td>0.5mL</td>
<td>2</td>
<td>Initial, 6–18 mo later</td>
</tr>
<tr>
<td></td>
<td>Havrix SKB</td>
<td>1440 EL.U.</td>
<td>1.0mL</td>
<td>2</td>
<td>Initial, 6–12 mo later</td>
</tr>
<tr>
<td></td>
<td>Vaqta Merck</td>
<td>50 U</td>
<td>1.0mL</td>
<td>2</td>
<td>Initial, 6–12 mo later</td>
</tr>
</tbody>
</table>

* SKB indicates SmithKline Beecham; EL.U., ELISA units; U, units.
† Children receiving 360 EL.U. or an unknown dose for the first injection should complete the series with two or more doses of vaccine (either a 360 EL.U. or a 720 EL.U. dose).
not always sensitive enough to measure low titers of antibody after administration of IG or vaccine.\textsuperscript{17} Antibody titers in clinical trials are expressed as milli-
international units per milliliter (mIU/mL) by comparison with the World Health Organization reference antibody.\textsuperscript{21,27} Although the minimal titer and functional class of antibody necessary to prevent infection and disease have not been established de-
finitively, a concentration of at least 20 mIU/mL seems protective.\textsuperscript{16,17}

Immunogenicity

Havrix generally has produced adequate IgG anti-
body titers in both adults and children over 2 years
using several two- and three-dose schedules.\textsuperscript{18-22} A single initial Havrix dose of 1440 EL.U. in adults
induced seroconversion (≥20 mIU/mL) by 15 days in
88% and by 1 month in 99%.

Three Havrix doses of 360 EL.U. given to children
aged 2 to 18 years at time 0, 1, and 6 months or 0, 1
and 12 months produced a 95% seroconversion rate 1
month after the first dose and 100% seroconversion
after the second or third doses.\textsuperscript{19,29} In both adults and
children, the second or third (booster) dose caused a
substantial increase in antibody titers, indicating an
anamnestic response (immunologic memory). Al-
though there is a rapid antibody response to the first
doze(s), antibody titers decline. Receipt of the booster
is necessary to induce high antibody titers and may
be needed for long-term protection.

Recently completed studies in children given 720
EL.U. as a two-dose schedule at 0 and 6 months
demonstrated 92% to 96% seroconversion 2 weeks
after the first dose and 97% to 100% one month after
the first dose, and 100% one month after the 6-month
booster dose.

Limited data exist about the use of HAV vaccine in
infants. In 53 infants without passively acquired ma-
ternal HAV antibody, administration of 360 EL.U. at
2, 4, and 6 months of age resulted in 98% serocon-
version at 8 months.\textsuperscript{30} All 25 infants with passively
acquired maternal anti-HAV antibody receiving HAV vaccine on the same schedule had detectable
antibody at 8 months, but the geometric mean titer
was one third that for infants without passive HAV
antibody.

Vaqta, when given as recommended, appears to be
as immunogenic and protective as Havrix in both
children and adults.\textsuperscript{23-27} Studies to determine
whether vaccines from different manufacturers
might be interchangeable are planned. Until this in-
formation is available, it is preferable to use vaccine
from the same manufacturer in the same patient.
However, because the two vaccines are similar, if a
patient presents for the booster dose and the manu-
facturer for the first dose(s) is not known, or both
vaccines are not available, completion of the booster
dose with vaccine from either manufacturer would
be preferable to initiating the entire schedule again.

Efficacy

The efficacy of Havrix was studied in a large,
double-blind, placebo controlled, randomized cli-
nical trial in Thailand involving 40 000 children 1 to 16
years old living in a region where HAV infection is
endemic.\textsuperscript{21} Three doses of 360 EL.U. were given at 0,
1, and 12 months. Eighty-four percent of the 38 cases
of HAV disease in the control group and both of the
two cases in the vaccine group occurred before the
12-month booster dose. Cases continued to occur
after the 12-month booster dose in the control group,
but not in the vaccine group. Calculated protective
efficacy was 94% after two doses, 100% after three
doses, and a cumulative 95% for two or three doses.

Clinical studies suggested a possible herd-immu-
nity effect if more than 80% of the estimated suscept-
able individuals were vaccinated.\textsuperscript{31} A single dose of
Havrix in Alaskan native villages with endemic
HAV disease resulted in a dramatic decrease in cases
within 8 weeks of vaccination.\textsuperscript{31} A similar abrupt
decrease in HAV cases was observed after two doses
of vaccine in two Slovak Republic villages experienc-
ing a large community outbreak.\textsuperscript{32} In the Vaqta trial
in New York State, no cases of clinical and confirmed
hepatitis A occurred in vaccine groups more than 21
days after the first dose, and the calculated protective
efficacy was 100%.\textsuperscript{27}

Duration of Protection

Because HAV vaccines have been undergoing
evaluation for only a short time, long-term efficacy or
the need for booster doses cannot be determined
currently. Detectable antibody, however, persists for
at least 4 years after a three-dose series in adults.\textsuperscript{33}
After the first year, antibody concentrations decline
approximately 14% per year, but kinetic models sug-
gest that protective levels will persist for up to 20
years. In the Vaqta trial in New York State, protec-
tion against HAV disease has persisted thus far for 4
years.\textsuperscript{32} (from Merck; data on file with the FDA.)

Vaccine in Immunocompromised Patients

The vaccine may be given to immunocompro-
mised individuals, but the immune response may be
suboptimal. A Havrix three-dose series of 720 EL.U.
resulted in protective levels of antibody in 77% of
HIV-positive homosexual men compared with 100%
of HIV-negative men.\textsuperscript{39} Data about HAV vaccine im-
munogenicity in immunocompromised children are
not available.

Effect of IG on Vaccine Immunogenicity

Simultaneous administration in adults of IG with
the first vaccine dose in a three-dose regimen did not
reduce the proportion of individuals with protective
concentrations of antibody compared with those re-
ceiving vaccine alone, although the final geometric
mean titer was slightly lower (2458 vs 3614 mIU/
ML).\textsuperscript{34} Five days after the initial injections, antibody
was detectable in serum of 92% of subjects receiving
IG alone or vaccine plus IG, but only 4% of those
receiving vaccine alone.\textsuperscript{34} These data suggest that
assurance of protective concentrations of antibody
within days after the first dose of vaccine may re-
quire concomitant administration of IG.
Adverse reactions have been mild and of similar frequency for recipients of Havrix, hepatitis B virus vaccine, and placebo. In children, reactions from Havrix most commonly consist of soreness at the injection site (18%), headache (12%), and fever (6%). Approximately 21,000 children have been immunized with Havrix during efficacy studies with no serious adverse effects reported thus far (from SKB; data on file with the FDA). More than 15,000 doses of Havrix have been administered in a travel clinic in Switzerland with no severe adverse event. Adverse reactions with Vaqta are also similar to placebo.

Precautions and Contraindications

The vaccine should not be administered to persons with a hypersensitivity to any of the vaccine components, such as alum and phenoxethanol. No data exist about administration to pregnant women, but the risk probably would be low to nonexistent because the vaccine is inactivated, purified virus protein.

Administration With Other Vaccines

HAV vaccine may be administered simultaneously with other vaccines and toxoids, but should be given from a separate syringe and at a separate injection site. HAV vaccine also may be administered simultaneously with another vaccine in the same muscle, if the two injections are given at least 1 inch apart. Simultaneous administration of Havrix and hepatitis B vaccines to military recruits did not increase reactogenicity or reduce immunogenicity of either vaccine. In more than 2000 adult travelers immunized simultaneously with Havrix and other vaccines (hepatitis B, live oral polio, tetanus with or without diphtheria, typhoid, yellow fever, cholera, or rabies) no interactive influence was observed. No information currently exists about the simultaneous administration of HAV and varicella vaccines. Studies are in progress evaluating simultaneous administration of Havrix, diphtheria and tetanus toxoids and pertussis, and Haemophilus influenzae type b vaccines to children.

Preimmunization Serologic Testing

Preimmunization testing for HAV antibody generally is not recommended for children. Testing may be cost-effective in individuals who have a high likelihood of immunity from earlier infection, such as those whose early childhood was spent in areas where HAV disease is endemic, those with a history of jaundice that may have been caused by HAV, and those older than 40 years.

Postimmunization Serologic Testing

Postimmunization testing for HAV antibody titer is not indicated in immunocompetent individuals because of the high seroconversion rates in both adults and children. Commercially available anti-HAV tests may not detect low but protective concentrations of antibody induced by vaccine. For immunocompromised persons, especially those with liver disease who are at risk of exposure to HAV, postimmunization testing is justified. If no HAV antibody is detected with a sensitive assay method, a repeat immunization series should be considered, preferably during periods of least immunosuppression.

HAV Vaccine for Postexposure Prophylaxis

Available data are insufficient to recommend HAV vaccine for postexposure prophylaxis. However, several studies suggest that HAV vaccine, with or without concurrent IG administration, may provide effective postexposure prophylaxis by engendering protective antibody levels before the usual 4-week incubation period for HAV infection. In trials using small numbers of chimpanzees, a single dose of Havrix, given 1 to 3 days after orogastric challenge with wild virus, protected against hepatitis and shedding of the virus in stool. In adults, one dose of the Havrix induced protective concentrations of antibody within 2 weeks in 88% of subjects and within 4 weeks in 99%. Concurrent administration in adults of IG with the initial dose of HAV vaccine has not resulted in diminished frequency of protective antibody 1 month after completion of a three-dose series. In a community with high rates of endemic HAV infection, one dose of Vaqta was 100% effective in preventing cases of HAV infection beginning 21 days after the dose.

RECOMMENDATIONS FOR IMMUNOPROPHYLAXIS

Pre-exposure Prophylaxis Against HAV (Table 2)

Foreign Travel

For susceptible persons traveling to or working in countries with intermediate or high endemic rates of HAV infection (Fig 2), immunoprophylaxis before departure is indicated. Such countries include those other than Australia, Canada, Japan, New Zealand, Western Europe, and Scandinavia. For persons 2 years and older, vaccine is preferable, but IG is an acceptable alternative. Factors to consider in choosing active and/or passive prophylaxis include the interval before departure, the relative costs and availability of IG and HAV vaccine, the duration of stay, and the likelihood of repeated exposure (see Table 2).

Existing data indicate that IG is protective against hepatitis A disease right after receiving the dose. The time required from administration of one dose of vaccine alone to onset of protection is not known. The usual incubation period for hepatitis A disease is 25 to 30 days. Since 88% to 96% of children and adults developed detectable anti-HAV antibody within two weeks of a single dose (from SKB; data on file with the FDA) and since 100% protective efficacy was observed within 21 days after receipt of a single dose of Vaqta in a community with ongoing endemic HAV disease, it is likely that protection occurs within a few days after the first dose of vaccine alone. However, the package insert for both vaccines suggests a 2-week interval and the CDC Advisory Committee on Immunization Practices rec-
ommends a 1-month interval. To insure protection in travelers whose departure is imminent, another option is to administer the usual protective dose of IG (Table 1) along with the first dose of vaccine (See “Effect of IG on Vaccine Immunogenicity,” p 1210). However, the addition of IG to the first dose of vaccine has not been evaluated in field trials, and the benefit may be marginal.

Whether vaccine alone or vaccine plus IG is given for the first dose, it is important to administer the second or third (booster) dose in order to produce high antibody titers and to ensure long-term protection. Children less than 2 years should receive only IG since vaccine is not yet approved for this age group.

Other Indications for HAV Vaccine

The following are specific groups for whom HAV vaccine is recommended. In addition, any healthy individual 2 years or older may receive HAV vaccine at the discretion of the physician and patient or parent.

1. Children 2 years and older in defined and circumscribed communities with high endemic rates and/or periodic outbreaks of HAV infection (eg, Native Americans, Alaskan Natives). HAV immunization is recommended for such children, as vaccine use has markedly diminished the occurrence of HAV cases. Younger children are most apt to be susceptible and should be given priority for immunization. In communities where HAV disease is endemic, children older than 10 to 15 years may have been infected already. Plans for implementation of age-specific immunization programs in such communities should be based on available seroprevalence and epidemiologic data and are best made in consultation with the local health authorities. For control of more widespread community outbreaks, too few data currently exist to recommend routine use of HAV vaccine. In some common-source outbreaks the source of infection has been removed before recognition of the outbreak; thus the subsequent risk to the community is low.

Widespread prophylactic use of IG during extended community outbreaks for other than close contacts of hepatitis A cases has not proved to be efficacious, because protection is of limited duration and spread of the virus may continue through several generations of incubation periods. Although in some community situations IG prophylaxis has been used for control, it cannot be recommended routinely.

2. Patients with chronic liver disease. Although limited data exist about the use of HAV vaccine in persons with chronic liver disease, no reason exists to suspect that the inactivated HAV vaccine would aggravate the chronic condition. Furthermore, such patients have an increased risk for severe hepatitis with HAV infection, and this may be prevented by immunization.

3. Homosexual and bisexual men.

4. Users of injection drugs and illicit drugs.

5. Those at occupational risk of exposure (eg, handlers of nonhuman primates and persons working with HAV in a laboratory setting).

Other Situations for Potential Use of HAV Vaccine

1. Child care center (CCC) staff and attendees. Approximately 14% of HAV cases are associated with CCCs. Recent serosurveys found only a small or no excess of HAV seroprevalence among CCC staff compared with community control populations. Given the cost of HAV vaccine, routine
immunization of all CCC staff is not justified. Administration of HAV vaccine, however, should be considered in CCC settings with ongoing or recurrent outbreaks and in communities where CCC cases contribute substantially to overall HAV disease.

The issue of HAV vaccine for CCC attendees is more problematic. In 1990, the National Child Care Survey estimated that 9.5 million children in the United States attended day care in CCC or family child care settings, and 27% were younger than 3 years. Transmission of HAV in CCCs usually occurs from asymptomatic infection in diapered children. Since HAV vaccine is not approved for children under 2 years, immunization of all these children is not possible or warranted currently.

2. Custodial care institutions. Epidemic HAV disease was reported in custodial care institutions in the 1970s and 1980s, but has not been a problem in recent years. However, HAV vaccine may be considered for staff and residents in institutions where HAV infection currently occurs or where HAV seroprevalence data indicate vaccination would be cost-effective.

3. Hospital personnel. Because hospital personnel generally do not have increased prevalence rates of HAV antibody compared with community control populations, routine pre-exposure use of HAV vaccine in hospital personnel is not recommended. Usually nosocomial HAV disease in hospital personnel has occurred through spread from acutely infected patients in whom the diagnosis of HAV infection was not recognized. If HAV vaccine is demonstrated to be effective in postexposure prophylaxis, immunization in such outbreaks would be indicated. In specific patient care areas with continued occurrence of clinical cases or where high rates of HAV antibody have been found, immunization may be effective clinically and economically.

4. Food handlers. Outbreaks from contaminated food or water account for approximately 4% of the clinical cases of HAV infection reported to the CDC. Food-borne outbreaks usually are associated with contamination of uncooked food during preparation by a food handler who is infected with HAV. The most effective way to prevent these outbreaks is by using careful hygienic practices during food preparation. Little information is available concerning prevalence rates of HAV antibody in food handlers compared with the general population. Therefore, routine HAV vaccination in this population is not indicated at this time. However, economic, medicolegal, and public relations implications of a food-borne HAV outbreak from a commercial establishment may indicate that HAV vaccine use should be considered in individual situations. Factors to consider in this decision include the nature of the food (eg, materials for salads), as well as the demographic characteristics, the average duration of employment, and the numbers of food handlers.

5. Patients with hemophilia. Outbreaks of hepatitis A infection in patients with hemophilia receiving solvent detergent-treated factor concentrates have been reported primarily in Europe. However, in the United States, three cases of hepatitis A were reported recently in patients with hemophilia who received factor VIII concentrate from one lot from one manufacturer. The United States seroprevalence data currently available about patients with hemophilia do not allow accurate determination of risk. Nevertheless, patients with hemophilia, especially those receiving solvent detergent-treated factor concentrates, may benefit from protection against HAV infection and should be considered for immunization with HAV vaccine. Preimmunization testing for anti-HAV antibody may be cost-effective, because limited data suggest higher seroprevalence rates among persons with hemophilia. Studies are planned to determine whether subcutaneous administration of the vaccine in hemophilic patients would be as immunogenic and safe as the intramuscular route recommended for other individuals.

Postexposure Prophylaxis Against HAV (Table 3)

IG

1. Household and sexual contacts. All household and sexual contacts of HAV cases should receive .02 mL/kg (minimal total dose, 25 mL; maximal total dose, 2 mL) of IG as soon as possible after exposure. Serologic testing of contacts is not recommended because it adds unnecessary cost and may delay the administration of IG. The use of IG more than 2 weeks after the last exposure is not indicated.

2. Newborn infants of infected mothers. Perinatal transmission of HAV is rare, but has been reported. Some experts have advised giving the infant IG (.02 mL/kg) if the mother’s symptoms begin in the period from 2 weeks before to 1 week after delivery. Efficacy, however, in this circumstance has not been established. Severe disease in healthy infants seems to be rare.

3. CCC employees, children, and their household contacts. Testing for HAV IgM antibody should be performed to confirm HAV infection in suspected cases. When an HAV case is identified in an employee or enrolled child in a CCC in which all children are older than 2 years and all are toilet trained, IG (.02 mL/kg) is recommended for employees in contact with the index case and for children in the same room as the index case. When an HAV infection is identified in either an employee or a child, or in the household contacts of two of the enrolled children in CCCs where children are not yet toilet trained, IG (0.02 mL/kg) is recommended for all employees and all enrolled children in the facility. During the 6 weeks after the last case is identified, new employees and children should also receive IG.

Studies are needed to determine the effectiveness of vaccine alone as a means to control such outbreaks. Vaccine alone could be considered as

...
an alternative option for prophylaxis of new employees if the risk of exposure is not high during their initial 2 weeks of employment, because a single dose induces seroconversion within 15 days in 88% of adults.33

Administration of IG to household contacts of a CCC case should be individualized and dependent on such factors as whether the child is toilet trained and the intimacy of contact (eg, primary care giver). Precise data concerning the onset of protection after a dose of IG are not available. However, allowing IG recipients to return to the CCC setting immediately after receipt of the IG dose seems reasonable.

If recognition of a CCC outbreak of HAV disease is delayed by 3 or more weeks from the onset of the index case or if illness has occurred in three or more families, the infection is likely to have spread widely. Although IG could be considered for use in these situations, it may not effectively prevent additional cases.50

Children and adults with acute HAV disease should be excluded from the CCC until 1 week after the onset of illness or beginning of the prophylaxis program, or as directed by the responsible health department.

4. Schools. Schoolroom exposure generally does not pose an appreciable risk of infection and IG administration is not indicated. However, IG could be used if transmission within the school setting is documented. Alternatively, vaccine should be considered as a means of prophylaxis, especially when a longer duration of protection is advisable. Children and adults with acute HAV infection should be excluded from school or work for 1 week after the onset of the illness.

5. Institutions and hospitals. In institutions for custodial care with an outbreak of HAV infection, residents and staff in close personal contact with infected custodial patients should receive IG (0.2 mL/kg). Administration of IG to hospital personnel caring for patients is not indicated routinely, unless an outbreak occurs.

6. Food or waterborne outbreaks. Such outbreaks usually are recognized too late for IG to be effective. Immune globulin may be effective if administered to exposed individuals within 2 weeks of the last exposure to the HAV-contaminated water or food.

**FUTURE DEVELOPMENTS**

Because the aforementioned recommendations for use of HAV vaccine are aimed at selected target populations, only a small portion of hepatitis A cases currently occurring in the United States will be prevented. Therefore, additional plans for control of cases of HAV infection are being considered.

**Infant Immunization**

Although most HAV infections occur in children, they are usually subclinical. Most HAV disease in the United States occurs in adults who have acquired infection in the community, often from children. Preven-

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