Hepatitis A

Medical Summary

Note: This article also contains information on the combination hepatitis A/B vaccine.

What's New

See Table CH-1 for the 2015 recommended childhood and catch-up immunization schedules and Table ADT-1 for the 2015 adult immunization schedule. There are no significant changes in hepatitis A recommendations from the 2014 schedules.

General Information

Introduction

Hepatitis A virus (HAV) replicates in liver cells, and the resulting immune response causes liver inflammation and hepatic dysfunction. Infection with any of the genotypes (4 of 7 affect humans) results in lifelong immunity against all strains of HAV. The incubation period is usually 15-50 days (average 28). While clinical disease usually lasts less than 2 months, about 10-15% of symptomatic patients are ill for up to 6 months. With HAV infections, relapsing hepatitis occurs; fulminant hepatitis is rare, and chronic hepatitis does not occur. A fatal course is rare in previously healthy individuals.

Mode of Transmission

Only humans harbor the virus. Transmission occurs through direct person-to-person contact via the fecal-oral route; contaminated water, ice or shellfish; or contaminated raw, inadequately cooked or frozen fruits, vegetables, or other foods. The virus is most often spread through contaminated food.

Transmission during oral-anal sexual acts also occurs. Blood-borne transmission, while uncommon, is possible via contaminated blood products.

Persons can shed the virus in stool beginning several weeks before onset of symptoms and for at least 1 week afterwards; viral concentration in stool is highest in the prodromal stage.

The virus survives well in the environment outside the human host; it can persist on hands for several hours and in room-temperature food for considerably longer. It is relatively resistant to heat and freezing.

Epidemiology

HAV infection is highly endemic in developing countries with inadequate sanitation, limited access to clean water, and poor hygienic conditions; rates are intermediate in developing countries with transitional economies and in some regions of industrialized countries where sanitary conditions are variable. While endemicity rates are low in developed countries with good sanitary and hygienic conditions, foci of high transmission in certain risk populations occur. In countries with very low HAV rates, disease may occur among travelers ingesting undercooked shellfish.

Risk

Current risk in travelers is estimated to be high (1-20/100,000 travelers per month of travel to developing countries); risk increases with duration of travel. For travelers to countries with intermediate or high levels of transmission, risk is highest for long-stay travelers; persons who live in or visit rural areas, eat or drink frequently in high-risk situations, or have close physical contact with local persons (especially young children) in settings with poor sanitary conditions; and those who travel outside pre-arranged, fixed itineraries (including common tourist packages).

However, cases can also occur with "standard" tourist itineraries, accommodations, and food- and beverage-consumption behaviors.

Risk of significant clinical illness or jaundice is practically nonexistent for infants < 12 months of age even if acutely infected. Those staying or residing in settings with good hygiene (i.e., babies who are breastfed or bottle fed using safe water for formula reconstitution; babies eating commercial baby food with no exposure to locally prepared foods that adults would eat) have low risk of actual infection. Asymptomatic or minimally symptomatic infants with acute infection may infect unvaccinated caregivers or close contacts upon return home.

Clinical Presentation

Infection can be asymptomatic or range in severity from a mild illness lasting 1-2 weeks to a severely disabling disease lasting several months. In young children, HAV usually causes either asymptomatic infection or very mild illness without jaundice; adults are more likely to have symptomatic infection.

Following an asymptomatic incubation period of 15-50 days, anorexia, nausea, abdominal pain, malaise, and fever may occur, followed within days by jaundice. Dark urine usually occurs before onset of jaundice and hepatic tenderness may also occur at this time. Severe hepatic and extrahepatic complications, including fulminant hepatitis and liver failure, are rare but more common in older adults and people with underlying liver disease.

Among older children and adults, the illness usually lasts < 2 months, although approximately 10-15% of infected people have prolonged or relapsing symptoms lasting up to a year. Chronic hepatitis and carrier states do not occur.

The overall case-fatality ratio is 0.1-0.3%, but can reach 1.8% among adults aged > 50 years.

IgG antibodies to HAV, which appear early in the course of infection, provide lifelong protection against the disease.

Prevention

Non-vaccine: Travelers should observe food and beverage precautions, regardless of immunization status. Good hygiene is vital, especially handwashing or use of hand sanitizer after using the bathroom, changing diapers, and before preparing or eating food.

Vaccine: Hepatitis A vaccines are highly immunogenic; a single dose of single antigen hepatitis A vaccine given any time before travel will provide complete protection for healthy persons; following 2 doses, protective antibodies are estimated to persist for at least 40 years in > 90% of adult vaccinees. (See *Literature Watch Review:* "Long-Term Protection against Hepatitis A: Serological and Cellular Studies.")

Since 2008, hepatitis A vaccine has been given routinely to children in the U.S. at 1 year of age; older children may or may not have had catch-up doses.

The protective efficacy of vaccine given within 1 week after exposure was shown to be 79% in 1 study.

A combined hepatitis A/hepatitis B vaccine is also available, and immunogenicity is equivalent to that of the monovalent hepatitis A and hepatitis B vaccines after completion of the recommended schedule.

Need for Medical Assistance

Persons with symptoms of hepatitis A infection or who have been exposed to HAV should seek medical attention.

Indications for Vaccination

Note: Shoreland's vaccine recommendations, which focus primarily on the risk to the individual traveler, reflect a synthesis and reconciliation of available advice from CDC, ACIP, AAP, and WHO, as well as ongoing global surveillance and the published literature. These recommendations may differ from those of individual countries' public health authorities.

Preexposure

Routine

Hepatitis A vaccine is routinely recommended for:

- All children in the U.S. at age 1 year (i.e., 12-23 months)
  - Children aged 2 years and older not vaccinated at recommended time (see above)
- Men who have sex with men and persons who use injection drugs
- Persons working with HAV-infected primates or with HAV in a research laboratory setting
- Persons with chronic liver disease (including persons waiting for or who have received liver transplants) and persons who receive clotting factor concentrates
- Unvaccinated persons who anticipate close personal contact (household or regular babysitting) with an international adoptee from a country with high or intermediate endemicity during the first 60 days after arrival of adoptee in the U.S. (The first dose should be administered as soon as adoption is planned, ideally > 2 weeks before arrival of the adoptee. The second dose should be given at least 6 months later to provide long-term immunity.)
- Any person seeking protection from HAV infection

Travel

Hepatitis A vaccine is recommended for:

- All susceptible persons aged ≥ 1 year, traveling to or living in developing countries and areas of intermediate or high risk for hepatitis A transmission, especially persons who plan frequent trips or have prolonged stays. This recommendation does not include travelers to North America (except Mexico), Australia (except remote interior regions), New Zealand, or Western Europe.
  - However, some experts recommend that travelers consider hepatitis A vaccination regardless of destination.
- Susceptible travelers to some non-developing countries who engage in risk behaviors (see "Risk")
- Risk-averse travelers desiring maximum pre-travel protection
- Note: At-risk travelers planning to depart in less than 2 weeks: see below.

Immune Globulin IM (IGIM) should be considered for:

- At-risk travelers who choose not to receive vaccine or who cannot receive vaccine due to allergy
- Infants aged < 12 months staying or residing in situations where there is significant exposure to local foods that adults would eat may be given IG if there is concern about transmission of hepatitis A to unvaccinated household contacts.
- Older adults, immunocompromised persons, and those with chronic liver disease or other chronic medical conditions who are planning to depart in ≤ 2 weeks should receive IG in addition to the initial dose of hepatitis A vaccine.

Combination HepA-HepB Vaccine is recommended for:

- Persons 18 years of age or older who are at risk for both forms of hepatitis

Postexposure Prophylaxis

Post-exposure prophylaxis is recommended after exposure to a clinical case of hepatitis A in these settings:

- Household and sex contacts
- Sharing illicit drugs
- Daycare center staff, attendees, and household members of attendees
- Common-source exposure (e.g., food handler)

- Schools, hospitals, and work settings, if there is close contact with the index patient
- Some experts recommend IG for newborn infants of acutely HAV-infected mothers, if the mother's symptoms began between 2 weeks before and 1 week after delivery.

Either hepatitis A vaccine or IG should be used as indicated below:

- Hepatitis A vaccine is preferred for healthy persons aged 12 months to 40 years.
- IG is preferred for persons aged > 40 years, but hepatitis A vaccine can be used if IG is not available.
- IG should be used for children aged < 12 months, immunocompromised persons, persons with chronic liver disease, and those for whom the vaccine is otherwise contraindicated.

Note: Because hepatitis A has a relatively long incubation period, the vaccine may not prevent the disease in individuals who have an unrecognized hepatitis A infection at the time of vaccination.

Vaccines

Vaccines - U.S.

Hepatitis A Virus Vaccines, Inactivated

Havrix (HepA; GSK)

- Approved for use in persons aged ≥ 12 months
- Formulations:
  - Pediatric: Each 0.5 mL dose contains 720 ELISA Units
  - Adult: Each 1 mL dose contains 1,440 ELISA Units
- Presentations: 0.5 mL and 1 mL single-dose vials and single-dose pre-filled syringes
- Contains aluminum, formalin, polysorbate 20, and neomycin
- Thimerosal-free and preservative-free
- The tip caps of the pre-filled syringes may contain natural rubber latex.

Vaqta (HepA; Merck)

- Approved for use in persons aged ≥ 12 months
- Formulations:
  - Pediatric/adolescent: 0.5 mL dose contains 25 units of hepatitis A virus antigen
  - Adult: 1 mL dose contains 50 units of hepatitis A virus antigen
- Presentations: 0.5 mL and 1 mL single-dose vials and single-dose pre-filled syringes
- Contains aluminum and trace amounts of formaldehyde, bovine serum albumin, and neomycin
- Thimerosal-free
- The vial stoppers, syringe plunger stoppers, and tip caps contain dry natural latex rubber.

Hepatitis A and Hepatitis B (Recombinant) Vaccine, Inactivated

Twinrix (HepA-HepB; GSK) is a combination of Havrix and Engerix-B.

- Approved for use in persons aged ≥ 18 years
- Each 1 mL dose contains 720 ELISA units of hepatitis A virus antigen and 20 µg of hepatitis B virus antigen.
- Presentations: 1 mL single-dose vials and single-dose pre-filled syringes
- Contains aluminum and trace amounts of neomycin, residual formaldehyde, polysorbate 20, and yeast protein
- Thimerosal-free and preservative-free
- The tip caps of the pre-filled syringes may contain natural rubber latex.

In contrast to immune globulin, hepatitis A vaccine is not derived from blood products. It is an inactivated, viral antigen vaccine.

See *Immune Globulin* for information on IG used for prevention of hepatitis A.

Vaccines – Available Outside the U.S.

Hepatitis A Virus Vaccines, Inactivated

Avaxim (Sanofi Pasteur): Canada, the EU, Australia, and elsewhere

- In Canada, Avaxim is available in both adult and pediatric (Avaxim Pediatric) formulations for ages ≥ 12 years and 1-15 years, respectively. (Either vaccine can be used for persons aged 12-15 years.) A booster is given after 6-12 months.
- In the EU, Avaxim is licensed for persons aged ≥ 16 years.
- In Australia, Avaxim is licensed for persons aged ≥ 2 years.
- This vaccine may have different approved age ranges and booster schedules in other countries. Check the package insert for the country of use.
- Each 0.5 mL dose contains 160 antigen units.
- Available in 0.5 mL pre-filled syringes
- Contains 2-phenoxyethanol, formaldehyde, aluminum hydroxide, polysorbate 80, and trace amounts of neomycin, and may contain bovine serum albumin
- Thimerosal-free

Havrix (GSK): Canada and Australia

- Havrix adult dose (≥ 19 years) contains 1,440 ELISA units/1 mL dose; Havrix Junior (1-18 years) contains 720 ELISA units/0.5 mL dose.
- Available in 0.5 mL and 1 mL single-dose vials and single-dose pre-filled syringes
- Contains aluminum hydroxide and trace amounts of neomycin, polysorbate 20, and formaldehyde
- Thimerosal-free

Vaqta (CSL/Merck): Australia (adult and pediatric/adolescent formulations)

- Same as U.S. vaccine, above

Note: Different strengths and/or concentrations of Havrix may be available or may be used for different patient populations in some countries. If questions arise concerning these other formulations, contact the manufacturer directly.

Hepatitis A Live Attenuated Vaccines (China)

- Vaccines (freeze-dried) are based on H2 strain or LA-1 strain
- Available in China for children aged ≥ 1 year
- H2 vaccine also licensed in India, Guatemala, Philippines, and Thailand
- Meta-analysis showed protective efficacy of both vaccines was 96%, equivalent to international inactivated vaccines.

Hepatitis A and Hepatitis B (Recombinant) Vaccine, Inactivated

Twinrix (HepA-HepB; GSK): Canada, Australia, and Europe in adult and pediatric (Twinrix Junior) formulations

- Available in 1 mL and 0.5 mL single-dose syringes in Canada and single-dose pre-filled syringes and vials in the EU and Australia
  - 720 ELISA units HAV/20 µg HBV per 1 mL dose

    - 360 ELISA units HAV/10 µg HBV per 0.5 mL dose (Twinrix Junior)
- Contains aluminum and trace amounts of formaldehyde, neomycin, and polysorbate 20; may contain yeast proteins

Combination Hepatitis A-Vi Polysaccharide Typhoid Vaccines, Inactivated

Several combined inactivated hepatitis A and Vi polysaccharide typhoid vaccines are available outside the U.S. Check package inserts carefully for full prescribing information.

Vivaxim (Sanofi Pasteur): Canada, Australia, and elsewhere

- licensed: ≥ 16 years
- One dose (1 mL) of the combination vaccine administered IM is followed by a booster dose of hepatitis A vaccine 6-36 months later.
- Protection against typhoid lasts about 3 years.
- Available in pre-filled, single-dose, dual-chambered syringe containing 0.5 mL purified Vi polysaccharide typhoid vaccine and 0.5 mL inactivated hepatitis A vaccine, which are mixed immediately prior to administration to produce a 1 mL dose
- Contains aluminum, 2-phenoxyethanol, formaldehyde, and traces of polysorbate 80, neomycin, and bovine serum albumin
- Thimerosal-free
- Contains no latex
- This vaccine is also known as Viatim in some countries.

Viatim (Sanofi Pasteur): Europe

- Same as Vivaxim, above.
- licensed: ≥ 16 years

Hepatyrix (GSK): U.K.

- licensed: ≥ 15 years
- One dose (1 mL) of the combination vaccine administered IM is followed by a booster dose of hepatitis A vaccine 6-12 months later.
- Contains 1,440 ELISA units HAV and 25 µg Vi polysaccharide of *Salmonella typhi* (Ty2 strain)
- Available in single-dose, pre-filled syringes
- Protection against typhoid lasts about 3 years.
- Contains aluminum
- Thimerosal-free

Administration: Hepatitis A Vaccine

See additional information in the *Administration* document.

Side Effects

Side effects tend to be mild and transient. The most frequently reported side effects following hepatitis A vaccination are pain, redness, and tenderness at the injection site. No serious adverse events have been observed.

Side effects of the combination hepatitis A/B vaccine (Twinrix) are reportedly similar in type and frequency to those of the individual vaccines (Havrix and Engerix-B) given concurrently.

Suspected allergic or adverse effects or medical care required after any immunization should be reported through the Vaccine Adverse Event Reporting System (VAERS). Also see Table ADV-1 and the VAERS form.

Havrix

In adults, the most frequent side effects are soreness at the injection site, headache, and malaise.

In children, the most frequent side effects are soreness and/or induration at the injection site, feeding problems, and headache.

Vaqta

In clinical trials with both children and adults, the most frequent complaints were injection site reactions (pain, tenderness, warmth, and swelling).

Some adults complained of headache, but this was less likely to occur in children and adolescents.

Twinrix

Per package insert, the most common reactions are pain, redness, and swelling at the injection site. Secondary respiratory tract infections have been reported.

Precautions and Contraindications

General

Consider postponing vaccination in persons with moderate or severe illness (with or without a fever) until recovery to minimize potential adverse effects.

Anaphylactic or other hypersensitive reaction to a previous dose contraindicates further immunization with that particular vaccine.

Anaphylactic or other hypersensitive reaction to a vaccine constituent contraindicates the use of vaccines containing that substance.

Persons who are allergic to a vaccine component or who choose not to receive the vaccine should receive a single dose of IG (0.02 mL/kg), which provides effective protection for up to 3 months. (See *Immune Globulin* for more information.)

Bleeding Disorders

This is an IM injection and may pose a risk for persons with bleeding disorders. See *Bleeding Disorders and Vaccination*.

Compromised Immunity

No special precautions need to be taken when vaccinating immunocompromised persons.

If this vaccine is administered to persons with malignancies, immune disorders, or those on immunosuppressive therapy, the expected immune response may not be obtained.

Also see *Immunocompromised Travelers* and *HIV- or AIDS-Infected Travelers*.

Pregnancy

The safety of hepatitis A vaccine during pregnancy has not been determined; however, because hepatitis A vaccine is produced from inactivated hepatitis A virus, the theoretical risk to the pregnant woman or developing fetus is expected to be low.

- The risk associated with vaccination should be weighed against the risk for hepatitis A in pregnant women who may be at high risk for exposure to hepatitis A virus.

- Immune globulin (IG) is a safe and effective means of preventing HAV, but immunization with hepatitis A vaccine gives a more complete and prolonged protection.

Per package insert, Twinrix should be given to pregnant women only if clearly indicated.

See *Pregnant Travelers* for additional information.

Compatibility

There is no known incompatibility with other immunizations.

Currently licensed hepatitis A vaccines can be used interchangeably.

Special Considerations

Pre-Vaccination Serologic Testing

Pre-vaccination serologic testing may be indicated for adult travelers who are likely to have had HAV infection, if testing costs less than vaccination and will not interfere with completion of the vaccine series. This is rarely done in clinical practice.

- This may include persons aged > 40 years, those with a history of hepatitis, older adolescents and adults in certain population groups (i.e., American Indians, Alaskan natives, and Hispanics), adults in certain groups that have a high prevalence of infection (e.g., men who have sex with men), and adults who were either born in or lived for extensive periods in geographic areas with a high endemism of hepatitis A infection.
- Anti-HAV IgM represents acute hepatitis A infection, and antibodies decline over several months. This is an inappropriate test for long-term immunity.
- Anti-HAV IgG or total anti-HAV represents previous hepatitis A infection, and protective antibodies persist for life.

Post-Vaccination Serologic Testing

Post-vaccination serologic testing is not indicated because of the high rate of vaccine response among adults and children. In addition, not all testing methods used for routine diagnostic use in the U.S. have the sensitivity to detect low but protective anti-HAV concentrations after vaccination.

- It is not yet known what level of anti-HAV antibody is needed to provide protection against infection.
- Persons tested for anti-HAV after immunization may not have detectable antibody but still may be protected.

Vaccination of an immune person is not contraindicated and does not increase the risk for adverse effects.
