Chapter 3: Hepatitis A

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I. Disease Description

Hepatitis A is caused by infection with the hepatitis A virus (HAV), a nonenveloped RNA agent that is classified as a picornavirus.[1] HAV replicates in the liver and is shed in the feces. Peak concentrations in stool occur during the 2 weeks before onset of illness. Virus is also present in serum, although in concentrations several orders of magnitude less than in feces. The most common mode of HAV transmission is fecal-oral, with the virus transmitted from person to person between household contacts, between sex partners, or by contaminated food or water. Because virus is present in serum during acute infection, bloodborne HAV transmission can occur, but it has been reported infrequently.

The incubation period of hepatitis A is 15–50 days, with an average of 28 days. The illness caused by HAV infection typically has an abrupt onset of signs and symptoms that include fever, malaise, anorexia, nausea, and abdominal discomfort, followed several days later by dark urine and jaundice. Hepatitis A usually does not last longer than 2 months, although some persons may have prolonged or relapsing signs and symptoms for up to 6 months. The likelihood of having symptoms with HAV infection is directly related to age. Among children younger than 6 years of age, most infections are asymptomatic; among older children and adults, infection is usually symptomatic. HAV infection occasionally produces fulminant hepatitis A. The case-fatality rate among persons of all ages with reported cases is approximately 0.3%, but it tends to be higher among older persons (approximately 2% among persons over 40 years of age).

HAV infection does not result in chronic infection or chronic liver disease.

II. Background

Among cases of hepatitis A reported to CDC during 2002–2004, the most frequently reported risk factor was international travel.

Historically in the United States, large nationwide epidemics occurred approximately every 10 years, with the last increase in cases being in 1995.[2] Even between these epidemics, disease rates were relatively high, and many communities experienced periodic epidemics. During the 1980s and 1990s, hepatitis A was one of the most frequently reported infectious diseases in the United States, with approximately 20,000–30,000 cases reported to the National Notifiable Diseases Surveillance System (NNDSS) each year. However, in recent years, hepatitis A incidence has declined precipitously. In 2004, 5,683 hepatitis A cases were reported, for a rate of 1.9 cases per 100,000 population.[2] This is the lowest rate of disease ever reported in the United States, which after correcting for underreporting and asymptomatic infections, represents an estimated 56,000 infections. This remarkable decline in cases can be attributed, at least in part, to hepatitis A vaccination of children in states with consistently elevated rates, which has been recommended by the Advisory Committee on Immunization Practices (ACIP) since 1999.[3]

Based on testing from the Third National Health and Nutrition Examination Survey (NHANES III) conducted during 1988–1994, 31.3% of the general U.S. population has serologic evidence of prior HAV infection. Anti-HAV prevalence is directly related to age, ranging from 9.4% among children 6–12 years of age to 74.6% among persons 70 years of age or older.[4]

Among cases of hepatitis A reported to CDC during 2002–2004, the most frequently reported risk factor was international travel (13.2%), followed by household or sexual contact with a person with hepatitis A (12.8%) and injection drug use (9.4%). An additional 10% of reported cases occurred among children and employees of child care centers and members of their households. Cases occurring during suspected foodborne outbreaks and those among homosexual or bisexual men each accounted for approximately 5%–12% of cases. The proportion of cases associated with being a homosexual or bisexual male and injection drug use varies from year to year (5%–30% of cases) as a result of periodic outbreaks occurring in these subgroups in certain communities. Fifty-six percent of persons with hepatitis A do not identify risk factors; their source of infection may be infected persons who are asymptomatic or have unrecognized infection.[2]

Since 1996, the ACIP has recommended routine hepatitis A vaccination of children living in communities with the highest hepatitis A rates. These communities often are relatively well defined, either geographically or ethnically, and include American Indian, Alaska Native, and selected Hispanic, migrant and religious communities. Historically, epidemics typically occurred every 5–10 years, with peak disease rates severalfold higher than the national average. Coincident with implementation of hepatitis A vaccination of children in recent years, dramatic reductions in hepatitis A rates have been seen in these communities. For example, since 2000, national hepatitis A rates among American Indians and Alaska Natives have been below the national average.

In 1999, recommendations for routine vaccination of children were extended to include children living in the 11 states, as well as in counties and communities in other states, with rates that were at least twice the 1987–1997 national average (i.e., >20 cases per 100,000 population). Routine vaccination was to be considered for children living in the six states, as well as in counties and communities in other states, with rates exceeding the 1987–1997 national average (i.e., >10 but <20 cases per 100,000 population).[3] Coincident with implementation of these recommendations, national disease incidence has declined to historic lows, with the largest declines occurring in the age groups and parts of the country in which vaccination is recommended. The majority of disease and the highest rates currently are in areas in which hepatitis A vaccination of children is not recommended.[5]

In 2006, ACIP expanded their recommendations for hepatitis A vaccination with the intention of further reducing hepatitis A morbidity and mortality in the United States and making possible the consideration of eventual elimination of HAV transmission.[5] Hepatitis A vaccination is recommended routinely for children, for persons who are at increased risk for infection, and for any person wishing to obtain immunity.

Vaccination of children

All children should receive hepatitis A vaccine at age 1 year (i.e., 12–23 months). Vaccination should be completed according to the licensed schedules (Tables 1, 2) and integrated into the routine childhood vaccination schedule. Children who are not vaccinated by age 2 years can be vaccinated at subsequent visits. States, counties, and communities with existing hepatitis A vaccination programs for children aged 2–18 years are encouraged to maintain these programs. In these areas, new efforts focused on routine vaccination of 12–23-month-old children should enhance, not replace, ongoing programs directed at a broader population of children. In areas without existing hepatitis A vaccination programs, catch-up vaccination of unvaccinated children aged 2–18 years can be considered. Such programs might especially be warranted in the context of rising incidence or ongoing outbreaks among children or adolescents.[5]

Vaccination of persons at increased risk for HAV infection

Persons traveling to or working in countries that have high or intermediate endemicity of infection, men who have sex with men, illegal drug users, persons working with nonhuman primates or with HAV in a research laboratory, persons with clotting-factor disorders, and persons who have chronic liver disease should be vaccinated against hepatitis A.[5]

III. Importance of Rapid Identification

Rapid identification and prompt reporting of cases of hepatitis A are important because measures can be taken to prevent transmission to other persons.

Pre- and postexposure prophylaxis

Immune globulin (IG) is a sterile preparation of concentrated antibodies (immunoglobulins) made from pooled human plasma. In the United States, only plasma that has tested negative for hepatitis B surface antigen (HBsAg), antibody to human immunodeficiency virus, and antibody to hepatitis C virus is used to produce IG. In addition, the Food and Drug Administration requires that the process used to produce IG include a viral inactivation step or that the final products test negative for HCV RNA.

IG provides protection against hepatitis A through passive transfer of antibody. When administered intramuscularly for preexposure prophylaxis, a dose of 0.02 mL/kg confers protection for more than 3 months, and a dose of 0.06 mL/kg confers protection for 3–5 months. When administered within 2 weeks following an exposure to HAV (0.02 mL/kg), IG is 80%–90% effective in preventing hepatitis A.[5] Efficacy is greatest when IG is administered early in the incubation period; when administered later in the incubation period, IG might only attenuate the clinical expression of HAV infection.

IG should be given to exposed persons as soon as possible, but not more than 2 weeks after the exposure. Recipients may include 1) persons with close contact (household, sexual, or needle sharing) with a person with hepatitis A; 2) staff and attendees at child care centers where a hepatitis A case is recognized; and 3) and persons in certain common-source exposure situations (e.g., patrons at a food establishment with an HAV-infected food handler, if the risk of transmission is determined to be high).[5]

IV. Importance of Surveillance

Disease surveillance should be used to 1) identify contacts of case-patients who require postexposure prophylaxis; 2) detect outbreaks; 3) determine the effectiveness of hepatitis A vaccination; 4) monitor disease incidence in all age groups; 5) determine the epidemiologic characteristics of infected persons, including the source of their infection; and 6) assess and reduce missed opportunities for vaccination. The interpretation of hepatitis A surveillance data depends upon an understanding of the local epidemiology.[6]

V. Disease Reduction Goals

The proposed disease reduction goal for hepatitis A calls for reducing the incidence of reported cases from a baseline of 11.3 cases per 100,000, reported in 1997, to no more than 5 cases per 100,000 by the year 2010.

An acute illness with a discrete onset of symptoms, and jaundice or elevated serum aminotransferase levels

VI. Case Definition

The following case definition for hepatitis A was adopted by the Council of State and Territorial Epidemiologists (CSTE), and was published in May 1997.[7]

Clinical case definition

An acute illness with

- A discrete onset of symptoms, and
- Jaundice or elevated serum aminotransferase levels

Laboratory criteria for diagnosis

- Immunoglobulin M (IgM) antibody to hepatitis A virus (anti-HAV) positive

Case classification

Confirmed. A case that meets the clinical case definition and is laboratory confirmed or a case that meets the clinical case definition and occurs in a person who has an epidemiologic link with a person who has laboratory-confirmed hepatitis A (i.e., household or sexual contact with an infected person during the 15–50 days before the onset of symptoms).

VII. Laboratory Testing

Serologic testing

IgM anti-HAV. Virtually all patients with acute hepatitis A have detectable IgM antibody to the capsid proteins of HAV (IgM anti-HAV). Therefore, the diagnosis of acute HAV infection is confirmed during the acute or early convalescent phase of infection by the presence of IgM anti-HAV in serum. IgM anti-HAV generally disappears within 6 months after the onset of symptoms. Persons who test positive for IgM anti-HAV more than 1 year after infection have been reported, as have likely false-positive tests for persons without evidence of recent HAV infection.

Total anti-HAV. IgG anti-HAV appears in the convalescent phase of infection, remains for the lifetime of the person, and confers enduring protection against disease. The antibody test for total anti-HAV measures both IgG anti-HAV and IgM anti-HAV. The presence of total anti-HAV and absence of IgM anti-HAV indicates immunity consistent with either past infection or vaccination. Commercial diagnostic tests are widely available for detection of IgM and total (IgM and IgG) anti-HAV in serum.

Serologic testing is necessary to establish a diagnosis for a person with symptoms of acute hepatitis.

CDC laboratory special studies

Serologic testing is necessary to establish a diagnosis for a person with symptoms of acute hepatitis. Molecular virologic methods such as polymerase chain reaction (PCR)-based assays can be used to amplify and sequence viral genomes. These assays may be helpful in investigating common-source outbreaks of hepatitis A. Providers with questions about molecular virologic methods should consult with their state health department or the Division of Viral Hepatitis, Laboratory Branch, CDC. For additional information on laboratory support for surveillance of vaccine-preventable diseases, see Chapter 22.

VIII. Reporting

In the United States, case reports of acute viral hepatitis are classified as hepatitis A, acute hepatitis B, or acute hepatitis C, or perinatal HBV infection, chronic HBV infection, and hepatitis C, past or present. Serologic testing is necessary to determine the etiology of viral hepatitis, and case reports should be based on laboratory confirmation (see above). Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[8] These regulations/laws list the diseases and conditions that are to be reported and describe those persons or groups who are responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, daycare facilities, and other institutions. Persons reporting these conditions should contact their state health department for state-specific reporting requirements.

Reporting to CDC

Case reports of hepatitis A and other reportable diseases are transmitted by the state health department weekly to NNDSS via the National Electronic Telecommunications System for Surveillance (NETSS). The NETSS core record includes basic demographic information (excluding personal identifiers)—age, race/ethnicity, sex, date of onset, date of report, and county of residence. The Division of Viral Hepatitis has developed an expanded Data Collection Worksheet to collect information about symptoms, risk factors and serologic data (Appendix 6). This worksheet can be used for case investigation and data can be directly entered into the state's electronic reporting system.

IX. Vaccination Schedules

Immune globulin (for hepatitis A postexposure prophylaxis)

For persons with recent exposure (within 2 weeks) to HAV who have not previously received hepatitis A vaccine, a single intramuscular dose of IG (0.02 mL/kg) should be given as soon as possible, but not more than 2 weeks after the exposure. Persons who have received one dose of hepatitis A vaccine at least 1 month before exposure to HAV do not need IG.

Hepatitis A vaccine

Two single-antigen inactivated hepatitis A vaccines are commercially available, HAVRIX® (GlaxoSmithKline) and VAQTA® (Merck & Co., Inc.). Both vaccines are licensed for persons 12 months of age and older. A combined hepatitis A and B vaccine, Twinrix® (GlaxoSmithKline), is also available for use in persons aged 18 years and older. Twinrix is made of the antigenic components used in HAVRIX and Engerix-B® (hepatitis B vaccine). These vaccines should be administered by intramuscular injection in the deltoid muscle or lateral thigh, with a needle length appropriate for the person's age and size. Hepatitis A vaccine is recommended for all children at age 12–23 months, children aged 2–18 years in selected areas of the country, travelers to areas of high or intermediate hepatitis A endemicity, users of illicit drugs, men who have

sex with men, persons with clotting factor disorders who receive therapeutic blood products, and patients with chronic liver disease (see "Vaccination of Persons at increased risk for HAV infection" above.). Any person 18 years old or older who has an indication for both hepatitis A and B vaccination can receive Twinrix.

The dose of HAVRIX is quantified in enzyme-linked immunosorbent assay (ELISA) units (EL.U.). HAVRIX is currently licensed in a two-dose schedule of 720 EL.U. per dose (0.5 mL) for children and adolescents (12 months through 18 years of age), and 1440 EL.U. per dose (1.0 mL) for adults (older than 18 years of age) (Table 1).

Table 1. Recommended doses of HAVRIX® (hepatitis A vaccine, inactivated)*

Group	Age	Dose (EL.U.)†	Volume	No. doses	Schedule§
Children and adolescents	12 months–18 years	720	0.5 mL	2	0, 6–12
Adults	>18 years	1,440	1.0 mL	2	0, 6–12

* *GlaxoSmithKline*

† *Enzyme-linked immunosorbent assay units*

§ *Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.*

The dose of VAQTA is quantified in units (U). The dose and schedule for children and adolescents (12 months through 18 years of age) is 25 U per dose in a two-dose schedule, and for adults (older than 18 years of age), 50 U per dose in a two-dose schedule (Table 2).

Table 2. Recommended doses of VAQTA® (hepatitis A vaccine, inactivated)*

Group	Age	Dose (U)†	Volume	No. doses	Schedule§
Children and adolescents	12 months –18 years	25	0.5 mL	2	0, 6–18
Adults	>18 years	50	1.0 mL	2	6–18

* *Merck & Co., Inc.*

† *Units*

§ *Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.*

The dose of Twinrix is quantified in ELISA units (EL.U.) and micrograms. Each dose of Twinrix contains at least 720 EL.U. of inactivated hepatitis A virus and 20 µg of recombinant hepatitis B surface antigen (HBsAg) protein. Primary vaccination consists of three doses, given on a 0, 1, and 6 month schedule, the same schedule as that used for single-antigen hepatitis B vaccine (Table 3).

Table 3. Recommended doses of TWINRIX® *

(combined hepatitis A and B vaccine for persons >18 years of age)

Group	Age	Dose (EL.U.† and µg)	Volume	No. doses	Schedule§
Adults	>18 years	20 µg (HBsAg protein) 750 EL.U. (Inactivated HAV)	1.0 mL	3	0, 1, 6

* *GlaxoSmithKline*

† *Enzyme-linked immunosorbent assay units*

§ *Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.*

X. Enhancing Surveillance

A number of activities can improve the detection and reporting of hepatitis A cases and improve the comprehensiveness and quality of reporting. Chapter 19 describes some general activities for enhancing surveillance; some specific recommendations for hepatitis A are listed below.

Appropriate serologic testing

Surveillance for acute hepatitis is challenging for several reasons. There are five different viruses (A–E) that account for nearly all human viral hepatitis. Because the clinical features of acute hepatitis caused by these viruses are similar, serologic testing is necessary to establish a diagnosis for a person with symptoms of acute hepatitis. Acute infection with several of the hepatitis viruses (HBV, HCV, and HDV) can progress to chronic infection, and review of serologic and clinical information of patients is necessary to make the differentiation between acute and chronic disease. A lack of understanding about the epidemiology of these diseases and underutilization of serologic testing may result in significant misclassification in reporting of acute viral hepatitis. For example, a provider may diagnose jaundice in a child as hepatitis A and not order serologic testing, when in fact the child may have another illness.

Aggressive case investigations of persons with acute disease provide the best opportunity to administer postexposure prophylaxis to contacts

To ensure accurate reporting of viral hepatitis and appropriate prophylaxis of household and sexual contacts, all case reports of viral hepatitis submitted to CDC should be investigated to obtain serologic testing information and risk factor data, and should be entered into the NEDSS base system and hepatitis extended record and reported by the state health department to CDC.

Provider education

Providers should be educated about the importance of reporting all cases of acute hepatitis A. A common risk factor for persons with acute infection is contact with a previously identified case-patient. Aggressive case investigations of persons with acute disease provide the best opportunity to administer postexposure prophylaxis to contacts of case-patients and have the potential to significantly reduce missed opportunities to prevent disease.

Case investigation

Aggressive case investigations of persons with acute disease provide the best opportunity to administer postexposure prophylaxis to contacts. Identifying risk factors among persons with acute disease can help better define the epidemiology of viral hepatitis at the state and local level. For example, recognition of hepatitis A outbreaks in child care centers, among men who have sex with men, or among injection-drug users can help target hepatitis A vaccination efforts. Analysis of risk factor data can identify populations where targeted interventions may be needed.

Monitoring surveillance indicators

Regular monitoring of surveillance indicators, including date of report, timeliness, and completeness of reporting, may identify specific components of the surveillance and reporting system that need improvement. Important hepatitis A program indicators that can be monitored through the surveillance, reporting and case investigation system include

- Cases of hepatitis A in vaccinated persons
- Cases of hepatitis A where death has occurred
- Cases of hepatitis A in children under 18 years of age

Laboratory reporting

Laboratories should be encouraged to report all persons with acute hepatitis. All IgM anti-HAV–positive results should be reported. To facilitate reporting, these IgM results could be included in the state's list of conditions reportable by laboratories.

Hospital-based reporting

Hospitals and infection control practitioners should be encouraged to report all persons with the ICD diagnosis codes of B15: hepatitis A. These patients may then be investigated to determine if they indeed have hepatitis A.

XI. Case Investigation

Guidelines for investigating a suspected case of viral hepatitis include 1) determining a discrete onset of illness, 2) confirming evidence of acute liver disease (jaundice or elevated aminotransferase levels), and 3) obtaining serologic laboratory results.[6]

Information to collect

The following information is epidemiologically important to collect in a case investigation. Additional information may also be collected at the direction of the state health department.

- Demographic information
- Clinical details, including
  - Date of onset of illness
  - Symptoms including abdominal pain and jaundice
- Laboratory results
- Vaccination status
- Risk factors
- Contact investigation and prophylaxis

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