Chapter 13
Hepatitis A

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Hepatitis A Infection

Etiology

Hepatitis A infection is caused by *Hepatovirus A* (HAV), a member of the *Picornaviridae* family. The naked capsid contains a single strand of positive-sense RNA. The region of the viral genome that encodes the three major HAV capsid proteins includes highly conserved clusters of rare codons that restrict the antigenic variability expressed on the exposed surface of the virion. As such, only one serotype of HAV exists, although multiple genotypes have been identified.

Reports of epidemic jaundice presumed to have been caused by HAV date back to the time of Hippocrates in the fifth century BC. The virus remains a common cause of viral hepatitis. Infections caused by HAV are clinically indistinguishable from other types of acute viral hepatitis. Asymptomatic infection, with or without elevations in serum hepatic transaminases, is common, especially in young children. Symptomatic infection is often, but not always, associated with the development of jaundice. Serologic test results that show the presence of HAV-specific immunoglobulin M (IgM) antibody are diagnostic.

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Epidemiology of Hepatitis A

Hepatitis A infections are vastly underreported due to the very high rates of asymptomatic and minimally symptomatic disease. Globally, the geographical distribution of HAV infection is closely tied to sanitation and hygiene standards, access to clean drinking water, and crowded living conditions. Worldwide, HAV infections occur sporadically and in large-scale epidemics. Explosive eruptions of disease, like the 1988 Shanghai epidemic that affected approximately 300,000 individuals, can be quite disruptive, causing serious strain on the public health system and substantial economic loss. Cyclic recurrences of HAV outbreaks are well documented. Globally, disease burden is greatest across Central and South America, Africa, the Middle East, Asia, and the Western Pacific island groups where HAV causes an estimated 1.4 million cases with 11,000 deaths each year.

The WHO recognizes four levels of disease endemicity. Most countries and regions with poor sanitation and hygiene are highly endemic for hepatitis A infection. High endemicity indicates that more than 90% of the population becomes infected by age 10 years. Natural infection confers lifelong immunity. Epidemics across these regions are rare because the majority of older children and adults are already immune. Infections in young children are typically asymptomatic, and the few with symptoms are almost always anicteric. For these reasons, countries and regions that are highly endemic for hepatitis A infection have low symptomatic disease rates, low morbidity, and low mortality. Despite its high endemicity, HAV does not pose a public health problem, and vaccination is a very low priority. Intermediate endemicity is the classification used to describe populations where 50% or more of individuals are infected by the age of 15 years. Intermediate endemicity is typical for countries and regions with transitional economies and variable sanitary conditions. The large pool of susceptible older children and adults is associated with high rates of symptomatic disease. Large outbreaks are a common occurrence. Regions with intermediate levels of HAV endemicity have the potential to benefit most from universal childhood immunization. Low endemic regions of HAV are defined as those where 50% or more of the population is infected by age 30 years, and very low endemic regions are those where fewer than 50% of individuals are infected by age 30 years. Low and very low levels of HAV endemicity are typical for developed countries with good sanitation and hygiene. Under these conditions, the majority of infections occur in high-risk group individuals, such as injecting-drug users, men who have sex with men, and travelers to regions of high endemicity. Index cases of infection in low and very low endemic communities can lead to outbreaks. In most cases, established sanitation and hygiene practices limit person-to-person transmission, thereby restricting the extent of any outbreaks. The source of many outbreaks originates from contaminated food products that are imported from countries with high or intermediate endemicity.

Hepatitis A Infection in the United States

Prior to vaccine licensure in the mid-1990s, large, nationwide epidemics of hepatitis A were common across the United States. Hepatitis A remained the most frequent cause of viral hepatitis until 2004. Between 1987 and 1997, 17 states (AZ, AK, AR, CA, CO, ID, MO, MT, OK, OR, NV, NM, SD, TX, UT, WA, and WY) accounted for 68% of all reported US infections. The implementation of a series of hepatitis A vaccine recommendations, first targeting high-risk individuals and later targeting all children living in states with the highest rates of disease, caused a gradual shift in the epidemiology of the infection. By 2002, reports of HAV infection nationwide were down, and the state-to-state differences in rates of infection had been eliminated.

Hepatitis A Transmission

Like other non-enveloped viruses, HAV can be stable in the environment for months. Virus can be inactivated by heat, formalin, or chlorine. Humans are the only natural host.

Virus is spread person-to-person via the fecal-oral route when a susceptible individual consumes food or water that has been contaminated with feces from an infected person. The average incubation period following exposure to HAV is 28 days but can be as long as 50 days. Virus replicates in the gastrointestinal tract, reaching its highest concentration in stool 2 weeks before symptom onset. Most infected individuals excrete virus in their stool for about 3 weeks. In young children, virus replicates to higher concentrations and is shed for a longer period of time. Hepatitis A is one of most frequent causes of foodborne infection. Its long incubation period complicates trace-back when investigating foodborne outbreaks.

Clinical Presentation

Infections caused by hepatitis A are very often clinically asymptomatic or so minimally symptomatic that the infected individual does not seek medical attention. Some asymptomatic infections are clinically inapparent, but most are better categorized as subclinical since laboratory test results will most often show an elevation in serum hepatic transaminase concentrations. The likelihood of developing symptomatic disease increases with age. Symptomatic illness associated with jaundice is described as icteric, and illness without jaundice is described as anicteric infection.

Symptomatic HAV infection most typically presents abruptly with low-grade fever, myalgias, malaise, anorexia, nausea, and vomiting with associated right upper quadrant abdominal pain. When present, clinical signs that indicate the presence of hepatic inflammation and/or dysfunction such as tea- or cola-colored urine, clay-like light-colored bowel movements, jaundice, scleral icterus, and/or hepatomegaly facilitate establishing the diagnosis by immediately raising the suspicion for viral hepatitis.

On average, symptoms last 2 weeks, although some adults have recovery times with intermittent relapses for 24 weeks or longer. Complete recovery with lifelong immunity to reinfection is expected. Unlike hepatitis viruses B and C, HAV does not cause chronic infection or chronic liver disease. Very rarely, HAV can lead to life-threatening fulminant hepatitis and acute liver failure.

Between 70% and 90% of children less than 6 years of age who are infected with HAV are asymptomatic, and those with symptomatic infection only rarely develop jaundice. In contrast, 76% to 97% of infected older children and adults develop symptomatic disease.

Management

There is no specific treatment available for infection caused by HAV. Symptomatic treatment, with careful attention to avoiding medications that are metabolized by the liver, or known to be hepatotoxic, can be used for pain relief or to reduce fever.

Hepatitis A Vaccine

Globally, several formulations of HAV vaccines are used. Live oral vaccines are available for use in China and in the private sector of India, but most available formulations are formaldehyde-inactivated whole-virus vaccines. They all show similar efficacy and side effect profiles. A two-dose series is recommended, although almost all vaccine recipients develop protective antibody levels within one month of receiving their first dose. Mathematical models predict that vaccine-associated protection will last 25 years or more.

Vaccines Available in the United States

Three formulations of formalin-inactivated whole-virus vaccines are available for use in the United States:

1. Vaqta, marketed by Merck Vaccines, gained FDA licensure in 1996. It is recommended as a two-dose series. The second dose should be administered 6 to 18 months after the first. Each adult dose, used for individuals 19 years of age and older, is a 1 mL intramuscular injection containing 50 U of the immunogen.

Each pediatric dose, used for ages 12 months to 18 years, is 0.5 mL containing 25 U of the immunogen, exactly half the adult dose.

2. Havrix, marketed by GlaxoSmithKline, gained FDA licensure in 1995. It is also recommended as a two-dose series. The second dose should be administered 6 to 12 months after the first. Each adult dose, used for individuals 19 years of age and older, is a 1 mL intramuscular injection containing 1440 ELISA units of the immunogen. Each pediatric dose, used for ages 12 months to 18 years, is 0.5 mL containing 720 ELISA units, exactly half the adult dose.
3. Twinrix, marketed by GlaxoSmithKline, gained FDA licensure in 2001 as a combination vaccine comprised of the same immunogens used to manufacture Havrix (inactivated whole HAV) and Engerix-B (recombinant hepatitis B surface antigen) monovalent vaccines. Twinrix is licensed for use in adults 18 years and older who require immunization against both hepatitis A and hepatitis B infections. Unlike Havrix, Twinrix is recommended as either a three- or four-dose series. The dosing schedule recommended for the three-dose series is at 0, 1, and 6 months. The four-dose series is recommended when an accelerated schedule is necessary or desired. Doses are given at 0, 7, and 21–30 days and then followed by a booster dose 12 months after the first dose. Each 1 mL intramuscular dose contains 720 ELISA units of the HAV immunogen and 20 mcg of the hepatitis B immunogen.

Immunizing Antigens, Additives, and Excipients

Vaqta is derived from a characterized HAV strain that is cultured in MRC-5 cells, then harvested, purified, and formalin inactivated. The immunogen is then adsorbed onto an adjuvant of amorphous aluminum hydroxyphosphate sulfate.

Havrix is derived from cell culture-adapted HAV strain HM175 virus propagated in MRC-5 cells and then purified from cell lysates via ultrafiltration and gel permeation chromatography. After undergoing inactivation with formalin, the immunogen is adsorbed onto aluminum hydroxide adjuvant.

Twinrix: The HAV immunogen is manufactured as described for Havrix. The hepatitis B immunogen is recombinant hepatitis B surface antigen that is produced by the yeast, *Saccharomyces cerevisiae* and then purified using a series of physical and chemical methods. Purified immunogen is adsorbed onto aluminum hydroxide adjuvant and then combined with the HAV immunogen to produce the final combination vaccine product.

ACIP Vaccine Recommendations in the United States

In 1996, shortly after the licensure of formalin-inactivated whole-virus HAV vaccine, the ACIP recommended it be administered to individuals 2 years of age and older identified to be at risk, including those living in communities with high rates of hepatitis A infection. The advice was directed, but not exclusive, to children

residing in certain American Indian, Alaskan Native, and Hispanic communities. In 1999, ACIP expanded the recommendation for routine vaccination to children 2 years of age and older who were residing in 17 states known to have HAV infection rates exceeding the national average of 10 cases/100,000 population. The vaccine's labeling indication was lowered to 12 months in 2005. Reported rates of HAV infection from the 17 states where HAV vaccine was being administered routinely to children had dropped well below the national average. In 2006, recognizing the shifting epidemiology of HAV infection and acknowledging the FDA's expanded age indication, ACIP broadened their recommendation for HAV vaccine to a universal childhood recommendation for all children starting at age 12 months. Figure 13.1 shows the total number of hepatitis A infections reported in the United States each year between 1966 and 2016 illustrating the impressive impact of vaccinating children on the total disease burden in the US population.

Currently, ACIP also recommends HAV vaccine for individuals at high risk due to any of the following circumstances listed in Table 13.1.

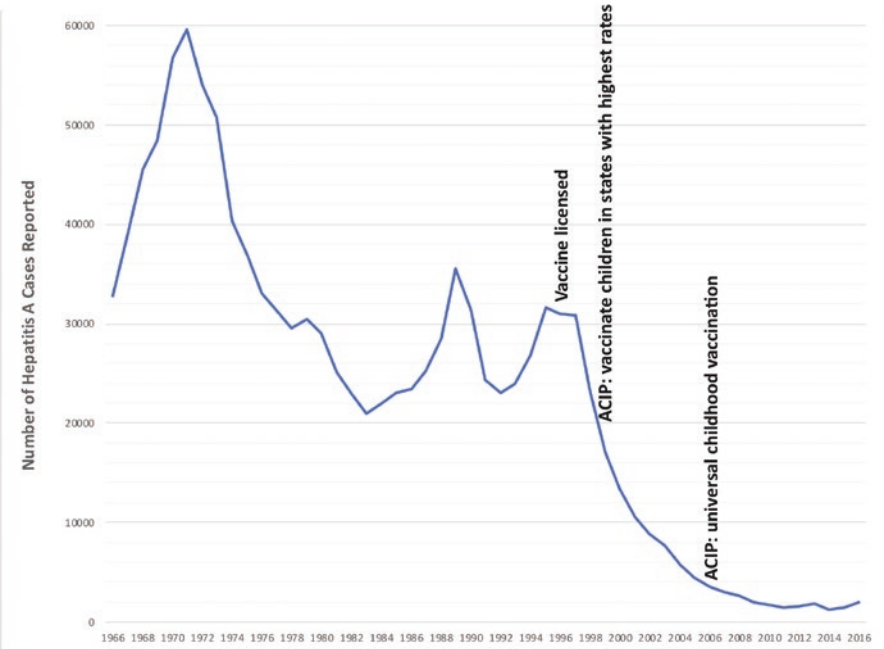

Fig. 13.1 Shown is the total number of hepatitis A cases reported in the United States each year from 1966 to 2016. Hepatitis A vaccine was approved for use by the US Food and Drug Administration in 1996. Later that year, ACIP recommended that the vaccine be given to children living in communities with high rates of infection. In 1999, ACIP expanded and clarified their recommendation to include children residing in 17 US states with high rates of infection. In 2006, ACIP recommended universal hepatitis A vaccination for all children starting at 12 months of age (see text). Source Data for graph: https://www.cdc.gov/hepatitis/statistics/SurveillanceRpts.htm

Table 13.1 Individuals and groups recommended to receive hepatitis A vaccine

Underlying medical conditions	Known or likely exposure	Social and behavioral risks
Chronic liver disease	Postexposure prophylaxis for people 12 months of age and older	Individuals who use drugs
Chronic hepatitis C infection	Household and close personal contacts of HAV-infected individuals	Men who have sex with men
Chronic hepatitis B infection	Working with HAV-infected patients or patient samples	Current or recent incarceration
Immunosuppression	Sexual partners of HAV-infected individuals	International travel to endemic areas
Individuals treated with clotting-factor concentrates	Close contact with an international adoptee from a country with high or intermediate endemicity	Individuals experiencing homelessness

Pediatric Immunization Schedule

HAV vaccine is recommended for all children 12–23 months of age as a two-dose series with catch-up recommended for children 2 years of age and older.

For those planning international travel, infants between 6 and 11 months should receive one dose prior to departure and then be revaccinated with two doses between 12 and 23 months of age as above.

Adult Immunization Schedule

Options for immunizing adults include the administration of a two-dose series of either Havrix or Vaqta using the recommended minimum dosing intervals. A three- or four-dose series of Twinrix can be considered for those who require vaccination against both hepatitis A and hepatitis B.

Global Vaccine Recommendations

The WHO recommends universal integration of HAV vaccination into national immunization schedules starting at 1 year of age. Some countries with more advanced progress in socioeconomic status and hygiene, such as Argentina, are opting for a single dose of inactivated HAV vaccine. This option provides comparable short- and intermediate-term effectiveness, is less expensive, and is easier to implement than a two-dose regimen.

Contraindications to Vaccine

Contraindications to HAV vaccine include previous life-threatening allergic reactions to prior doses or to any vaccine components. Those with an ongoing moderate or severe illness should postpone immunization until fully recovered.

Warnings and Precautions for Vaccine Use

Syncope or near-syncopal episodes can occur following the administration of any injectable vaccine.

Side Effects and Adverse Events

Self-limiting side effects may include soreness or redness at the injection site, low-grade fever, headache, and/or tiredness. Rare side effects have included dizziness, fainting, shoulder pain on the side of the injection, and allergic reactions. Serious allergic reactions that include hives, facial swelling, tachycardia, dizziness, and/or weakness are estimated to occur at less than 1 in a million doses.

The safety profile of Havrix was evaluated in clinical trials involving approximately 37,000 subjects. Localized pain at the injection site was reported by 56% of adults and 21% of children older than 2 years. The most common local reactions reported in children less than 2 years of age were injection site pain (32%) and injection site redness (29%). Systemic reactions in this age group included irritability (42%), drowsiness (28%), and loss of appetite (28%). A similar safety profile was shown in clinical trials using Vaqta. Children less than 2 years of age experienced injection site pain (37%), redness (21%), and fever (16%). The most common adverse reactions reported by adults included injection site pain (67%), injection site warmth (18%), and headache (14%).

Vaccine Efficacy and Immunogenicity from Clinical Trials

Overall, inactivated whole-virus hepatitis A vaccines result in seroconversion of more than 95% of children and adults after a single dose and 100% seroconversion after two doses. In addition, two doses of Havrix vaccine, administered 1 month apart, was shown to be 94% effective at preventing hepatitis A infection among 40,000 Thai children, aged 1–16 years, living in highly endemic villages. Seroconversion rate after the two-dose series was 99% or higher. Similarly, Vaqta vaccine was shown to be 100% effective in preventing hepatitis A infection among

1000 New York children 2 to 16 years of age who received one dose while living in a community with high rates of disease. Seroconversion following two doses was documented in 100% of two-dose vaccine recipients.

Impact of Vaccine on Disease Burden

Globally, by 2016, at least 16 countries have added universal HAV vaccine to their national pediatric immunization programs. In each case, as childhood vaccination rates increased, the national incidence of hepatitis A infection in all age groups decreased dramatically underscoring the role that young children play in the transmission of this disease. The impact of implementing universal pediatric hepatitis A vaccine programs on nationwide incidence of hepatitis A is shown in Table 13.2. For example, the Panamanian Ministry of Health added a single dose of HAV vaccine to their universal childhood immunization schedule in 2007 targeting children older than 12 months. The mean incidence of hepatitis A infection reported between 2000 and 2006 was 51 per 100,000 population. By 2010, single-dose vaccine coverage rates had reached 71% and the reported incidence of hepatitis A had dropped 93% to 3.7 per 100,000.

Similar successes have been achieved in the United States. Following the 1996 ACIP recommendations to immunize American Indian and Alaskan Native children living in communities with high rates of hepatitis A infection, the incidence of disease in those communities dropped by more than 95%, from 104 to 5 cases per 100,000 population.

Following the 1999 expanded ACIP recommendations to immunize all children in 17 states with rates of infection that exceeded the national average, there was an 88% decline in hepatitis A cases reported from the targeted states. In 2014, an all-time low of 1239 cases of hepatitis A were reported across the United States, representing a 96% decline since vaccination efforts had begun.

Table 13.2 Examples of the global impact of universal pediatric hepatitis A vaccine programs

Country	Start of vaccine	Target age	Mean vaccine coverage rates	Years compared	Incidence per 100,000 population	Decline in hepatitis A disease
Argentina	2005	1 yr	2006–2011: 96.8%	2000–2002 vs. 2006–2011	66.5 vs. 7.9	88%
Israel	1999	18 mos	2003–2010: 88%	1993–1998 vs. 2008–2012	50.4 vs. <1.0	>98%
Panama	2007	>12 mos	2010: 71% (one dose)	2000–2006 vs. 2010	51.1 vs. 3.7	93%
Uruguay	2007 2008	1–5 yrs. >12 mos	2010: 74% (one dose)	2005 vs. 2010	69.6 vs. 2.7	96%

A resurgence in disease that began in late 2016 has been more challenging to control because of the large numbers of high-risk individuals from groups that are historically harder to reach. Outbreaks continue in individuals who use drugs, in those experiencing homelessness, and among men who have sex with men. More than 15,000 cases, 8500 (57%) hospitalizations, and 140 deaths from HAV infection have been reported across these risk groups.

Inactivated whole-virus HAV vaccines are safe and highly effective. Universal vaccination programs that target young children have led to dramatic declines in disease incidence, at least in part by interrupting disease transmission from young children to other members of the community. Young children shed higher amounts of virus during infection, often lack quality hygiene practices, and are very often asymptomatic during infection. Weeks of uninterrupted transmission can occur under these conditions since the outbreak may not become evident until an adult contact develops symptomatic disease with jaundice and the incubation period for the infection can be as long as 50 days.

References and Suggested Reading

Links

World Health Organization:

https://www.who.int/news-room/fact-sheets/detail/hepatitis-a
https://www.who.int/immunization/diseases/hepatitisA/en/

U.S. Centers for Disease Control and Prevention:

https://www.cdc.gov/hepatitis/hav/index.htm

Vaccine Information Sheet

https://www.cdc.gov/vaccines/hcp/vis/vis-statements/hep-a.html

Contagion Live

https://www.contagionlive.com/outbreak-monitor?z=no&type=sub&category=Hepatitis+A

Havrix Package Insert

https://www.fda.gov/media/79349/download

Vaqta Package Insert

https://www.fda.gov/media/74519/download

Twinrix Package Insert

https://www.fda.gov/media/74182/download

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