INTRODUCTION

Hepatitis A virus (HAV), the causative agent of viral hepatitis type A, was first identified almost thirty-five years ago. It is one of the most common causes of acute viral hepatitis in the United States. Epidemics occur sporadically throughout the world. HAV causes only acute hepatitis and does not go on to chronic liver disease. While vaccination has decreased the incidence of HAV, severe fulminant HAV can occur in healthy individuals as well as persons with chronic liver disease. Thus, HAV remains an important illness to consider in the evaluation of patients presenting with acute hepatitis.

VIROLOGY

HAV is a positive-stranded RNA virus which, unlike the Hepatitis C virus, lacks a lipid envelope. It is a member of the Picornaviridae family. Much of the understanding of HAV is derived from studies of the prototype picornavirus, poliovirus. The HAV genome is packaged within a icosahedral protein capsid composed of sixty copies of each of three major structural proteins: VP1, VP2, and VP3. Several features of the HAV replication cycle distinguish it from other picornaviruses: slow and protracted time course, low virus yields, and a propensity to establish persistent infection in cell culture, despite the fact that it does not cause persistent infection in-vivo (1).

The precise oral infective dose of HAV in humans remains ill-defined. After oral inoculation, HAV is thought to be transported across the intestinal epithelium by a vectorial transport process that is poorly understood and is taken up by hepatocytes. Uptake by HAV specific receptors is uncertain. The liver is the only target organ of injury and HAV genomic replication occurs exclusively in the cytoplasm of the hepatocyte. From the liver, HAV is transported through the biliary tree to the intestine. It’s resistance to inactivation by bile and intestinal proteolytic enzymes allow it to be shed in feces and facilitate fecal-oral transmission.

EPIDEMIOLOGY

HAV has a worldwide distribution and causes approximately 1.5 million cases of clinical hepatitis each year. Cases occur mainly in countries with high or intermediate risk of transmission (Figure 1), where poor sanitary conditions prevail. In 1995, HAV vaccination was recommended to persons at risk, and in
1999 this recommendation was extended to children living in areas with high prevalence of acute hepatitis A. As a result of these recommendations, the incidence of HAV declined substantially in the U.S. In 2001, a historically low 10,609 cases of HAV were reported in the U.S. (3.77 cases/100,000) (2). The actual number of cases was probably much higher. Other factors that have led to the decline in incidence include advances in hygiene, improved water supplies, enhanced sewage disposal, reduced crowding, and augmented food safety, among other factors. In the U.S., there have been cyclic outbreaks every five-to-10 years for decades. The incidence of HAV is higher in western states and among people five-to-39 years of age. Approximately one-third of the U.S. population has serologic evidence of previous HAV infection with a prevalence of 9% among children six-to-11 years old and 75% among persons 70 years and older (3).

The virus is typically transmitted from person to person through the fecal-oral route and through ingestion of contaminated food or drinks. Greater than 75% of adults with acute HAV have symptoms while 70% of children less than six years of age are asymptomatic (4). These characteristics contribute to the stealth and efficient spread of the virus. It is spread easier from asymptomatic young children to other young children and to adult contacts. Thus, young children are thought to be the primary reservoir and dominant source of transmission in the community. Fecal shedding of HAV starts before the onset of symptoms of acute infection and lasts as long as three months after initial diagnosis, providing ample time for the fecal-oral transmission to susceptible hosts (5). Parenteral transmission of hepatitis A via blood or blood product transfusions has been documented (6,7) and may partially explain the increased prevalence of acute hepatitis A infection among injection drug users.

Evidence suggests that the epidemiology of HAV is heterogeneous. CDC surveillance program showed that 52% of patients could not identify the source of infection (8). Household or sexual contact with a person with HAV (12%) and history of injection drug use within six months before onset of illness (14%) were the two most commonly recognized risk factors. Other risk factors include attendance or employment at daycare center, male homosexual activity within the previous six months, and recent international travel to countries where HAV is endemic (8).

**CLINICAL FEATURES**

HAV is an acute disease, with rare but well documented relapses that may occur between 30 to 90 days after the primary episode (9). Extrahepatic manifestations can occur in rare cases (Table 1). No chronic sequelae occur once HAV has resolved. Rarely, HAV-related nephrotic syndrome and subsequent chronic kidney disease has been described (10). There is no chronic carrier status. There are four main clinical presentations of symptomatic HAV (11):

1. **Classical HAV**—A mild prodromal illness (fever, headache, malaise, fatigue, nausea, vomiting, and diarrhea) develops one week before onset of dark urine. This usually prompts patients to seek medical attention. This may be followed by clay-colored stools and jaundice. On physical exam, the patient may have tender hepatomegaly, splenomegaly, and posterior cervical lymphadenopathy. This usually heralds the resolution of prodromal symptoms (convalescent phase). This presentation occurs in over 80% of symptomatic cases, is self-limited, and is usually less than eight weeks in duration.
2. **Relapsing HAV**—occurs in 4%–20% of symptomatic patients. There are usually two or more bouts of acute HAV over six-to-10 weeks with symptom-free intervals (9).

3. **Cholestatic HAV**—occurs in 10% of symptomatic cases. It is characterized by a prolonged course lasting weeks to months including fever, marked pruritus and jaundice. Serum bilirubin may remain elevated for months, but complete resolution by six months after initial presentation is the norm (12).

4. **Fulminant HAV**—accounts for 0.35% of all HAV cases and approximately 3% of patients presenting with acute liver failure in this country (13). It is the most severe form of symptomatic HAV. The presentation usually consists of worsening jaundice, encephalopathy, and prolongation of the prothrombin time within the first week (55%) or first month (80%) of symptom onset. Patients above age 40 (14,15) and chronic liver disease patients, particularly those with chronic hepatitis C, are at higher risk of fulminant hepatic failure from acute HAV. The development of renal insufficiency, need for vasopressor agents and intubation predict a poor outcome often necessitating liver transplantation (13). Patients evolving to fulminant failure typically have low or undetectable HAV-RNA levels in blood and high serum bilirubin levels. This suggests that liver failure may be due to an excessive immune response associated with marked reduction in viral load (16).

A variety of extrahepatic manifestations of HAV have been described (Table 1). An evanescent rash and arthralgias are the most common, occurring in approximately 11% and 14% of patients, respectively. The development of extrahepatic manifestations may be more common in patients who have protracted disease, such as relapsing or cholestatic hepatitis.

Acute hepatitis A during pregnancy may be associated with a higher risk of maternal complications. A recent series from Israel (17), reported an increased incidence of premature rupture of membranes, premature contractions and vaginal bleeding among pregnant patients developing acute hepatitis A. Consultation with high-risk obstetrics specialist is recommended when acute hepatitis A is diagnosed during pregnancy.

### Diagnosis

The diagnosis of acute HAV infection rests on the clinical presentation together with typical serologic findings. Liver related enzyme test abnormalities are not specific for HAV. Enzyme elevations do not correlate with disease severity or prognosis. A prolonged prothrombin time may reflect extensive hepatocellular necrosis and may predict mortality.

The detection of anti-HAV IgM in the appropriate clinical context is diagnostic. HAV-IgM is detected one-to-two weeks after exposure to HAV and persists for three-to-six months. HAV-IgG is detectable five-to-six weeks after exposure and persists for decades. It may confer lifelong protection against HAV. Total anti-HAV measures both IgM and IgG. A positive total anti-HAV with negative HAV-IgM indicates immunity (post-infectious or vaccination).

### Treatment

Treatment is largely supportive and the management is usually on an outpatient basis. Acute infection can be prevented with immune globulin treatment within two weeks of exposure, or by administering the hepatitis A vaccine within three-to-four weeks of travel. Approximately 13% of acute cases require hospitalization due to the presence of dehydration, coagulopathy, encephalopathy, or other evidence of severe disease (8). Most patients
experience complete clinical and biochemical resolution within three-to-six months from disease onset.

PREVENTION

The development of HAV replication in cell culture over 25 years ago resulted in the ability to produce large quantities of the virus, paving the way to vaccine development. Over the years, several vaccines have been developed (18). Good general hygiene is central to the prevention of HAV, especially in environments such as day-care centers. Good public water sanitation and food hygiene are also important (4).

Standard immunoglobulin is most often used for post-exposure prophylaxis of HAV infection (Table 2). It is at least 85% effective in preventing symptomatic HAV when given within two weeks after exposure (4). It should be given to an unvaccinated person who has household or sexual contact with someone with HAV. Other situations when the administration of standard immunoglobulin should be considered include attendees and employees at day-care centers where HAV has been identified, coworkers of food handlers with HAV, and possibly persons exposed to HAV through a common source outbreak (19). In cases of recent exposure, HAV vaccine should also be considered and administered at a separate site to provide long-lasting immunity. For post-exposure prophylaxis, the dose is 0.02 mL/kg. For travelers, the dose of 0.02 mL/kg protects for up to three months while 0.06 mL/kg protects through five months. Hepatitis A vaccination administered to travelers at least two weeks prior to departure may be as effective as the immune globulin and, if followed by a second injection in six to 18 months, will provide long-lasting immunity.

Two inactivated HAV vaccines are FDA approved for administration in the U.S. Havrix (GlaxoSmithKline) and VAQTA (Merck & Co., Inc.) are the two approved vaccines. Havrix contains a preservative (2-phenoxethanol), where VAQTA does not. A combination hepatitis A/hepatitis B vaccine (Twinrix; GlaxoSmithKline) is approved for use in adults. Two doses are needed of the HAV vaccine, given six-to-18 months apart. The second dose is important to achieve sustained immunity against HAV. Protective antibody levels should last at least five-to-ten years and perhaps longer. Both vaccines are well tolerated, although anaphylaxis has been reported.

The Centers for Disease Control (CDC) recommends hepatitis A vaccination for the following persons (Table 2): travelers to countries with high or intermediate rates of disease, men who have sex with men, users of illicit drugs, persons who have chronic liver disease or who have received or will receive a liver transplant, persons who use clotting-factor concentrates, and laboratory personnel who work with the hepatitis A virus or with non-human primates that are infected with hepatitis A (8). Recently, the Advisory Committee on Immunization Practices of the U.S Centers for Disease Control and Prevention recommended universal childhood immunization against HAV.

The current average estimate of HAV infection in non-immune travelers is 0.1 per 1000 per trip to an at-risk destination (19). Most experts, including the WHO and CDC, recommend immunization of “all susceptible persons” visiting at-risk destinations. Consultation with a travel clinic can be helpful for travelers in this regard.

| Table 2 |
| Indications for HAV vaccine or immune globulin |
| HAV vaccine |
| • Children 2 years of age in areas with high rate of infection |
| • Travelers of at least 2 years of age to areas with high or intermediate rates of disease |
| • Homosexual men |
| • Users of illicit drugs |
| • Persons with chronic liver disease or who have received or will receive a liver transplant |
| • Persons who use clotting-factor concentrates |
| • Laboratory personnel who work with HAV or with non-human primates that are infected with HAV |
| Immune globulin |
| • Persons traveling to countries with high or intermediate rates of disease within next two weeks |
| • Children younger than two years of age traveling to countries with high rates of disease |
| • Post-exposure prophylaxis, within 14 days after exposure: persons who have been exposed to food that was handled by someone with acute HAV who had either poor hygiene or diarrhea or persons exposed to a family member with acute HAV |
Patients with chronic liver disease also deserve special attention in relation to HAV vaccination. A number of studies have shown that acute HAV superimposed on chronic liver disease is associated with a more severe clinical course and a higher mortality rate (20–24). A meta-analysis of 18 publications examined the clinical course of acute hepatitis A in patients with chronic liver disease; the mortality rate ranged from 0% to 100% but was generally high in most reports (24). The CDC includes patients with chronic liver disease as candidates for vaccination against HAV. A large multicenter study supports this recommendation (25). The safety and immunogenicity of the vaccine has been confirmed in patients with mild-to-moderate chronic liver disease, although patients with advanced or decompensated liver disease were excluded, and are less likely to respond (25). HAV vaccination should be administered early in the natural history of chronic liver disease to maximize response. Pre-vaccination testing for anti-HAV is reasonable in this population, as higher levels of prior exposure to HAV have been documented among patients with chronic liver disease (26). Post-vaccination testing to confirm a response is generally not recommended due to the high likelihood of antibody response in healthy subjects and patients with mild-to-moderate chronic liver disease.

CONCLUSION

Hepatitis A remains an important cause of acute hepatitis in the United States and throughout the world. Improved sanitation and hygiene as well as vaccination has led to declines in HAV infection rates in developing countries. However, sporadic outbreaks still occur. Older adults and patients with chronic liver disease represent patients in which HAV can have a severe clinical course. Universal childhood immunization against HAV in all regions of the country, as recently recommended by the Advisory Committee on Immunization Practices of the U.S. Centers for Disease Control and Prevention, may help decrease the incidence and impact of HAV in this country. ■

References