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Hepatitis A:

Epidemiology, Natural History, Unusual Clinical Manifestations, and Prevention

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Keywords

Hepatitis A virus; Hepatitis A vaccine; Acute liver failure; Hepatitis A outbreak; Hepatitis A prevention

INTRODUCTION

Early studies in viral hepatitis noted 2 distinct patterns of infection, suggesting the involvement of multiple hepatitis viruses.[1] For several years, these 2 patterns of infection were dubbed “infectious hepatitis” for clinically apparent infection and “serum hepatitis” for clinically inapparent infection. After discovery of the Australia antigen, serum hepatitis was renamed hepatitis B, and infectious hepatitis was renamed hepatitis A.[2] The hepatitis A virus (HAV) was characterized in 1973 by Feinstone and colleagues.[3] It is transmitted by a fecal-oral route, causing a self-limited infectious hepatitis, but can also cause large epidemics through person-to-person contact.[4] HAV is a positive-sense RNA virus in the *Herpavirus* genus of the Picornaviridae family, with 4 genotypes characterized in humans. It is a nonenveloped small (27 nm) particle in an icosahedral shape.

Most HAV infections that occur in developing countries are not clinically apparent and cause no symptoms, likely because of partial immunity in endemic areas. In contrast, infections in developed countries often are characterized by jaundice and an acute hepatitis, especially in adolescents and adults. HAV cannot cause chronic infection, unlike hepatitis B and C.[4] Diagnostic testing for HAV is readily available as is a commercial HAV vaccine[5] (Table 1).

EPIDEMIOLOGY

HAV infections are seen around the globe, with greater prevalence in developing countries and low-income regions.[6] HAV is hyperendemic in sub-Saharan Africa and South Asia, with nearly no at-risk adults because of the frequency of early childhood exposure. Intermediate

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DISCLOSURE

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endemicity is seen in Latin America, the Middle East, North Africa, Eastern Europe, and middle-income regions in Asia.[7] Countries with stronger economies, such as the United States and countries in Western Europe, have lower rates of HAV infection, but the susceptibility of their nonimmune adult population becoming ill from HAV is much higher than the lower-income countries.[8,9] There is a paradoxic effect with regards to HAV in countries that are demonstrating upward mobility intheir economy. The first HAV exposure in their citizens occurs later in life when compared with lower-income countries, ultimately posing a difficult public health problem in their HAV epidemiologic transition.[10]

HAV is transmitted feco-orally between people in close contact with each other.[11] Transmission commonly occurs from children to their parents, one of the reasons that daycare centers are often implicated in HAV spread.[12] HAV from food and water contamination often involves a food service worker who did not appropriately wash hands and sanitize after defecation.[13] Fresh produce can be a culprit in spreading HAV infection, because the virus is difficult to wash off surfaces of fruits and vegetables.[14] Contaminated water, whether by inadequate chlorination or by poor irrigation infrastructure, leads to both contained and epidemic infections.[15] Transient viremia after initial acquisition is responsible for rarely seen parenteral transmission.[16] Risk factors in developed countries include men having sex with men (MSM), travel to an endemic country, and intravenous drug use.[17–19] Developed countries remain with locales where HAV is endemic, as seen in Native American tribes in the western United States.[20]

HAV outbreaks occur and commonly are associated with poor sanitary conditions. Outbreaks are often related to water contamination and inadequate sewage disposal in both developing and developed countries.[21] Outbreaks in higher-income nations are often linked to a source of contaminated food or water.[22] Shellfish are associated with HAV transmission because of their water filtration effect, which effectively concentrates the virus, and have been the cause of prior large epidemics.[23]

A recent HAV outbreak that reached international attention was the San Diego outbreak, with 590 confirmed cases between November 22, 2016 and June 21, 2018 of genotype 1b HAV in San Diego, California. Most cases were either boys or men, and major risk factors included homelessness, injection drug use, and MSM. Approximately 17% of cases were hepatitis C virus coinfected, and 5% of cases were hepatitis B virus (HBV) coinfected. The San Diego outbreak, and more recently, an outbreak in Michigan highlight that the epidemiology of HAV outbreaks may be shifting from contaminated food and water to poor sanitation revolving around homelessness, overcrowding, and injection drug use.[9] The same pattern is being seen in the now ongoing Kentucky outbreak, with more than four thousand infections and 43 deaths.[24] The outbreak is largely spread by patients using drugs and without stable housing, as was the case in San Diego. Challenges in hepatitis A vaccination in rural Kentucky and limited funding and resources to acquire vaccine were thought to be the major reasons this outbreak is now the largest and deadliest in the United States.[25]

NATURAL HISTORY

After a nonimmune subject acquires HAV, the virus is taken up through the enterohepatic circulation and enters the liver, where it replicates.[26,27] HAV has been shown to be able to infect enteric cells in culture,[28] but there seems to be no evidence of significant replication in the gut. Virions can be detected in stool and blood before onset of symptoms. Several days later, serum transaminases rise. Prodromal symptoms occur about a month following exposure and can consist of fever, malaise, nausea, vomiting, and anorexia. Prodromal symptoms are common in adult infections but not as much in children.[4] Adult infections will typically also be characterized by jaundice, diarrhea, and hyperbilirubinemia, peaking 7 to 10 days after the onset of jaundice. Jaundice will typically resolve much faster than the malaise and anorexia, which can last for months. Pediatric infections will often be asymptomatic or have very few symptoms.[29]

UNUSUAL CLINICAL MANIFESTATIONS

Acute liverfailure from HAV is rare, occurring in about 1 in every 300 cases, and very infrequently results in death or the need for liver transplantation.[30] A relapsing hepatitis is infrequently seen in adult infections with recurrent symptoms typically occurring within 6 months of prior infection. Relapsing hepatitis is characterized by shedding of HAV in the stool and elevated transaminases. Occasionally, the elevation in transaminases will be asymptomatic.[31] Hepatitis A–associated prolonged cholestasis has also been reported after infection, for periods up to 1 year.[32,33] Extrahepatic manifestations previously reported include rash, kidney injury, myocarditis, and Guillain-Barre syndrome.[34]

DIAGNOSIS

Diagnosis of HAV infection is typically confirmed by serologic evidence of a recent infection, that is, detection of immunoglobulin M (IgM) antibodies against HAV. Concordance between assays is high, but there is about a 10% reported rate of discrepancy.[35] IgM antibodies typically peak about a month after exposure and can persist for up to a year. False negative results can be seen in early infection, while the patient is viremic and interval antibody retesting should be considered.[26,36] False positive results have been reported in a variety of scenarios, including patients with rheumatoid factor or other autoimmune disease.[37] IgM antibodies to HAV can be detected in the setting of recent HAV immunization or recent HAV vaccine boosting.[38,39] IgG response typically follows IgM response after 1 week, typically persists for life, and confers neutralizing activity to future HAV exposures. Durability of IgG response may be limited in immunosuppression, as previously demonstrated in human immunodeficiency virus (HIV) -infected persons with an absence of detectable HAV antibodies several years after vaccination[40] (Fig. 1).

Serum detection of HAV RNA can be technically done but rarely used in diagnosis of acute hepatitis A infection. Hepatitis A viremia is detectable in serum of immunocompetent hosts within a few days of infection and persists for 3 to 4 weeks.[41] Immunosuppressed patients may have persistent hepatitis A viremia beyond 4 weeks.[42] HAV RNA has also been detected in stool and saliva of infected hosts, but at much lower concentrations than serum.[43]

RNA can be detected by real-time polymerase chain reaction (PCR) or nested PCR methods. Molecular characteristics of HAV, although not important in diagnosis, have been used in epidemiologic studies and can assist in phylogenetic analysis of early outbreaks and epidemics.[35]

TREATMENT

The treatment of acute hepatitis A is supportive.[44] Liver failure from hepatitis A is rare, but is estimated to occur in less than 5% of cases.[45] Immediate referral to a transplant center is critical for cases of HAV-associated fulminant liver failure.

Therapeutics has been previously investigated for cases of HAV-associated liver failure. ALF-5755, a C-type lectin, was administered to 10 subjects with HAV-associated liver failure. There was no evidence of improvement in transplant-free survival rate.[46] N-acetylcysteine, although shown to be very effective for acetaminophen-induced liver failure, does not seem to confer any benefit for HAV-associated acute liver failure.[47]

Interferon (IFN) as a treatment of acute hepatitis A infection has been previously evaluated and shown to be effective in cell cultures.[48] Case reports of IFN treatment of acute hepatitis A are limited, and its utility is unclear.[49] Direct-acting antivirals have been evaluated in cell culture systems and shown to have potential effectiveness in inhibiting HAV replication and in antiviral activity.[50–52] Drug development and clinical trials are limited by difficulty in enrolling subjects before they resolve their infection to measure potential outcomes of intervention.

PREVENTION

Sanitation measures play an important role in HAV infection prevention, including but not limited to careful attention to hygiene, particularly in the food service industry.[53] Food service workers who are ill with jaundice of unclear cause should be restricted from work. Hospitalized patients with HAV should be on enteric precautions for 1 week after the onset of jaundice, when viral shedding in the stool is at its highest.[54]

Prevention of HAV by vaccine is the standard approach across much of the world, and many countries have adopted universal vaccination against HAV in their children[55] (Table 2). HAV vaccine is also a mainstay of postexposure prophylaxis.[56] The United States offers 2 commercially available hepatitis A vaccines and 1 combination HAV-HBV vaccine.[57] The HAV vaccine is typically administered in 2 doses, 6 months apart, whereas the HAV-HBV vaccine usually requires 3 doses.[58] Live-attenuated HAV vaccines are used in China with good success.[59]

The efficacy of both live-attenuated and inactivated vaccines has been well established in large trials across the globe collectively encompassing nearly 750,000 patients.[60] Both vaccines confer a protective effect against hepatitis A when given before exposure. Immunogenicity of the 2 HAV vaccines in the United States, when compared head to head, was equal.[61] An antibody titer greater than or equal to 20 mIU/mL is thought to be protective.[62] Lower protection rates following vaccination are observed in

immunosuppressed persons, including HIV infection, inflammatory bowel disease, and organ transplant recipients.[63]

Nonvaccinated persons traveling to HAV endemic regions should have a single dose of vaccine before their departure.[64] Persons with chronic liver disease, the elderly, and the immunocompromised should receive both vaccine and immunoglobulin at 0.02 mL/kg at a separate injection site.[56,65] Postexposure prophylaxis for HAV is best achieved with either HAV vaccine or immunoglobulin, and both seem to be equally effective.[66,67]

SUMMARY

HAV continues to be a global health issue, with the highest rates in lower-income countries. Infections are typically linked with contaminated food or water and almost always tied to poor sanitary conditions. Treatment is supportive, and there are no drug therapies available for acute hepatitis A infection. Vaccination is the most effective form of prevention and is also used in postexposure prophylaxis. Universal vaccination for HAV in children should be adopted whenever possible and has been shown to reduce HAV burden around the globe.

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KEY POINTS

- Hepatitis A occurs around the world and causes an acute hepatitis, which is typically subclinical.
- Clinical illness is not common in endemic areas because of early childhood exposures, but poses a large risk to travelers from nonendemic areas.
- Diagnosis of hepatitis A typically requires serologic testing.
- Jaundice, anorexia, right upper quadrant pain, and elevated alanine aminotransferase levels are classically described in acute hepatitis A.
- Hepatitis A is preventable through vaccination.

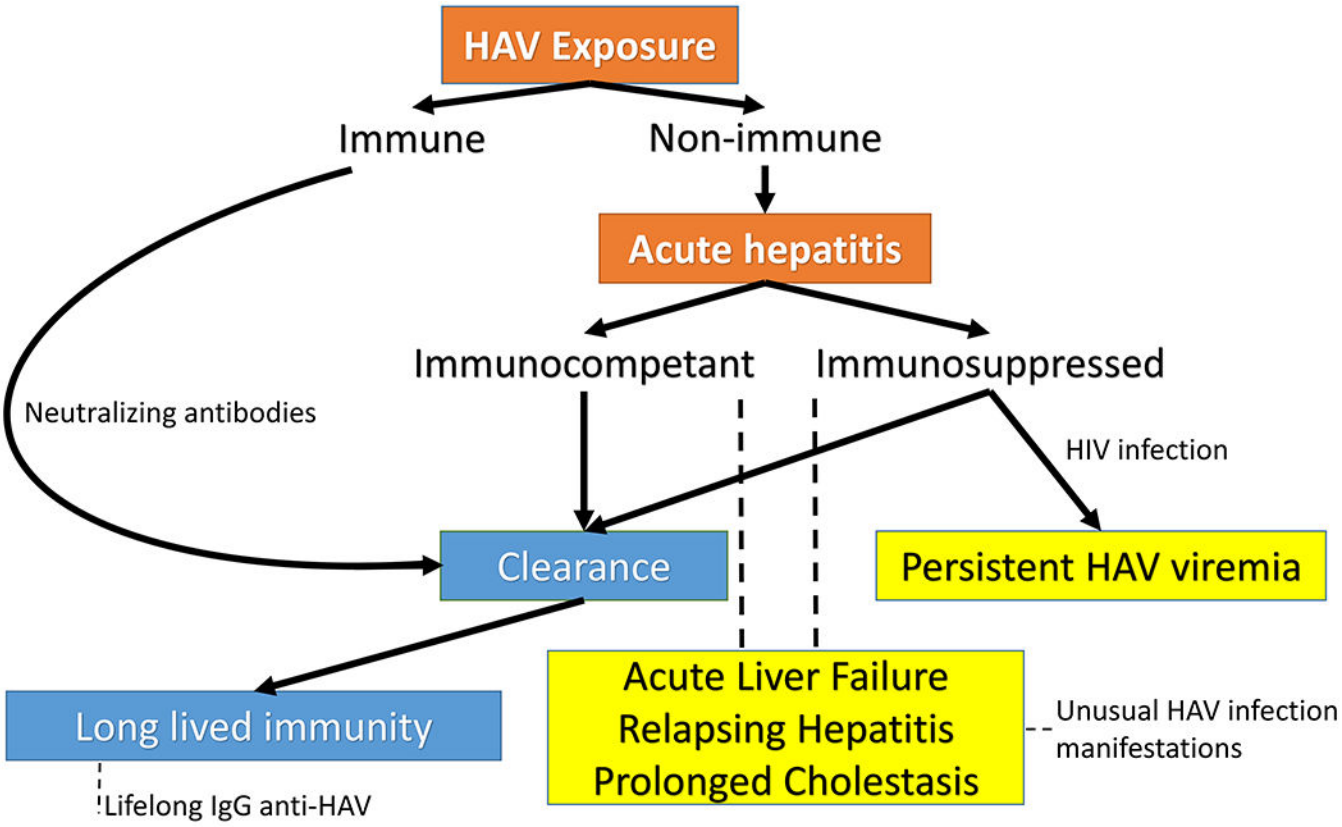

Fig. 1.

Effects of HAV exposure in immunocompetent and immunosuppressed patients. Patients immunized against HAV before exposure can clear the virus via preformed neutralizing antibodies. Nonimmune patients who are immunocompetent typically clear the virus after the infectious hepatitis, whereas immunosuppressed patients may sustain a chronic viremia. In rare cases, both immunocompetent and immunosuppressed hosts may manifest an unusual presentation of HAV, including but not limited to liver failure, relapsing hepatitis, and prolonged cholestasis.

Table 1

Hepatitis A in a nutshell

Epidemiology	Estimated 1.4 million cases per year globally Infections can be sporadic or epidemic
Transmission	Fecal-oral via Person-to-person contact Consumption of contaminated food or water
Diagnosis	Presence of IgM antibodies to HAV
Treatment	Supportive
Classical presentation	Children Asymptomatic Adults Jaundice, hyperbilirubinemia, RUQ pain, anorexia
Unusual presentations	Relapsing hepatitis Prolonged cholestasis Acute liver failure
Prevention	HAV vaccine
Postexposure prophylaxis	HAV vaccine HAV immune globulin

Abbreviation: RUQ, right upper quadrant.

Table 2

Vaccine preparations in the United States and populations that are recommended to receive HAV vaccine

Vaccine Name	Protects Against	Dosing Schedule	Relevant Populations
Havrix	HAV	Two doses 6 mo apart	Children 1–2 y old
Vaqta	HAV	Two doses 6 mo apart	Travel to endemic area
Twinrix	HAV, HBV	Three doses at 0, 1, and 6 mo	MSM PWID Chronic liver disease Health care workers

Abbreviation: PWID, people who inject drugs.