Enterically Transmitted Viral Hepatitis: Hepatitis A and Hepatitis E

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Acute hepatitis is an important public-health concern as a substantial majority are caused by a variety of hepatitis viruses. By the 20th century, it was clear that acute hepatitis consisted of two separate diseases, namely infectious hepatitis and serum hepatitis, acquired through enteric and parenteral routes, respectively. Enterically transmitted viral hepatitis caused by hepatitis A virus (HAV) and hepatitis E virus (HEV) are associated with both sporadic infections and epidemics in areas with poor sanitation and weak public-health infrastructures. Recently, the geographical distribution and modes of transmission of these agents and their clinical presentations have been shown to be much broader than were previously believed. This review focuses on the subject of HAV and HEV infection, an area of continuing expansion of knowledge and change. The genomic structure of the nucleotide sequence variation within the 5′ non-coding region, structural protein regions, non-structural protein regions, and a 3′ non-coding region. The large open reading frame (ORF) of the HAV genome is divided into three functional regions. The aminoterminal third of the viral genome encodes the major capsid polypeptides, and the remaining two thirds encode nonstructural proteins largely required for viral replication. The nucleotide sequence variation within the VP1/2A region of the genome has been used to define genotypes and subgenotypes. The seven genotypes are differentiated into four human clusters (I-III and VII) and three simian strains (IV-VI). Genotype I is most prevalent worldwide, and subgenotype IA is more common than IB.

Epidemiology: Worldwide, the endemcity of HAV infection varies according to regional hygienic standard, and the highest prevalence of infection occurs in regions with the lowest socioeconomic levels. Although the incidence of hepatitis A has declined over the past decade, primarily because of hepatitis A immunization, it remains a frequently reported disease. The most common reported source of infection is household or other close contact with an infected person. Other potential sources of infection include men having sex with men, travel to regions of high HAV endemicity, and illicit drug use. Contaminated food and water are an infrequent source of infection, although they have been associated with outbreaks. Rarely, transmission by parenteral route has been documented following blood transfusion or the use of blood products.

Clinical Manifestations and Outcomes: The clinical spectrum of HAV infection ranges from asymptomatic infection to fulminant hepatitis. After an incubation period of 15 to 50 days (average period, 28 days), most patients develop nonspecific constitutional signs and symptoms followed by gastrointestinal symptoms. Clinical manifestations of hepatitis A are dependent on the age of the patients. In children younger than 6 years of age, 70% of infections are asymptomatic. In contrast, infection is usually symptomatic with jaundice occurring in more than 70% of older children and adults. Mortality and the need for hospitalization increase with age. There is no evidence of chronic liver disease or persistent infection following infection. However, 15 to 20% of the patients have prolonged or relapsing disease lasting up to 6 months, with prolonged excretion of HAV. Fulminant hepatitis is a rare complication of hepatitis A, with a reported incidence from 0.015 to 0.5%, and the highest rates occur among young children and older adults with underlying chronic liver disease. Fortunately, HAV-related fulminant hepatitis resolves spontaneously more frequently than fulminant hepatitis of other etiologies. Unlike hepatitis E, acute hepatitis A does not increase mortality in pregnant women, although, it is associated with a higher risk of maternal complication and preterm labor, despite the relatively mild features of the disease.

Extrahepatic manifestations of hepatitis A, such as autoimmune hemolytic anemia, aplastic anemia, pure red cell aplasia, pleural or pericardial effusion, acute reactive
arthritus, acute pancreatitis, acalculous cholecystitis, mononeuritis, and Guillain-Barré syndrome, have been rarely reported.

**Diagnosis:** Current serologic tests provide the foundation for diagnosis of hepatitis A and HAV infection. The determination of IgM anti-HAV in serum has been used as the primary marker of acute HAV infection. It can be detected at the early onset of symptoms and usually remains positive for approximately 4 to 6 months after the onset of infection. A small proportion (8%-20%) of vaccinated persons have a transient IgM anti-HAV response. IgG anti-HAV is also positive at the onset of the disease and remains detectable usually for life. It is interpreted as a marker of previous infection.

Recent advances in methods to identify and characterize nucleic acid markers of viral infection have provided the foundation for the field of molecular epidemiology of hepatitis A. The determination and analysis of molecular biomarkers (e.g., nucleic acid sequencing or phylogenetic analysis) have been used to determine the genetic relatedness of organisms to identify and track modes and chains of transmission in host populations.

**Treatment:** Hepatitis A is usually a self-limiting disease, and in most cases will resolve without sequelae. Therefore, treatment typically consists of supportive care including adequate hydration, nutritional support, use of antiemetics for severe vomiting, and cautious use of antipyretics for high fever. Considering that acute kidney injury or hemolytic anemia may complicate hepatitis A, regular renal function testing along with complete blood analysis should be performed. In the case of cholestatic variants of acute hepatitis A, corticosteroids are used to relieve severe symptoms. Although, persistent aminotransferase elevation and viral excretion with progressive hepatic fibrosis have been reported. Therefore, corticosteroid treatment should be used with caution for a relatively benign variant.

**Prevention:** Sanitary measures and immunoprophylaxis are the principal means of prevention for HAV infection. The inactivated hepatitis A vaccines available worldwide are safe and effective. A single dose provides excellent short-term protection for up to 2 years in young adults, and the second dose is important for long-term protection. Recommended target populations for the hepatitis A vaccine include persons at increased risk of acquiring infection or having poor prognosis after infection, such as travelers to areas with poor hygiene standards, patients with underlying chronic liver disease, hemophiliacs, intravenous drug users, and men who have sex with men.

For post-exposure prophylaxis, passive immunization with immunoglobulin should be administered within 2 weeks of exposure. However, from the basis of encouraging results from a randomized trial comparing the effect of immunoglobulin and hepatitis A vaccine after exposure, the use of hepatitis A vaccine has been preferred over immunoglobulin. Hepatitis A vaccine as post-exposure prophylaxis offers a number of advantages over immunoglobulin including long-term protection, easy administration, and more abundant supply. However, immunoglobulin remains the first choice for post-exposure prophylaxis in older persons or those with chronic liver disease who are likely to have severe illness if infected with HAV.

**Hepatitis E**

HEV was initially called the enterically transmitted non-A, non-B hepatitis virus. Subsequently, it was named as the HEV, based on its enteric transmission and association with hepatitis epidemics. This single-stranded, positive-sense RNA virus is classified in genus Hepeviridae of the family Hepeviridae. Four major genotypes of mammalian HEV have been recognized as species genotype 1 and 2 strains exclusively infect humans, whereas genotype 3 and 4 strains infect humans and several other mammalian species. The genome contains short 5' and 3' nontranslated regions which consist of three overlapping ORFs. The ORF1 encodes a nonstructural polyprotein containing domains with methyltransferase, papain-like cysteine protease, helicase and RNA-dependent RNA polymerase, which are required for viral replication. The ORF2 encodes for the capsid protein, which is involved in virion assembly and immunogenicity. The ORF3 overlaps the capsid gene and encodes a small protein that may have regulatory properties.

**Epidemiology:** An estimated one third of the world’s population living in the developing countries has been infected with HEV. Over a wide geographic area, two distinct epidemiological patterns have been observed. In high-endemic regions, such as tropical and subtropical countries in Asia, Africa, and Central America, HEV presents as outbreaks and also as sporadic cases with acute self-limited hepatitis. The transmission is feco-oral, usually through contaminated drinking water following heavy rainfall or leaky water pipes passing through sewage-contaminated soil. HEV isolates from these regions mainly belong to genotype 1 and 2 whereas genotype 3 and 4 viruses have been isolated from some sporadic cases. The animal reservoirs of HEV responsible for maintaining the disease in high-endemic regions remains unclear. In regions with low endemicity, such as the US, Western Europe, and developed countries of Asia-Pacific, the disease was previously believed to be associated with travel to endemic areas. However, in recent years, several observations suggest that autochthonous (locally-acquired) hepatitis E in these areas is possibly caused by zoonotic spread of infection from pigs, wild boars or deer. Contaminated shellfish have also been proposed as a potential vehicle. The HEV isolates from such cases have belonged to genotype 3 and 4, which also infect animals.

**Clinical Manifestations and Outcomes:** In high-endemic areas, a self-limiting acute icteric hepatitis is the most common recognizable form of illness, indistinguishable from that caused by other hepatotropic viruses. However, HEV infection may be largely asymptomatic, since most of the seropositive individuals in these regions do not recall having jaundice. The incubation period after exposure to HEV has ranged from 2 to 10 weeks, with an average of 6-7 weeks. Two phases of illness have been described: 1) the prodromal and pre-icteric phase is characterized by flu-like symptoms, and 2) the icteric phase is usually heralded by the appearance of darkening of urine before jaundice becomes apparent. Hepatitis E predominantly affects adolescents and young adults aged 14-40 years with an overall fatality rate of 0.5% to 4% among hospitalized patients, although case-fatality rates in population surveys during outbreaks are much lower (0.07%-0.6%). Some patients experience a prolonged cholestatic hepatitis, though usually with good outcome. HEV superinfection may occur in patients with pre-existing liver disease who can present as acute-on-chronic liver disease with a higher risk of a poor outcome. During outbreaks, pregnant women have a higher disease attack rate, and have a poor prognosis with mortality rates of up to 30%.
In areas with lower disease prevalence, clinical presentations in these regions are generally similar to those in high-endemic areas, except that most patients are middle aged or elderly men with co-existing illnesses. Hence, hepatitis E is frequently misdiagnosed as drug-induced liver injury since tests for HEV infection are neither available nor routinely done. The mortality rate is somewhat higher in these populations, probably due to older age and underlying disease. Of particular concern in these regions is the development of persistent HEV infection among organ transplant recipients, HIV infected and other immunocompromised individuals who had HEV infection with genotype 3 and have recently developed unexplained chronic hepatitis. Serial liver biopsies in such cases showed development of liver fibrosis, suggesting the possibility of progression to cirrhosis.

**Diagnosis:** The diagnosis of hepatitis E in individual patients remains problematic. HEV nucleic acid detection using amplification techniques can provide detection of HEV infection and also allow identification of viral genotype. Unfortunately, the detection of HEV nucleic acid is not useful to diagnose acute infection as it is undetectable in the symptomatic phase of the illness. Thus, the diagnosis of hepatitis E primarily depends on serological tests for anti-HEV antibodies. Commercially available enzyme immunoassays are based on immunodominant parts of the ORF2 and ORF3 proteins. In endemic countries, the detection of IgM anti-HEV indicates acute HEV infection, although the assay may fail to detect about 40% of the patients. In non-endemic areas, IgG anti-HEV has been used to screen for acute hepatitis in travelers who have returned from endemic areas. However, recent reports of high anti-HEV seroprevalence rates in these regions suggest that this may not be an appropriate approach.

**Treatment:** Considering that the illness is usually self-limited, the mainstay of therapy is supportive care. Patients with liver failure need admission to an intensive care unit, and should be considered for liver transplantation. There is no available data on the role of antiviral drugs in acute HEV infection. However, pegylated interferon alpha or ribavirin for 3-12 months have been used to induce a sustained virological response in patients with chronic HEV infections.

**Prevention:** As with other enterically transmitted diseases, effective prevention relies primarily on public sanitation and education about personal hygiene. During outbreaks, boiling and chlorination of water are useful to inactivate the virus. In areas with zoonotic transmission, sanitary handling and proper cooking of pig and deer meat is recommended. Isolation of affected persons is not recommended as person-to-person transmission is uncommon. However, infected persons should not be involved in preparation and handling of food until their symptoms have fully resolved.

Experimental hepatitis E vaccines based on recombinant protein derived from the capsid gene of HEV have been shown efficacious in macaques conferring cross-protection against various genotypes. To date, only two vaccine candidates have progressed to the stage of clinical evaluation. In a Phase II trial among 2,000 volunteering Nepalese soldiers, three doses of the rHEV vaccine expressed in baculovirus achieved 100% seroconversion and protective efficacy of up to 95% over a 2-year follow-up. Recently, a phase III trial of three doses of the HEV 239 vaccine involved 112,604 healthy Chinese adults and showed a protective efficacy of 100% and no vaccine-related adverse events during a 13-month follow-up. Despite the successful trials of the vaccine, no approved vaccine against hepatitis E is commercially available, possibly because pharmaceutical companies are not assured of a sufficient market.

**CONCLUSION**

Although hepatitis A and E, the enterically transmitted hepatitis viruses, are mostly self-limiting and rarely fatal, they lead to substantial diseases, and economic burden. Improved sanitation and hygiene as a result of socioeconomic development, and health education are crucial for preventing transmission of hepatitis A and E. The strategy of active immunization against hepatitis A locally depends on endemicity of the infection. UnlikeHAV, an approved HEV vaccine is not available. Hence, prevention of HEV infection should rely on personal, food, and environmental hygiene. Continuous monitoring of the seroprevalence of both viruses is essential to inform the latest epidemiological pattern for public health interventions.