Jorge L. Herrera, M.D., Series Editor

Hepatitis E Virus Infection

by S. Bennet Hooks, C. Julian Billings, Jorge L. Herrera

INTRODUCTION

The hepatitis E virus (HEV) is a single stranded RNA virus that is transmitted via the fecal-oral route. This virus has been the etiology of large-scale hepatitis outbreaks in developing countries and has been identified as being the single most important cause of acute clinical hepatitis among adults throughout Central and Southeast Asia. It was initially identified in 1983, cloned in 1991, and has been studied more carefully over the last decade (1). Investigation of this virus has revealed a more widespread prevalence than expected. In the immune competent host, hepatitis E does not cause chronic liver disease, but the endemic nature of this disease in developing countries and its mortality associated with pregnancy make this an important illness to consider in patients presenting with acute hepatitis, particularly after recent travel to endemic areas.

VIROLOGY

HEV is a nonenveloped, single stranded, positive-sense RNA virus. It consists of three overlapping open reading frames. ORF-1 is believed to encode nonstructural proteins, ORF-2 is postulated to encode the capsid protein, and ORF-3 encodes a very small protein whose function is unknown. HEV has structural genes at the 3′ end and non-structural genes at the 5′ end, opposite of the genomic structure of the hepatitis A virus (HAV). Currently there are four genotypes of HEV virus; genotype 1 is most frequently associated with human disease (2). Genotype 1 is found most often in Asia, genotype 2 is found in Central and South America. Genotype 3 is similar to the HEV swine virus found in domesticated pigs in the mid-1990's. Genotype 4 has both human and swine strains and is typically found in Taiwan. After oral ingestion and uptake into the portal circulation viremia ensues. The virus accumulates in high concentrations in the bile and is excreted via stool. It is unknown if the virus replicates in the small bowel. Humoral immune response occurs providing diagnostic clues to the presence of HEV. IgM antibodies to HEV appear first, followed by IgG. The duration of IgG anti-HEV is unclear, but it may not last as long as HAV. Although the hepatitis A and E viruses are similar and cause a clinical picture that is indistinguishable without serologic testing, there are important virologic and clinical differences between the viruses, highlighted in Table 1.

S. Bennet Hooks, M.D., C. Julian Billings, M.D., Jorge L. Herrera, M.D., University of South Alabama College of Medicine, Mobile, AL.

EPIDEMIOLOGY

HEV is acquired via the oral-fecal route, similar to HAV. In endemic areas seroconversion of anti-HAV Ab typically occurs prior to five-years of age; in contrast, antibodies to HEV are typically not detected until early adulthood, with the exception of Egypt, where the prevalence of antibodies to HEV exceeds 60% by age 10 (2). In the world, hepatitis E is endemic to Asia, Northeast Africa, the Middle East and Mexico. Prevalence rates up to 70% have been found in these areas. Surprisingly in some areas of the United States, up to 20% of blood donors are seropositive for HEV; the prevalence is highest in those states that are large producers of swine (3).

HEV can infect humans, chimpanzees and certain species of macaques. Some strains of HEV are endemic in swine herds worldwide and are believed to be one source of human infection. Waterborne transmission is the most common cause of epidemic or

Table 1
Comparison for HEV and HAV

	Hepatitis E	*Hepatitis A*
Family	Hepeviridae	Picornaviridae
Genus	Hepevirus	Hepatovirus
Genotypes	Five (1,2: human; 3,4: human, swine; 5: avian)	Six (1,2,3: human; 4,5,6: simian)
Genome	Positive sense, single stranded RNA	Positive sense, single stranded RNA
Endemic seroconversion	1st decade of life	3rd decade of life
Incubation	~40 days	~30 days
Elevation of bilirubin	Yes, more common than HAV	Yes
Overall mortality	1%–4%	0.1%–2%
Mortality in Pregnancy	Up to 20%	no increase
Sex	No difference (except in pregnancy)	No difference
Chronicity	Possible if Immunocompromised	No

cluster cases of HEV. This has occurred in both tropical and subtropical regions. Bile (4) and others recorded epidemics of hepatitis E cases in Somalia along the Shebeli and Lower Shebeli Rivers. The rise in cases with the peaking river staging along with the higher attack rate in villages right on the river supports the waterborne transmission of this disease (4). The breakdown of a water purification plant in Pakistan in 1993 resulted in an outbreak of HEV with an attack rate of 10% of the population. The highest attack rate was in the communities in which the source of drinking water was exclusively from the treatment plant that malfunctioned. Termination of water supply from the aforementioned treatment plant resulted in a decrease of cases (5). In both of these epidemics it was noted that the attack rate was highest in individuals in their third decade of life.

Zoonotic transmission of hepatitis E from both domesticated and wild animals has been identified. The genotype 3 human HEV is similar to swine HEV suggesting the possibility of zoonotic transmission (6). Multiple cases of fulminant hepatic failure from HEV believed to be transmitted from pig livers exist in the literature (7,8). Other animals including wild boar, deer, cats and mongoose have been identified as reservoir and cases of consumption of undercooked meat have resulted in human HEV infection.

While hepatitis E is classically transmitted via the fecal-oral route, higher hepatitis E antibody prevalence has been found among patients in endemic zones who have undergone multiple transfusions as opposed to a control population implicating possible bloodborne transmission of HEV (9).

Vertical transmission of the HEV from mother to child is controversial. Vertical transmission to five newborns was described during an epidemic of waterborne infection (10). Others have demonstrated the presence of HEV-RNA in cord or newborn blood of children born to mothers in the United Arab Emirates (11).

CLINICAL FEATURES

Overall HEV infection is an acute self-limited hepatitis in the immune-competent host. Patients infected with HEV present with nausea, vomiting, anorexia, jaundice, abdominal pain, fever, and hepatomegaly. The clinical presentation of HEV is similar to that of acute hepatitis A. Laboratory features include elevated ALT and bilirubin levels (12). The disease ranges from subclinical presentation to fulminant hepatic failure. Mortality rates are 1%–4% in men and non-pregnant women, but higher in pregnant women and patients with cirrhosis.

(continued on page 15)

(continued from page 12)

CLINICAL COURSE

The incubation period for this virus ranges from 25–45 days. After the incubation period patients will typically enter the icteric phase with elevation of bilirubin and hepatic transaminases in addition to the typical symptoms of hepatitis. The icteric phase can last from two-to-60 days. In a study by Chauhan and others HEV RNA was detected in the serum on day 22 and disappeared by day 46 (13). Stool samples detected HEV RNA during this similar time period. Serum HEV IgG usually appears at the peak of ALT elevation. Persistent HEV IgG detection has been present for >8 years in study subjects.

Compared to acute hepatitis A infection HEV affects older individuals, and is more likely to cause jaundice. HEV afflicted patients have higher bilirubin levels, prolonged prothrombin times, and more severe hypoalbuminemia when compared to HAV counterparts (14). The incubation period of HEV averages 40 days, which is 10 days longer than HAV.

SPECIAL POPULATIONS

While HEV infection in most adults is a self-limited disease with relatively low mortality, the disease can be much more aggressive in certain groups of patients as shown in Table 2.

Pregnancy

HEV infection in pregnant women is more severe, leading to hepatic failure and death in 15% -20% of those acutely infected (15). A recent prospective cohort confirmed the mortality risk in pregnancy. Patra, et al (16) followed prospectively pregnant patients in New Delhi, India who presented with symptoms of acute hepatitis and found that HEV was the cause of 60% of acute viral hepatitis in pregnant females. The study confirmed the increased mortality rates during pregnancy and revealed that fulminant hepatic failure was more common in HEV infected women, particularly if the infection occurred during the third trimester compared to other types of viral hepatitis during pregnancy. They also found that women with HEV infection (as opposed to other infectious hepatitis causes) have more frequent obstetric complications including antepartum hemorrhage and increased intrauterine death. The reason for the aggressive nature of HEV during pregnancy is unknown, but immunologic changes associated with pregnancy may be implicated in the pathogenesis (17).

Cirrhosis

It is known that acute HAV infection in patients with cirrhosis is associated with increased morbidity and mortality. Current guidelines recommend vaccination of cirrhotics without immunity against hepatitis A infection. Acharya, et al proposed that acute HEV infection in cirrhotics would have a similar outcome. They found that mortality in HEV infected cirrhotics was significantly higher both at four weeks and at 12 months (18). In their study HEV-RNA was used for detecting the virus thus confirming active infection, not prior exposure.

DIAGNOSIS

Hepatitis E infection can be diagnosed by the detection of IgM anti-HEV in the serum by ELISA testing. IgM

Table 2
Special Populations With Increased Risk of Complications from Hepatitis E Infection

Underlying Risk Factor	*Outcome*
Pregnancy, particularly 3rd trimester	Increased mortality
Cirrhosis	Increased mortality
Solid organ transplant recipients	Potential for chronic HEV infection

anti-HEV is generally present by the time the patient presents with symptoms of acute hepatitis. Because the currently available serologic tests for HEV can vary in specificity and sensitivity, confirmation of the infection by detecting HEV-RNA by PCR in serum or feces is recommended. Unfortunately, PCR testing for HEV-RNA is not currently commercially available in the US, but can be obtained by contacting the CDC. Fecal detection of HEV-RNA starts approximately one week prior to the onset of symptoms and typically becomes negative two weeks later, although prolonged fecal shedding of virus up to 52 days has been documented.

Serum HEV-RNA is positive in all patients who are symptomatic with acute HEV infection and persists for approximately two weeks. Intermittent positivity in serum has been documented for four-to-16 weeks after initial presentation.

IgM-anti HEV precedes the development of IgG by a few days and persists for four-to-five months after resolution of the acute illness. IgG anti-HEV persists for four-to-five years or longer and serves better as a marker for prior infection rather than acute infection. Tests for IgM and IgG anti-HEV antibodies are commercially available in the US through reference laboratories.

POTENTIAL FOR CHRONIC HEV INFECTION

Traditionally, HEV is thought of as an acute self-limited infection. The presence of HEV-RNA in serum has been documented in 1.5% to 4% of healthy volunteer blood donors in endemic areas, indicating that probably subclinical HEV infection occurs commonly in these areas. These asymptomatic cases could serve as an HEV reservoir in humans. In immunocompetent hosts, chronic infection with HEV associated with abnormal liver tests and or symptoms has not been documented.

Recently, there have been several cases of chronic HEV infection described in immunocompromised patients—specifically those with solid organ transplants. All of the reported cases of chronic HEV infection have been infected with genotype 3 HEV infection. This chronic infection led to cirrhosis in one of the patients (19) and is believed to be the etiology of cirrhosis in a kidney transplant recipient (20). Kamar, et al (21) reported 14 cases of acute HEV infection in solid organ transplant recipients, eight of which developed chronic hepatitis, all were infected with genotype 3 HEV. These reports have raised awareness of the possible risk of HEV infection becoming chronic in the immunocompromised host and await further confirmation.

HEPATITIS E VACCINE

Currently there is no approved vaccine for HEV, but arguments can be made for vaccinating subjects in endemic areas at particularly increased risk such as those with cirrhosis, women of child-bearing age, those on the waiting list for organ transplant and travelers to endemic areas.

Development of a HEV vaccine is in progress. Antibody to HEV capsid protein appears to be protective and passive immunization studies in animals are promising. Development of an attenuated or killed vaccine is hampered by the lack of an efficient cell culture system to grow the HEV virus.

A genotype 1 HEV recombinant protein vaccine was found to provide protection against HEV in non-human primates (22) and has been studied in humans (23). Recently, the vaccine was tested in 2,000 healthy adults susceptible to HEV in Nepal (24). Recipients of all three doses of the vaccine had a 95.5% protective effect of clinically overt HEV infection. In the intention to treat analysis, the vaccine efficacy was 88.5%. This analysis included nine subjects who developed hepatitis E after the first dose of the vaccine, and presumably were incubating the infection at the time of inoculation. The vaccine was well tolerated, except for a greater amount of injection site pain in the subjects receiving the vaccine compared to placebo. Many questions on the effectiveness of this vaccine remain to be answered, particularly duration of induced protective efficacy, its efficacy in preventing asymptomatic HEV infection, as well as the populations that should receive vaccination.

CONCLUSIONS

Hepatitis E infection has only recently been recognized as a distinct entity, despite the fact that it is a common cause of acute hepatitis around the world. While in most cases HEV infection causes a self-lim-

ited illness, there are groups at risk of severe disease and even potential for chronicity. A vaccine against hepatitis E infection holds the promise of preventing significant illness in developing countries where the disease is endemic, but with such a small potential market in industrialized countries, it is not known if an effective vaccine will ever be marketed. ■

References

1. Balayan MS, Andjaparidze AG, Savinskaya SS, et al. Evidence for a virus in non-A, non-B hepatitis transmitted via the fecal-oral route. *Intervirology*, 1983;20:23-31.
2. Emerson SU, Purcell RH. Hepatitis E Virus. *Rev Med Virol*, 2003;13:145-154
3. Meng XJ, Wiseman B, Elvinger F, et al. Prevalence of antibodies to hepatitis E virus in veterinarians working with swine and in normal blood donors in the United States and other countries. *J Clin Microbiol*, 2002;40:117-122.
4. Bile K, Isse A, Mohamud O, Allebeck P, Nilsson L, Norder H, Mushahwar IK, Magnius LO. Contrasting roles of rivers and wells as sources of drinking water on attack and fatality rates in a hepatitis E epidemic in Somalia. *Am J Trop Med Hyg*, 1994;51:466-474
5. Rab MA, Bile MK, Mubarik MM, Asghar H, Sami Z, Siddiqi S, Dil AS, Barzgar MA, Chaudhry MA, Burney MI. Water-borne hepatitis E virus epidemic in Islamabad, Pakistan: a common source outbreak traced to the malfunction of a modern water treatment plant. *Am J Trop Med Hyg*, 1997;57:151-157.
6. Meng XJ, Purcell RH, Halbur PG, Lehman JR, Webb DM, Tsareva TS, Haynes JS, Thacker BJ, Emerson SU. A novel virus in swine is closely related to the human hepatitis E virus. *Proc Natl Acad Sci*, 1997;94:9860-9865.
7. Kato M, Taneichi K, Matsubayashi K. A mini-outbreak of hepatitis E infection in those who enjoyed Jokiniko party: One died of fulminant hepatitis. *Kanzo*, 2004;45:1326-1332.
8. Yazaki Y, Mizuo H, Takahashi M, Nishizawa T, Sasaki N, Gotanda Y, Okamoto H. Sporadic acute or fulminant hepatitis E in Hokkaido, Japan, may be food-borne, as suggested by the presence of hepatitis E virus in pig liver as food. *J Gen Virol*, 2003;84: 2351-2357.
9. Khuroo MS, Kamili S, Yattoo GN. Hepatitis E virus infection may be transmitted through blood transfusions in an endemic area. *J Gastroenterol Hepatol*, 2004;19:778-784.
10. Khuroo MS, Kamili S, Jameel S. Vertical transmission of hepatitis E virus. *Lancet*, 1995;345:1025-1026.
11. Kumar RM, Uduman S, Rana S, et al. Sero-prevalence and mother-to-infant transmission of hepatitis E virus among pregnant women in the United Arab Emirates. *Eur J Obstet Gynecol Reprod Biol*, 2001;100:9-15
12. Smith JL. A review of Hepatitis E virus. *J Food Prot*, 2001;64:572-586
13. Chauhan A, Jameel S, Dilawari JB, Chawla YK, Kaur U, Ganguly NK. Hepatitis E virus transmission to a volunteer. *Lancet*, 1993;341:149-145
14. Chau TN, Lai SK, Tse C, et al. Epidemiology and Clinical Feature to Sporadic Hepatitis E as compared with Hepatitis A. *Am J Gastroenterol*, 2006;101:292-296
15. Khuroo MS, Teli MR, Skidmore S et. al. Incidence and severity of viral hepatitis in pregnancy. *Am J Med*, 1981;70:252-255.
16. Patra S, Kumar A, Sagar S, et al. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann Intern Med*, 2007;147:28-33.
17. Pal R, Aggarwal R, Naik SR, et al. Immunological alterations in pregnant women with acute hepatitis E. *J Gastroenterol Hepatol*, 2005;20:1094-1101
18. Kuma R Acharya S, Kumar Sharma P, Singh R, Kumar Mohanty S, Madan K, Kumar Jha J, Kumar Panda S. Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death. *J Hepatol*, 2007;46:387-394.
19. Haagsma EB, van den Berg AP, Porte RJ, Benne CA, Vennema H, Reimerink JH, Koopmans MP. Chronic hepatitis E virus infection in liver transplant recipients. *Liver Transpl*, 2008;14:547-553.
20. Gérolami R, Moal V, Colson P. Chronic hepatitis E with cirrhosis in a kidney-transplant recipient. *NEJM*, 2008;358:859-860.
21. Kamar N, Selves J, Mansuy JM, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *NEJM*, 2008;358:811-817.
22. Tsarev SA, Tsareva TS, Emerson SU, et al. Recombinant vaccine against hepatitis E: dose response and protection against heterologous challenge. *Vaccine*, 1997;15:1834-1838.
23. Safary A. Perspectives of vaccination against hepatitis E. *Intervirology*, 2001;44:162-166
24. Shrestha MP, Scott RM, Joshi DM, Mammen Jr MP, Thapa GB,Thapa N, et al. Safety and efficacy of a recombinant hepatitis E vaccine. *NEJM*, 2007;356:895-903.