

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Hepatitis E Virus Infection: More Common Than Previously Realized?

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**G&H** In which geographic regions is hepatitis E virus infection most common, and how is the infection transmitted?

**KES** In terms of population exposure, hepatitis E virus (HEV) infection is most common in countries that have poor sanitation systems, such as India, Bangladesh, and parts of South America. HEV infection is probably also common in parts of Africa, but the disease has been less well characterized there.

Like hepatitis A virus, HEV is spread through fecal-oral transmission. The majority of exposure appears to be associated with contaminated water. Large-scale epidemics primarily occur during monsoon seasons in India, when flooding causes runoff of sewage into the drinking water supply. Outbreaks during these periods can involve tens of thousands of people. In such regions, HEV infection is ubiquitous; virtually everyone becomes infected at some point during their lifetime.

**G&H** What is the prevalence of HEV infection in regions where the virus is not endemic?

**KES** HEV infection is quite prevalent even in nonendemic regions. An analysis of samples collected as part of the third National Health and Nutrition Examination Survey (NHANES III), which was conducted by the Centers for

Disease Control and Prevention, found that approximately 20% of patients in the United States have been exposed to HEV. Prior to this study, no one knew that HEV existed in the United States, except perhaps in individuals who had recently travelled abroad.

**G&H** How were these infections missed?

**KES** Many HEV infections are subclinical, in which case patients may not feel sick enough to visit a doctor; in other cases, patients are symptomatic, but the clinician does not consider HEV as a possible diagnosis. In this regard, HEV is similar to hepatitis A virus. If a serosurvey were conducted of people in Cincinnati, Ohio, it would find that 30–40% of individuals have been infected with hepatitis A virus, but if researchers ask people if they have ever been infected, 99% would say no. Similarly, HEV shows high rates of infection when researchers consider serologic evidence of prior exposure, but patients often have few or no symptoms, or they have symptoms but are not diagnosed with HEV infection.

**G&H** Do most patients recover without treatment?

**KES** Yes, almost everyone will recover without treatment, unless they develop fulminant hepatic failure. While liver failure from enterically transmitted viruses can occur due to either hepatitis A virus infection or HEV infection, such occurrences are uncommon. However, HEV infection can cause a very high risk of mortality in pregnant women in some parts of the world.

## G&H What factors predispose US patients to HEV infection?

**KES** According to data from the NHANES III survey and other sources, infection occurs most often in people who eat organ meats, farmers or other individuals who are exposed to pigs, veterinarians who care for large animals, patients who are infected with hepatitis C virus, individuals who have multiple sex partners, and men who have sex with men. Military personnel also have higher rates of HEV exposure than the general population, although these individuals may have been exposed to HEV while deployed abroad.

## G&H What is the connection between animal exposure and HEV infection?

**KES** HEV seems to be mainly associated with pigs, as these animals have high rates of HEV infection. In one study that was conducted in Spain, about 15% of female pigs had active HEV infection, and the virus was transmitted to almost all of their piglets. The animals then recovered, and most were no longer infected by the time they were slaughtered. In another study, however, investigators went to grocery stores in the United States and found that HEV was present in 11% of pig livers. While HEV can be inactivated by cooking meat thoroughly, people sometimes prepare pig livers for foods like liverwurst, in which case it may not be cooked adequately.

## G&H Could eating infected pork cause infection in humans?

**KES** Eating infected meat is thought to be one source of exposure. Rates of HEV infection are approximately 20% in the United States overall, and these rates are highest in the Midwest (22%). We think that people acquire HEV by being exposed to pigs, eating pig organ meat that has not been properly prepared, and possibly through contact with wild deer and/or consumption of infected venison.

## G&H Can you briefly describe the study you and your colleagues published in 2009 in *Emerging Infectious Disease*?

**KES** This study examined the prevalence of HEV antibodies in patients with chronic liver disease and a control group that did not have known liver disease. This study included a total of 167 patients: 129 patients with chronic hepatitis and 38 healthy controls. Chronic liver disease was due to hepatitis C virus or hepatitis B virus infection (sometimes with HIV co-infection), autoimmune hepatitis, and idiopathic hepatitis.

We found that the likelihood of HEV infection was significantly greater in patients who had chronic liver disease. Overall, nearly 30% of patients with chronic liver disease had evidence of HEV infection, which is significantly higher than the rate seen in the general US population. HEV infection may be more common in patients with coexisting liver disease because these individuals have higher-risk exposures in terms of what they eat, how they live, and their exposure to fecal contamination.

## G&H How is HEV infection diagnosed?

**KES** The standard testing method involves the use of serologic assays. There are both immunoglobulin (Ig)G and IgM assays, but the tests that have been utilized in the United States are not very accurate. In other countries, efforts are underway to develop better commercial assays.

In addition to limitations in available assays, another problem is that physicians do not think to order these tests. Until recently, US physicians were taught that they only needed to consider HEV infection in patients who had traveled to countries where the virus is endemic. Thus, HEV infection is not among the diseases that US gastroenterologists, primary care physicians, and infectious disease doctors typically consider. This omission of HEV infection in the differential is why this condition is now an emerging infectious disease; the disease is not new to the country, but for a long period of time, it simply has not been recognized.

## G&H What are the most likely misdiagnoses if clinicians fail to recognize HEV infection?

**KES** HEV infection is indistinguishable from other forms of acute hepatitis. Attributions are made in a variety of ways. In some cases, clinicians simply diagnose the patient as having acute hepatitis—cause unknown; even without a specific diagnosis, supportive care will typically allow for eventual recovery. In other cases, acute hepatitis is misattributed to another cause. For example, research suggests high rates of HEV infection in patients with chronic liver disease; these patients may have both acute and chronic liver disease processes. If a patient who is known to have chronic liver disease appears to rapidly decompensate, their decompensation has historically been attributed to the underlying liver disease, but it may actually be due to HEV infection. In addition, electronically published data in *Gastroenterology* show that a percentage of cases included in the Drug-Induced Liver Disease Network were due to acute HEV infection. Even though these cases were reviewed by a group of expert hepatologists, the diagnosis of HEV infection was often missed.

### G&H When should US physicians consider a diagnosis of HEV infection?

**KES** HEV infection should be considered as a possibility in any patient with acute hepatitis. HEV infection should also be considered in any patient with chronic liver disease who exhibits a sudden decompensation.

### G&H Does correctly diagnosing HEV infection change how these patients are managed?

**KES** If the physician knows that the patient is suffering from an acute process, then he or she can provide supportive care, and the patient will eventually recover. For example, if a patient with otherwise stable liver disease shows signs of decompensation, knowing that this decompensation is due to HEV infection changes the prognostic outlook completely. Rather than telling the patient that his or her chronic disease has worsened and that nothing can be done, the clinician can provide supportive measures that may lead to clinical stabilization.

From a research standpoint, knowing that someone was exposed to HEV would allow us to learn more about the epidemiology of the disease in the United States. Researchers could then begin to look more closely at the behaviors that led to the infection and instruct people on ways to avoid exposure, as researchers do for other outbreaks that are spread by fecal-oral contamination. Because HEV infection has not been recognized clinically, researchers have not focused on what individuals might need to do to prevent infections. Finally, a greater appreciation of the significance of HEV infection may lead to widespread use of a protective vaccine in at-risk populations.

### G&H What future studies are needed to determine the prevalence of HEV infection?

**KES** First, we need to have high-quality assays for both IgG and IgM. We also need to be able to perform viral testing, at least in reference laboratories. The period of viremia is very short, but phylogenetic analysis of the virus's genetic material is needed to identify the source of an outbreak.

Second, we need better characterization and recognition of HEV infection in patients with chronic liver disease who are at risk for hepatic decompensation. Once we better understand this scenario, we then need to educate patients about risk factors so that they can reduce their chances of acute infection.

Third, research is just beginning regarding HEV infection in the setting of organ transplantation, specifically kidney and liver transplantation. Acute HEV infection in this population appears to result in liver injury that was previously unrecognized or misclassified; in addition, acute HEV infection appears to lead to chronic disease in some of these patients. A few case reports have described efforts to treat such chronic infections with either interferon or ribavirin, but further research is needed. Immunosuppression is thought to prevent clearance of the virus in transplant recipients, but questions remain as to how often HEV infection occurs in this setting and how to manage it.

Finally, at least 2 effective HEV vaccines have been developed, and evidence suggests that they are effective, but neither is licensed in the United States. The eventual availability of such vaccines and development of vaccination programs could play an important role in preventing HEV infection over the next 1–2 decades.

### Suggested Reading

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