Hepatitis E: What We Think We Know

Aradhna Seth, M.D., and Kenneth E. Sherman, M.D., Ph.D.

BACKGROUND

Until 1980, hepatitis A virus (HAV) was considered to be the only enterically transmitted form of viral hepatitis, earning it the designation in common medical parlance of “infectious hepatitis” (also known as “infective hepatitis” in the United Kingdom). For prior decades, water-borne outbreaks of hepatitis with jaundice in India, central and southeast Asia, the Middle East, and North Africa were considered epidemiologically to be viral in nature, and had been attributed to HAV even though formal testing to make this determination was not routinely available. Indeed, infectious hepatitis was the first viral disease for which a

Abbreviations: ACLF, acute-on-chronic liver failure; ALF, acute liver failure; BEAST, Bayesian Evolutionary Analysis by Sampling Trees; HAV, hepatitis A virus; HEV, hepatitis E virus; SOT, solid organ transplant.

From the Division of Digestive Disease, University of Cincinnati College of Medicine, Cincinnati, OH.

A.S. is a Gastroenterology and Hepatology Fellow at the University of Cincinnati College of Medicine. K.S. is the Gould Professor of Medicine at the University of Cincinnati.
water-borne route of infection was generally accepted.\(^1\) An outbreak of infectious hepatitis in 1978—characterized by a high case fatality rate in pregnancy—that occurred not far from Srinagar, the summer capital of Kashmir in India, led to the recognition of a hitherto unknown hepatitis virus that was distinct from HAV. This outbreak caused colossal human suffering, with an estimated 52,000 icteric cases and about 1,700 deaths.\(^2\) As the Cold War waned, Russian virologist Mikhail Balayan used an old but historically relevant method of discovery—he infected himself. In 1983, he investigated an outbreak of non-A, non-B hepatitis in Tashkent, Uzbekistan.\(^3\) Lacking the ability to refrigerate samples, he ingested a pooled fecal extract from ill patients. Subsequently, he came down with acute viral hepatitis. He passaged his own stool into monkeys and showed that they then produced virions visible on electron microscopy similar to that seen in his own stool. Serologically, this virus was not HAV and became known as hepatitis E virus (HEV), the same virus that had caused the 1978 Kashmir epidemic.\(^2\)

HEV is a small, non-enveloped, positive sense, single-stranded RNA virus that is part of the Orthohepevirus genus under the Hepeviridae family, which has a fascinating evolutionary history (Fig. 1).\(^4,5\) It is suspected that hepatitis E has been afflicting human beings for centuries, as evidenced by medieval literature illustrating jaundice. About 1344 years ago, the HEV progenitor evolved into two variants, anthropotropic and enzootic variants. The anthropotropic variant progressed into genotypes 1 and 2 and the enzootic variant into genotypes 3 and 4, as we know them today.\(^5\) Depending on the classification system, there are 7 to 10 distinct genotypes. Genotypes 1 and 2 infect only humans and non-human primates, with genotype 1 being predominant in Asia and North Africa and genotype 2 having a predilection for Mexico and central Africa. Other genotypes may also rarely infect humans. Genotypes 3 and 4 are zoonotic forms that easily cross to humans from animals, particularly swine and deer. Genotype 3 virus infection in humans has been reported throughout Europe, pockets of North and South America, and Japan, whereas genotype 4 has remained isolated to eastern Asia (Fig. 2 and Table 1).\(^5,6\)

Epidemiologically, HEV falls into four distinct categories of global distribution. Hepatitis E is hyperendemic, meaning it has persistently high levels of disease occurrence in Mexico, central, southern, and southeast Asia, as well as eastern, western, and northern Africa. It is endemic, meaning HEV has a constant but not unusually high presence, in much of the Middle East, parts of southeast Asia, and regions of South America. Hepatitis E is sporadic in developed or industrialized countries and typically goes unrecognized with a low disease burden. Egypt is the sole country to have a distinctive pattern zone in the sense that the majority of the population develops immunity to the disease early on, and infection in pregnancy is minor or asymptomatic.\(^5\) This may be related to near-constant exposure to water from shallow wells in the Nile river drainage. However, given the advent of globalization, HEV should be on the differential for any patient with acute hepatitis with recent travel to any endemic region or known exposure to animals known to harbor the virus.

The incubation period of HEV is typically 4 to 5 weeks postexposure. This is similar to hepatitis A and shorter than hepatitis B or C.\(^6\) Other viruses (e.g., West Nile, Yellow fever) that can cause viral hepatitis with jaundice as part of their spectrum of disease cannot be separated from HEV or HAV by the incubation period.\(^7\) Hepatitis E is typically underdiagnosed because of lack of clinician recognition, as well as the fact that there is no diagnostic assay currently approved by the US Food and Drug Administration. Commercial assays vary widely in sensitivity and specificity because of differences in binding and sensing. Adding to the challenge, the presence of HEV RNA is very transient in the serum, although it is shed in the stool for much longer. However, stool testing is challenging and rarely performed.\(^8\)

The most common mode of HEV transmission is fecal-oral, and the majority of epidemic outbreaks have been associated with contaminated water supplies, particularly during periods of flooding from monsoons and other

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storms. Foodborne transmission of genotype 3 occurs after ingestion of undercooked pork or wild boar, although shellfish are sometimes implicated.4 Hunters who handle reservoir species are at particular risk. A study among German boar hunters found a 21% prevalence rate of prior HEV infection, which is significantly higher than the background population. This observation has prompted some authors to suggest that hunters wear gloves while handling blood or body fluids of these animals.9 Blood transfusion–associated transmission of hepatitis E is thought to be rare, but well-documented cases are described and seem to be increasing in Europe.4,10 In response to the increasing incidence of HEV in Europe, multiple European countries including Ireland, the United Kingdom, and the Netherlands have begun HEV RNA screening of blood donations. Germany and France perform screening in blood intended for high-risk populations; however, Denmark has decided not to partake in HEV RNA screening because of look-back studies of living recipients with no evidence of transfusion-transmitted HEV.11 The United States does not routinely test donor blood for HEV RNA because there has been only one reported case of transfusion-associated transmission and an exceedingly low presence of HEV RNA in donor blood.12,13 Evaluation of 18,829 blood donations from six geographic regions of the United States found that only two donations tested positive for HEV RNA and had a PCR that was not quantifiable.13

Hepatitis E must be on the differential in a patient with cirrhosis who has decompensated for unclear reasons. Treatment of HEV in the acute setting is not indicated; however, physicians must be hypervigilant because patients may experience development of acute-on-chronic liver failure (ACLF), causing rapid decompensation and even death. A retrospective study in India, a hyperendemic country for HEV, found that 61% of their 121 patients experienced ACLF caused by HEV. The 3-month mortality rate in these patients was 44%.14 Supportive care is the mainstay of treatment. Prevention of acute HEV in patients with chronic liver disease is critical, and patients should be

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**FIG 1** Evolutionary history of the HEV.5 A Bayesian analysis of HEV as calculated by BEAST to determine the times to the most recent common ancestors for all four genotypes. Reproduced with permission from *World Journal of Gastroenterology*.5 Copyright 2016, Baishideng Publishing Group, covered under the Creative Commons Attribution-Noncommercial.
counseled on appropriate precautions when traveling to endemic regions.

Although HEV is typically an acute and self-resolving illness, risk for progression into chronic infection has been noted in immunosuppressed patients such as organ transplant recipients, patients with HIV, and those with underlying chronic liver disease that may warrant treatment of hepatitis E. An observational cross-sectional study in the United States found that almost 30% of their patients with underlying chronic liver disease possessed HEV IgG antibodies. These patients were more likely to be older in age and male. In addition, a prospective, predominantly European study of 85 solid organ transplant (SOT) recipients revealed that 66% of their patients experienced development of chronic hepatitis E. A multivariate analysis found that the independent predictive factors associated with chronic HEV development were the use of tacrolimus versus cyclosporine and a lower platelet count at the time of diagnosis. Regarding treatment, 32% of patients had resolution of infection and viral clearance simply with reduction in tacrolimus dosing after a mean time of almost 20 months. Notably, no patient experienced acute cellular rejection with reduction of immunosuppression. For those SOT patients who do not respond with reduction in immunosuppression or those who warrant treatment of HEV for reasons other than those mentioned earlier, ribavirin and pegylated interferon therapies have been studied.

**FIG 2** Global distribution of HEV genotypes. Hepatitis E is distributed unevenly based on differences in source of infection, which is highly associated with HEV genotype. Reproduced with permission from *World Journal of Gastroenterology.* Copyright 2016, Baishideng Publishing Group, covered under the Creative Commons Attribution-Noncommercial.

**TABLE 1. HEPATITIS E GENOTYPES**

| Genotype | Endemic Areas | Host          |
|----------|---------------|---------------|
| 1        | Asia, North Africa | Human         |
| 2        | Mexico, central Africa | Human         |
| 3        | Europe, North America, South America, Japan | Human, pig, deer |
| 4        | Eastern Asia | Human, pig, deer |
| 5        |              | Wild boar     |
| 6        |              | Wild boar     |
| 7        |              | Camel         |
Ribavirin should be first-line therapy in SOT recipients because of interferon’s notorious side effects and risk for graft rejection, particularly in kidney and heart recipients. A retrospective, multicenter study found that 78% of SOT patients achieved SVR after about 3 months of ribavirin therapy.

In patients with HIV with low CD4 counts and subsequent severe immunosuppression, coinfection with HEV can accelerate liver fibrosis and lead to decompensated cirrhosis. In addition, HEV should be considered in patients with HIV with unexplained and persistently elevated transaminases.

Hepatitis E has been associated with neurological, renal, and hematological extrahepatic manifestations. The most notable and morbid neurological manifestations include Guillain-Barré syndrome and meningoencephalitis. Renal manifestations include membranoproliferative glomerulonephritis, membranous glomerulonephritis, and cryoglobulinemia. Neurological and renal manifestations are the most common; however, there have been cases of autoimmune hemolytic anemia, aplastic anemia, thrombocytopenia, and pancreatitis.

Among hepatologists, there are many “truths” that are frequently cited, even if they are not true. We will explore some of the common assertions made by experts regarding HEV.

**HEV INFECTION DURING PREGNANCY IS USUALLY FATAL**

Acute HEV infection has been implicated in causing acute liver failure (ALF) and maternal mortality during the third trimester in up to 20% to 25% of cases. Apart from maternal morbidity, HEV during pregnancy has been associated with miscarriage, premature delivery, or stillbirth. The placenta secretes certain enzymes and cytokines that suppress cell-mediated immunity at the interface of maternal-fetal circulation, thus allowing a method for HEV transmission. In addition, there have been reports of HEV replicating within the placenta. Proposed mechanisms include the greater virulence of genotypes 1 and 2, because those are the only genotypes known to cause complications in pregnancy, together with immunological and hormonal changes during pregnancy. Pregnancy is postulated to cause suppression of T cell–mediated immunity including suppression of CD4 cells and increased steroid hormone production leading to augmented viral replication.

Although HEV has an ostensible role in mortality during pregnancy, there are notable regional differences that cannot be overlooked. Hepatitis E is particularly feared in northern India. A large, prospective study in New Delhi found that HEV comprised almost 60% of cases of acute hepatitis among pregnant women, a result comparable with prior studies. In the patients with HEV infection, a staggering 41% of them developed ALF with significantly higher maternal mortality, antepartum hemorrhage, and intrauterine fetal demise in HEV-infected women as compared with non-HEV-infected patients. In contrast, other areas where HEV is endemic, such as Egypt and southern India, have experienced minimal to no mortality from HEV. These regional discrepancies beg the question of whether there are other factors such as age of exposure, nutritional status, or lack of access to health care that are also playing a neglected but pivotal role in disease outcomes.

The age-specific prevalence of antibodies to HEV is variable and may be fundamental to understanding why mortality among pregnant women is discordant. By the age of 15, 90% of Egyptians have been exposed to hepatitis E and possess antibodies. Conversely, the Indian antibody prevalence rate peaks at just 40%, and this comparatively dismal rate of population immunity does not develop until the late teenage years. Conceivably, women in India have their initial exposure to HEV at an older age, coinciding around the time of pregnancy, given the mean age of 22 years in the New Delhi study. Therefore, although high mortality during pregnancy does occur in some places, this appears to be an epidemiological artifact of exposure. It is well known that children infected with hepatitis A have few symptoms but jaundice; morbidity and mortality are significantly more common when adult infection occurs. The same seems to be true of hepatitis E.

Pregnant women once again became collateral damage in the wake of a HEV outbreak in Africa’s Lake Chad region, fueled by thousands of refugees escaping the political violence inflicted by Boko Haram. Per a World Health Organization report, by May 2017 there were 282 cases of HEV in Niger, with 26 out of 27 deaths occurring in pregnant women. It is no coincidence that this outbreak occurred in the setting of unsanitary living conditions in
refugee displacement camps, where residents are often forced to dig latrines in the same area in which they cook and sleep. To make matters worse, heavy rains caused flooding and spread contaminated water.\textsuperscript{25} Risk factors associated with infection included sharing of sanitation facilities, lack of soap during hand washing, and animals sleeping inside living quarters.\textsuperscript{26} In addition, there is often a dearth of access to health care and food supplies inside a refugee camp. One can argue that the deleterious effects of unsanitary living conditions, limited access to health care, and poor nutritional status are what are killing pregnant women in these HEV outbreaks. Perhaps we find solace in blaming HEV for the death of these women rather than our own human-made deplorable living conditions during a humanitarian crisis.

EATING PROCESSED FOODS IS BAD

In the United States, our diet consists of processed foods. Some blame this lifestyle as the root of our epidemic of obesity and nonalcoholic fatty liver disease. Many call for a return to farm-to-table eating. The bucolic life of collecting one’s fresh pork sausage from your local farmer barely exists in regions of the country. Instead, most Americans can find a grocery store aisle of neatly packaged sausages bearing minimal resemblance to their original state—exactly how Americans prefer their food nowadays. In contrast, Europeans still believe in the concept of open-air farmers’ markets and frequenting their local charcuterie (from the French, literally pork butcher shop) (Fig. 3). However, this zest for fresh pork may come at a heavy cost. Since 2005, Europe has experienced a 10-fold surge in the number of HEV infections over the span of a decade, the bulk of which occurred in France, Germany, and the United Kingdom. The majority are secondary to genotype 3, which happens to be the same genotype isolated in European pigs.\textsuperscript{27} In the United Kingdom, sausages, pork pie, and ham were found to be the guilty culprits.\textsuperscript{28} In the United States, rates of HEV antibody prevalence have decreased over the last two decades, a sharp contrast with our European friends (Fig. 4).\textsuperscript{29-32} In this case, processed food makes our food supply safe, and we should be thankful for the frozen, precooked breakfast sausage we eat.

CONCLUSION

Hepatitis E infection has long been an underrecognized entity causing acute hepatitis and also underappreciated for the impact it can have in developed nations. It has been thought of as a disease unrelated to the Western world because of its associations with unsanitary living conditions and contaminated water supplies in developing countries and war-torn regions. Perhaps now that it is affecting patients in developed nations, because of exposure from blood and food products, and affecting affluent populations that have benefited from the miracle of organ transplantation, it is now being more

FIG 3  The European versus American palate: raw versus processed. In Europe, locally processed meats that may harbor HEV are consumed. Insufficient cooking can lead to transmission of HEV from pork, venison, rabbit, and other products. In the United States, similar meat products are highly processed, precooked, and carefully monitored for microbial contamination.
closely scrutinized. The first essential stepping-stone in the quest to rein in HEV is to broaden recognition among physicians. Second, we must have reliable diagnostic assays. Finally, we need effective treatment for the chronically infected. Thus far, ribavirin holds the most promise for the treatment of HEV, but it is not globally effective and it is difficult to tolerate. Although there is an effective vaccine in use in China, its applicability to other genotypes is unknown. The incidence of HEV in Europe continues to increase, but prevention seems distant.

SERIES EDITOR'S POSTSCRIPT

Depending on whether your historical point of view is sociopolitical or evolutionary, one could say that the history of HEV either barely dates back to 1978 to an outbreak in India of waterborne acute hepatitis that was ultimately distinguishable from hepatitis A, or had affected humans for centuries according to descriptions of jaundice in medieval sources and Bayesian analysis of viral molecular sequences that are related by an evolutionary tree, respectively. Irrespective of one’s historical perspective, both approaches are explained in this admirable essay by Aradhna Seth and Kenneth E. Sherman, which describes the discovery, isolation, and identification of HEV; delineates its viral genotypes and their global geographical distribution and epidemiology; describes its myriad clinical features; and highlights the significance of its detection, especially in patients who might otherwise be thought to have nonviral liver injury. The realization that this classically viral cause of acute hepatitis can persist chronically in immunosuppressed individuals seems all the more surprising because infection with HAV, which is so similar to HEV in many ways, does not yet appear in chronic form even though relapsing cases do exist. Finally, it is intriguing to be disabused of the convictions that HEV infection in pregnancy is usually fatal and that eating processed foods is bad. In the case of meat products that are contaminated with HEV, processing makes the food supply safe.

CORRESPONDENCE

Kenneth E. Sherman, M.D., Ph.D., Gould Professor of Medicine, Director, Division of Digestive Disease, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0595. E-mail: shermake@ucmail.uc.edu

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FIG 4  Seroprevalence of hepatitis E in the United States versus Europe. Estimates of seroprevalence of HEV vary widely, but overall age-specific prevalence appears to be declining in the United States. Higher rates of HEV are now seen in much of Europe, with the highest rates in the southern regions.
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