The Enigma of Hepatitis E Virus

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Abstract: Globally, hepatitis E virus (HEV) is the most common cause of acute viral hepatitis. HEV is endemic in many developing countries, yet it is far more common in industrialized, nonendemic countries than previously recognized. Nonetheless, HEV remains poorly characterized and is frequently unidentified or misdiagnosed by clinicians. Manifestation of disease, source of infection, and route of transmission vary by HEV genotype and epidemiology in endemic and nonendemic settings worldwide. HEV infection can be acute or chronic, further complicating the presentation, diagnosis, prognosis, and natural history of disease. However, accurate identification and diagnosis of HEV has important implications for patient management, disease control, prevention efforts, and characterization of mechanisms of transmission and epidemiology. Acute HEV infection is rarely diagnosed in industrialized, nonendemic countries; however, recent seroprevalence data collected using modern, highly sensitive testing assays demonstrate a surprisingly high prevalence of anti-HEV antibodies in these settings, suggesting common subclinical or unrecognized infection. These data suggest widespread underestimation of the global burden, population seroprevalence, and importance of HEV infection. Enhanced capacity for disease recognition, accurate diagnosis, and clinical awareness are critical to improving the management and reducing the burden of HEV infection worldwide.

First described as a new epidemic form of viral hepatitis in 1956 yet unrecognized until 1980,[1-3] hepatitis E virus (HEV) has emerged as an important but often missed or misdiagnosed etiology of hepatitis. Interestingly, a disease that may have a seroprevalence of more than 20% in some regional populations in the United States[4] and near-universal infection of the populace in some regions of the world[3] remains poorly characterized, clinically unrecognized, and often forgotten. Much of this is because of disparate presentations due to unique epidemiologic transmission patterns that are highly associated with the presentation of disease. Add in the significant influence of genotypic variability in clinical presentation and host range and the importance of the host

immunologic milieu, and clinicians are presented with a confusing range of presentations and natural histories for this global disease process. To dissect the role of each of these factors, this article explores in detail the interlocking complexities that lead to observed (and missed) disease presentations and their associated natural histories.

Natural History of Hepatitis E Virus

Burden

HEV infection is a global health problem that occurs in both developing and industrialized countries. Each year, an estimated 20 million HEV infections occur worldwide, leading to 70,000 HEV-related deaths.[5,6] However, only 3.3 million (17%) of these 20 million HEV-infected individuals experience symptoms that are directly attributed to HEV.[5,6] A large proportion of HEV infections are often symptomatic, but the protean symptoms are not intrinsically suggestive of a hepatitis process. This represents a substantial challenge for diagnosis, treatment, and infection control efforts. Furthermore, it enhances the opportunity for missed diagnoses of a potentially fatal and sometimes chronic disease. Seroprevalence data suggest a lifetime exposure risk of HEV infection in one-third of the world's population.[7] Control and prevention of HEV are further exacerbated by the wide range of disease presentations among individuals infected with HEV and by the emerging changes observed in recent years to the chains of infection and the course of the disease.[8]

Clinical Presentation

Clinical presentation of individuals infected with HEV varies between disease-endemic developing countries and nonendemic, industrialized settings. In disease-endemic areas in the developing world, HEV commonly manifests both as epidemic infections and as sporadic waterborne cases.[3,9] However, the recent discovery of locally acquired (rather than travel-related) sporadic and zoonotic cases of HEV in developed countries represents one of the emerging changes in the understanding of HEV infections.[3] Although autochthonous cases in industrialized countries are few in absolute number, serosurveys have documented substantial HEV seroprevalence.[10-12] A better understanding of the exposure and clinical implications of these locally acquired cases may help explain the mystery of the natural history of HEV. Differences in HEV genotype play an important role in the presentation of cases infected with HEV.

In acutely infected individuals, HEV is indistinguishable from acute hepatitis caused by other hepatotropic viruses.[9] The majority (>90%) of patients with HEV infection experience an asymptomatic infection with spontaneous clearance of the virus; a minority of patients develop and present with a more typically symptomatic HEV infection.[7,13] Acute HEV infection can result from genotypes 1 and 2 (restricted to humans) or genotypes 3 and 4 (zoonotic agents; Table 1).[1,3,14] A smaller proportion of patients infected with HEV genotype 1 have particularly severe disease and present with fulminant hepatitis and acute liver failure; higher rates of fulminant hepatitis and acute liver failure may be observed among pregnant women that result in increased maternal mortality (10%-20% mortality rate).[9,14,15] Animal studies using primate models demonstrated that the viral inoculum dose determines the severity of the liver injury; lower doses were associated with subclinical infection, although this has not yet been determined in humans.[16] Other research examining the association between HEV genotypes isolated from patients with acute viral hepatitis vs fulminant hepatic failure suggests the possibility of correlation between disease severity and HEV isolate genotype.[17]

Table 1. The Relationship Between Hepatitis E Virus Genotype and Disease Natural History

Genotype	Acute Disease	Chronic Disease
1	√	
2	√	
3	√	√
4	√	√

Although HEV most commonly manifests as a self-limiting, acute infection,[3,8] chronic HEV infection can occur,[9] specifically after infection with HEV genotype 3 and possibly genotype 4.[14] However, chronic HEV infection has never been reported from genotype 1–endemic countries (Table 1).[9] Chronic HEV infection is usually asymptomatic and seen in immunosuppressed patients, including people living with HIV and transplant recipients[3,18]; however, chronic HEV infection can be associated with extrahepatic symptoms.[8] Among patients with chronic liver disease due to other causes, the likelihood of HEV infection is significantly greater and may be a cause of disease in those characterized as cryptogenic hepatitis (ie, disease that is unexplained by conventional clinical, laboratory, and histologic findings[19]).[18,20,21]

Disease Severity and Genotype

Phylogenetic analysis of the HEV RNA allows grouping of HEV into genotypic families that have both epidemiologic and clinical significance. While there are 4 major genotypes that primarily circulate in humans, other genotypes may occasionally infect humans as well.

HEV genotype also appears to play a key role in disease transmission patterns. HEV genotype 3 replicates at high prevalence in swine, deer, and other animal populations.[3,9,22] Humans are incidental hosts, with transmission associated with consumption of foods derived from infected animals that have not been heated to levels consistent with viral inactivation. This includes food products such as cold-smoked pig liver sausage (figatella) and raw shellfish. HEV genotype 4 has also been implicated in animal-sourced infections. In contrast, HEV genotypes 1 and 2 appear to only cause disease in humans and nonhuman primates. Progression from acute to chronic disease is almost exclusively seen in patients with HEV genotype 3 infection, although a recent report implicates HEV genotype 7, which was presumably transmitted from a camel to man[23]; cases of HEV genotype 4 chronicity have also been reported.[24]

Diagnosis of Hepatitis E Virus Infection

The diagnosis of HEV infection is difficult. Unlike other viral hepatitis agents, knowledge regarding HEV among clinicians is limited. Therefore, HEV is rarely considered in the evaluation of liver transaminase abnormalities. Indeed, even among hepatologists, HEV infection may be missed. In the National Institutes of Health–sponsored Drug-Induced Liver Injury Network, cases of suspected liver injury from a drug etiology were evaluated by a jury of expert hepatologists.[25] The diagnosis of HEV was not considered, and many cases were judged to be due to the drug in question. Subsequent testing revealed that 7 of 318 (2.2%) cases in which expert opinion ruled that a drug-induced liver injury was likely were found to be due to acute HEV infection instead.[25] Similar to hepatitis A virus, many cases of HEV are subclinical, and specific testing is not performed, even if it is easily available. However, HEV testing is not routinely available. There is no HEV diagnostic assay approved by the US Food and Drug Administration. Multiple test comparison panels of commercial assay products reveal wide variation for both HEV immunoglobulin (Ig) G and IgM antibodies. HEV RNA is very transient in the setting of acute infection and is difficult to obtain in most clinical laboratories. HEV RNA is shed in stool longer than the typical period of viremia; however, stool testing is cumbersome and rarely performed except in targeted epidemiologic studies of disease outbreaks. The lack of routine HEV diagnostic testing impacts the understanding of the significance and prevalence of HEV infection worldwide.

Challenges in diagnosing HEV fuel missed diagnostic opportunities and misdiagnoses of HEV infection. The subclinical nature of many HEV infections may result in a lack of care-seeking by case patients; thus, no clinical diagnosis is made (Table 2). However, for some symptomatic patients, practitioners may fail to consider and test for acute HEV infection, which is often indistinguishable from other forms of acute hepatitis (Figure).[20,26,27] Other HEV infections that clinicians fail to recognize include those in patients with both acute and chronic liver disease and those with suspected drug-induced liver injury.[18,28] Correct identification and diagnosis of HEV in patients with acute or chronic infection has important implications for patient management, disease control and prevention, and clinicians' understanding of the transmission and epidemiology of HEV.

Transmission of Hepatitis E Virus

The average incubation period of HEV ranges from 2 to 10 weeks during HEV outbreaks, but normally occurs over 4 to 5 weeks postexposure.[1,3] Five major routes of HEV transmission characterize the disease distribution geographically in endemic and nonendemic settings, and include: (1) waterborne transmission via the fecal-oral route due to fecal contamination of drinking water, (2) foodborne transmission via the ingestion of products derived from infected animals, (3) zoonotic transmission via exposure to infectious bodily fluids of infected animals, (4) parenteral transmission via transfusion of infected blood products, and (5) vertical (materno-fetal) transmission.[3,29,30] Evidence of person-to-person transmission has been proposed[31,32] but remains a matter of controversy.[30,33] During outbreaks, nosocomial transmission of HEV in hospital patients and health care workers[34,35] and in hemodialysis units[36] has been reported on occasion.[30] Zoonotic transmission of HEV due to consumption of camel, cow, and goat milk has been documented.[23,37,38] In pregnant women, HEV transmission can be transplacental, resulting in increased risk of abortions and stillbirths, and increased rates of liver necrosis and deaths in newborns.[39,40] Transmission from HEV-infected mothers to neonates via HEV RNA in breast milk is considered an unlikely route of transmission and requires additional research; however, isolation of HEV RNA in breast milk has been documented, suggesting that breastfeeding could be a potential route of mother-to-child transmssion.[30,41]

Presence of Preexisting Antibodies

Locoregional transmission patterns appear to influence the age of the patient at HEV acquisition and are directly related to the source of point exposures. In the Nile River Valley, early HEV exposure appears to be the rule rather than the exception. By the age of 20 years, more than 70% of people have antibodies to HEV.[29,42] The

Table 2. Diagnostic Opportunities and Errors

Clinical Situation	HEV Infection Misdiagnosis
Subclinical infection; patient does not seek care	No diagnosis made
Symptomatic infection; practitioner does not consider HEV infection	Non-HEV diagnosis
Indistinguishable acute HEV infection	Acute hepatitis, cause unknown Chronic liver disease (in a patient with known chronic liver disease) Flare of disease in a patient with chronic autoimmune hepatitis[27] Acute liver injury[26] Liver injury from a drug etiology[28]
Chronic HEV infection	Chronic liver disease due to HBV or HCV Chronic liver disease due to HBV/HIV or HCV/HIV coinfection[18] Autoimmune hepatitis[18] Idiopathic hepatitis[18] Acute cryptogenic hepatitis[18,21] Acute cellular rejection
HEV-induced neuralgic amyotrophy	Neuralgic amyotrophy[73]
HEV-associated Guillain-Barre syndrome	Guillain-Barre syndrome, unknown etiology

HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus.

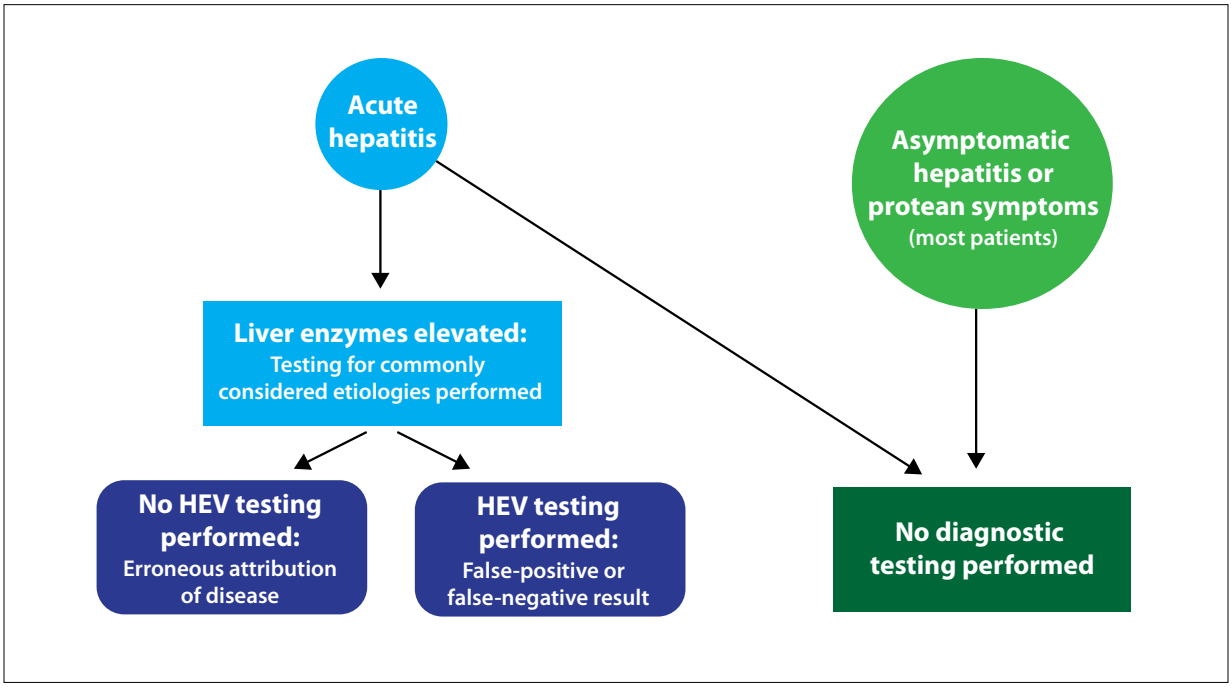

Figure. A flowchart showing the reasons clinicians may fail to diagnose HEV infection.

HEV, hepatitis E virus.

Table 3. Epidemiologic Triad of Hepatitis E Virus Transmission and Implications for Missed Diagnoses

Virus Genotype	Host (Source)	Environment	Potential for Missed Diagnosis
1	Human	Developing, endemic countries	Cases in low-endemic regions, sporadic cases in hyperendemic regions
2			
3	Human, swine (including pork products), deer, wild boar, mongoose, macaque, sheep, yak, and cattle[22,37]; oyster, shellfish, cat, and rodent[74]; camel[23,75]; soft fruit[76]; goat[38]	Developed, nonendemic countries	Cases with chronic, asymptomatic, or unrecognized infection
4			Cases with asymptomatic or unrecognized infection

source of HEV infection is thought to be groundwater or well water that is used to provide the water supply for many villages and towns. In contrast, exposure in India is mainly associated with periods of flooding during the monsoon season.[43] In the United States, transmission is mainly zoonotic and presumably foodborne, although the specific source of infection is almost never identified. Antibodies are present in 40% of the population by age 16 to 25 years.[44] Seroprevalence rates are highest in the Midwest and rise with age, indicating either a cohort effect or a slow but continuous exposure during an individual's lifetime.

Because antibodies appear to be protective or at least modulatory of clinical disease features, the age of acquisition appears to affect disease presentation. For example, HEV-associated acute liver failure is common among pregnant women in India, presumably in part because young women do not necessarily have prior exposure to disease.[43,45] In contrast, acute liver failure is relatively rare following acute HEV exposure or infection in Egypt, including in pregnant women, suggesting that early-age prior exposures provide protection. Family members that reside with individuals infected with acute HEV (ie, index cases) in Egypt appear to be protected from the development of symptomatic disease if they have anti-HEV antibodies present.[11,46-48] Additional research in pregnant women is indicated, as many factors may influence disease presentation.

Epidemiology of Hepatitis E Virus

The diagnostic challenges, numerous routes of transmission, and seroprevalence previously discussed complicate the understanding of HEV epidemiology. In HEV-endemic areas, generally considered to be in the developing world, the rates of IgG seropositivity reflect the greater frequency of HEV infections due to frequent waterborne outbreaks of HEV genotypes 1 and 2 (Table 3).[12] Outbreaks of HEV genotype 1 infection documented in India,[49] Egypt,[47] China,[50] Somalia,[51] and Uganda[31] have affected thousands of people through prolonged epidemics resulting from continued exposure to a contaminated water source.[29] As for developed countries, small outbreaks have been reported of HEV genotype 3 in Japan[52,53] and the United Kingdom,[54] and HEV genotype 4 in Italy[55] has been associated with zoonotic and foodborne transmission.[56] To date, no large outbreaks of HEV genotype 3 or 4 etiology have occurred.[43,56]

Hepatitis E Virus in Developing Countries

Estimates of HEV seroprevalence in developing countries range from 30% to 80%.[33] Diagnostic testing for acute HEV infection is rarely completed in any setting; thus, estimates of HEV incidence worldwide are likely too low. In HEV-endemic countries, symptomatic infections are most common in individuals ages 15 to 40 years, whereas asymptomatic or mild anicteric cases are more common in children.[43] Modeling analyses using population-based epidemiologic studies project annual incidence rates of roughly 0.5% to 1.0% for ages 0 to 15 years, 1.0% to 1.4% for ages 15 to 20 years, and a decrease to 0.2% or less for ages older than 30 years (data for ages 20-30 years are not presented in a manner allowing for estimation).[13] This pattern of seroprevalence is consistent with data across HEV genotype 1 endemic regions, in which antibodies to HEV begin to rise in adolescence and peak between the second and third decades of life.[43]

As previously noted, the presence of HEV antibody does reflect previous exposure to HEV, although it is dependent on the population tested and the assays used.[12] A comparison of HEV testing using a widely accepted gold standard assay (Walter Reed Army Institute of Research Enzyme Immunoassay [WRAIR EIA]) vs a modern assay (Beijing Wantai Pharmacy Enterprise, Co, Ltd Enzyme-Linked Immunosorbent Assay [Wantai ELISA]) estimated that the overall population

seroprevalence for anti-HEV antibodies in Bangladesh was 26.6% vs 46.7%, respectively.[57] Another study of HEV seroprevalence using the Wantai ELISA (sensitivity, 94.4% vs 53.9% for WRAIR EIA)[57] detected surprisingly high and similar age-standardized seroprevalence of anti-HEV antibodies in Nepal (47.1%), Bangladesh (49.8%), and southwest France (34.0%), despite differences in the epidemiology and circulating genotype in each country.[58] The currently available HEV global burden estimates rely heavily on studies that used the WRAIR EIA, thus suggesting widespread underestimation of population seroprevalence and global importance of HEV.[13,57]

Hepatitis E Virus in Developed Countries

Genotypic variability and HEV host range differ in important clinical respects in developed countries. HEV infection in this setting mainly occurs as sporadic cases caused by HEV genotypes 3 and 4 with symptoms similar to those of many causes of acute hepatitis. Locally acquired HEV genotype 3 infections are thought to represent a zoonotic source, but identification of a common food source or animal contact in individual cases is unusual. Symptomatic HEV in the developed world is most common in middle-aged and elderly men (median age, 63 years; male-to-female ratio, 3.5:1).[3,59] However, few data exist to explain this trend, and seroprevalence data suggest that exposure is unrelated to age or sex.[60]

The seroprevalence data from industrialized countries in which acute HEV infection is rarely diagnosed challenge the current view of HEV epidemiology. It is now known that the high prevalence of HEV IgG antibodies in settings previously considered to have low incidence, such as the United States (21%-40%),[10,44] France (22%-52%),[61,62] and the United Kingdom (42%),[63] actually represents common subclinical or unrecognized infection.[12,59] The prior notion that HEV seroprevalence in developed countries was low (<5%) or that seropositivity indicated a travel-related exposure was propagated by first-generation serology assays that lacked sufficient sensitivity.[59] In fact, improved diagnostic assays have identified a number of hot spots of HEV infection in European countries.[59] The incidence of locally acquired, zoonotic HEV infection remains unclear, yet evidence is increasing such that HEV is now considered endemic in many developed countries,[59] including The Netherlands (high incidence in blood donors),[64,65] the Czech Republic (>400 laboratory-confirmed cases),[66] France (very high seroprevalence rates),[3,58] Japan,[67] and China.[59,68,69] Data from England estimated more than 100,000 cases of locally acquired (nontravel-related) HEV infections between 2014 and 2015, which accounted for 5% of patients presenting with hepatocellular jaundice.[63,70] However, only 800 cases were laboratory-confirmed, suggesting that the majority of patients (>90%) produce no symptoms,[59] which creates a diagnostic challenge.

Conclusion

The epidemiology and natural history of HEV are complex and intricately linked to issues of geography, culture, weather, and host-viral genetic variability. Although it is beyond the scope of this article, the potential impact of vaccination and effective viral treatment may also modulate natural history, transmission, and maintenance cycles. Indeed, an effective vaccine (Hecolin, Xiamen Innovax Biotech Co, Ltd) is available in China,[7,71] but it is currently not known how its use is altering HEV epidemiology. Chronic HEV infection in the setting of solid organ transplantation can be cured in more than half of cases,[72] which may improve the health of the individuals but may also impact HEV disease spread. Overall, disease recognition and accurate diagnosis remain the primary issues in the United States and abroad, and clinicians should become more aware of HEV infection and clinical outcomes. Only then will the enigma of HEV become transparent and manageable.

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