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TOPIC HIGHLIGHT

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Hepatitis E: Epidemiology and prevention

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Abstract

Hepatitis E is caused by the hepatitis E virus (HEV), the major etiologic agent of enterically transmitted non-A hepatitis worldwide. HEV is responsible for major outbreaks of acute hepatitis in developing countries, especially in many parts of Africa and Asia. The HEV is a spherical, non-enveloped, single-stranded, positive sense RNA virus that is approximately 32 nm to 34 nm in diameter and is the only member in the family Hepeviridae and genus *Hepevirus*. There are four distinct genotypes of HEV (genotypes 1-4). While genotype 1 is predominantly associated with large epidemics in developing countries, genotype 3 has recently emerged as a significant pathogen in developed countries. The clinical manifestations and the laboratory abnormalities of hepatitis E are not distinguishable from that caused by other hepatitis viruses. However, high mortality among pregnant women particularly during the third trimester distinguishes HEV from other causes of acute viral hepatitis. Specific etiologic diagnosis among infected cases can be made by serological testing or detection of viral nucleic acid by reverse transcription polymerase chain reaction. Although there are vaccine candidates that had been shown to be safe and efficacious in clinical trials, none are approved currently for use. There is no specific therapy for acute hepatitis E as treatment remains supportive.

Key words: Hepatitis E virus; Acute viral hepatitis; Outbreak; Epidemiology; Serology; Prevention

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INTRODUCTION

Hepatitis E virus (HEV) is a significant international public health problem and it is estimated that 2.3 billion people are infected globally[1]. HEV is the leading cause of acute viral hepatitis in the world, especially in developing countries. The first retrospectively confirmed outbreak of hepatitis E occurred in 1955-1956 in New Delhi, India and resulted in more than 29 000 symptomatic jaundiced persons[2]. Since that time, many large outbreaks have occurred in Asia, Africa and Mexico[3,4]. In addition, sporadic hepatitis E outbreaks commonly occur in developing countries of Asia and Africa as well as in industrialized countries[5,6]. Although there is a distinct epidemiologic picture of HEV infection in North America, Europe, and Japan, this review article will summarize the current epidemiology of HEV infection in the developing world.

HEV

The discovery of HEV followed the development of serological tests for hepatitis A virus (HAV) and hepatitis

B virus (HBV) infections in the mid 1970s. With the ability to diagnose HAV and HBV infections and after ruling out HAV as the cause of the large 1955-1956 jaundice epidemic in New Delhi, the search for the causative agent of the enterically transmitted non-A non-B hepatitis intensified. In 1983, virus-like particles were observed, using immune electron microscopy, in the stool of a human volunteer experimentally infected with what eventually became to be recognized as the HEV[7]. The HEV genome was first cloned in 1990.

HEV is a spherical, non-enveloped, single-stranded, positive-sense RNA virus that is approximately 32 nm to 34 nm in diameter[8]. The organization of the HEV genome is substantially different from other viruses and it has its own family, the hepeviridae, genus *hepevirus*, species *HEV*[9,10]. The HEV genome is arranged in three overlapping open reading frames (ORF). The three coding frames are used to express different proteins. ORF1 encodes a polyprotein of about 1690 amino acids that undergoes post-translational cleavage into multiple non-structural proteins required for virus replication, including a methyltransferase, a putative papain-like cystein protease, an RNA helicase and an RNA-dependent RNA polymerase. ORF2 does not overlap with ORF1; it is located at the 3'-end of the genome and encodes the principal structural protein, the capsid protein of 660 amino acids. ORF3 begins with the last nucleotide of ORF1; it overlaps with ORF2 and encodes for a small immunogenic 123 amino acid phosphoprotein which associates with the cytoskeleton, suggesting its possible role in the assembly of virus particles[11]. The organization of the ORF differs slightly according to genotype however the function remains the same. Compared to the HAV, the HEV is less resistant to environmental conditions such as temperature.

EPIDEMIOLOGY

HEV is classified into at least four major genotypes 1-4 and 24 sub-types[8]. However, HEV has only one serotype. Genotype 1 is the most frequent cause of epidemic and sporadic hepatitis E in the developing world. HEV genotype 2 was first identified from the 1986 epidemic in Mexico and subsequently from Chad and Nigeria[4]. Meng *et al*[12] first described an HEV isolate which was genetically divergent from Burmese and Mexican strains and that was highly prevalent in the swine population. This strain was eventually isolated from a case in the United States that occurred in a person for whom no clear risk factor for infection was identified[13]. HEV genotype 3 is prevalent globally in the swine population and is now being increasingly identified in human cases in the developed world[14]. Genotype 4 was first described in Taiwan and subsequently found in China, Japan and India. Genotypes 3 and 4 also have been isolated from swine in the United States, Africa and Asia. There are clear differences in the epidemic potential of the various genotypes and epidemics occur exclusively in developing countries where the predominant circulating human strain is HEV genotype 1. The geographic distribution, the virulence, the nature of reservoirs and the epidemic potential of the four genotypes that are associated with human disease is shown in Table 1.

The epidemiologic characteristics of epidemic hepatitis E have remained consistent since the first described outbreak in New Delhi with the highest attack rates among young adults and a high mortality among women in the third trimester of pregnancy[2,3]. This latter characteristic has remained to be the hallmark of HEV associated acute viral hepatitis that leads to the initial suspicion of an epidemic in the absence of capacity for serological diagnosis.

To date, few studies have attempted to quantify the incidence of hepatitis E in the general population. Labrique *et al*[15] followed a randomly selected cohort of 1134 subjects from rural southern Bangladesh where the baseline prevalence of antibodies against HEV was 22.5% and found serological incidence of 60.3 per 1000 person-years during the first 12 mo of follow up. Conversely, there are several studies that have examined the prevalence of antibodies against HEV in different population groups. However, the interpretation of these seroprevalence data is immensely challenging. Challenges include the inconsistency of results due to lack of standard tests with comparable sensitivity and specificity, the high seroprevalence in populations where disease rarely occurs or is virtually absent, the presence of multiple genotypes with different disease patterns and the failure of serological tests to distinguish between genotypes.

The prevalence of markers of infection with HEV is much lower in children than for comparable markers of HAV infection in countries endemic for both infections. In a study in Pune, India, researchers found that the prevalence of anti-HAV increased rapidly and reached a peak of around 90% by age 10 years. However, the prevalence of anti-HEV remained low until age 15 at which point it started to increase and peaked at around only 50%[16]. There is no clear explanation for the relatively low prevalence of immunoglobulin G (IgG) antibodies against HEV but it may be due to a rapid loss of serological evidence following natural infection.

In epidemic conditions, HEV is transmitted mainly by drinking fecally contaminated water. In Southeast Asia, outbreaks have usually occurred during the rainy season when flooding can contaminate drinking water supplies[2]. However, many outbreaks also have occurred during the dry season or in conditions where there was no clear flooding or contamination of the drinking water supplies. Recent evidence suggests significant person-to-person transmission in outbreak situations although it is not clear whether this mode of transmission is of comparable magnitude to the person-to-person transmission of HAV infection[17]. There have been reports of transfusion-related transmission and nosocomial transmission of isolated cases of HEV infection[18,19]. Vertical transmission of HEV from a pregnant woman to her unborn fetus is

Table 1 Comparison of the four hepatitis E virus genotypes by select characteristics

Characterstics	Genotype 1	Genotype 2	Genotype3	Genotype 4
Viral discovery	1983	1986	1995	2003
Geographic distribution	Developing countries	Mexico, West Africa	Developed countries	China, Taiwan, Japan
Food-borne transmission	No	No	Yes	Yes
Fecal-oral transmission	Yes	Yes	?	No
Water-borne transmission	Yes	Yes	?	No
Person-to-person transmission	Yes	Unknown	Yes	Unknown
Zoonotic transmission	No	No	Yes	Yes
Occurrence of epidemics	Common	Smaller scale epidemics	No epidemics	Uncommon
Highest attack rate	Young adults	Young adults	Persons ⩾ 40 yr of age	Young adults
Gender	Male preponderance	Not discriminatory	Mostly male	Not discriminatory
Mortality rate	0.5%-3%	0.5%-3%	Not determined	0.5%-3%
Mortality among pregnant women	High	High	Not determined	High
Chronic infection	None	None	Yes	None
Severe disease among immuno-compromised	Not reported	Not reported	Yes	Not reported
Interspecies transmission	Only humans and non-human primates	Only humans and non-human primates	Humans Pigs	Humans Pigs
Subtypes	5	2	10	7

very well documented. Khuroo *et al*[20] investigated fetal outcomes of HEV infection in pregnant women and found in utero transmission with fetal outcomes ranging from intrauterine fetal death to symptomatic and asymptomatic neonatal liver infection. To date, there has been no evidence for sexual transmission of HEV.

Sporadic hepatitis E is also common in countries where epidemic hepatitis E occurs. The mode of transmission or risk factors for sporadic HEV transmission is not known. There are data that show that a significant proportion of acute viral hepatitis in epidemic prone countries is caused by HEV[3,5,6]. The global burden of HEV infection is due much more to the contribution of sporadically transmitted hepatitis E cases than to cases consequent to epidemic hepatitis E. In India alone, it is estimated that 2 million cases of hepatitis E occur annually compared to an estimated 1.4 million cases of hepatitis A[3,6].

In parts of Africa (Sudan, Chad, Uganda, Kenya, and Somalia) a number of large hepatitis E outbreaks have occurred among persons living in refugee camps or internally displaced persons camps[21]. Persons living in such camps may not have adequate access to clean water and sanitary conditions. Furthermore, such populations may be vulnerable to infectious diseases because of crowded living and poor nutrition, leading to higher risk of exposure to infectious agents and poor immune response during infectious exposures. Available medical care services may not be optimal and thus mortality from serious complications of infection may be high. This may explain in part the observed high mortality during hepatitis E outbreaks in Africa[22]. Outbreaks have been reported among migrant workers who move to cities and reside in crowded urban slums[23].

The clinical presentation and sero-epidemiology of hepatitis E (caused by HEV genotype 1) is not consistent globally. Serological data from Egypt have shown that the seroprevalence of anti-HEV can reach close to 100% in a population; similar to that seen with the seroprevalence of anti-HAV. Studies among pregnant women in the Nile Delta have found very high seroprevalence rates without any clinical consequence[24]. Furthermore, a high clinically manifest infection rate has been recorded in young children in the same region[25]. The HEV strain circulating in Egypt is HEV genotype 1 subtype 3. On the basis of this finding some researchers have suggested that HEV genotype 1 subtype 3 may be less virulent but highly contagious.

The persistence of IgG anti-HEV following natural infection has been one area of interest for researchers. In Kashmir, researchers conducted serological follow up of 320 persons who were known to have hepatitis E during the 1978 HEV outbreak. In 50% of the cases there was detectable IgG anti-HEV 14 years after infection[26]. In another short term follow-up study, researchers found that 100% of persons maintained evidence of past infection 3 years later[27]. However, the implication of the persistence of antibodies is not clear. The fact that the prevalence of anti-HEV in the population does not reach the same levels as HAV and that attack rates are higher among young to middle aged adults suggests that infections may not confer lifetime protection. This intriguing finding is also complicated by the recurrence of outbreaks in countries where one would surmise that following past epidemics the population would have developed immunity to prevent future outbreaks. The question of how long anti-HEV IgG remains present following natural infection and the protective efficacy of naturally acquired anti-HEV antibodies is important because of its implications for vaccine development.

Prolonged excretion of HEV in stool following symptomatic/asymptomatic infection is rare. While in HAV it is known that neonates and young children can shed virus for long periods of time, such associations have not been established for HEV. Researchers have however found that HEV RNA from human or animal

(pig) waste can contaminate drinking water, survive and remain infectious for long periods[28]. In genotype 3-associated food borne outbreaks, there has been a clear link between consumption of pig or wild boar liver and development of disease[29,30]. US researchers have isolated HEV RNA from pig livers in grocery stores[31]. In Egypt, consumption of unwashed produce was associated with higher prevalence of anti-HEV IgG, suggesting that produce could be contaminated by human or animal waste before harvest[24]. The reservoir of HEV during inter-epidemic periods is not clearly understood. There are many animal species including rats, cattle, deer and wild boar from whom anti-HEV antibodies or HEV RNA have been isolated. Kuniholm *et al*[32] have shown that having a pet dog was associated with HEV seropositivity, based on the National Health and Nutrition Survey conducted between 1988 and 1994 in the United States.

CLINICAL PRESENTATION, DIAGNOSIS AND TREATMENT

The incubation period of HEV infection ranges from 15 d to 60 d (mean 40 d). Research among non-human primates showed a direct association between infective dose and severity of disease with an inverse relation to the incubation period[33]. HEV causes a range of clinical manifestations including asymptomatic infection, unapparent infection, and icteric hepatitis. The clinical presentation of acute hepatitis E is indistinguishable from other acute viral hepatitis. Hepatitis E is an acute disease with abrupt onset of non specific symptoms followed by right upper quadrant pain, jaundice, anorexia, malaise, nausea and vomiting. Asymptomatic infections occur more often among children than adults. In a study by Khuroo *et al*[3] the symptomatic to asymptomatic ratio for children was 1:12 while for adults it was only 1:3. The symptomatic hepatitis E attack rate during an outbreak can reach up to 15%. The attack rate is always higher among adults even in countries where HEV epidemics have occurred repeatedly. Furthermore, the attack rate varies by gender. In many epidemics men were found to have higher attack rates. However, in a recent HEV outbreak in Uganda, women were more likely to have symptomatic hepatitis E than men and this difference was significant for women aged 15-45 years[21]. Although the outcome of disease is worse in pregnant women, there is no evidence to suggest that they are more susceptible to infection or are at higher risk of infection. HEV infection in pregnant women is typically severe during the third trimester of pregnancy[34,35]. Mortality rates among pregnant women in the third trimester range from 10%-25%. To date, it is not clear what the disproportionately high mortality among pregnant women is due to[36]. The causes of death include fulminant liver failure and obstetric complications including excessive bleeding[37,38]. In contrast, the high mortality observed in many Asian and African countries was not observed among HEV infected pregnant women from Egypt. Stoszek *et al*[24] detected no deaths among more than 2000 pregnant women with serological markers for infection. Other researchers also found very high seroprevalence with little to no symptomatic infections in highly endemic rural Egyptian communities[39]. The commonly circulating HEV isolate in Egypt belongs to genotype 1 subtype 3 and this may explain in part the different morbidity and mortality patterns found there.

Another group prone to develop severe morbidity following HEV infection is persons with pre-existing chronic liver disease. Persons with advanced liver disease including cirrhosis can develop acute hepatic failure when super-infected with HEV[40]. The same phenomenon has been observed with hepatitis A super-infection of persons with chronic liver disease and was the basis for administration of hepatitis A vaccination to persons with chronic liver disease[41]. This will have to be considered when HEV vaccine becomes available.

The frequent occurrence of HEV infection among persons undergoing immunosuppressant therapy for solid organ transplantation in developed countries raises the question of HEV infection among those with AIDS. To date, there are few case reports of acute, chronic or reactivated HEV infection among persons with acquired immune deficiency syndrome (AIDS). However, these reports are from Europe where the causative HEV agent belonged to genotype 3[42]. A few studies have examined anti-HEV seroprevalence among AIDS cases in Africa, but there were no reports of acute or chronic hepatitis caused by HEV. Dalton *et al*[43] found that HEV was the culprit in a number of cases diagnosed as drug-induced liver injury. In developing countries, the high prevalence of HIV/AIDS and drug-induced liver injury should be taken seriously and a systematic search for HEV infection should be part of the management of liver abnormalities in such populations.

The laboratory abnormalities in liver enzymes and liver function tests are similar in HEV to findings with other forms of acute viral hepatitis and include elevated serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, and γ-glutamyltransferase[11,44]. Abnormalities in liver function typically coincide with onset of clinical symptoms. Histopathological changes in the liver during acute infection include focal necrosis and modest inflammation[45]. Cholestatic hepatitis is common and a "pseudoglandular" alteration of hepatocyte plates has been noted. HEV is not thought to be cytopathic and it is possible that disease is due to immunological reactions, although this has not been confirmed. Resolution of biochemical abnormalities generally occurs within 1 wk to 6 wk after onset of illness. Chronic infection with HEV is virtually absent among healthy individuals, and has never been reported from HEV genotype 1 endemic countries[46]. Also, there is no evidence to suggest recurrent HEV infection in endemic countries. However, chronic hepatitis E after infection with HEV genotype 3 has been reported among persons receiving immunosuppressive treatments following organ transplants.

HEV infection elicits both immunoglobulin M (IgM) and IgG antibodies against HEV. The IgM antiHEV response is rapid, occurring about a month after infection and peaking at the time of onset of biochemical abnormalities and/or symptoms[47,48]. HEV RNA can be detected in both blood and stool at the peak of the acute serological response. There are a number of commercial enzyme immunoassays to detect IgM and IgG anti-HEV in serum although there is considerable variability in their sensitivity and specificity, thereby making the diagnosis of HEV infection difficult. Drobeniuc *et al*[49] conducted a pangenotypic validation of six commonly available IgM assays and found that only two of these assays had sensitivity and specificity above 95%. Reverse-transcription polymerase chain reaction can be used to detect HEV RNA in serum and stool but is not available routinely in commercial laboratories. Interpretation of test results can be difficult, and in low endemic regions a definitive diagnosis generally requires use of multiple tests, consideration of risk factors, and exclusion of other causes of acute hepatitis.

The reported mortality rate from hepatitis E during an epidemic has ranged from 0.5%-4%. Two recent investigations have shown that the mortality rate among young children is also high. In Uganda, the mortality rate among children younger than 2 years of age was 8% while in the Kazakhstan the mortality rate among children was 5%[21,50]. Tsega *et al*[51] reported no deaths among more than 400 cases of acute hepatitis E in young soldiers in Ethiopia. Unfortunately, in recent investigations of HEV outbreaks, it has become apparent that HEV is a fatal disease not only of pregnant women or very young children. There is growing evidence that HEV can result in fatal illness in otherwise young and healthy adults. HEV super infection may also increase mortality in otherwise stable individuals with chronic liver disease.

There is no specific therapy for hepatitis E, and treatment currently is supportive. The disease typically resolves within 4-6 wk of the onset of symptoms, usually without any long-term consequences[52]. Patients with severe complications of hepatitis E require hospitalization and it is generally believed that hepatitis E may be more severe than hepatitis A[53]. Vulnerable populations like pregnant women and persons with preexisting chronic liver disease should be identified and be given necessary supportive treatment. To date immune globulin has not been demonstrated to be effective in preventing hepatitis E in HEV-infected persons although there is some evidence to suggest that prior infection protects from disease[54-56].

PREVENTION

In HEV outbreaks, as in other fecal orally transmitted infection outbreaks, the provision of clean drinking water and improving the sanitary disposal of human waste are the two most important preventive approaches. There are challenges in implementing such strategies in a timely manner in areas where such epidemics occur. The outbreak in Uganda resulted in more than 10 000 cases despite attempts to provide clean water and increased access to latrines[21]. The outbreak in Darfur raised questions about the optimal level of chlorination to eliminate HEV from drinking water[57]. In contrast, the lack of specific risk factors for sporadic hepatitis E makes it more difficult to develop prevention strategies.

In Nepal, a phase Ⅱ trial of recombinant HEV vaccine made by expressing the ORF 2 protein in baculovirus has demonstrated that the vaccine is safe and highly efficacious[58]. However, this trial only included men and thus yielded no information on the vaccine's safety and efficacy in women and children. Recently, Zhu *et al*[59] reported a phase Ⅲ trial of another recombinant vaccine expressed in *Escherichia coli*. The trial included almost 110 000 persons randomized to receive vaccine or placebo (hepatitis B vaccine). This trial found a vaccine efficacy of 99%, but did not enroll children and pregnant women. There are other vaccines at different stages of development.

The two vaccine candidates that have undergone phase Ⅱ and phase Ⅲ trials, respectively, are recombinant proteins from truncated ORF 2 of the SAR 55 strain. As HEV has only one serotype, it is expected that these vaccines will be equally protective from infection by any of the four HEV genotypes. Given the experience in Asia that recurrent outbreaks can occur in a population and that the population level prevalence of markers of immunity against HEV are not as high as that against HAV, it seems likely that the vaccine will prove to be the magic bullet for prevention of HEV transmission during outbreaks in these countries. While the results from the recent vaccine trials are promising, many questions remain to be answered before the vaccine can be rolled out for use in the field. The most important question is the safety and efficacy of a vaccine among the most vulnerable populations including pregnant women, young children, and those with pre-existing chronic liver disease. Other questions include the efficacy of a vaccine when used in the immediate post-exposure situation in preventing and controlling transmission during an outbreak, the cost of the vaccine, the length of vaccine induced immunity, and when to vaccinate.

Understanding the global burden of HEV disease will help to develop vaccination policy when vaccines become available. However, there is a lack of epidemiological data from most countries where HEV could be the leading cause of acute viral hepatitis. The available information is mostly limited to data collected during outbreaks or epidemic investigations. To benefit optimally from the vaccine, it will be important for countries to start conducting surveillance for viral hepatitis with emphasis on etiologic rather than syndromic diagnosis. Information on baseline prevalence of markers for past HEV infections also would be useful in informing the target recipients of the vaccine.

CONCLUSION

HEV is the leading cause of non-A, non-B enterically-transmitted acute viral hepatitis in the world. Although HEV has only one serotype, the different genotypes appear to be associated with different epidemiological profiles in the developing world compared to industrialized countries. In most of the developing world, the disease affects mainly young adults and results in very high mortality among very young children and pregnant women. In epidemic settings, the basic premises for prevention of HEV infections are provision of safe drinking water and sanitary disposal of human waste. As the risk factors for transmission in sporadic hepatitis E are not clearly understood, it remains difficult to recommend prevention strategies. However, the same strategy that prevents outbreaks should closely be adhered to, as HEV and other feco-orally transmitted or water-borne infections could be prevented. Specific attention should be given to persons at higher risk of severe illness by giving priority to the prevention of infection in this vulnerable group during outbreaks. Given the huge global burden of epidemic and sporadic hepatitis E, the high mortality among pregnant women and very young children, the severity of autochthonous hepatitis E, and the threat caused by the widespread prevalence of HEV infection in different populations worldwide, expansion of epidemiologic and intervention studies, especially clinical trials of promising hepatitis E vaccine candidates, should be pursued.

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