REVIEW

Hepatitis E virus: An ancient hidden enemy in Latin America

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Abstract

Hepatitis E virus (HEV) infection is a common cause of acute clinical hepatitis worldwide. HEV is an RNA-containing virus and the only member of the genus *Hepevirus* in the family *Hepeviridae*. Human HEV is classified into four genotypes widely distributed across the world. The virus is mainly transmitted *via* the fecal-oral route, and water-borne epidemics have become characteristic of hepatitis E in developing countries, including those in Latin America. The zoonotic potential of HEV is broadly recognized. Thus, there is an urgent need to re-evaluate virus transmission scenarios and to enforce epidemiological surveillance systems. Additionally, it is known that HEV infections, initially defined as self-limiting, can also take chronic courses in immunocompromised patients. Moreover, we recently reported a high seroprevalence of HEV in samples from cirrhotic patients with no other etiological agents present, suggesting the potential role of HEV in the development of chronic liver illness. In this review, HEV genomic variability, transmission, chronic infectious course, zoonotic potential and treatment are discussed. Focus is placed on the impact of HEV infection in Latin America, to support the development of specific control strategies and the handling of this important and typically imperceptible viral infection.

Key words: Emerging diseases; Zoonosis; Viral genotypes; Mexico; Hepatitis E virus-chronic infection

Core tip: Despite the widespread presence of hepatitis E virus (HEV), this pathogen is not commonly considered from a global public health perspective. Active research on hepatitis E both in animals and humans has provided novel insight into HEV pathogenesis, zoonotic potential and its role in chronic liver disease. Detailed guidelines for tracking cases need to be developed to contain the virus. This action is particularly necessary in endemic and emerging situations in regions with a higher risk of developing the infection, including Latin America.

INTRODUCTION

Multiple outbreaks of viral hepatitis have been documented around the world since ancient times. In Latin America, viral hepatitis may have been implicated in the extermination of more than half the population of Mesoamerica in colonial times[1]. In the past century, hepatitis A virus (HAV) and hepatitis B virus (HBV), followed by the more recent description of hepatitis C virus (HCV), have been identified as causative agents of viral hepatitis. Hepatitis E virus (HEV), although probably also ancient, was not recognized as a new virus-causing hepatic disease until 1980[2], which is the main reason for the limited information on this viral disease.

HEV infection is responsible for the half of all outbreaks of acute liver disease in endemic areas[3]. HEV, which was formerly known as non-A, non-B hepatitis-causing infectious virus, is mainly transmitted *via* the fecal-oral route through contaminated water and is primarily found in areas with inadequate sanitary conditions. Other routes, such as organ transplants and zoonotic transmission, may possibly play important roles in transmission. Although the disease is usually associated with rather low fatality and mortality rates (0.2%-3.0%), in some highly susceptible populations the estimated infection rates have been reported in the range 15%-20%[4]. Of interest, in HEV-positive pregnant women, mortality due to fulminant hepatic failure has been reported to reach up to 25% in infected individuals[4,5], which is the highest value reported so far for HEV-caused fatalities.

HEV infection and HEV-associated diseases represent a major public health problem. It is estimated that 2.3 billion people are infected globally. HEV is responsible for nearly 50% of acute viral

Table 1 Hepatitis E virus genotypes reported for Latin America

Genotype	Region	Species[1]			Detection method/input specimen[2]	
		Humans	Swine	Other[3]	RT-PCR	Serum
Genotype 1	Uruguay	X			X	X
	Venezuela	X			X	
	Cuba	X				X
	Mexico	X			X	X
Genotype 2	Mexico	X	X		X	X
Genotype 3	Argentina	X	X	X	X	X
	Brazil	X	X	X	X	X
	Bolivia	X				X
	Cuba	X			X	
	Venezuela	X			X	
	México		X	X	X	
	Uruguay	X			X	
	Chile	X			X	X
	Costa Rica		X		X	
Genotype 4	China, Japan, Taiwan (not in Latin America)	X	X		X	X

[1]According to reports found in PubMed, indicates infection regardless of disease condition of the host (with or without clinical signs). [2]Origin of the host in analyzed samples. Reverse Transcription PCR (RT-PCR) was the method used to detect genomic RNA of HEV. When serum was the input material, the detection of anti-HEV specific antibodies (seroconversion) was indicative of current contact (active infection) or past infection. [3]Host or developed in chickens, deer, rodent and other mammals.

hepatitis in developing countries in Asia, Africa and Latin America[6]. Acute infections mostly affect adults, 15 to 40 years of age and are symptomatically mild. Studies from Asian endemic regions indicate a high seroprevalence, with rates ranging from 15% to 60%[3]. Chronic disease related to HEV has been reported in immune-suppressed individuals, such as organ transplant recipients, patients receiving chemotherapy, and HIV-infected patients[3,6], in whom chronic HEV infection may lead to the development of hepatic fibrosis and cirrhosis[7].

HEV, the etiological agent of hepatitis E disease, has been classified into at least four genotypes and several subtypes (Table 1). HEV genotypes 1 and 2 are hyper-endemic in Asia and Africa, and frequently cause outbreaks of acute hepatitis. HEV genotype 3 is prevalent in developed nations, where sporadic acute hepatitis has been reported[3,6]. HEV genotype 4 is almost exclusive to Asia, and it is recognized as the most frequent cause of the sporadic hepatitis E cases that affecting humans in China[8].

Initially considered an infection associated with the use of low-quality water sources, its importance has increased due to animal reservoirs. In the last decade, HEV has gained increasing attention as depicted in Figure 1. The detection of HEV in animals raised concerns about the risk of zoonotic transmission to humans. Thus, the need to involve animal health into
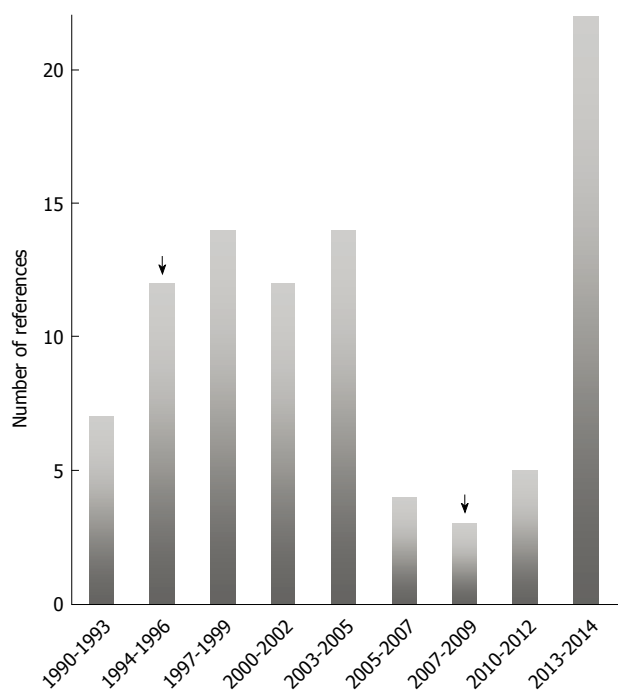
Figure 1 Timeline of the number of papers about hepatitis E virus. Based on references found in PubMed when hepatitis E virus (HEV) was used as a search keyword. All the years prior to 1990 clustered at first time point. Awareness was more prominent following the demonstration of chronic hepatitis as caused by HEV. Arrows highlights first report of zoonotic transmission (left arrow), and the demonstration of chronicity due to HEV infection (right arrow).

a single approach was recently recognized as the One Health initiative stated of the World Health Organization (WHO), which was developed to cope with such multi-source causes of disease. Human HEV outbreaks have been reported in Latin America, and specifically, twice in Mexico[2]. In both reported cases, the viral genotype 2 was detected, and this remains the only viral variant from this country[2]. HEV has also been detected in pigs from Mexico and Costa Rica[6]. Moreover, recent reports demonstrated that HEV circulates in Uruguay[6] and central Argentina[9]. Additionally, it is endemic in the Brazilian Amazon[10] and is postulated to be present in Bolivia based on the detection of antibodies against HEV[11]. Based on the limited knowledge available about the distribution of HEV viral variants in Latin America, in this review a general scientific landscape is presented to update HEV epidemiology literature and to assess the epidemiological risk for humans in this region.

VIRUS CAUSING HEV DISEASE

Hepatitis E disease is due to infection with HEV virus, a member of the *Hepaviridae* family[3]. This family includes the genus *hepevirus*, which contains viruses isolated from humans, avian species, mice, rats, and several other mammals such as boars, rabbits, camels, goats, ferrets, and mongooses. The viral particle is a non-enveloped sphere with approximately 32-34 nm in diameter. The viral genome consists of a single-stranded, positive-sense RNA molecule 7.2 kb in size. The genome organization includes a 7-methylguanosine cap structure attached to the 5' end, a noncoding region in 5' end, an open reading frame 1 (ORF1) and two other ORF2 and ORF3, which are partially overlapping. HEV RNA also has a non-translated region at the 3' region spanning approximately 27-35 nucleotides (nt), and the 3' end is extended by a poly A tract[5] (Figure 2).

The first genomic region, ORF-1, gives rise to a protein of approximately 1693 amino acids (aa) that encodes non-structural proteins and enzymes involved in viral replication, transcription and protein processing[12]. The most downstream region, ORF-2, consists of 1980 nt, ending with 65 nt before a poly-A tail signal, which encodes a 660-aa, a glycosylated protein corresponding to the structural protein of the capsid[3,6]. The ORF-2 protein contains epitopes that induce the neutralizing antibodies located mainly near the carboxyl end. The intermediate region, ORF-3, overlaps with a single nt at its 5' end with ORF-1 and with 328 nt with ORF-2. ORF-3 encodes for 123 aa, a small, approximately 13.5 kDa protein, that is phosphorylated[5]. Also known as phosphopeptide, this small protein was reported to be associated with the hepatocellular cytoskeleton and forms a complex with the major capsid protein ORF-2, suggesting their involvement in virion assembly. ORF-3 might also have regulatory functions involved in the modulation of cellular signaling transduction[5,13]. Additionally, the ORF-3 protein is thought to contain neutralizing epitopes toward its 3' end[12,13], which highlights its importance during the viral infection cycle.

HEV SEROEPIDEMIOLOGY IN LATIN AMERICA

Because HEV is primarily transmitted *via* the fecal-oral route, most outbreaks have been described as originating from a source of water. This situation occurs mainly in developing countries with a temperate climate, high population density and poor sanitary conditions[4]. Since the first epidemics described in New Delhi, India (1955-1956), many others have occurred in India (Kashmir), Nepal (Kathmandu) and China (Xinjiang Province, 1986-1988)[3]. In Latin America, the only major outbreak of HEV occurred in Mexico from 1986-1987[2,14].

The total prevalence of antibodies against HEV in endemic countries is variable (3%-27%)[4]. In contrast to other enteric viruses, such as polio or HAV, the prevalence of IgG anti-HEV is lower in children and young people than it is in adults[2]. In non-endemic areas with proper sanitary conditions and a well-controlled water supply, the prevalence of antibodies against HEV in the general population is relatively high (up to 7%-10%), and is even higher in certain endemic areas[2]. In Mexico, a study analyzing the
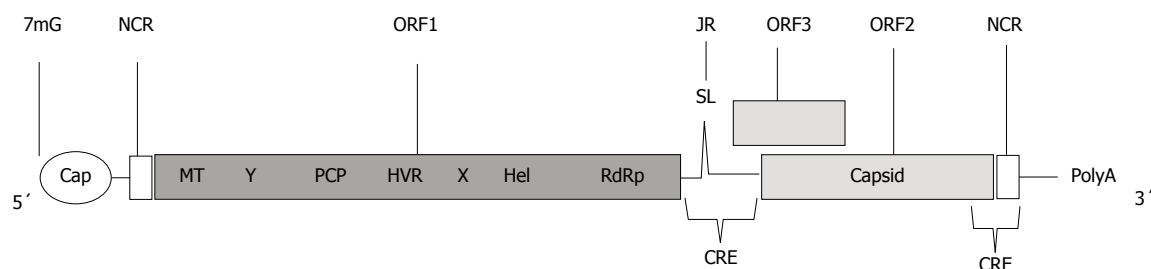
Figure 2 A schematic representation of the RNA- hepatitis E virus genome. RNA encodes for multiple proteins from three Open Reading Frames (ORFs). ORF1 comprises the methyltransferase (MT), Y domain, a papain-like cysteine protease (PCP), hypervariable region (HVR), X macrodomain, helicase (Hel), and RNA-dependent RNA polymerase (RdRp). ORF 2 encodes the capsid protein, and ORF3 encodes a cytoskeleton-associated phosphoprotein. 5´Cap and 3´PolyA modifications are also depicted. The junction region (JR), stem-loop structure (SL), and cis-reactive element (CRE) have been described elsewhere[12].

serum samples of 3549 individuals found a HEV seroprevalence of 10.5% in young adults and children of different socioeconomic status and from various regions within the country. This seroprevalence increased with age, from 1.1% in children under five years old up to 14% in people between 26 to 29 years of age[14,15]. Age, the type of community, and the level of education have been described as risk factors for infection[2]. A seroprevalence of 6.3% with a clear predominance of men older than 50 years was then confirmed in the same Mexican study[15]. In Mexico, HEV has also been detected as a cause of disease in the State of Hidalgo[16], and circulates in pig populations[17]. So far, no studies have evaluated HEV zoonotic potential or the risk of transmission in the food chain in Mexico.

From recent studies, it seems that HEV has been found in several other regions in Northern Mexico. Analysis of blood samples from 557 low-income, pregnant women in El Paso, Texas (United States) and 307 women in Ciudad Juarez showed a seroprevalence for HEV of 0.4% and 1.6%, respectively[18]. Additionally, a study of 273 serum samples from rural adults in Durango state revealed a higher (36.6%) seroprevalence than that reported in other Mexican regions[19]. This same study reported serological evidence of HEV exposure in 150 Mennonites in the same geographical area. However, Mennonites had a lower seroprevalence (6.7%) of HEV antibodies than the general rural population (40.7%) and, as reported for other groups, the seroprevalence in Mennonites increased with age[20]. The findings of a higher prevalence in older age subjects could represent a latent infectious stage in which the virus circulates in a subclinical form, or the constant permanence within an undetected animal reservoir.

An evaluation of HEV presence in higher risk population has been conducted in Mexico. The study of 439 pregnant women in Durango, Mexico revealed an HEV seroprevalence of 5.7% and an association between unpasteurized cow milk consumption and HEV exposure[21]. In Latin America, HEV has also been found in Brazil[22,23], Chile[24], Argentina[9], Costa Rica[25], Bolivia[6,11] and Uruguay[26] (Table 1). Currently,

it is accepted that in these regions, HEV has a high prevalence.

HEV GENOMIC VARIABILITY: THE CASE OF LATIN AMERICA

As an RNA virus, HEV has been recognized to exhibit broad genetic diversity although no serotype variation has been identified so far. A single serotype has been described and is composed of at least four different genotypes differing in geographic distribution and host (Table 1). Studies characterizing the genome of HEV from the same outbreak have found sequence similarities in the range of 95%-98% at the nucleotide level and 95%-100% at the amino acid level[27,28]. Support for the quasispecies nature of HEV relies on this reported genetic heterogeneity, but its impact on epidemiology has not been assessed. The genomic sequence dissimilarity has been proposed to extend the classification to incorporate HEV variants detected in many animal species, but the virus that infects humans belongs to the same four genotypes previously recognized[29]. Two additional genotypes have been proposed following the detection of HEV in wild boar in Japan, and the taxonomy of Hepeviridae is currently under revision[30]. At present, HEV is still classified into the same four genotypes, which were further subdivided into subtypes[29]. Most viral diversity relies on RNA, and alternative protein sequence-based methods could be useful for this multi-host pathogen (see Table 1) to avoid multiple subdivisions and fragmentation of this single-serotype virus. Notably, the availability of a detailed description of viral epitopes[30] could permit the use of immune-oriented methods to understand current and upcoming sequence diversity.

HEV genotypes 1 and 2 have been isolated from humans and associated with HEV outbreaks[5]. Genotype 1 is considered endemic in some areas of Asia and Africa and was also detected in Cuba and Venezuela[6,27]. In Uruguay, an indigenous HEV, genotype 1, was recently described[26]. Genotype 2 has been reported in Mexico and some local variants from Africa[2,6,27]. HEV genotypes 3 and 4 were initially
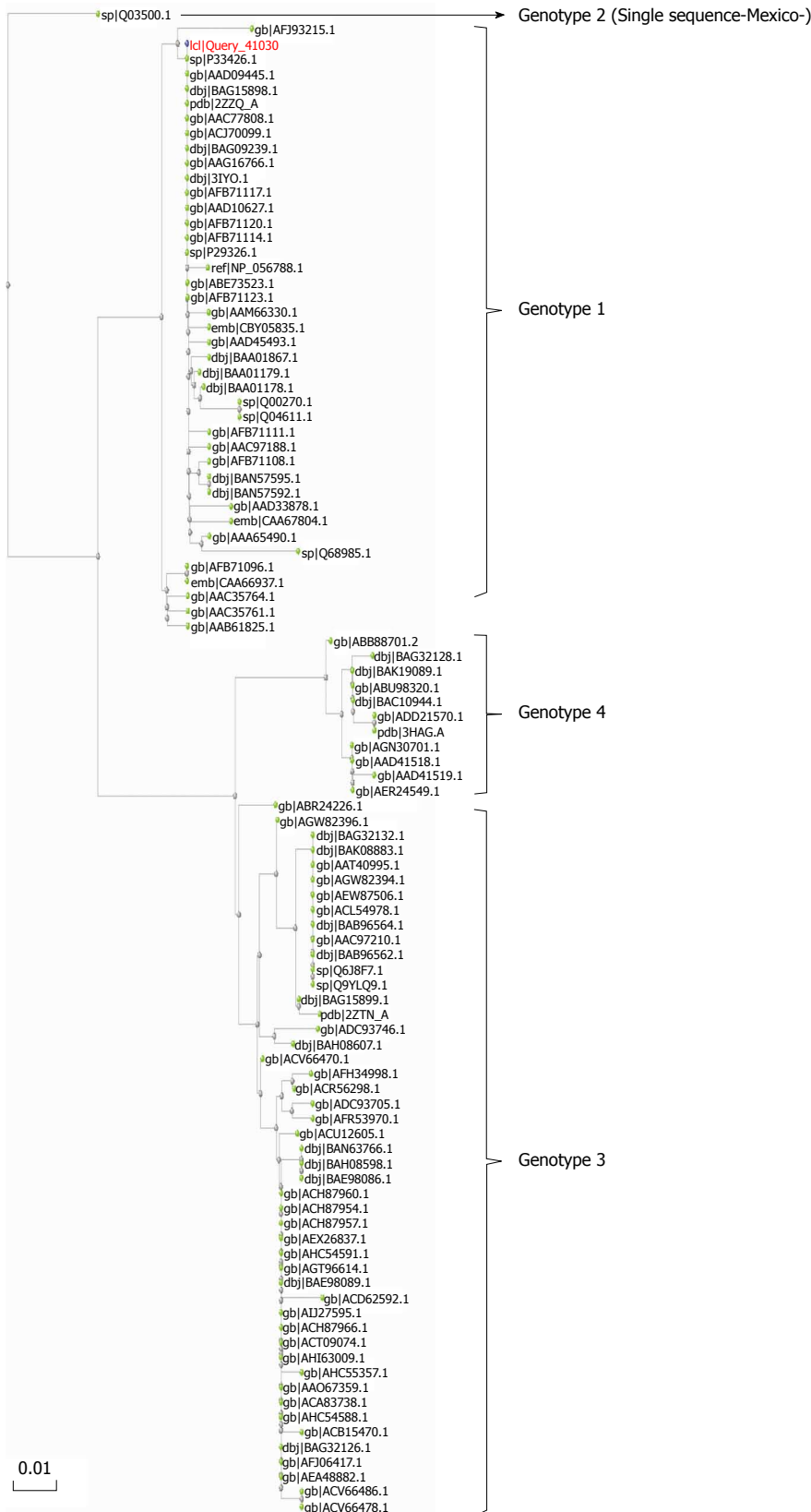
Figure 3 A phylogenetic tree for hepatitis E virus according to their amino-acid sequences from the recognition domain E2 (E domain, residues 455 to 606, based on US-1 strain) in the open reading frame capsid protein. This region corresponds with the binding domain of neutralizing Mab 8C11[32,33]. It contains all epitopes demonstrated to elicit neutralizing antibodies. This region is sufficient to provide protection, and is the basis of the current recombinant vaccine Hecolin 293 approved in China. The analysis was based on 100 sequences representing the diversity of HEV sequences. The tree was constructed by the Maximum Likelihood method using PhyML software, as implemented in server http://phylogeny.lirmm.fr[33]. The scale bar represents amino-acid substitutions and the statistical support was obtained from 100 Bootstrap replicates.

Figure 4 Patterns of hepatitis E virus infection. The typical clinical courses taken by hepatitis E virus (HEV) infections are depicted. The scheme is base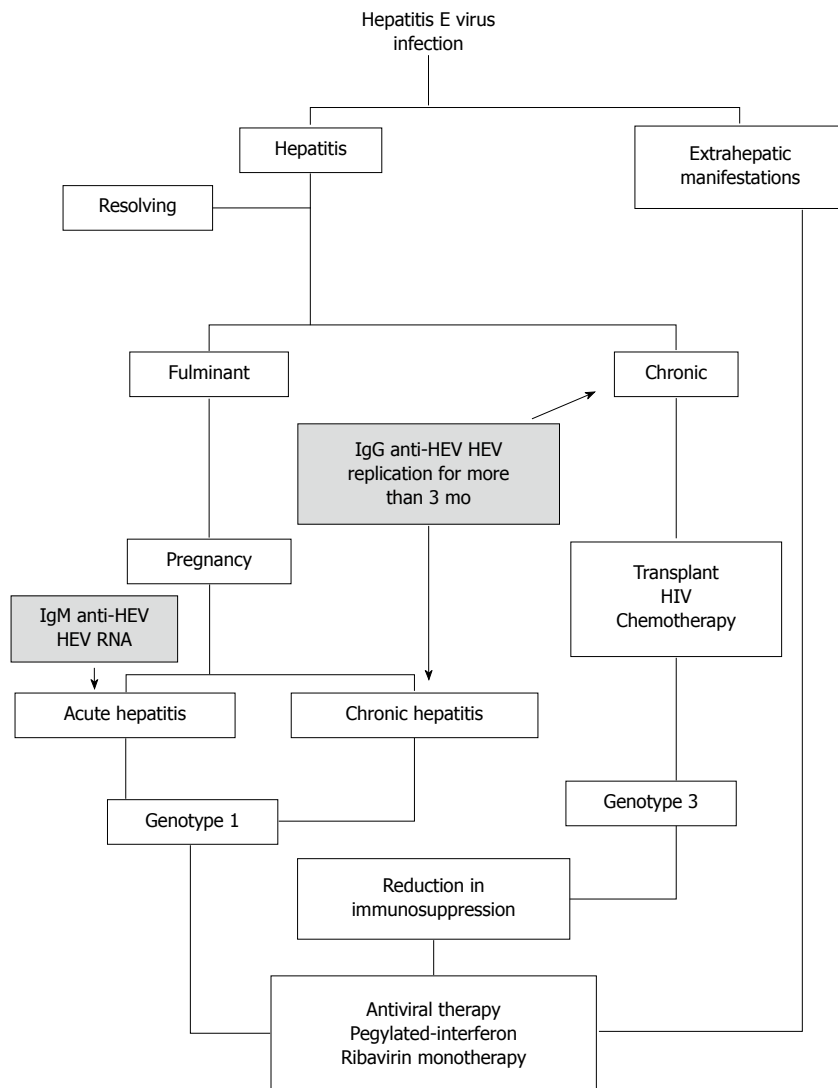d on the clinical approach followed at different institutions, as first revised in Kamar *et al*[13]. The shaded text corresponds to the clinical laboratory markers used to classify the degree of disease caused. This model is based mainly on infections with HEV from genotypes 1 and 3, as shown. Fewer data are available for genotypes 2 and 4, but the same general model may apply.

isolated after causing infection in humans and animals, mainly pigs. In humans, these genotypes 3 and 4 have been associated with acute hepatitis sporadically during outbreaks[10]. HEV genotype 3 includes isolates from non-endemic regions (the United States, Italy and Greece), and its occurrence is considered to be related to traveling to endemic regions, representing a group of more diverse sequences[4-6,10]. HEV genotype 4 is found in Asia, and is particularly endemic in China, and Central Europe[3,4]. HEV genotype 3 is the most frequent genotype found in South America, where the HEV epidemiology appears to be composed of at least three of the four known genotypes[3,4,6] (Table 1). It is interesting that the clinical manifestations of HEV have been associated with distinct ages depending on the infectious genotype. In the Indian outbreak, which primarily consisted of genotype 1, the age group with the highest incidence of infection was between 20

and 29 years. Characterization by extensive sequence analysis of three regions of HEV genome from Uruguay revealed that these viruses were closely related to a set of European strains[26] and, thus, dissimilar to Brazilian, Argentinean and Bolivian isolates[6]. The outbreaks reported in Mexico and those associated with genotypes 1 and 2 in developing countries have shown the highest incidence among individuals in the same age range. In contrast, sporadic infections in industrialized countries have been associated with genotypes 3 and 4, with an average age of highest incidence of 60 years. HEV detected from Argentina and Brazil are more related to viruses from industrialized countries (North America and Europe), whereas the HEV in the Caribbean and Mexico include viral genotypes more closely related to outbreaks in Africa and Asia[2,6]. The heterogeneity of HEV viruses in Latin America can be demonstrated by the

phylogenetic analysis of their sequences as detailed in Figure 3[28,29], and particularly according to their amino-acid sequence from recognition of the E2 domain in ORF2 that corresponds to the major recognition epitope for neutralizing antibodies[30-32]. The prevalence observed in this region and its genetic heterogeneity highlight the urgent need to improve our knowledge of the molecular epidemiology of HEV in Latin America. Thus, single or multiple re-introductions of HEV may be detected to prevent further outbreaks.

TRANSMISSION

HEV is primarily transmitted *via* the fecal-oral route. As such, the epidemics of hepatitis E in endemic areas are due to contaminated water[2]. The optimal circumstances for hepatitis E epidemics arise when untreated wastewater comes into contact with drinking water during times of heavy rain. Examples of these circumstances included the 1950s epidemic in Delhi (India), which was preceded by heavy rains and floods[6], and outbreaks in Mexico, which have coincided with the rainy season. There is a direct correlation between a high incidence of positive serology of HEV and the use of superficial waters without boiling for food consumption or personal hygiene[6]. Some studies have described the presence of viral particles and RNA in the wastewater of cities after the slaughter of swine in industrialized countries[33,34]. However, subsequent studies have not confirmed any risk of HEV infection *via* this type of water contamination in industrialized countries[35]. This discrepancy may reflect the difficulty of detecting pathogens in water samples, particularly in the case of HEV RNA, which is very labile. Clearly, there is still a great need for systematic studies that identify the risk represented by such water conditions in Latin America because many areas are considered to have poor health conditions and deficient sanitary treatment of the potable water systems.

The incidence of HEV transmission from person to person is low, representing between 1 and 2% of the total number of cases described[5]. In contrast, the rate of HEV transmission from mother to child, though variable, is quite high (30% to 100%)[20,21]. Up to two-thirds of pregnant women infected with HEV may have premature births and high neonatal mortality[36]. Reports of HEV RNA in the blood of newborns, when the virus could not be detected in the mothers, have also been published as a possible case of vertical transmission[37]. Additionally, the presence of HEV in multiple animal reservoirs shows that the origin and transmission of HEV disease are in need of urgent revision. Thus, animal reservoirs used as a food source cannot be discarded as risk factors for spreading

HEV[13].

PATHOGENESIS

After entering the body, HEV virus shows exquisite tropism for the liver, *via* as-yet-unknown mechanisms. The virus accumulates in the bile, reaches the intestine through the bile duct, and then can be found in the feces after approximately two weeks of infection. During the first two weeks, anti-virus specific antibodies can be found in the serum[4,5]. HEV has been reported in the blood or feces for longer periods, up to 16 wk, depending on unknown conditions. The more prolonged maintenance of HEV in asymptomatic individuals may result in reservoirs during inter-epidemic stages over time, resulting in sporadic infections among persons exposed to contaminated food or water[4]. HEV is shed in the feces of infected individuals as infectious, nonenveloped virions with their genome encapsidated in a naked protein shell[10,13]. However, recent reports suggest that HEV circulates during acute infection in a membrane-wrapped form in which the encapsidated RNA is completely enveloped and sequestered from neutralizing antibodies, and yet has an infectivity equivalent to that of naked virus particles. These membrane-wrapped forms of HEV differ from classical enveloped viruses in that the surrounding lipid bilayer appears to be devoid of virally encoded proteins[13]. This would allow the extracellular virus to masquerade as a host-derived exocytic vesicle and likely facilitates its dissemination within the host, but this hypothesis remains to be tested.

During the infection cycle, typical humoral responses have been described with less information available for the corresponding cellular component of the immune response. The role of the host response in the self-damage to liver cells is poorly understood, and there is agreement regarding the prominent role of the immune system plays in the resultant liver damage[3]. The identification of specific IgM antibodies for HEV in the serum coincides with the appearance of symptoms. HEV-specific IgG antibodies can be detected shortly after the emergence of IgM antibodies, and IgG values increase during the acute phase of the disease and remain detectable in the serum for several years[3,4].

The lack of a cellular or animal model hampers the progress of studies regarding the pathogenesis of HEV virus. Attempts to culture the virus have given rise to a few reports on cells lines permissive for HEV replication while in culture[10,13]. However, no standard methodology for viral isolation has been established, and the characterization of infection is performed using only serological and molecular methodologies (Table 1). The understanding of viral pathogenesis is in urgent

need for *in vitro* methods and *in vivo* approaches that might evoke the viral life cycle.

HEV-chronic infection in immunocompromised patients

Although HEV infections are defined as acute and self-limiting, we previously reported a high seroprevalence of HEV in samples from cirrhotic patients with no other etiological agents, suggesting the potential role of HEV in the development of chronic liver illness[2]. In fact, it has been recently accepted that HEV infections may take chronic courses under specific circumstances, such as in immunocompromised individuals. Although chronic HEV infections have been mainly diagnosed in the organ transplanted population[38-43], chronic HEV infections have also been found in patients receiving chemotherapy[44] and in patients coinfected with HIV[45,46].

HEV and transplants

The HEV seroprevalence is high in liver transplant recipients[38]. The prevalence of HEV infection in organ transplant patients (OT) ranges from 2.3% to 43.9%, depending on the serological test employed[47-53]. The incidence of HEV RNA in OT with increased liver enzyme levels ranges between 4.3% and 6.5%[38,53]. To date, HEV is considered to cause chronic infection with rapidly progressive cirrhosis within 1-2 years of infection in organ-transplanted patients[53,54], faster than reported in HCV-infected OT. This rapid progression is found in liver and non-liver transplant patients[54]. The administration of immunosuppressive medication to prevent organ rejection appears to be an important risk factor for developing a chronic infection caused by HEV. In particular, tacrolimus, a potent immunosuppressant, has been associated with chronic HEV infection[55-57]. Advances in the description of optimal immunosuppressive protocols for HEV-infected patients are currently in progress[58,59].

A diagnosis of chronic hepatitis infection is defined by the presence of genomic viral content for more than six months. However, in the setting of organ transplantation, it has been found that no spontaneous clearance of HEV occurs between 3 and 6 mo after an acute infection[13]. Thus, chronic HEV infection should be considered when HEV replication persists for more than 3 mo. Moreover, given the liver enzyme abnormalities often attributed to hepatic graft-versus-host disease or drug-induced liver injury in liver transplant recipients, the misdiagnosis of HEV is frequent. Symptoms are present in only 32% of OT patients, with fatigue being the main symptom and, in contrast to acute hepatitis A virus infection, clinically apparent jaundice is uncommon. Liver enzyme levels are increased (300 IU/L) but are lower than those observed in immunocompetent patients (1000 to 3000 IU/L)[57]. Considering that HEV infection may occur in donors, this emphasizes the need for HEV screening not only after transplantation but also in donors presenting liver function abnormalities[60]. HEV diagnosis in OT with elevated liver enzymes is advised and is based on HEV RNA testing as antibody assays are typically not sensitive enough. HEV seroconversion may be delayed and may not occur in some patients. Thus, the molecular detection of HEV RNA is essential to exclude an HEV infection in patients who are negative for anti-HEV IgM and to assess the evolution of infection. To date, no cases of chronic HEV genotypes 1, 2 or 4 have been reported. All chronic cases have been associated with HEV genotype 3. Interestingly, fulminant hepatitis in pregnant women has been related to viral genotype 1[13]. Thus, the determination of genotypes may be crucial to predicting the disease outcome.

HEV, chemotherapy, and HIV co-infection

The systematic analysis of the incidence of chronic HEV infection among hematological patients receiving chemotherapy has not been conducted. Among the small number of reported cases are patients treated for lymphoma, chronic myelomonocytic leukemia, and B-cell chronic lymphocytic leukemia[59-62]. The incidence and HEV seroprevalence among stem cell transplantation patients is in progress. Preliminary, evidence from two independent studies report an anti-HEV seroprevalence of 36% and 5.6% among cell transplanted patients. However, in both studies, ongoing HEV infection was absent[63,64]. This piece of information has induced clinicians to screen patients in chemotherapy with abnormal function tests for HEV RNA. Similarly, chronic infection with HEV has been described in individuals with HIV infection. Based on the limited number of analyzed cases, the seroprevalence of anti-HEV IgG in HIV-positive patients ranges from 1.5% to 11.2%[65-75]. However, the incidence of HEV infection defined by the presence of HEV RNA in the serum is low, ranging from 0 to 1.3%[66,70-75].

A small number of cases of HEV coinfection confirmed by the detection of genomic viral content have been documented around the world[45,66-68,71,73,76-78]. A high HEV seroprevalence in HIV-infected patients has been documented in both HIV-infected patients with unexplained liver disease[79] and HIV-infected patients in the absence of chronic liver infection[80]. As detailed above, genotype 3 has been the HEV variant detected among HEV-related cirrhosis cases in HIV co-infected patients[67,68,70,81]. The clinical presentation in patients receiving chemotherapy and in the HIV co-infected patients is similar to that found in OT patients. Moreover, HEV infection can even result in extra-hepatic manifestations both during and after the resolution of infection[80]. However, data regarding the epidemiology of hepatitis E in particular populations is limited. Further studies are required to determine the exact role of HEV in the development of liver damage in immunocompromised and immunocompetent indi-

viduals.

ZOONOSIS

HEV is widely recognized as a zoonotic infectious agent[82-84]. Recently, a re-visited American population had a 6% seroprevalence of anti-HEV antibodies in the general population. For this US-based study, Hispanic race, and "meat" consumption were identified as factors associated with HEV-seropositivity. No significant association was observed with low socioeconomic status, water source, or level of education. In the multivariate analysis, only older age remained predictive of HEV seropositivity[81,84]. Of note, in previous studies in the United States, having a pet in the home was identified as another important factor for HEV-seropositivity[83,84]. From studies in other countries, it seems that the presence of anti-HEV antibodies in pet dogs could be approximately 1%, and this factor could also become another component to understanding the epidemiology of HEV[85,86].

In the 1990s, the presence of antibodies against HEV in swine was described for the first time[84,86] (Figure 1). Subsequently, the experimental infection of swine with swine HEV or isolates of human origin demonstrated that infected animals exhibited viremia, releasing the virus along with their feces while showing no evidence of clinical or biochemical disease. Studies in America, Asia, and Oceania, have shown very high prevalence rates, ranging between 20% and 100%[86]. In Latin America, HEV circulates in animal species, including swine, as reported in Brazil[87] and Argentina[88]. A study analyzing the presence of antibodies against swine HEV in Mexico and Thailand found positivity for IgG anti-HEV in 81% of the swine analyzed in Mexico[6,17]. The sequence analysis of a total of 44 positive samples isolated from Mexico and Thailand were genotype 3, supporting the notion that only genotypes 3 and 4 have zoonotic potential[17,89-94]. This finding is of particular interest as it considers the genotypes found in industrialized countries, suggesting that the mechanism of infection in these regions could be zoonotic. Moreover, the study of 87 livers collected from pigs destined for human consumption in Nuevo Leon, Mexico revealed that between 19.54% and 22.5% of the livers were positive for genomic HEV[89]. These findings indicate that HEV-infected meat may constitute a source of contamination[82,89]. The initial suggestion that HEV could potentially be a zoonotic agent has been supported by data showing a high prevalence of anti-HEV antibodies in farms in both endemic and non-endemic areas[82]. Moreover, swine isolates are genetically more related to human variants in the same geographical region than to swine strains from other parts of the world, which supports the zoonotic nature of transmission. Furthermore, the described cases of acute hepatitis after ingesting raw meat from HEV-infected deer demonstrate the potential zoonotic characteristics of HEV[90,91].

In addition to swine, HEV infections have been detected in other animal species. Anti-HEV antibodies and the HEV RNA genome have been detected in animals such as cattle, sheep, dog, deer, cat, goat and nonhuman primates[82,90]. The presence of specific antibodies only (seroprevalence) has been described by several studies in chickens, dogs, cattle, cats and rodents[82,94-103]. In most cases detecting and analyzing HEV genome, sequencing results obtained from a particular location have been very similar regardless of the species of origin. Altogether, these observations confirm of the zoonotic circulation of HEV virus crossing the species barrier frequently[84,96].

Experimentally, a rabbit HEV strain was successfully demonstrated to be transmitted to pigs, indicative of the ability of HEV to cross the species barrier[91]. The zoonotic transmission of HEV from deer[90] and pet cats[95] to humans has also been reported[82,84]. In addition, it has been demonstrated that avian HEV, although genetically less related to human HEV compared to swine, shares antigenic epitopes with both[98]. At least three genotypes of HEV have been documented from chickens worldwide[92-94], and these are different from the genotypes described for mammals. HEV infection in chickens is enzootic and affects 71% of chicken flocks in the United States. HEV infection in chickens is mostly subclinical, although 30% of chickens were seropositive for avian HEV antibodies[92,94]. While the evidence of avian infection in humans is currently lacking[93], the spread of bird-to-bird infection has been reported[94]. HEV has been isolated from a variety of animal species ranging from bats, chicken, camel, cutthroat trout, deer, ferret, fox, mink, mongoose, moose, pigs, rabbits, rats and wild boar[91-96].

The high incidence of HEV infection in Mexican swine requires adequate epidemiological surveillance in high-risk groups near farms. Also, although some studies have revealed that domestic pet veterinarians are at no increased risk of hepatitis E compared to the general population[83], the data have primarily come from Asia and Europe. Specific studies in Latin American countries are required to determine the potential risk of infection in this group. Descriptions of genotypes in rural areas with poor sanitary conditions are needed to provide the necessary data for controlling these infections, the incidence of which at present has been underestimated.

TREATMENT

There is no specific prophylactic treatment for acute hepatitis E infection. The results obtained in animal models suggest that the use of specific Ig, when faced with high HEV titers, can be useful during outbreaks[3]. The existence of a single serotype of HEV supports the possibility of generating a vaccine that has broad cross-reactivity against all known genotypes. The availability of such vaccine would be useful to protect against HEV

infections and to prevent local outbreaks in developing countries, especially in immunosuppressed individuals, inhabitants of endemic regions and travelers to endemic areas. In 2011, the first vaccine against HEV (Hecolin, based on strain HEV-239), was licensed in China[97]. This vaccine is not yet available in the rest of the world. In the absence of a vaccine, the availability of clean water and good hygiene practices such as washing hands properly and the consumption of only properly cooked food is very helpful in controlling HEV virus spread[98].

In the case of immunocompromised patients, particularly in OT patients, intervention strategies should be considered in cases of acute or chronic HEV infection[99]. The first-line approach includes reducing of immunosuppressive medication because these drugs may influence viral replication and the course of liver disease. Oral ribavirin and pegylated-interferon have antiviral activity against HEV[59,100]. A twelve-week course of pegylated interferon, ribavirin or a combination of the two agents leads to viral clearance in about two-thirds of patients with chronic hepatitis E[100]; however, treatment failure may occur[59]. For patients with severe infection, ribavirin monotherapy should be considered to expedite viral clearance and recovery. Although ribavirin therapy is contraindicated in pregnancy owing to teratogenicity, the risks of untreated HEV to the mother and fetus are high and specific treatments are yet to be developed[100]. Given that specific therapies should be indicated for particular populations, the determination of the optimal dose, duration, and quantitative goals of ribavirin or pegylated-interferon treatment are still in progress[99].

CONCLUSION

In 2009, the WHO Expert Committee on Biological Standardization endorsed a proposal by the Paul-Ehrlich-Institut to prepare an International Standard for HEV RNA for use in NAT-based assays. This standard is currently available and should be implemented in all epidemiological studies with the aim of harmonizing methods globally[101].

To date, there are limited established guidelines and regulatory mechanisms for the study of highly dynamic diseases of public health impact, such as HEV, in Latin America. Careful scrutiny of the host distribution of the viruses that cause hepatitis E in Latin America, changes in the pathways of transmission, or the evolutionary dynamics of the genotypes of these circulating viruses, are required to support handling strategies of the disease, to define clinical treatments, and to prevent potential outbreaks. The common finding of this virus in epidemiological studies[102,103] represent a risk that must be properly handled.

Despite the widespread presence of HEV, this pathogen is not commonly considered from a global public health perspective. Limitations in medical and laboratory infrastructure and the absence of awareness of the disease caused by HEV may hinder surveillance studies and thus facilitate viral spread. There are now sensitive diagnostic assays and well-defined validation reagents to support the identification and preparedness to prevent HEV outbreaks[101]. A detailed guideline for following cases in endemic as well as in emergency situations needs to be developed to contain the virus (Figure 4). Active research on hepatitis E both in animals and humans has provided novel insights into HEV pathogenesis. More research is recommended to understand chronic and extra-hepatic infections to determine better treatment approaches.

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