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Hepatitis E: Insights Into Molecular Virology, Epidemiology, And Pathogenesis

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ABSTRACT

Background: Hepatitis E is a significant public health concern, especially in developing countries, due to its association with waterborne outbreaks. It accounts for a large proportion of enteric-transmitted liver diseases worldwide. In developed nations, cases of hepatitis E are rare and typically linked to travellers from endemic regions or individuals without identifiable risk factors.

Objective: To provide an overview of the hepatitis E virus (HEV), including its virology, transmission, zoonotic potential, and treatment options.

Methods: A review of current literature on HEV epidemiology, virology, modes of transmission, and treatment approaches, with a focus on genotype distribution and its impact on public health.

Results: HEV is a single-stranded, non-enveloped RNA virus with one serotype and four genotypes. Genotypes 1 and 2 are primarily found in developing countries and exclusively infect humans, while genotypes 3 and 4, common in industrialized countries, infect humans and other mammals, especially pigs. HEV is increasingly recognized as a zoonotic.

KEYWORDS: Hepatitis E virus (HEV), Enteric-transmitted liver disease, Zoonotic infection, Genotype distribution, Acute hepatitis E, Chronic hepatitis E, Waterborne outbreaks, Vaccine development.

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INTRODUCTION

In 1980, strain E of acute hepatitis was defined using blood samples taken from a massive epidemic of fecally transmitted hepatitis that hit New Delhi, India, in 1955 and 1956. 1 It was determined that hepatitis virus (HAV) was not the causative agent of that pandemic based on demographic and clinical data as well as the presence of anti-HAV antibodies. In 1983, the "non-A enteric hepatitis virus," now known as hepatitis E virus (HEV) (E for enteric and epidemic), was identified as the pathogen responsible for this disease. A genomic sequence of it was completed in 19913. Although hepatitis E seems to be ubiquitous in developed nations like the US and Europe, it is primarily a public health concern in underdeveloped nations where it accounts for a disproportionate share of hepatitis E infections. The pollution of water supplies and inadequate sanitary

conditions in impoverished nations are the key factors that cause HEV epidemics. (Orosz, Sárvári, Dernovics, Rosztóczy, & Megyeri, 2024).

Travelers from endemic areas and occasional cases without risk factors are the only known sources of acute hepatitis E in industrialized countries. Different HEV strains in affluent and developing nations provide credence to the idea that HEV infection in the former originated locally. Thus, hepatitis E has been postulated as a potential culprit in epidemics resembling the Indian epidemic that plagued Europe throughout the late 19th and early 20th centuries, a time when sanitation was severely lacking. Because it has only ever been found in pigs, chickens, deer, mongooses, rats, and rabbits—and because no other hepatitis virus has animal reservoirs—hepatitis E is widely believed to be a zoonotic illness. (Zhu & Feng, 2024).

Acute liver infections that resolve on their own and severe instances of oral-faecal transmission are both caused by HEV, according to clinical observations. Nevertheless, there have been reports of chronic infection with this virus in patients undergoing liver and kidney transplants. This adds this virus to the list of causes of chronic liver infection with viruses B, C, and D, and it opens up a promising avenue for further research. Histoplasmosis infection is associated with a greater death rate (1–4%, or 1–15% during epidemics, or 20–30% in pregnant women) compared to hepatitis A (0.1–2%). While the faecal-oral route of HEV transmission is well-established, there have been reports of individuals in Japan6 who contracted the virus through blood transfusions or food consumption, suggesting that other plausible routes of transmission exist (vertical, blood transfusions, person-to-person contact, zoonotic). (Letafati et al., 2024).

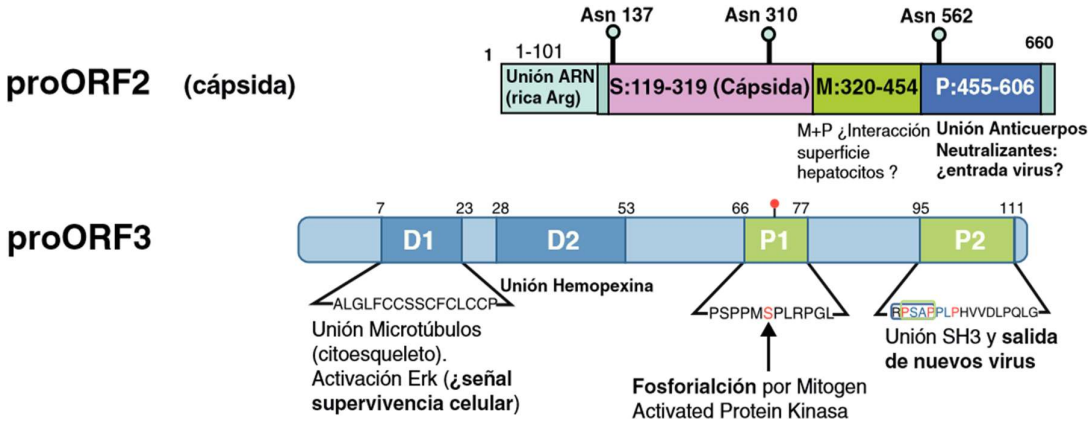
HEV virology

The fecal-oral transmission route is made possible by an unencased icosahedral particle of approximately 32 nm9 (fig. 1A) that is resistant to inactivation by the mild acidic and alkaline conditions of the intestines. One strand of positive-sense RNA, measuring approximately 7.2 kilobase pairs (kb), makes up the viral genome. It contains three open reading frames (ORFs)—ORF1, ORF2, and ORF33—that code for proteins. Two untranslated regions (NTRs) flank the 5' and 3' ends of the strand. The 5′ NTR region, an alphavirus-homologous sequence in the middle of the RNA, and a conserved 58-nucleotide length of ORF1 all fold into "stem and loop" structures (Fig. 1B), which are crucial for HEV10 transcription and replication. Proteins encoded by ORF2 and ORF3 (which overlap with ORF2) are derived from a single bicistronic subgenomic RNA that contains two AUG codons situated in the central region of the genome that is similar to alphaviruses. ORF1 is translated from a full genomic transcript, which is the HEV-RNA itself, and functions as a messenger (figure 1B). (Luo et al., 2024).

Located at the 5′ end of the viral genome, ORF1 occupies 60% of it and codes for a big polyprotein, proORF1, which is 1,693 amino acids long (Fig. 1C). This protein contains various structural and functional motifs that are involved in viral replication, such as methyltransferase (MetTrf), cysteine-protease similar to papain (Cys-Prot), helicase for RNA (Helic), and RNA-dependent RNA polymerase (RNA-pol) (fig. 1B). An important 5'-methyl-guanosine residue required for HEV infection and replication is located in the 5' of the RNA, which provides support for MetTrf. The active site of this enzyme seems to be the crucial GDD motif of the RNA-Pol region. The viral capsid, which consists of 660 amino acid proORF2 dimers that interact with the 5′ end of the genome through its N-terminal region rich in arginines (aa:1101), is encoded by the ORF2 region in the 3′ position of the viral genome. The protein is glycosylated in asparagines 137, 310, and 562 (Fig. 1C). (Ayyub, Thomas, & Hodeify, 2024).

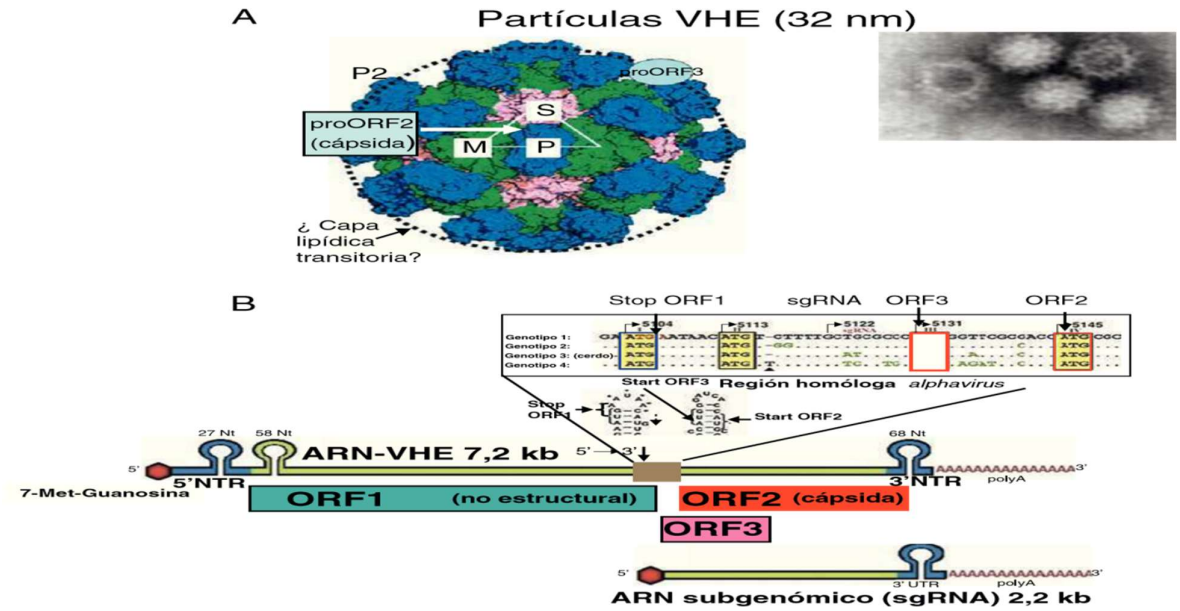
Three linear domains make up the proORF2 protein. The first, the S domain, is located at amino acids 119–319 and is responsible for forming the capsid. The second, and third, domains, M and P, are located at amino acids 320–454 and 320–606, respectively, and are associated with the capsid. The P domain, which is accessible from the outside of the capsid, is being developed as a vaccine target and may serve as a binding site for neutralizing antibodies. The 114-amino acid phosphoprotein referred to as proORF3 is encoded in the ORF3 region (Fig. 1C). It is translated from the subgenomic messenger RNA starting at a third AUG codon, which involves a reading frame change (+1) relative to the AUG codon in ORF2, almost entirely overlapping with ORF2. Ape infection seems to necessitate this protein, even though it is unnecessary for replication in vitro. Its cysteine-

rich N-terminal end forms a complex with the viral capsid and binds to the viral RNA. The viral particle is momentarily covered by a lipid coating as it exits the infected cell.(Nagoba & Rayate, 2024).



Multiple multifunctional domains located in the C-terminal region of proORF3 interact with many cellular proteins that are involved in viral particle formation and infectivity. Eleventh: Mitogen-activated protein-phosphatase interacts with hydrophobic domain D1 (Fig. 1C). Infected individuals have decreased plasma levels of hemopexin and haptoglobin, two acute phase glycoproteins; -kinase, which is colocalized with the cytoskeleton, activates extracellularly regulated kinase (ERK), which may serve as a cell survival signal. D2 interacts with hemopexin. By reducing the intensity of the acute phase inflammatory response, proORF3 seems to suppress the host's innate immune response. P1 has the 80-serine residue that is phosphorylated and is present in all HEV strains except the Mexican strain. The other proline-rich area, P2, has a PxxPxxP motif that binds many proteins. Domains homology-src3 (SH3) contain, and are linked to, the virus's production (Maria Casares-Jimenez et al., 2024).

It seems that ProORF3 interacts with multiple intracellular pathways to control the host cell environment. Binding to and suppressing the phosphatase that inhibits ERK activation is how it works. Extended ERK activation would produce a signal for cell growth and survival. To protect cells infected by HEV, proORF3 interacts with various cellular components in a way that promotes viral replication. This, in turn, prolongs the life of infected cells by lowering the intrinsic death pathway and downregulating the innate immune response. (Borlang, Murphy, Harlow, Osiowy, & Nasheri, 2024).



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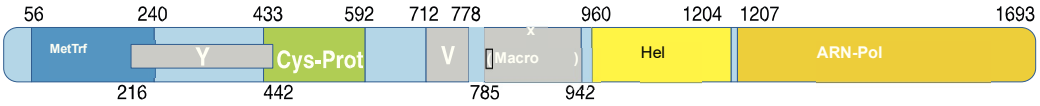

proORF1

(MAPK)

Graphic 1. A) The crystal structure of pseudoviral particles and electron microscopy image of HEV viral particles (derived from Xing et al.) reveal the potential localization of proORF3, as well as the packaging of the capsid proORF2 proteins (Fig. 2C). During the outflow of the viral particles, the dashed circle represents the transitory lipid layer. Structure of the HEV genome (B): The positive-sense RNA strand is approximately 7.2 kilobase pairs long and contains the following: a 7-methylguanosine (7-Me-Guanosine) residue at the 5′ ends (cap), a poly-A tail at the 3′ ends, the untranslated regions 5′NTR and 3′NTR (with "stem-loop" folded fragments), three open reading frames: ORF1, ORF2, and ORF3, as well as the alphavirus-homologous central region, which contains the stop codon of ORF1, the start (ATG) of ORF3 and ORF2, and the start position of the 2.2 kb subgenomic RNA that functions as a transcript for ORF2 and ORF3. C) Hybrid Ebola Virus protein sequence diagrams (Brüggemann, Klöhn, Wedemeyer, & Steinmann, 2024).

- ProORF1 is a non-structural polyprotein that encodes several enzymes, including MetTrf, Cys-Prot, Hel, and RNA-dependent RNA polymerase. Moreover, there are two sections, X (the macrodomain) and Y, that are similar to non-structural proteins found in other positive-strand RNA viruses. Hinge function is possible in Region V, which is an Arg-rich region.
- ProORF2 is a structural protein that is a part of the capsid of the virus. It appears that the M and P domains—one of which extends from the capsid; Fig. 1A—are involved in cellular receptor identification and contain the neutralizing epitopes; the S domain produces polymers that give birth to the capsid structure.
- There is a protein called proORF3 that has multiple functions. Domains P1 and P2, which are rich in proline, and hydrophobic domains D1 and D2 are shown (see text).

VHE replication cycle

The capsid pattern that recognizes the virus's cellular receptors is unknown, although it may be situated in the P214 domain's neutralizing epitope. Its similarities to other RNA viruses have led to the proposal of a model for its replication cycle. Here, following HEV infection, the genomic RNA—now devoid of capsid—is translated in the cytosol to generate the non-structural polyprotein proORF1. Then, cellular proteases (MetTrf, Cys-Prot, Helic, and RNA-Pol) work in tandem with HEV's own Cys-Prot protease to cleave proORF1 into its parts. To create new viral particles and proORF1 messenger, RNA-Pol replicates the positive HEV-RNA strand into negative HEV-RNA intermediates. These templates are also used to synthesize the subgenomic HEV-positive RNA, which is a messenger for proORF2 (the viral capsid) and proORF3. (Salemane et al., 2024).

Figure 1B shows that the viral RNA, which seems to function as a promoter, is responsible for the transcription of these two proteins. An unidentified process removes the lipid coating from circulating virions, leaving the viral genome packaged within the capsid. On the surface of the capsid, proORF3 binds with the genome. Last but not least, with the potential involvement of proORF3, the newly formed virions will leave the cell via a poorly characterized mechanism. Positive and negative strand HEV RNA has been found in the livers of monkeys and pigs that were experimentally infected, however, there is no data from experiments to support this potential replicative cycle.(Zahmanova, Takova, Lukov, & Andonov, 2024).

HEV classification and phylogeny

Classification changes have resulted in HEV's reclassification from the Caliciviridae family to the Hepevirus genus, where it now stands as the sole member of the Hepeviridae family of class IV positive-sense RNA viruses. According to studies on HEV variety both inside and between patients, the virus has a quasispecies structure, with a rate of base substitutions ranging from 1.40-1.72×103 per site and per anus, which is comparable to other viruses. RNA, with ORF1 comprising a hypervariable region and highly polymorphic sections, and well-conserved terminals at both ends of ORF2, the capsid gene. Based on their evolutionary tree, four distinct genotypes17 and twenty-four distinct subtypes19 have been identified for mammalian HEV (Fig. 2A). We don't yet know which subgroups are clinically relevant. See Figure 2B for a breakdown of the HEV genotype distribution by region.(Modiyinji et al., 2024).

Humans are the only known hosts for genotype 1, which has only recently been detected in the United States as well as in endemic regions of Asia and North Africa. There is a 90% degree of similarity between the various isolates. A single strain from an outbreak in Mexico and strains from epidemics in Central Africa6 make up the human-exclusive genotype 2. It shares an 86% amino acid identity with genotype 120 and a 75% nucleotide identity. Human and swine HEV strains belonging to genotype 3 originate from developed nations such as the US, Europe (particularly the UK, France, Holland, Spain, Greece, Austria, and Italy), Oceania (including Australia and New Zealand), and Argentina. It has also been found in wild boar and deer. (Fantilli et al., 2024). Isolates from humans have been found in pigs and non-human primates, suggesting that they may be able to transcend species boundaries despite having just 75% similarity with genotypes 1 and 2. In rare instances of acute hepatitis in Asia and infrequently in Europe, genotype 4, which encompasses both human and porcine HEV strains, has been detected. In endemic places, significant waterborne epidemics are linked to genotypes 1 and 2, which are exclusive to humans. In non-epidemic regions, sporadic instances of hepatitis E are mostly caused by genotypes 3 and 4, which are shared by humans and other mammals. Virus transmission and illness severity may be correlated with viral genotype. Pathogenicity appears to be higher in genotypes 1 and 2 compared to genotypes 3 and 4, with genotype 4 exceeding 321,22.(Saadat et al., 2024).

In underdeveloped nations, older children and young adults were more likely to experience clinical involvement in hepatitis E infections caused by genotypes 1 and 2, whereas in developed countries, genotypes 3 and 4 typically manifest in infected individuals at older ages. It appears that the elderly or those with impaired immune systems are more susceptible to contracting HIV from the "less pathogenic" genotypes 3 and 4, which are considered to be less dangerous overall. There are some places where the swine and human HEV strains

are very different. For example, in the Netherlands, the human strains are subgenotype 3f, while the swine strains are 3c. This is even though swine HEV isolates of genotype 3 or 4 are similar to human isolates. (Chen et al., 2024).

In other HEV-infested nations, such as India, where swine strains are genotype 4 and human strains are genotype 120, or China, where human and swine strains are subgenotypes of genotype 424, this separation between the two is more pronounced. It appears from these numbers that pig-human infection is rare in these nations. According to HEV infection outbreaks, genotypes 1 and 2 are more efficient at infecting people by the faecal-oral route, while genotypes 3 and 4 are mostly found in animals and can only infect humans very rarely through zoonotic transmissions, like eating undernourished pig liver. Cooked. It seems that the genotype distribution is changing rather fast over time.(Karnsakul & Schwarz, 2025).

Genotype 4, which was first detected in China in 2000, is thus more prevalent there, but genotype 1, which caused one of the worst hepatitis E epidemics in China in 1986 and 1988, seems to be declining. Other types of herpesviruses have also been identified and studied; for example, avian herpesviruses seem to form a new genus of the virus and do not infect primates. Another type of herpesvirus was found in Chinese farm rabbits and may be a variant of genotype 3, which could infect animals like humans and pigs. However, no evidence of this has been found. Lastly, a herpesvirus was found in rats in Germany, which has only 60% homology with human HEV and 50% with avian HEV, respectively, and could represent a new genotype of hemovirus.(Piralla et al., 2024).

Pathogenesis of hepatitis E

Although oral entry is the primary mode of HEV infection, there is a lack of clinical evidence on the possibility of extrahepatic replication. Nonetheless, mononuclear cells have been found to contain HEV-RNA. One week before the start of the illness and up to two weeks later, HEV was found in the faeces of the volunteers. Almost all patients have HEV-RNA detectable in their serum within 2 weeks of disease onset30, and this positivity can last anywhere from 4 to 16 weeks. In primates, HEV antigens can be seen in the liver 7 days after infection. During the peak of viral replication, 70 to 90% of hepatocytes show these antigens. During this time, HEV can also be seen in bile and faeces, either before or at the same time as the beginning of alanine aminotransferase (ALT) elevation and morphological changes in the liver. This suggests that HEV is released into bile and faeces before the ALT peak and liver morphological changes.(Ahmad et al., 2024).

By the start of an infection, HEV-RNA levels in blood and stool are extremely high; by the end of the infection, when the body mounts a strong immune response against the virus, they drop dramatically. Hepatitis E may have an immune-based pathogenic mechanism unrelated to the cytotoxic action of HEV, according to concordance between pathological, virological, and serological results. Primate infections with low doses of HEV can cause subclinical infections but can still transmit the illness to other animals. The severity of the virological, immunological, and pathological effects of HEV infection is heavily dependent on the infectious dose. (Yu & Zhang, 2024).

Due to a lack of experimental replication, the pathogenic processes causing the extremely high mortality rate (20-30%) in pregnant women from fulminant liver failure remain unknown. As a result of hormonal and immunological changes that occur during pregnancy, disseminated intravascular coagulation is frequently linked to severe liver damage in humans. Thus, in comparison to non-pregnant women, pregnant women infected with HEV show a shift towards Th2 in the Th1/Th2 balance. But how it affects the severity of a herpes simplex virus infection is unclear. There is proof that the(Santos-Silva et al., 2024)

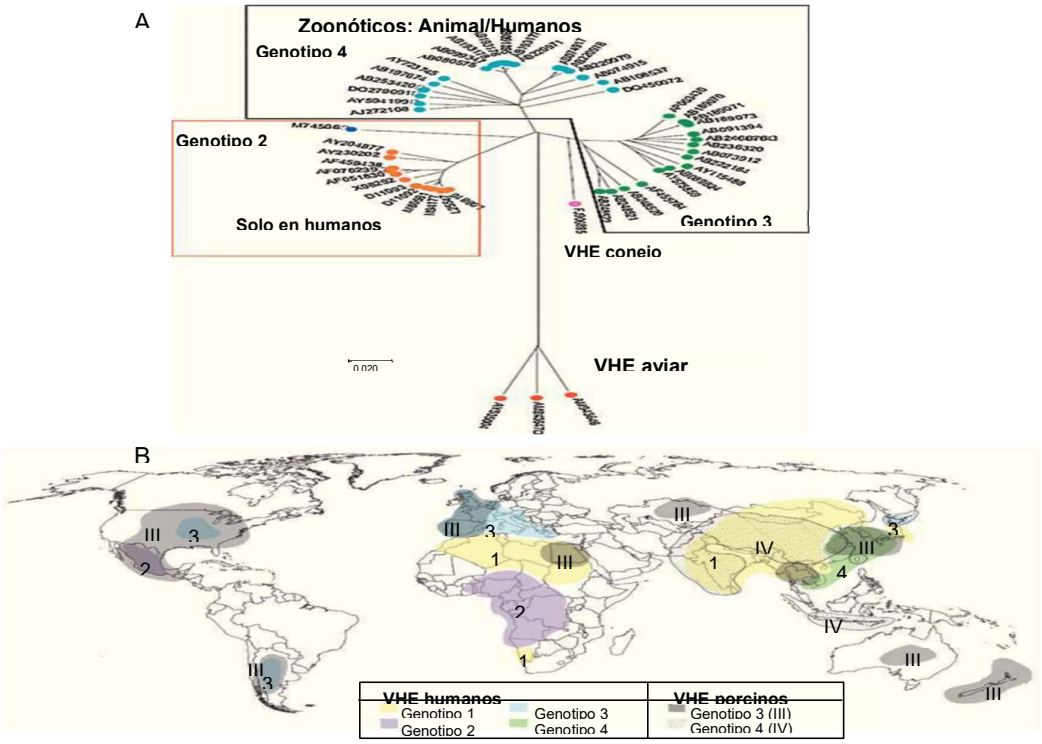

Illustration 2. It is possible to see the many HEV genotypes on the evolutionary tree. Adapted from Pavio et al., the numbers represent the GenBank sequence identifiers. Section B, adapted from Purcell and Emerson, shows the worldwide distribution of HEV genotypes in pigs and humans. Human herpesvirus genotypes are shown on solid backgrounds and numbered 1–4, while pig genotypes are shown on dotted backgrounds and numbered I–IV. (Roberts, 2024).

There was an increase in estrogen, progesterone, and HCG levels compared to HEV-negative patients and controls, and a higher risk of maternal and fetal mortality in pregnant women with jaundice and acute hepatitis C virus infection compared to those infected with other forms of viral hepatitis. There may be links to both genetics and the environment; therefore, a new theory proposes that HEV infection during pregnancy can lead to a loss of immunity and eventual death by selectively suppressing the NFB factor and removing p65 from the transactivation complex.(Harlow, Dallner, & Nasheri, 2024).

Incubation period and transmission routes

While hepatitis E1 outbreaks can last anywhere from 2 weeks to 10 weeks, the incubation period in human volunteers is typically 4-5 weeks29. There are five reported pathways for HEV gearbox, listed below in descending order of significance:

a) due to fecal-oral contamination by agua potable ministers' waste;
b) harmful, uncooked, or undercooked foods; and, less often
c) as a result of receiving contaminated blood transfusions;
d) transmitted from mother to child in a vertical fashion,
e) through coming into close touch with people who are sick.
Establishing the mode of infection is not always easy, particularly in non-endemic areas and in occasional cases within endemic regions.
Because inactivation mechanisms appear to be inadequate for non-enveloped viruses, it is important to consider that blood supplies are susceptible to their transmission by parenteral injection (route c) of HEV. Molecular testing has revealed cases of hepatitis E associated with blood transfusions in countries that are not endemic, including France, Japan, and the UK. (Cao, Chen, Liu, Yang, & Zhang, 2024);

Acute hepatitis was caught by another patient who had a meal with the donor in one of these cases; the donor had contracted HEV infection through roast pork (path b). There is a possibility for parenteral transmission of these "zoonotic" genotypes of hepatitis E as all transfusion-related cases have been caused by HEV strains of genotypes 3 and 4. Therefore, prospective post-transfusion infections involving human hepatitis E virus (HEV) should be evaluated in the future, considering blood transmission. Very few cases occur in the home environments of individuals with acute HEV infection, indicating that person-to-person transmission is extremely inefficient. (Kobayashi et al., 2024).

Epidemiology of HEV infection

An estimated one-third of the global population has been infected by HEV, making it the most prevalent cause of acute hepatitis globally. In Central America and Southeast Asia, HEV is the leading cause of acute hepatitis in adults. In the Middle East and North Africa, it is second only to hepatitis B virus. On the other hand, in developed nations, where HAV is the leading cause, HEV accounts for a negligible fraction of cases. Although HEV sickness is more commonly found in some regions, HEV antibodies are more widely distributed around the world. Developing nations, where HEV clinical disease is common, have the highest prevalence rates. (Wißing et al., 2024).

In Egypt, for example, there have been very few reported cases of hepatitis E and no epidemics, yet the prevalence of anti-HEV antibodies is very high, reaching as high as 70%. This virus creates paradoxes in many countries. The situation is very similar in the US, where anti-HEV antibodies are more common than anti-HAV antibodies, yet hepatitis E cases are rare. The only places where HEV poisoning of water causes epidemic outbreaks are in underdeveloped nations; in industrialized nations, infections tend to be sporadic and non-epidemic. (Huang et al., 2024).

The possibility of zoonotic transmission from contaminated food (raw or undercooked seafood or meat) or from close contact with diseased animals may account for some of these isolated incidents. Controversy surrounds the "true" estimate of human HEV infections. Consequently, there are at least twice as many cases of subclinical infections in people as there are of clinical infections. While the percentage of symptomatic HEV infections in adults is poorly defined (7–21%) in industrialized nations, it is a meagre 2.1% in China. (He et al., 2024).

It is reasonable to infer that many HEV infections in industrialized nations go undetected because the population there is exposed to low doses of the virus and smaller doses of the virus seem to generate fewer symptoms43. In a similar vein, subclinical infections can cause a weak immune response to HEV, but they nevertheless cause viremia and faecal excretion of HEV, which means they add to the reservoir of HEV and can be transmitted. The spread of herpes simplex virus appears to follow two distinct patterns: one in economically developed nations and another in areas where epidemics are most common. (Abravanel et al.).

Epidemic pattern: hepatitis E in endemic regions

Drinking water tainted with faeces is a common cause of hepatitis E epidemics in these areas, which can impact hundreds or even thousands of individuals. India, China, Southeast and Central Asia, the Middle East, and portions of northern and western Africa have all been affected by these epidemics. Mexico has also seen two separate outbreaks between 1986 and 1987. It frequently follows periods of heavy rain and flooding, which encourage the mixing of human waste with water supplies for drinking, and the outbreaks last anywhere from a few weeks to over a year.(Hafkesbrink, Schemmerer, Wenzel, & Isenmann, 2024).

In outbreaks of hepatitis E, the morbidity rate can be anywhere from 1% to 15%; the virus mostly strikes young adults, with a higher prevalence of males than females. An increased risk of perinatal death and obstetric prematurity is connected with hepatitis E outbreaks, which in turn cause a significant rate of morbidity and mortality in pregnant women (19% compared to 2.1% in non-pregnant women or 2.8% in men)41. Acute

sporadic hepatitis, which has a clinical picture comparable to epidemic cases, is also found in these regions to be caused by HEV, accounting for a substantial proportion of cases (70% in India). (Wei et al., 2024).

Samples of wastewater that contained HEV-RNA suggest that the virus is still widely distributed in the community, potentially producing isolated cases of infection, even when no epidemic is underway. Remember that, even during epidemics, the transmission of HEV from person to person is extremely rare (0.7-2.2% among relatives of patients with hepatitis E vs. 50-75% in hepatitis A), in contrast to other enteric-transmitted illnesses. (Mitra & Mohapatra, 2024).

A common source of primary infections (such as waterborne) rather than transmission from person to person is likely to account for the short time interval in infections within the same family. It is highly improbable that these areas are infected with HEV zoonosis since human and animal HEV isolates are of different genotypes. For instance, in India, human and animal HEV isolates are of genotype 1, respectively. The presence of a disease-carrying reservoir in these areas is highly improbable. The significant number of people who have subclinical HEV infection may serve as the primary reservoir, ensuring the infection persists through faecal contamination. (Adeel et al., 2024).

Non-endemic pattern: hepatitis E in non-endemic regions

Hepatitis E accounts for a small percentage of acute viral hepatitis in countries where epidemics do not occur; up until recently, the majority of cases were associated with travel to regions where HEV infection is common. U.S., European, and developed Asia-Pacific nations have all reported instances of indigenous hepatitis E transmission in recent years. This includes Japan, Taiwan, Hong Kong, and Australia. (Liu et al., 2024).

Although most rare cases still lack an established path of infection, zoonosis appears to be the most likely explanation given the spread of human herpesvirus strains to pigs and, subsequently, to primates. The fact that anti-HEV antibodies are present in large numbers in several animal species and that HEV genomic sequences have been found in pigs that are quite similar to human HEV isolates provide credence to this theory. (Park et al., 2024).

The great heat stability of HEV particles explains why raw or undercooked hog liver was ingested in the majority of sporadic hepatitis E cases in Japan. Compared to the general population, those who work with pigs, such as veterinarians and farmers, have a higher prevalence of anti-HEV antibodies, which suggests that the virus can be transmitted by direct contact. Interestingly, while HAV has declined from 57.4% to 3.1% during the same period, HEV-RNA has remained detectable in 30% of wastewater samples from a metropolitan area (Barcelona) in Spain. The existence of external animal reservoirs of HEV could explain this finding, which suggests that changes in population health do not impact the prevalence of HEV infection.(Alexandrova et al., 2024).

The fact that genotype 3 in Europe and genotype 4 in Japan show "identity" between animal and human sequences provides strong evidence that hepatitis E is native to these countries and spreads mostly through pigs. The increased seroprevalence of anti-HEV antibodies in veterinarians and pig farm workers, as well as proven cases of foodborne transmission, provide evidence supporting this conclusion. Consequently, we need to think about the high serological frequency of the infection in pigs and the viral activity assessed by HEV-RNA in faeces. (Rau et al., 2024).

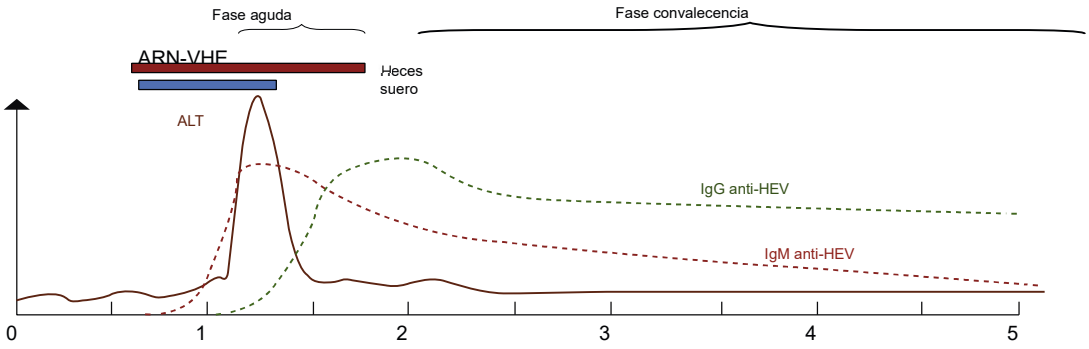

Figure 3. Seroprevalence of anti-HEV IgG antibodies (modified from Chandra et al.).

Seroprevalence of HEV-IgG antibodies: evidence of HEV exposure

Evidence of HEV exposure, in the form of anti-HEV IgG antibodies (Fig. 3), has been discovered in otherwise healthy people all over the globe. Figure 4 shows that compared to wealthy nations with a low frequency of clinical cases of hepatitis E, developing countries with extremely unclean drinking water tend to have higher prevalence rates. North Africa and the Middle East have a prevalence of 26% in Egypt (70% in some adult series) and 17% in Saudi Arabia; South and Central Asia have a prevalence of 20-30% in China, 45% in rural Malaysia, and up to 20% in India. Although hepatitis E outbreaks are common in endemic countries like India, the anti-HEV seroprevalence rate is lower (4-20%) compared to hepatitis A (HAV). The opposite is true in Egypt, where anti-HEV is found in as many as 70% of adult samples, even though there have been no reported cases of the disease20. The prevalence of anti-HEV seroprevalence is often lower, ranging from 1-3 per cent, in industrialized nations such as the United States (Miao et al., 2024)

Months after infection

Figure 4. Profile of laboratory markers in acute self-limited HEV hepatitis (modified from Krawczynski et al.). Cases exceeding 20% in specific groups or regions (such as states with considerable swine farming activities in the US) were recorded in Germany (2.1%), and France (0.9%).20,50. With a significant age gap between the youngest affected persons (1% of the total) and the oldest (3.6%), Spain's claimed prevalence rates range from 2.2% to 7%. Despite the low prevalence of clinical HEV illness in these regions, the seroprevalences in these places seem to be greater than anticipated. (Molina et al.).

According to the epidemiology section, there are states in the US where anti-HEV is more common than anti-HAV, even though the frequency of hepatitis E is low. The comparatively high frequencies of anti-HEV antibodies are noticed even if antibody levels decrease after primary HEV infection. For instance, at 14 years old, 47% of individuals impacted by a HEV epidemic outbreak still have detectable levels of anti-HEV, and at 30 years old, only 25% do. There is a noticeable disparity in the prevalence of antibodies that target HEV. Factors in social and occupational settings, as well as related diseases, etc., are associated with HEV. Consequently, the incidence is greater among pig farmers and veterinarians in the US, the Netherlands, Moldova, and China compared to the overall population. (Antonopoulou et al., 2024).

These findings demonstrate the zoonotic character of HEV infection and imply that pig infection is a major factor in the high incidence among humans who have regular direct contact with pigs. So, HEV is prevalent among pigs that have high levels of anti-HEV antibodies (e.g., nearly all pigs in the US and Mexico, 90% in NZ, 46% in Laos, and 98% in Spain) and that have the same 3 and 4 genotypes as humans in areas where the virus is not endemic.(María Casares-Jimenez et al., 2024).

Subclinical HEV infection is more than twice as common as symptomatic infections in endemic countries, hence it needs to be considered when calculating prevalence rates. The fact that analytical tests vary in their

sensitivity and specificity raises the possibility of inaccurate prevalence estimations, the former of which are more commonly caused by false negatives than false positives. This, along with the fact that anti-HEV titers have been declining over time, raises the possibility that the actual seroprevalences and overall number of HEV infections are more than what has been documented. Even with the advent of next-gen testing, it appears doubtful that seroprevalence numbers will undergo a substantial shift in the years to come.(Takahashi et al., 2024).

HEV infection clinic

Acute HEV hepatitis

When compared to other hepatotropic viruses, the clinical manifestations of HEV infection are virtually identical. Acute hepatitis is the most frequent type of this illness; it typically affects people aged 15 to 40 and develops 3 to 6 weeks after exposure; it is self-limiting and does not leave any lasting effects. Jaundice, anorexia, nausea, vomiting, and sometimes fever can accompany acute infections ranging from mild (anicteric) to severe (cholestatic) hepatitis, which can persist anywhere from one week to six weeks. About 1% of cases can lead to fulminant liver failure (FHF), which is more dangerous for pregnant women and people with chronic liver disease (54-55). These have a worse obstetric and fetal prognosis and a higher mortality rate (15-20%) compared to other types of viral hepatitis. None of the existing diagnostic tools can determine the disease's prognosis, and the causes of FHF remain a mystery. Epidemiological research has shown that endemic and non-endemic regions are distinct from one another. (Sadio, 2024):

Areas with endemic HEV infection

There is a high prevalence of HEV infection in these regions, particularly genotypes 1 and 2 (Fig. 2B), in young adults. Infected individuals can exhibit a wide range of symptoms, the most common of which is self-limiting acute jaundiced hepatitis, which is similar to other hepatotropic viral infections.3,49. Compared to other viruses like HAV, there is a higher proportion of severe cases of acute liver failure; fatality rates range from 0.5% to 4% (or 0.7% to 0.6% during epidemics). Asymptomatic infection or test evidence of anicteric hepatitis E (elevated liver enzymes [ALT] and normal serum bilirubin values) is preferred due to the high prevalence of anti-HEV antibodies in endemic places and the lack of acute hepatitis symptoms. Patients suffering from chronic liver disease due to any cause can have their prognosis worsened by superimposing acute liver lesions and a clinical appearance resembling acute liver infection caused by HEV superinfection. (Sacristán et al., 2024).

Non-endemic areas for HEV infection

When patients over the age of 60 present with unexplained hepatitis, serological testing is typically utilized to identify HEV infection, which is caused by genotypes 3 and 4 (Fig. 2B) in non-endemic countries. 50 The clinical illnesses seen in these individuals are comparable to those in endemic regions, except jaundice hepatitis is more common. In contrast to instances from endemic areas, the majority of patients are middle-aged or older men, and they frequently have a history of diseases. This tends to explain why their prognosis is worse.(Yadav et al., 2024).

Chronic hepatitis due to VHE

It was formerly thought that HEV, similar to HAV, just caused acute liver infections and fulminant liver failure that resolved on their own, and had nothing to do with chronic liver diseases. Nevertheless, there have been reports of immunosuppressed individuals, including those receiving solid organ transplants, haematological patients, or those undergoing chemotherapy, developing chronic liver disease and eventually developing cirrhosis as a result of HEV infection. the virus that causes AIDS in humans(Traore et al., 2024).

At first, evidence of HEV infection was found in 14 solid organ transplant recipients with elevated ALT levels; 8 of these patients had viremia (HEV-RNA) and continued elevation of their ALT levels. Subsequent reports of similar incidents have also been made, this time in individuals undergoing a liver, kidney, or pancreas

transplant. A histological pattern of portal hepatitis with dense lymphocytic infiltrate and varying degrees of fibrosis was observed in patients with chronic hepatitis E infection, as was a decrease in CD2, CD3, and CD4E lymphocyte levels compared to cases with resolved self-limited HEV infections. In certain cases, retransplantation was necessary as the infection progressed to cirrhosis.(Martino et al., 2024).

It has been noted that kidney transplant recipients can develop liver cirrhosis from chronic HEV genotype 3 infections, indicating that HEV infection can lead to cirrhosis. People with impaired immune systems are the only ones who contract HEV chronically; this may be because this genotype is more common in the regions where these infections have been detected. The potential for HEV genotype 1, which is prevalent in HEV-endemic areas, to induce persistent infection requires additional research. According to a retrospective study conducted by Kamar et al., 60% of 85 cases of solid organ recipients infected with HEV developed chronic hepatitis as a result of this agent. This finding raises concerns about the potential role of tacrolimus, an immunosuppressant, in chronification and the association between viral clearance and dose reduction.(Primadharsini et al., 2024).

When considered as a whole, these findings challenge our previous assumptions about the course of HEV infection and provide more evidence that a type of chronic HEV infection is present, causing gradual liver damage that can lead to cirrhosis. While this does not happen very often, it does have a major impact on immunosuppressed patients and needs to be studied more. (Hinrichs et al., 2024).

Laboratory diagnosis of HEV infection

Serological testing and viral RNA detection are the cornerstones of a correct hepatitis E diagnosis because the virus does not manifest clinically differently from other forms of acute viral hepatitis (Fig. 4). Universal diagnostic enzyme immunoassays, like ELISA, may detect specific antibodies (anti-HEV) of the IgG and IgM kinds, irrespective of the HEV genotype, because all four HEV genotypes belong to the same serotype. The commercial methods for detecting anti-HEV IgG or IgM antibodies rely on the detection of antibodies against the HIV capsid protein encoded by ORF242, which is both highly conserved and immunogenic. When diagnosing HEV infection, the variations in serological methods' sensitivity and specificity become particularly apparent. As a result, there are notable variations in specificity (ranging from 78% to 98%) and sensitivity (ranging from 72% to 98%) among six anti-HEV IgM enzyme immunoassays, two of which were developed in-house and four of which were purchased.(Jose-Abrego, Trujillo-Trujillo, Laguna-Meraz, Roman, & Panduro, 2024).

The fundamental reason for these variations is that anti-HEV detection is not very sensitive during the convalescent phase, resulting in more false negatives than false positives. An additional factor impacting the analytical efficiency of these assays is the intricate kinetics of the anti-HEV response, which might vary in duration against each epitope. Similarly, this reaction could be lacking, particularly in the early stages of infection, and it drops sharply following an acute infection. Conventional and real-time non-commercial, in-house (non-standardized) reverse transcription PCR (RT-PCR) techniques are utilized for the detection and genotyping of the HEV-RNA viral genome at the virological level. to examine samples of blood, excrement, and wastewater for the presence of HEV RNA(Joshi et al., 2024).

Serological and virological markers of HEV infection

Typically apparent during the outset of sickness, patients' anti-HEV serological responses display a characteristic pattern of anti-HEV IgM and IgG42 (Fig. 4). During the acute phase of the disease, Anti-HEV IgM can be detected as early as 4 days after jaundice begins. Being detectable for four to five months, it is an excellent marker for the diagnosis of acute infection, since it is seen in more than 90% of patients within two weeks of disease onset, with a peak during the symptomatic period. Recent research into the potential utility of anti-HEV IgA detection in acute infection diagnosis has shown that, compared to HEV-RNA detection, anti-HEV IgA detection (either alone or in combination with anti-HEV IgM) has longer duration and higher specificity in diagnosing E62 infection. To determine this new marker's actual utility, however, further research is required.(Ansari et al., 2024).

Very early on, in the process of developing alongside or perhaps concurrently with the IgM response63, is the anti-HEV IgG response. The peak of ALT elevation occurs three to four weeks after inoculation in macaques, and during the symptomatic phase of infection in human volunteers, anti-HEV IgG is identified in serum. During the acute phase and convalescent stage, which last for years following infection, levels of anti-HEV IgG grow; however, these levels subsequently drop. It is possible that variations in the efficacy of the assessment tools are to blame for the observed differences in the lengths of anti-HEV IgG persistence. This means that concordance rates of 40–70% have been seen with several commercially available anti-HEV IgG assays. Thus, the presence of IgGanti-HEV without IgM suggests a previous infection, whereas the presence of IgManti-HEV without IgG suggests a current infection. Nevertheless, both IgG and IgM antibodies might be found in the acute phase because IgGanti-HEV antibodies manifest relatively early.(Khattak, Vongsavath, Haque, Narwan, & Gish, 2024).

As will be seen later on, HEV-RNA is the sole virological marker that is of any use, but its utility is severely limited. Even before ALT rises, it can be identified in serum and faeces using RT-PCR34, which is useful during the acute phase of illness. By detecting HEV-RNA, viral replication can be initiated and its genotype can be subsequently characterized. The short intervals of viremia (about 2 weeks in serum and around 4 weeks in faeces, with cases ranging from 8 to 12 weeks) mean that HEV-RNA is not very useful for diagnosing acute infection; hence, its absence does not allow us to rule out the possibility of a diagnosis of acute HEV infection. (Vasconcelos et al., 2024).

Testing for anti-HEV IgM in serum and/or HEV RNA in serum or faeces are thus the cornerstones of acute hepatitis E laboratory diagnosis. Acute herpes simplex virus (HSV) infections are typically characterized by the presence of IgM (and IgA, if validated by additional research) and even anti-HEV IgG, although only the latter is indicative of prior infection and is thus more useful from a serological perspective. On the subject of seroprevalence. Include HEV-RNA detection in the workup of immunocompromised patients if seroconversion is delayed or nonexistent. Regardless, it is important to remember that there are specificity and sensitivity issues with detecting IgM-HEV, as mentioned before.(Subramaniam, Fares-Gusmao, & McGivern, 2024).

Prevention and antiviral therapy of HEV infection

Sanitation, distribution system adaptations, and public education on personal hygiene are the primary means of preventing the spread of HEV, which is mostly transmitted through faecal material contamination of drinking water. Aside from not eating raw or undercooked meat, proper food management is crucial. Protective efficacy against HEV has not been proven by using serum immunoglobulins. With only one HEV serotype known, it should be possible to create a vaccine that is highly cross-reactive and thus effective against HEV infection. Research on animals has shown that certain recombinant proteins that mimic the viral capsid and are produced from proORF2 can prevent HEV infection by stimulating the production of antibodies that target the virus specifically.(Di Cola, Fantilli, Pisano, & Ré).

So far, two vaccines that use peptides extracted from the viral capsid (proORF2)—which contain neutralizing epitopes shared by several genotypes—have shown promise in human volunteers. A 56kD recombinant peptide, which is a shortened version of proORF2, induces an anti-HEV response that is dose-dependent. A randomized study involving 2,000 Nepalese Army volunteers found that those who received this vaccine had a lower incidence of acute hepatitis E compared to those who did not receive it 66. Pregnant women, children, and other risk groups, like those with chronic liver disease, require safety testing because the vast majority of participants in this trial were young males (mean age, 25 years).(Yoshida et al., 2024).

Further research is needed to determine how long this vaccination provides protection, as this one found that 44% of vaccinated people had anti-HEV levels below the protective threshold after the follow-up period (mean 800 days). Similar to the first vaccine, HEV-23967 contains a shortened recombinant peptide of proORF2 (amino acids 376 to 606). It was created more recently. Despite the lack of safety and security data, Zhu et al. found that this vaccination effectively prevented HEV infection in a phase III trial including vaccinated individuals, as opposed to 15 infected cases in the placebo group who got the HBV vaccine. Infectious disease

potential. The length of time these vaccines provide protection is an important question that needs further research. (Sedgwick, ElBohy, & Daly, 2024).

Despite the positive results of these pilot studies, it is unclear whether or not these vaccinations will be commercialized. This is because, despite the clear need, the prospective market in developed nations is tiny, likely consisting mostly of military personnel and civilians visiting endemic regions. However, these vaccines would be extremely helpful in underdeveloped nations, particularly during pregnancy, but their price tag would have to be reasonable for those economies to purchase them.(Schmitz et al., 2024).

Particular features of hepatitis E virus (HEV) infection warrant investigation into potential treatment modalities, including the fact that it is more severe in pregnant women, that it exacerbates chronic liver damage, and that it manifests in immunocompromised people. So far, preliminary reports of pegylated interferon-based antiviral treatment for chronic HEV infection in transplant patients have shown a persistent viral response in four out of five cases. Additionally, ribavirin monotherapy has been investigated, and in 5 out of 7 reported cases, a sustained viral response was noted, showing performance similar to pegylated interferon.(Usuda et al., 2024).

Recent research has demonstrated that ribavirin medication is effective in reducing HEV-RNA levels to undetectable levels in a heart transplant recipient with chronic hepatitis E and in a severe acute hepatitis patient caused by HEV73. Research into the biochemical and structural properties of HEV's non-structural proteins, including its proteases, helicases, and duplicates, to create inhibitors of these proteins, could be a future direction for an antiviral treatment against HEV. New treatments for HEV infection may be based on these medications, which are now in clinical use for other infections.(BOMGNING, TSAGUE, FOTIO, NGUELEFACK-MBUYO, & NGUELEFACK, 2024).

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