Review

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Zoonotic Hepatitis E Virus Infection: Where Are We and Where Should We Look?

Zoonotik Hepatit E Virüs Enfeksiyonu: Neredeyiz ve Nereye Bakmalıyız?

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ABSTRACT

Zoonotic hepatitis E virus (HEV) causes a worldwide problem. Generally transmitted via infected animals/eating contaminated food. Fully understanding the distinctive biology, transmission routes, and clinical consequences of zoonotic HEV strains is essential for developing efficacious prevention and control tactics. Current knowledge gives prominence to animals, with pigs in particular being recognized as reservoirs, and examines the clinical variances between zoonotic and strictly human HEV genotypes. This analysis further explores recent advances in diagnostics, immunization efforts, and protective measures while identifying gaps in our comprehension, requiring additional research to better address HEV as a public health menace. Furthermore, strategies aiming to reduce potential zoonotic transmission through improved hygiene standards and strict inspection of the food supply chain merit consideration.

Keywords: Hepatitis E virus, zoonotic, diagnosis, epidemiology, prevention, vaccine

ÖZ

Zoonotik hepatit E virüsü (HEV) dünya çapında bir soruna neden olmaktadır. Genellikle enfekte hayvanlar/kirlenmiş gıdaların yenmesi yoluyla bulaşır. Zoonotik HEV türlerinin kendine özgü biyolojisinin, bulaşma yollarının ve klinik sonuçlarının tam olarak anlaşılması, etkili önleme ve kontrol taktikleri geliştirmek için kesinlikle gereklidir. Mevcut bilgiler, başta domuzlar olmak üzere rezervuar görevi gören hayvanları ön plana çıkarmakta ve zoonotik ve tamamen insani HEV genotipleri arasındaki klinik farklılıkları incelemektedir. Bu analiz ayrıca, teşhis, bağışıklama çabaları ve koruyucu önlemlerdeki son gelişmeleri araştırırken, HEV'i bir halk sağlığı tehdidi olarak daha iyi ele almak için ek araştırma gerektiren kavrayışımızdaki boşlukları belirlemektedir. Ayrıca, hijyen standartlarının iyileştirilmesi ve gıda tedarik zincirinin sıkı bir şekilde denetlenmesi yoluyla potansiyel zoonotik bulaşmayı azaltmayı amaçlayan stratejiler de dikkate alınmalıdır.

Anahtar Kelimeler: Hepatit E virüsü, zoonotik, epidemiyoloji, tanı, korunma, aşı

Introduction

Overview of HEV Types and Genotypes

Hepatitis E virus (HEV) is a virus from the *Hepeviridae* family according to the 10th report of the International Committee on Taxonomy of Viruses (ICTV) (1). It has a (+)- chain ribonucleic acid strain various gene size of 7.2-7.4 kb (2), single-stranded, positive-stranded, has measurement between 27 and 34 nanometres in diameter (nm) (3,4,5,6). It was initially recognised as a cause of certain types of hepatitis (non-A, non-B) (7). This virus encompasses both animal-based strains, which can infect humans, and variants restricted to animals, which complicates the epidemiology and transmission dynamics of HEV (3,4,5,6).

According to the 10th ICTV report, HEV consists of two types of genera: *Orthohepevirus* and *Piscihepevirus* (1). *Piscihepevirusincludes* genus exclusive to *Oncorhynchus clarkii* virus, while *Orthohepevirus* includes class of *aves* and *mammalia* HEV isolates. Four different types of *Orthohepevirus* are as follows: A, B, C, and D, and are divided into at least 8 genotypes (1,8,9,10). Genotypes 3 and 4 are the primary cause of zoonotic infections; other strains also show potential (Table 1) (10,11).

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Table 1. Currently classification of HEV

Family	Genera	Species	Genotypes
Hepeviridae	*Orthohepevirus*	A, B, C, D	I, II, **III***, **IV***, V, VI, VII, VIII
	Piscihepevirus		

*: Zoonotic, HEV: Hepatitis E virus

There are genotypes and subtypes of HEV associated with host species and geographic origin (12). Studies have detected an association with clinical outcomes, while others have not observed such an association (13,14).

Genomic analyses indicate that *Hepeviridae* may have arisen from ancient recombination between *Alphatetraviridae* and *Astroviridae* (15). The HEV strains that infect humans are members of the *Orthohepevirus A* species, which ICTV has recently, renamed *Paslahepevirus balayani (P. balayani)* (16). Subtypes 1g, 3k, 3l, 3m, and 8a are now included in the revised list of suggested reference sequences for *P. balayani* subtype classification (17). The ongoing identification of diverse HEV strains suggests that *Hepeviridae* taxonomy will continue to evolve (1).

Zoonotic Transmission and Primary Animal Reservoirs

It is not known exactly which hosts HEV infects, because most infections are asymptomatic and virus replication is low. Because virus release is irregular, detecting HEV-RNA in different host species is difficult and resource-intensive. Furthermore, it is difficult to detect infected individuals, as viral load is usually low. Every strain of HEV has the same serotype, which prevents differentiation of infections with different strains (18).

HEV has potential hosts that can be detected in many animal species such as domestic pigs, wild boars, chickens, mice, rabbits, deer, fish, cattle, sheep, and bats, and the virus is constantly expanding its host range. Other possible hosts are still under investigation, making the spread of HEV more complex (19). Recent findings have revealed that HEV *homologues* are found in fish (20), amphibians (21), moose (22), kestrels (23) and many other organisms, suggesting that the *Hepeviridae* family, like the *Herpesvirales* order, may exhibit a wide range of hosts and that HEV has the ability to cross interspecies barriers (24).

HEV isolates are classified into eight species. Species A includes isolates from humans, pigs, deer, hares, camels, and mongooses. Species B comprises *aves* class HEV isolates from birds. Species C includes isolates from rodent family members (Indian bandicoot rat, Asian musk shrew, and various rodent species), while Species D consists of isolates from bats. Only isolates that infect humans have 8 genotypes and belong to species A. Genotypes 1 and 2 infect only humans, while genotypes 5, 6, 7, and 8 infect wild boar, humans, and camels, specifically *Camelus bactrianus* (8).

HEV Biology and Genomic Characteristics

HEV Genome Structure and Replication

The *mammalia* HEV genome, a single-stranded, positive-sense RNA, is approximately 7200 nucleotides long, while the *aves* HEV genome is approximately 6650 nucleotides long (25). Although animal models and cell transfection are used to study the biology and pathogenesis of HEV, its structure and replication cycle are still difficult to understand because of slow replication, ineffective cell cultures, and unknown receptors (2,6,7,18,21,25,26,27,28,29,30,31,32,33). Though its molecular specifics are unclear, the uncoating process is associated with polysaccharide-binding sites (26).

The HEV genome includes functional regions such as the methyltransferase Y domain papain-like cysteine protease enzymatic, RNA helicase, phosphoprotein [open reading frame 3 (ORF3)], capsid (ORF2), and RNA-dependent RNA polymerase. It has a 5′ non-coding region, 5′ and 3′ untranslated regions, and three ORFs (ORF1, ORF2, ORF3) (Figure 1) (33). ORF1 encodes a polyprotein for replication, ORF2 encodes a capsid protein, and ORF3 encodes a protein involved in virion morphogenesis. HEV-3 strains are divided into 13 subtypes. The genome is 7.3 kb, and HEV virions are non-enveloped in feces, and semi-enveloped in blood. Two virus-like particle types exist: T=1 (270 Å) and T=3 (320-340 Å). The capsid protein exists in two forms, ORF2S and ORF2C, with four cis-regulatory elements crucial for replication (2,5,6,7,8,16,18).

Researchers on HEV have found that there is a conserved receptor binding motif in the capsid protein (26), a potential binding site in the M domain (27), and interactions with heparin sulphate proteoglycans (28). It was also suggested that a 55 kDa protein may play a role as an entry receptor, but it was emphasized that this hypothesis requires further confirmation (29). It has been suggested that HSC70 and Grp78 may play a role in intracellular transport processes rather than receptor functions (30).

HEV enters cells through a clathrin- and dynamin-2-dependent pathway, utilizing different routes for enveloped (quasi-enveloped) and non-enveloped virions. This process involves the small GTPases Rab5 and Rab7. Although HSP90 inhibitors block the intracellular transport of the virus, they do not interfere with its entry into the host cell (32). Semi-enveloped HEV (eHEV) virions enter cells via clathrin-mediated endocytosis and are also known to require Rab5 and Rab7 GTPases. Figure 2 presents a model of cell entry of naked and semi-eHEV virions (33).

Hepatocytes also allow eHEV particles to be released into the circulation from the cellular surface into the blood. Therefore, eHEV can be detected in blood and urine, while non-eHEV (naked HEV) can only be found in bile and feces (33,34).

The replication process starts with viral RNA producing a negative sense intermediate, which is used as a template to produce both positive sense genomic RNA and subgenomic bicistronic mRNA (35). Viral RNA replication proceeds slowly and peaks 8 days after transfection of reporting genes such as green fluorescent protein or luciferase (36).

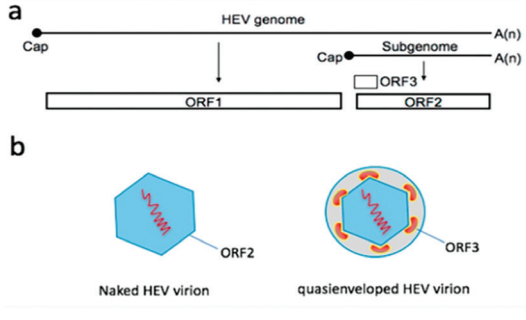

Figure 1. The HEV genome, its encoded proteins (a), and two types of virions (b)

HEV: Hepatitis E virus, ORF: Open reading frame

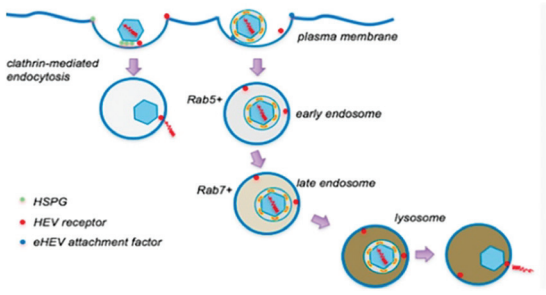

Figure 2. Model for cellular entry of naked and quasi-enveloped HEV virions

HEV: Hepatitis E virus, eHEV: Enveloped HEV, HSPG: Heparan sulfate proteoglycan

A recent study suggests that the eHEV envelope likely originates from the trans-Golgi network (TGN) and is derived from HEV intracellular membranes. The study emphasizes the role of TGN in forming the envelope of HEV particles and the dynamic processes of TGN membranes in virus discharge and bloodstream passage (4). Another study found that HEV genotypes 1 and 3 successfully replicated in primary intestinal cell cultures. HEV RNA and ORF2-specific antigens were detected in a chronic infection patient's intestinal crypts, indicating that HEV proliferates in the intestines and replicates before passing to hepatocytes (37).

Differences Between Zoonotic and Human-restricted Strains

The genetic dissimilarities between zoonotic and human-restricted strains of HEV center around genetic diversity, evolutionary adaptations, and host interactions. Zoonotic strains like genotype 3 and genotype 4 exhibit greater genetic diversity owing to their ability to infect multiple animal species, leading to swift evolutionary changes and intricate genome architectures. They also demonstrate notable variation in structural proteins such as ORF2, allowing them to adapt to different types of hosts and settings. Comparatively, human-restricted strains like genotype 1 and genotype 2 are more genetically stable and primarily infect humans, resulting in less genetic fluctuation and fewer mutations. They are more genetically stable and evolve within a single host species, which reduces their flexibility (2,3,8,9,12).

Research has revealed that before the identification of genotypes of the wild boar and camel origins (HEV-5 to HEV-8), the ancestors of all *Orthohepevirus A* species were enzootic (38).

Over the past decade, exploration into HEV's cross-species transmission has made progress, though questions remain. ORF1 is a key determinant, but further investigation is needed to recognize precise domains. Comprehending HEV's interactions with host cells is crucial for understanding its targeting and infection, and decoding these interactions will help in understanding the full range of HEV cross-species transmission mechanisms (12).

Zoonotic Transmission and Pathogenesis of HEV: Host Tropism and Adaptations Enabling Cross-species Transmission

Modern HEV strains, which emerged around 6800 years ago due to pig domestication and agricultural intensification (39), while *Orthohepevirus A*, which infects rabbits, camels, and swine, originated in Asia around 4500-6800 years ago (40).

The HEV genome is diverse across different genotypes, often linked to specific host species. Genetic recombination in HEV genomes contributes to their genetic diversity and facilitates cross-species transmission. Factors influencing HEV's ability to spread from animals to humans include: viral determinants like ORF1, host-specific factors like cellular receptors and immune responses, and alterations in translation efficiency and viral genome packaging. These factors contribute to HEV's ability to infect multiple species (40,41,42,43,44). Underlying mechanisms for cross-species HEV infection are unclear, with specific cellular receptors and virus entry mechanisms being poorly understood (44).

HEV has evolved several adaptations to facilitate its zoonotic transmission. These include genetic diversity, host range, and species-specific modifications (12). One study suggested that HEV ancestors may have evolved from animal hosts to humans (38), while another research report states that *Orthohepevirus A*'s first host was humans and then evolved into cross-species and human-exclusive genotypes (40). HEV has evolved mechanisms to evade immune responses in various hosts, allowing it to infect a wide variety of animals (12). In addition to the divergence of enzootic and human-limited genotypes, the evolutionary history of *Orthohepevirus A* also includes the divergence of genotypes that infected camels during camel domestication. The divergence of HEV-3ra coincided with rabbit domestication (40).

A study found a bias in HEV-1's ORF2 protein production in deer cells, which could be corrected by introducing a short 5' RNA sequence from HEV-3. This suggests that translation efficiency can vary significantly depending on the host strain, potentially restricting the viral species' host range. The study underscores the complexity of interactions between host and virus and provides insights into how host-specific factors shape HEV's zoonotic potential (41).

A study in Singapore analyzed viral populations from 15 chronic HEV patients to identify lineage and points of interest for mutation. In this study, 21 viral RNA samples were examined from a single hospital between 2012 and 2017. Phylogenetic analysis identified the whole sequences spanning the HEV-3a subclass, indicating a unique local ancestry (42).

Recent studies have identified genetically distinct HEV variants from various animal species, identified in specific isolates from specific animals. Recombination events have been observed in both animal reservoirs and human patients. Chronic HEV infection in immunocompromised individuals creates a human host carrying genes of virus strains, suggesting potential for adaptation and host-virus interactions (43). Exosome-released HEV particles are shielded from neutralizing antibodies, potentially facilitating HEV spread (4). Natural selection is a crucial process for virus fitness in specific environments (45). Transmission with frequent cross-species contact may emerge as parallel evolution due to adaptation to new host environments (46). HEV's large host range may be due to evolutionary conservation of host factors, but further investigation of HEV's strategies to evade distinct host immune responses is needed (44).

The exact method of transmission between species in HEV remains unclear. Knowledge of the host and viral factors involved has advanced, with the majority of the research to date focused on HEV ORFs and evolutionary events (12).

Epidemiology

Global Epidemiology of Zoonotic HEV Strains

HEV has established itself globally as the primary factor for acute hepatitis in many areas, with the majority of infections going unnoticed or asymptomatic, and as the fifth recognized cause of human viral hepatitis (47). Historically thought to occur only in resource-poor regions, HEV is now recognized as predominantly zoonotic in nature, endemic even in developed countries. Genotype 3 (and genotype 4) has especially garnered attention given our evolved understanding of its ubiquity and position as a dominant source of community-acquired hepatitis across Europe (48).

Approximately 20 million people fall ill from HEV each year worldwide. Though not all experience symptoms, over 70,000 die as a result of infection. Outbreaks have plagued refugee camps and regions with inadequate sanitation infrastructure. Though sporadic cases, also surface outside of epidemics, countries from Africa to Central/South America, through temperate East Asia, and into the Middle East witness the virus's effect (49,50). Most recent World Health Organization data indicate HEV led to over 44,000 deaths in 2015 alone, constituting 3.3% of viral hepatitis mortality rate globally (50). Genotypes 1 and 2 have periodically sparked large outbreaks across parts of Asia, Africa, and Mexico, linked to heavy rain and the subsequent contamination of water supplies (50,51,52,53). According to the study by Li et al. (53), Figure 3 shows the distribution of HEV genotypes globally.

HEV infections are an increasingly grave public health issue, particularly in developing regions where close contact with livestock like pigs, goats, sheep, and cattle in conjunction with traditional meat consumption habits and subpar hygiene exacerbate transmission risks. Multifarious determinants including agricultural techniques, meat handling protocols, and inadequate preventive health infrastructure compound the infection risks. To stymie the spread, thorough cooking, improved sanitation, and regulated animal agriculture and hygienic practices are indispensable (51,52,53,54,55).

HEV is rampant in less developed nations with deficient clean water access and sanitation (51). It has surfaced in persistently affected areas like Asia, the Middle East, Africa, and even in parts of Central America, which have been categorized as developing regions (52). A meta-analysis of 419 studies showed that more than 12% of people worldwide have encountered the virus. At-risk populations include raw meat eaters, soil handlers, blood donors, travelers to endemic areas, canine companions, rustics, and poorly educated groups. The study implies nearly 939 million individuals have had HEV (53).

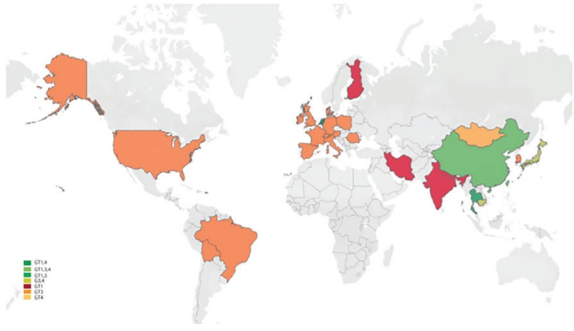

Figure 3. The global distribution of HEV genotypes
HEV: Hepatitis E virus

A meta-analysis of HEV seroprevalence in industrialized countries found that rates fluctuate from 5% to 50%, depending on location and demography. While certain divergences may relate to serological testing techniques, current understanding of transmission avenues fails to thoroughly clarify these dissimilarities. The work emphasizes pronounced inconsistencies, notably in research utilizing the Wantai HEV-IgG ELISA screening (54).

A meta-analysis of 432 studies from 2003 to 2015 found that HEV seroprevalence in Europe is between 0.6% and 52.5%, increasing with age but not gender. Rates varied by test type, with higher rates in individuals in contact with swine and wildlife. Geographical region, test type, and exposure status also influenced seroprevalence. France had the highest rates, while Italy had the lowest (55).

A meta-analysis of HEV infection seroprevalence in Middle Eastern countries revealed a total of 21.3%, with Egypt having the highest rate at 35%. Pregnant women had the highest rates at 47.9%, while kidney transplant patients had a lower rate at 30.8% (56).

Information on anti-HEV seroprevalence in Türkiye is limited. A 2018 meta-analysis in Türkiye found that HEV prevalence ranged from 0 to 12.4%, with lower rates in children. While the incidence is 7-8% in pregnant women, it is 13% and 35% in patients with chronic hepatitis B, C, renal failure and agricultural workers, respectively. HEV seroprevalence among those migrating from Türkiye to Europe was determined to be 10.3% in Italy and 33.4% in the Netherlands. This study emphasized that the studies were not reflecting the entire population and excluded immunocompromised patients and solid organ recipients, suggesting that HEV was endemic in Türkiye (57). In a review study conducted in Türkiye, high rates of HEV seroprevalence in hemodialysis patients and low rates in children were reported, especially in the regions of Eastern Anatolia and Southeastern Anatolia. However, considering the epidemiologic characteristics of HEV infection, HEV seroprevalence varies according to age, location and underlying special risk group status (58).

In a meta-analysis examining the prevalence of HEV IgG antibody in pregnant women, seroprevalence was found to be 16.51% according to data from 15 studies. The highest prevalence, 61.29%, was found in Sudan, and the lowest prevalence, 3.41% was found in Italy. High heterogeneity was observed among the studies, and the results show that HEV seroprevalence varies according to geographical regions (59).

A study on HEV's seroprevalence in pigs and the environment highlights its potential for transmission through water, food, and humans. The high prevalence in domestic animals, like pigs, suggests that the virus can spread in the environment and meat supply chains. Detection in water sources and animal products increases infection risk, highlighting the need for further research in animal markets (60).

Transmission Routes of HEV

HEV is primarily transmitted via ingestion of food or water that has come into contact with and been contaminated by the feces of infected individuals or animals (fecal-oral route). Typical routes of transmission include drinking untested water sources, eating undercooked meat (particularly pork) products, and lacking proper hygiene practices (49,52,60,61,62). Although HEV3 and HEV4 are usually transmitted zoonotically, these viral variants have still been found polluting untreated wastewater, pig manure storage tanks, and surrounding river waterways (63).

HEV also has a zoonotic transmission route where it can be passed from animals (especially pigs, deer, and other livestock) to humans through consumption of infected meat (60). Additionally, bloodborne transmission can occur through blood transfusions or organ transplants from infected donors (51). HEV can also be spread via contaminated medical equipment, though this is rare. Lastly, there is a possibility of environmental transmission through contact with contaminated surfaces or soil, but this route is less frequently reported (62). Vertical transmission can happen during pregnancy, leading to complications for both the mother and fetuses (64).

HEV can also transmit zoonotically, with humans becoming ill after consuming inadequately cooked meat from infected pigs, deer, and livestock. Bloodborne spread through tainted blood donations or organ transplants is another potential path of transmission (51). Rarely, the virus might spread through contaminated medical equipment. It's also possible, yet less reported, to contract HEV by touching surfaces contaminated by infected excrement or soil (62). During pregnancy, vertical transmission in the womb can endanger both expectant mothers and their fetuses.

HEV3 and HEV4 have been found in several animal species, including domestic animals, wild boars, and sika deer, and are common in domestic pigs worldwide. Pigs aged three to five months have the highest excretion of HEV. These animals can transmit HEV to humans. Although HEV3 and HEV4 infection remain asymptomatic, the virus is retained in herds thanks to the high amount of excreted virus in the faeces of infected animals (65).

Scientists have identified HEV3 and HEV4 within numerous animal populations as well, such as domesticated pigs and boars, sika deer, and even household pets. Pigs between three and five months of age have been found to carry the highest viral loads in their feces. These swine can pass HEV on to humans who handle or consume them. While asymptomatic in pigs, the virus persists in herds because of immense quantities excreted by infected swine.

Clinical Manifestations of Zoonotic HEV Infection

Symptomatology and Complications in Zoonotic HEV Infection

Infection with HEV poses significant risk to pregnant women, infants, the elderly, those with immunocompromised systems, individuals with chronic liver conditions, and people who work closely with host animals of HEV (61,66,67). HEV infections can result in various clinical manifestations, including acute and self-limiting hepatitis, acute-on-chronic liver disease, chronic hepatitis, cirrhosis, and liver failure (67).

Chronic HEV infection can develop in immunocompromised patients. The host immune response may mediate liver damage caused by HEV, and its clinical manifestation may vary, especially in high-risk groups (61). Zoonotic and non-zoonotic HEV infections share common symptoms (61,66,67). Zoonotic HEV (genotypes 3 and 4) is more likely to cause chronic infection, especially in immunocompromised individuals, and is associated with extrahepatic complications such as neurological disorders, glomerulonephritis, and autoimmune responses. In contrast, non-zoonotic HEV (genotypes 1 and 2) are generally self-limiting in healthy individuals but pose a higher risk of severe outcomes in pregnant women, including acute liver failure (ALF), stillbirth, and preterm delivery, especially in the third trimester. While zoonotic HEV can lead to chronic hepatitis and cirrhosis in susceptible populations, non-zoonotic HEV is more likely to cause acute infection with a better prognosis in most individuals, except in pregnancy (49,50,67).

Zoonotic HEV (genotypes 3 and 4), which are usually spread by undercooked pork or animal products, are linked to extrahepatic complications like neurological disorders, glomerulonephritis, and autoimmune reactions. It is also more likely to cause chronic infection, particularly in immunocompromised individuals. Non-zoonotic HEV (genotypes 1 and 2), on the other hand, is mainly waterborne and spreads through contaminated water in unsanitary areas. While certain conditions are generally self-limiting in healthy individuals, pregnant women are at a higher risk of serious complications, such as ALF, stillbirth, and preterm delivery, particularly during the third trimester. With the exception of pregnancy, non-zoonotic HEV is more likely to produce acute infection with a better prognosis in most people, compared to zoonotic HEV, but zoonotic HEV can induce chronic hepatitis and cirrhosis in vulnerable populations.

Acute Hepatitis

Acute HEV infection typically manifests with a prodromal phase lasting around one week. It possesses an incubation period averaging six weeks, though it can extend from two to nine weeks (49). It often induces mild symptoms such as malaise, fever, body aches, nausea and vomiting prior to progressing to dark urine and jaundice. Occasionally, acute HEV infection accounts for only five to thirty percent of overall HEV cases. Other common symptoms include abdominal pain, loss of appetite, joint pain, and itchy skin (11,49,67).

The convalescent phase resolves icteric symptoms, with HEV1 causing more severe acute hepatitis presentations than HEV2. Older men are susceptible to severe infections from HEV3 and HEV4, while patients with chronic liver disease can develop acute-on-chronic liver failure (ACLF) (67).

Pregnant women and immunocompromised individuals has critical time window for diagnosis and management, which crucial for improving patient outcomes (11,49,67). These women, especially in their second and third trimesters, face high risk of symptomatic disease and ALF from HEV1, leading to mortality rates as high as 25% (68,69,70). In the third trimester, HEV1 can endanger mothers through eclampsia, hemorrhaging, and liver failure. Babies are vulnerable to transmission during birth or breastfeeding, known as vertical transmission (71).

Newborns face severe risks due to maternal-fetal transmission of HEV, often leading to clinical symptoms like hypoglycemia, hepatitis, and neonatal death (70). A recent study investigating risk factors associated with vertical transmission of HEV found that 46.09% of HEV-IgM-positive mothers passed the virus to their fetuses. Among 29.41% of newborns, delivered by mothers with ALF tested, are positive for HEV-RNA.

The research highlighted that viral load was a salient predictor of the transmission of the infection from mother to child, along with hemoglobin and folate levels. Researchers developed a novel risk evaluation system incorporating such elements from these indicators to more precisely foresee the likelihood of vertical transmission. This model reinforced that a higher viral burden plays a pivotal role in impacting whether HEV transfers to the fetus (64).

Chronic Hepatitis

Although HEV generally emerges as an acute infection, it is able to induce chronic HEV in immunocompromised patients (such as those receiving organ transplants or those with human immunodeficiency virus). Hepatocellular carcinoma (liver cancer), cirrhosis, and progressive liver damage can all be brought on by a persistent infection. Antiviral therapy and ongoing monitoring are necessary for chronic infections because chronic infections can result in serious, long-term liver damage (11,49,67).

Zoonotic HEV (genotypes 3 and 4) infections, spread primarily via undercooked pork, have been tied to several extrahepatic manifestations including neurological issues, glomerulonephritis, and autoimmune responses. Moreover, it often results in chronic infection, particularly in immunocompromised individuals. Non-zoonotic HEV (genotypes 1 and 2) is mainly waterborne and is transmitted through contaminated water in unsanitary areas. Generally, a stronger immune system in healthy individuals can prevail without complications, but pregnant women are at a higher risk of serious complications, such as ALF, stillbirth, and preterm delivery, particularly during the third trimester. Non-zoonotic HEV often causes an acute infection with a favorable prognosis for disease (with the exception of pregnant women), but zoonotic HEV can cause chronic hepatitis and cirrhosis in susceptible groups (49,50,61,67).

Hepatic Fibrosis and Cirrhosis

HEV infection has been shown to expedite the progression of liver fibrosis, inevitably leading to cirrhosis in individuals with a chronic case, especially those with pre-existing liver conditions (such as existing chronic liver disease).

Individuals with pre-existing liver disease may experience further hepatic decompensation from HEV superinfection, while recipients of solid organ transplants and those with severe immunosuppression may experience asymptomatic acute HEV infection (49). Cirrhosis can raise the risk of complications including hepatocellular cancer and liver failure over time (61,66,67).

However, studies cannot provide sufficient evidence for a conclusive inference when different studies are examined. A study found higher anti-HEV IgG and HEV-RNA positivity rates in cryptogenic cirrhosis patients compared to healthy controls. However, a positive correlation was observed between HEV-RNA levels and liver enzymes (AST and ALT), suggesting HEV infection may contribute to liver damage in these patients. This suggests a possible association between HEV and cryptogenic cirrhosis, but further research is required to confirm this association (72).

Extrahepatic Manifestations

HEV infection can cause neurological, renal, pancreatic, and hematological complications, complicating diagnosis due to mild liver function tests (67,73). Neurological issues include polyradiculopathy, Guillain-Barre syndrome, Bell's palsy, ataxia, and mental confusion. Renal issues include nephritis and a specific type of glomerulonephritis. Hemolytic anemia has been linked to HEV infection in immunocompromised individuals, and rare cases can cause pancreatitis (67,74).

While previous analyses had examined HEV's interactions with human-derived monocytes and macrophages, a new investigation revealed that monocytes, macrophages, and bone marrow-derived macrophages from humans exhibit tolerance to HEV infection. These immune cells, crucial for defense mechanisms, can be reservoirs for persistent infections, especially in individuals with compromised immunity. This persistence could lead to chronic infection and complicate patient management, especially in patients with immunodeficiencies or immunosuppressive treatments. The life cycle of HEV in human bone marrow-derived macrophages could be linked to the development of hematological conditions that manifest as extrahepatic symptoms, such as anemia and thrombocytopenia. However, there is a significant gap in understanding the full spectrum of extrahepatic manifestations associated with HEV, especially in immunocompromised patients. Further research is needed to clarify the mechanisms by which HEV affects various organ systems and contributes to non-liver-related symptoms (75).

Co-infection with Other Viruses

Infections with other hepatotropic viruses (as hepatitis B or hepatitis C) can coexist with zoonotic HEV infections, particularly in immunocompromised people. In this case, co-infection makes diagnosis and treatment more difficult, which results in severe conditions such as liver disease (76,77).

Autoimmune Phenomena

HEV infection can cause autoimmune reactions, particularly in people with less than ideal immunity. These reactions might manifest as rheumatic symptoms like arthritis and myalgia (pain in the muscles) or autoimmune hepatitis, in which the immune system unintentionally targets liver cells (78).

Diagnosis of HEV Infection

Both diagnostic and epidemiologic uses have led to the development of serological and nucleic acid testing (NAT) for the detection of HEV. The identification of HEV antigen, HEV-RNA, and serum antibodies against HEV [immunoglobulin A (IgA), IgM, and IgG] is necessary for the laboratory diagnosis of HEV infection (48,79).

Anti-HEV IgG antibodies can persist for over ten years, indicating distant exposure, but anti-HEV IgM antibodies can be found during the acute stage of the illness, and can continue for four to five months, indicating recent exposure. Therefore, the

presence of anti-HEV IgM, HEV antigen, and HEV-RNA, is used to diagnose acute infection, but anti-HEV IgG is the primary basis for epidemiological studies (79).

Acute HEV is diagnosed by detecting HEV IgM in serum; HEV-RNA in serum or stool specimens confirms the serologic diagnosis. Long-term, serial detection suggests chronic HEV infection. The United States of America Food and Drug Administration does not approve diagnostic tests for (specific condition or purpose).

HEV infection, but some establishments provide screening services.

The diagnostic laboratory within the Centers for Disease Control and Prevention's Viral Hepatitis Diagnostic Reference Laboratory division can offer testing assistance to identify HEV-specific antibodies (IgM and IgG) in patient samples and can provide an assay to detect HEV-RNA in blood and fecal samples (49).

Anti-HEV antibodies are frequently undetectable in immunocompromised individuals with chronic HEV, and NATs are the only accurate diagnostic method in these situations. When HEV-RNA is detected for three months or more, it is considered a chronic case of HEV. Viral load testing is utilized in these chronic instances to detect recurrent infections, and assess how well patients respond to changes in immunosuppressive medication or antiviral therapy (48).

In summary, the current European Association for the Study of the Liver guide recommends using a comb for the diagnosis of acute HEV infection (48).

The convalescent phase resolves icteric symptoms, with HEV1 and HEV2 causing more severe acute hepatitis presentations. HEV3 and HEV4 may cause severe infections in older men and ACLF in chronic liver disease patients (67).

Pregnant women and immunocompromised individuals are at risk for severe outcomes, and early diagnosis and timely management are crucial for improving patient outcomes (11,49,67). Pregnant women are at a high risk of developing symptomatic disease and ALF, leading to, mortality rates of 15-25% in specific trimesters, for those who develop these conditions (68,69,70). Acute HEV1 infections, particularly during the third trimester, can cause maternal morbidity and up to 20% maternal mortality due to eclampsia, hemorrhagic complications, and liver failure (69). Vertical transmission refers to the transfer of a virus from parent to child during childbirth or through breastfeeding (71). The application of serology and NAT tests diagnoses HEV infection, while the application of NAT tests specifically diagnoses chronic HEV infection (48).

Treatment

HEV infection usually has spontaneous viral clearance without treatment. No set approach is required for acute HEV infection; there is no approved treatment for chronic HEV infection. There is no vaccine approved by the (United States) Food and Drug Administration (66). Ribavirin therapy for severe acute HEV infection has very few available case reports. Within a few days of starting ribavirin medication, liver functions returned to normal, and HEV-RNA was no longer detected. There have been documented cases of ribavirin therapy for HEV genotype 1 and HEV genotype 3 infections. In one instance, liver synthetic function quickly improved (80). Individual cases of ALF that were later shown to be caused by HEV infection have been treated with corticosteroids. In these instances, steroid treatment was linked to better liver function metrics (48). But currently, there isn't enough data to support corticosteroid therapy for individuals with ALF brought on by HEV infection (81).

Risks for Public Health

HEV causes significant human infection in European Union/European Economic Area countries, with over 21,000 reported acute cases and 28 fatalities over the past decade, which shows a tenfold increase in reported cases. The majority of these cases (80%) have been from France, Germany, and the United Kingdom. However, as HEV infections are easy to miss and surveillance practices vary, the actual number of cases is likely higher than reported cases. Food-borne transmission, primarily through pigs and wild boars, is considered a major route of HEV infection in Europe. Both outbreaks and sporadic cases have occurred in immune-competent individuals, especially in those with high-risk conditions such as pre-existing liver conditions, immunosuppressive diseases, or those undergoing immunosuppressive treatments (82).

Preventive Measures and Vaccination Strategies

HEV is primarily transmitted through exposure to contaminated food and environmental factors. However, the propagation rate of HEV through these transmission routes can vary depending on factors such as the virus genotype, environmental conditions, hygiene practices, and the food consumed (83).

Waterborne transmission is the most common way for genotypes 1 and 2 for large outbreaks. The determination of zoonotic strains with the ability to traverse cross-species lines has expanded the host range and raised public health concerns due to its larger impact area. Every animal species is a possible host for HEV, and contact or consumption of host animals pose risks for infection, especially swine (19).

Development and Current Status of HEV Vaccines

Vaccine development for HEV in Europe is limited, with HEV-239 only being available in China for 10 years. Challenges in vaccine development include differences in genotype distribution, transmission routes, risk groups, and immune responses in vulnerable groups. This time, possible vaccine types focus on enhancing the immune system by stimulating proteins to induce protective antibody responses. The HEV-239 trial aimed to prevent acute symptomatic infections, but it is unclear if immunocompromised individuals have worse outcomes. Development of passive immunization or monoclonal antibody therapy, which has a neutralizing effect, is promising. Created vaccines should show clear effectiveness across all variations and maintain a strong safety standard (84).

Future Directions and Research Priorities

Future research on HEV should focus on improving epidemiological surveillance, developing diagnostic tools, vaccines, and therapeutics to control and prevent the spread of this disease. Key areas of surveillance include creating global networks to track HEV outbreaks, identifying asymptomatic infections, and studying HEV prevalence in animal populations. Rapid, affordable, and easy-

to-use diagnostic tools are essential for early detection. Portable genomic sequencing technologies can enable widespread viral monitor, track mutations, and understand HEV's evolution. Vaccine research should focus on universal vaccines, improve accessibility, and explore monoclonal antibodies. Host-based therapeutic approaches targeting immune responses or cellular mechanisms involved in HEV replication could complement antiviral therapies for chronic infections. Research into HEV's life cycle will help develop personalized treatments and prevent HEV-related liver cancer.

Conclusion

Zoonotic and non-zoonotic HEV infections are prevalent in different regions without discriminating the economic classifications and transmitted by various agents.

Zoonotic HEV is primarily spread from animals, particularly pigs, and can cause mild illness in healthy individuals with an healthy immune system but can lead to chronic liver damage in immunocompromised patients. Non-zoonotic HEV is generally acute and self-limiting but can cause severe complications, especially in pregnant women. Both types can cause extrahepatic manifestations, but zoonotic HEV is more likely to lead to chronic conditions.

While knowledge regarding HEV epidemiology and genetics has expanded in recent decades, surveillance shortcomings, diagnostic ambiguities, and vaccination barriers remain. Moving forward, prioritizing the differentiation of zoonotic from strictly human genotypes, enhancing diagnostic precision, and innovating preventive inoculations should be emphasized. A cohesive and integrated approach combining epidemiology, molecular biology, and vaccine development will be crucial for dealing with the complex nature of HEV.

In this disease, which does not discriminate between economic conditions, developed countries can take the lead and establish an information exchange structure with easy access to digital methods for worldwide monitoring and standardized reporting. This will create pivotal and ideal conditions for mitigating HEV's impact and improving global public health.

Footnotes

Authorship Contributions

Concept: M.A., Design: M.A., Literature Search: S.A., İ.E., M.A., Writing: S.A., M.A.

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