Review

Research progress of human Hepatitis E virus infection

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ABSTRACT

Hepatitis E virus (HEV) infection is a global health concern, with a large number of new infections reported every year. In developing countries with poor sanitation condition, HEV1 and HEV2 are mainly transmitted by the fecal-oral route due to water contamination. HEV3 and HEV4 are zoonotic diseases in humans consuming undercooked pork, mainly in developed countries. Usually, HEV infection is an acute self-limited course, and chronic infection can occur in immunocompromised individuals. The diagnosis of HEV infection relies on serological tests, including RNA and anti-HEV antibodies. Currently, ribavirin is a proven effective drug; the treatment options for immunocompromised and pregnant individuals are limited. To date, only China has approved vaccines for HEV prevention. Therefore, more research is needed to understand the etiology.

Key words: antiviral therapy, diagnosis, epidemiology, genotypes, hepatitis E virus

INTRODUCTION

Hepatitis E virus (HEV) is one of the five most common viruses causing hepatitis globally; it belongs to the Hepeviridae family.[1] In 1983, Russian virologist Balayan[2] tested the virus for the first time and observed the HEV in his own feces through an electron microscopy. Although our understanding of HEV has improved since its discovery, the origin of HEV remains unclear. HEV infects approximately 20 million people annually worldwide, causing more than 3 million clinically apparent symptoms and 70,000 deaths.[3] Although HEV often causes self-limiting acute viral hepatitis, HEV-related infection remains a huge public health burden in developing countries with poor sanitation. The mortality due to acute HEV infection in pregnant women and infants is rather high due to unknown mechanisms.[4] In addition, it has been reported in recent years that HEV infection can lead to the rapid progression of chronic hepatitis E to cirrhosis in immunocompromised and other special populations.[5] In China, HEV genotype 1 (HEV1) was previously the most common genotype. However, HEV genotype 4 (HEV4) overtook HEV1 to become the predominant genotype in recent years, most likely due to the

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Access this article online

Website: https://www.hksmp.com/journals/cai
DOI: 10.54844/cai.2022.0079
Submitted: 08-03-2022 **Revised:** 21-04-2022
Accepted: 17-05-2022 **Published:** 29-06-2022

How to cite this article: Wang J, Wang Y, Deng B. Research progress of human Hepatitis E virus infection. Community Acquir Infect 2022;9:5.

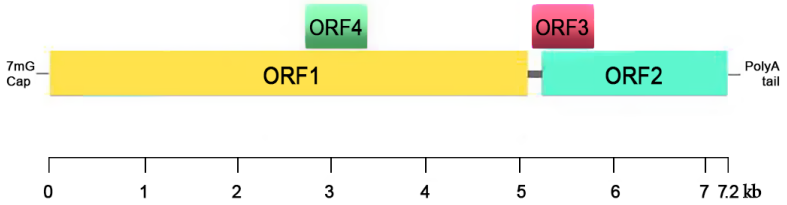

Figure 1. A schematic diagram of the open reading frames (ORFs) with the HEV genome. HEV: hepatitis E virus.

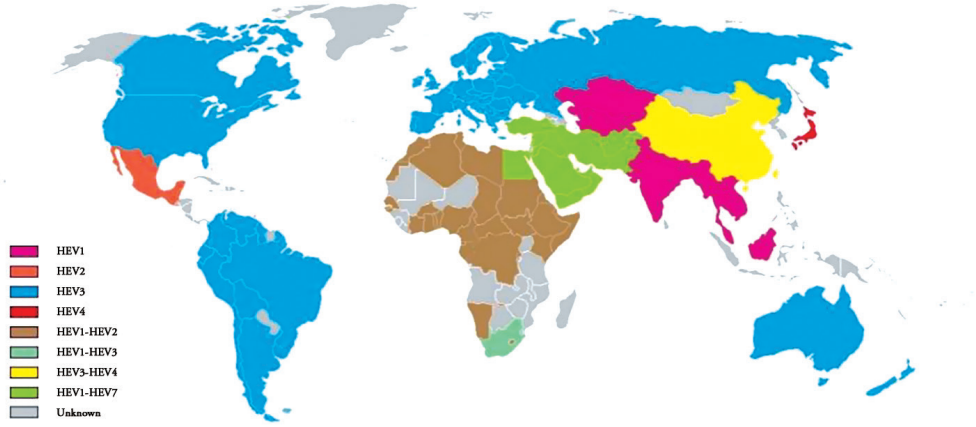

Figure 2. The distribution of the different HEV genotypes in the worldwide. HEV: hepatitis E virus.

improvements in living standards and sanitation.[6] It is important to follow the changing trend of hepatitis E worldwide, research the progress of etiology, grasp the trend of, and better prevent infection. This study aimed to provide an update on the etiology, clinical manifestations, diagnosis, and treatment of HEV infection.

Etiology

HEV is a small, icosahedral, nonenveloped, single-stranded RNA virus with a diameter of 27–34 nm; it is the only member of the Hepeviridae family and Hepevirus genus. HEV has three open reading frames (ORFs) (Figure 1). ORF1 encodes a nonstructural protein responsible for viral processing and replication, ORF2 encodes capsid proteins, and ORF3 encodes a protein involved in the release of new virions.[7] The recently discovered ORF4 is an additional ORF of HEV1 and plays a key role in the normal functioning of HEV RNA polymerase.[8] Viruses that infect humans belong to the Orthohepevirus family and can be divided into groups A to D. Although Group A comprises the predominant species infecting humans, a strain belonging to Group C has also been recently identified in humans in contact with rats.[9] Group B (avian) and D (bat) that infect animals but are not transmissible to humans. Group A includes eight genotypes. Only HEV1 (Asia, India, and North Africa) and HEV2 (Mexico and West Africa) infect humans, while HEV3 and HEV4 (Asia, North America, and Europe) can infect humans and animals and are mainly prevalent in pigs.[10] HEV5 and HEV6 have only been reported in wild boar, HEV7 has been reported in dromedary camels and in people who consume camel meat or milk, and HEV8 in Bactrian camels in the Middle East.[11,12] In addition, rodent (as an intermediate host)-associated HEV can also infect humans, and cases of murine HEV infection in humans have been reported in Hong Kong.[13] Other zoonotic hosts, including moose, ferrets, and dolphins, exist. It is not clear whether the corresponding HEV strains are capable of infecting humans.

Hepatitis E infecting humans is mainly caused by the first four of the eight Orthohepevirus A genotypes[14] (Figure 2). HEV1 and HEV2 are obligate human pathogens. In South Asia, Africa, rural China, and Mexico, HEV infection can cause large outbreaks due to poor sanitation. HEV is transmitted by the fecal-oral route through water source pollution.[15] HEV3 and HEV4 are zoonotic diseases, and pigs are the main hosts.[7] Genotype 3 is widely found and identified in North America and Europe. Genotype 4 is mainly found in China and Japan, with related cases also occurring in Europe.[10] HEV infections continue to increase every year in developed countries. Statistics reveal at least 2 million new infections annually in Europe.[16] HEV has been found in pigs worldwide, and the consumption of infected pig meat products, which have been undercooked, is a major route.[17] In addition, HEV has also been found in many other foods, mainly including shellfish, fruits, and vegetables.[18] Noteworthy, parenteral transmission through blood transfusion has been identified as a new occult infection route.[19] Reports confirm that China and Germany have a higher prevalence of viremia compared with other countries in the world, 0.281% and 0.12%, respectively.[20,21] However, only a small minority of infections through blood transfusion cause symptomatic hepatitis E. Approximately 70% of infections remain asymptomatic. This makes

the detection of infected blood donors extremely difficult. The development of chronic HEV infection is possible only when infected blood or blood products are administered to immunosuppressed individuals.

Clinical manifestations, diagnosis and pathology

A majority of clinically HEV-infected patients experience an acute self-limiting hepatitis course. After an incubation period of 2–9 weeks, an average of 6 weeks, patients develop symptoms such as fatigue, loss of appetite, nausea, vomiting, abdominal distension, and liver pain. The prevalence of cholestasis and jaundice is high. HEV1 and HEV2 are mainly found in young adults and pregnant women, while HEV3 and HEV4 typically affect middle-aged and older adults; their prevalence is higher in male patients than in female patients.[22] Most immunocompetent people with HEV can clear the virus spontaneously and rarely develop acute liver failure. People with underlying liver diseases (alcoholic liver disease, fatty liver, and so on) are at risk of developing decompensation or acute liver failure.[23] In patients with diabetes, HEV3 may cause severe disease and acute liver failure has been reported.[24] In women during late pregnancy, HEV1 infection can cause up to 25% mortality,[4] most deaths occurring due to fulminant liver failure or obstetric complications. The recently discovered HEV4 infection has also been linked to pregnancy and can lead to preterm labor and miscarriage. However, overall, no excess maternal mortality was found in HEV3 and HEV4 infection.[25] The causal mechanisms underlying death during pregnancy are still not fully understood. Further research is needed to reveal the interactions between various hormones and viruses in the body during pregnancy.[26]

HEV may contribute to immunocompromised patients (e.g., solid organ transplant [SOT] patients,[27] patients receiving chemotherapy for hematological malignancies,[28] patients with rheumatism using steroids and other immunosuppressive drugs,[29] and patients with Human Immunodeficiency Virus [HIV][30]) develop chronic hepatitis. To date, all chronic infection cases are caused by HEV3 and HEV4, and no related report of HEV1 or HEV2 exists.[31] Chronic hepatitis E can lead to changes in the structure of liver tissue. Pathologically, lymphocytic infiltration in the portal area can be observed, as well as hepatocyte necrosis, with varying degrees of fibrosis and rapid progression to liver cirrhosis.[32,33] The mechanism of chronic HEV infection is relatively complex; it is mainly closely related to the host immune status. Chronic HEV infected patients have low autoimmune function due to the intake of immunosuppressants, chemotherapy or HIV infection, which prevents timely clearance of the virus, resulting in chronic infection. In addition, massive transfusions of blood products, plasma exchange, and stem cell transplantation increase the risk of blood-borne infection in these patients. Defining chronic HEV infection has been controversial. In 2013, Kamar designed a study in a cohort of 69 HEV-infected SOT recipients; of these, 28 cleared the virus within 3 months and 41 remained infected for more than 6 months. Therefore, it was concluded that 3 months were defined as the cutoff for chronic HEV infection in SOT recipients.[34] At present, most clinics define chronic HEV infection as the continuous detection of HEV RNA in the blood or feces of patients for more than 6 months. In the "EASL Hepatitis E Virus Infection Clinical Practice Guidelines" issued by the European Association for the Study of the Liver (EASL) in 2018, HEV RNA detection for more than 3 months can be considered as chronic HEV infection.[35] With the development of organ transplantation and new immunosuppressive drugs, more immunosuppressed people may be detected, and chronic HEV infection may also become a new problem faced by clinicians.

In addition to acute and chronic hepatitis manifestations, Hepatitis E can also show a variety of extrahepatic manifestations.[36] The first is neurological disease. Guillain-Barre Syndrome (GBS) is one of the most common extrahepatic complications of HEV infection. HEV-related GBS cases have been reported in many countries around the world. In Europe, a prospective study showed 16.5% of symptomatic HEV cases presented with neurological symptoms.[37] In addition to GBS, facial palsy, neuralgic amyotrophy (NA), polyradiculopathy, mononeuritis multiplex, viral meningitis, encephalitis, and myelitis have all been suggested to be potentially associated with HEV infection. It is unclear whether neurological manifestations are the result of immune-mediated mechanisms or a direct cytopathic effect of HEV. Besides, hematological, and renal diseases also have been reported in both acute and chronic HEV infection, especially HEV3. Pancreatitis has been reported in patients with acute HEV1 infection.[36,38]

It is well known that HEV is a hepatitis virus that mainly manifests as liver damage, but various studies have shown that the ability of HEV to replicate in extrahepatic tissues.[33] *In vivo* models can provide better insight into the pathogenesis of extrahepatic manifestations, there are a variety of animal models of infection with different genotypes, including pigs, rhesus monkeys, rabbits, BALB/c mice, etc.[39] However, a drawback of such models is that not all genotypes of isolates can actively infect animal models. A new small animal model, human liver chimeric mice can be infected with HEV of different genotypes. This model breaks through previous flaws will be a valuable tool for the *in vivo* study of HEV infection.[40] In addition, in terms of *in vitro* cell culture, due to the cell passage of primary cells derived from organs is difficult and has poor reproducibility. Researchers design stem cell-based primary cell model.[41] We can study the host immune response to HEV through different *in vivo* and *in vitro* models.

The HEV should be considered in hepatitis that cannot be explained by other causes. The EASL guidelines recommend serology as a first-line test.[35] The diagnosis of acute HEV is complicated due to the lack of a standardized assay. Although a variety of commercial test kits are available, specificity and sensitivity vary widely. Generally, the initial test method is an anti-HEV Immunoglobulin M (IgM) assay; IgM is a marker of acute infection that appears in the early phase and persists for 4–5 months.[42] HEV RNA assays are required to confirm the diagnosis due to poor specificity. For chronic HEV infections, it is necessary to detect HEV RNA in

serum or stool for more than 3 months. The anti-HEV Immunoglobulin G (IgG) assay is of limited utility in chronic infections. Therefore, EASL recommends using a combination of serology and nucleic acid amplification technique (NAT) testing to diagnose HEV infection and NAT testing to diagnose chronic HEV infection.[35,43] Diagnostic and treatment algorithm of HEV infection is shown in Figure 3.

In clinical practice, the diagnostic methods of HEV infection are limited to the aforementioned serological methods, and the differential diagnosis of complex cases is quite troublesome. Acute hepatitis E is easily misdiagnosed as drug-induced liver injury.[44] Given the time limit and specificity of serological testing, histopathology is more acceptable as the gold standard. Some scholars showed[45] that ORF2 protein (pORF2) in HEV-infected paraffin-embedded (FFPE) liver tissue was easier to observe than pORF1 and pORF3, and its immunohistochemistry could be used for diagnosis. This provided us with a histopathological diagnosis. Actually, at present, there are few pathological studies of HEV infection, related characteristic changes and concepts have not been reported, and the pathological diagnosis is challenging.

Treatment and vaccine

In general, most HEV infection is spontaneously cleared and does not require antiviral therapy. As with other forms of acute viral hepatitis, bed rest, symptomatic and supportive treatment, and close monitoring of liver function are needed to observe illness progression.

However, immunosuppressed patients with chronic infections do require intervention. The EASL clinical practice guidelines recommend reducing immunosuppression first, if not get virus clean, and then initiating ribavirin therapy.[35] About one third of chronically infected patients achieve sustained viral clearance by reducing immunosuppressive therapy; also, ribavirin monotherapy has been shown to be effective in patients with reduced immunosuppression but still unable to clear the virus.[46] A large-scale European multicenter retrospective study of 255 SOT recipients found that the sustained virological response (SVR) rate was 81.2% after taking ribavirin, and when relapsers received a second course of ribavirin, the SVR rate increased to 89.8%.[47] In liver transplant recipients, pegylated Interferon-α (pegIFN-α) may be an alternative, but in heart or lung transplant recipients, it is contraindicated due to the possible high risk of graft rejection.[35] Chronic or persistent hepatitis in HIV patients or patients receiving chemotherapy for hematological malignancies can be treated in the same way with ribavirin.[48] For pregnant women who may develop liver failure after infection, ribavirin has been clearly proven to have teratogenic effects and is contraindicated. Some patients are still treated with ribavirin, and no teratogenic cases have been observed due to the high mortality rate of acute hepatitis E during pregnancy.[49]

So far, in addition to ribavirin and interferon entering clinical applications, two other drugs have been approved in experimental

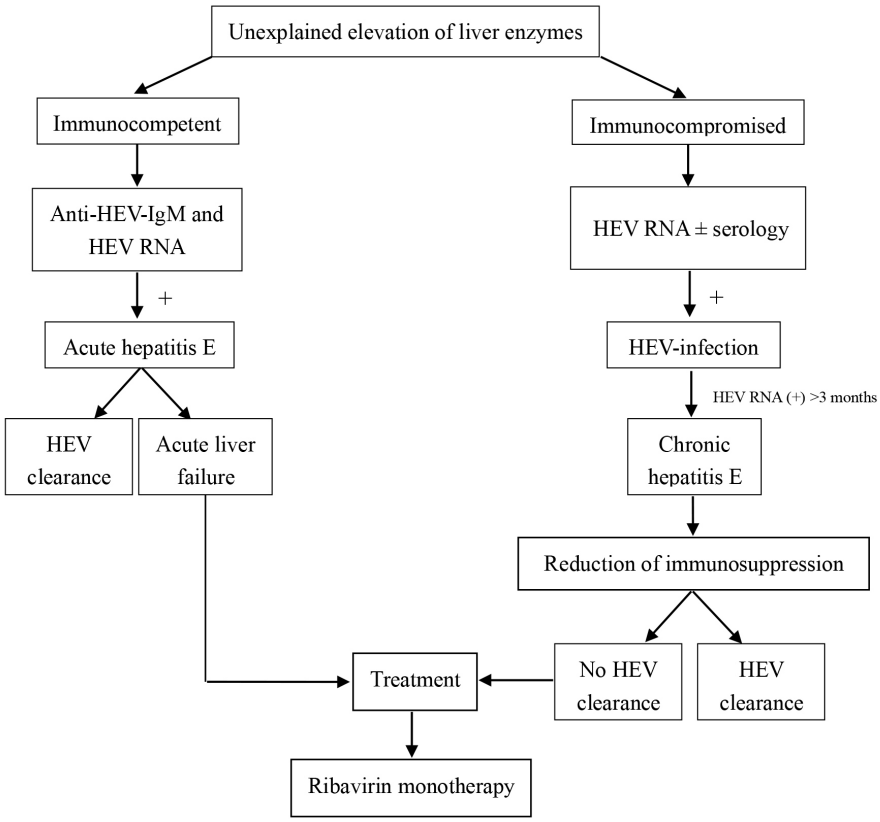

Figure 3. Diagnostic and treatment algorithm of HEV infection. HEV: hepatitis E virus; IgM: Immunoglobulin M.

settings other than *in vitro* cells culture, among them, sofosbuvir has entered the clinical trial stage, and silvestrol has entered the *in vivo* trial stage.[50]

Currently, treatment options are limited for ribavirin-unresponsive and contraindicated populations. Research data show that sofosbuvir can be used in this condition. Sofosbuvir is an NS5B polymerase inhibitor used to treat hepatitis C. It has been reported to have antiviral activity against HEV *in vitro*.[51] A phase II pilot trial in Germany investigated the antiviral efficacy and safety of sofosbuvir monotherapy in 10 patients with chronic HEV infection who failed to achieve hepatitis E virus clearance with ribavirin or developed contraindications to ribavirin. Although many patients initially had a significant reduction in viral load, none achieved SVR.[52] Therefore, the antiviral effect of sofosbuvir on HEV remains uncertain. Silvestrol is a natural compound found only in plants of the genus Aglaia.[53] The pan-genotypic effect of this compound is demonstrated in HEV infection experiments, the inhibitory effects were also consistent for different genotypes covering HEV1-4. Besides, HEV RNA levels reduced in feces of special treated mice.[54] Therefore, this compound may be considered as a future therapeutic strategy for chronic hepatitis E in immunocompromised patients.

Apart from the above, there are a number of studies confirming the use of some drugs for the treatment of HEV infection, but all *in vitro* tests, none of them have been validated in clinical trials.[50] One of the studies designed a HEV replication system for drug screening using GT3 isolates, by which the researchers found that Type III IFNs (IFN-λ1-3) can effectively inhibit the growth of HEV.[55]

The recombinant vaccine HEV 239 (Hecolin; Xiamen Innovax Biotech, Xiamen, China), which Chinese scholars successfully developed, was certified by the China Food and Drug Administration (CFDA) in 2012 and has become the world's first vaccine for hepatitis E prevention. In phase III clinical trial of 97,356 clinical volunteers aged 16–65 years, using the 0, 1, and 6-month regimens, 15 people in the placebo group were infected with HEV within 13 months after three doses of vaccine following the standard protocol. The vaccine efficacy was 100.0% in the vaccine group.[56] The extended follow-up lasted for 4.5 years. Finally, 60 cases of hepatitis E were found; seven cases (0.3/10,000-years) in the vaccine group and 53 (2.1/10,000-years) in the control group; the vaccine efficacy rate was 86.8%.[57] Currently, no globally approved vaccine is available to prevent hepatitis E; the focus is on preventing infection and cutting off the route of transmission. Major improvements in sanitation, better personal hygiene, and better management of manure and water sources are needed in developing countries. Attention should be on the food chain in developed countries. As mentioned, pork products are the main vehicle. Hence, it is recommended to avoid eating raw pork or eat only if it has been cooked for more than 2 min at 70°C. In addition, attention needs to be paid to the transmission of HEV through blood transfusion.

CONCLUSION

In the past, HEV was considered to be a disease endemic in underdeveloped areas with poor sanitation. However, a surge in HEV infections has been reported in recent years worldwide, including in developed countries; it has gradually become a new global health problem. Identifying novel HEV genotypes in different animals and hosts increases the likelihood of cross-species infection. Meanwhile, blood transfusions also increase the risk of infection. Typically, the infectious process is self-limited, but a chronic infection has recently been reported in immunocompromised patients and the number of cases is increasing. In addition to acute and chronic hepatitis, HEV infection has a variety of extrahepatic manifestations, with GBS being one of the most common neurological lesions. Ribavirin (RBV) and pegIFN-α can be used to treat chronic hepatitis E, and many other drugs are in *in vitro* cell trials, and vaccine is only available in China. Under the guidance of EASL guidelines, we can better diagnose and manage chronic patients.

Source of funding

This study was supported by the Natural Science Foundation of Liaoning Province, China (Grant No. 2019JH2/10300031-05), the National Natural Science Foundation of China (Grant No.12171074), the National Science and Technology Major Project (Grant No. 2017ZX10103007-005).

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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