Liver Research 8 (2024) 11–21

Contents lists available at ScienceDirect

Liver Research

journal homepage: http://www.keaipublishing.com/en/journals/liver-research

Review Article

Viral hepatitis E: Clinical manifestations, treatment, and prevention☆

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ARTICLE INFO

Article history:
Received 17 September 2023
Received in revised form
17 November 2023
Accepted 3 January 2024

Keywords:
Hepatitis E
Chronic hepatitis
Screening
Antiviral therapy
Vaccination

ABSTRACT

Hepatitis E is a globally distributed infection that varies in seroprevalence between developed and developing regions. In the less developed regions of Asia and Africa, a high seropositivity rate has been reported for hepatitis E virus (HEV) antibodies. Although acute hepatitis E is often self-limited and has a favorable prognosis, some populations experience severe manifestations, which may progress to liver failure. Moreover, some immunocompromised patients are at risk of developing chronic HEV infection and cirrhosis. Proactive screening, reducing misdiagnosis, improving patient management, timely antiviral therapy for severe and chronic cases, and vaccination of high-risk groups are important measures to reduce the morbidity of hepatitis E. This review focused on the clinical presentation, management, and prevention of hepatitis E.

1. Introduction

Hepatitis E virus (HEV) is the most prevalent causative pathogen of acute viral hepatitis. The first outbreaks of acute hepatitis were named non-A, non-B viral hepatitis and were first documented in Delhi, India in 1955 and, subsequently, in Kashmir, India in 1978.[1,2] In 1983, Russian virologists achieved a significant breakthrough when viral particles in fecal samples from affected patients were visualized using immunoelectron microscopy.[3] In 1989, the viral genome was successfully sequenced, and this pathogen was formally designated as HEV.[4]

HEV infection has long been thought to only lead to self-limiting acute hepatitis and typically has a favorable prognosis. However, a study conducted in 2008 revealed that chronic hepatitis secondary to HEV infection occurred among organ transplant recipients.[5] Another reported case involved a 16-year-old adolescent who was infected with HEV, which progressed to liver cirrhosis after bone marrow transplantation for acute lymphocytic leukemia.[6] This discovery underscored the potential of HEV infection to manifest as a chronic condition in immunocompromised individuals and, in some instances, progress to cirrhosis.[7] Furthermore, specific demographic groups, such as the elderly, pregnant women, and individuals with preexisting liver diseases, may develop severe symptoms, including acute liver failure (ALF), upon acquiring HEV infection.[8] Recognizing the historical lack of attention paid to viral hepatitis E and the substantial strides in related research in recent years, China introduced the “Consensus on Prevention and Treatment of Hepatitis E” in 2022.[9] This consensus aims to address the urgent needs of healthcare institutions by providing clinical guidance for healthcare professionals on the diagnosis, treatment, and prevention of HEV infection.

In clinical practice, the diagnosis of HEV infection is typically established by serologic and molecular biology examinations. Nonetheless, because of the insufficient awareness of hepatitis E among primary healthcare facilities and nonspecialist physicians, certain regions face challenges in implementing adequate screening for HEV infection. Furthermore, the limited availability of HEV ribonucleic acid (RNA) testing contributes to the underdiagnosis of HEV infection. Indeed, in individuals predisposed to the severe and chronic outcomes of infection, failure to promptly diagnose and treat HEV infection can lead to grave consequences. Consequently, in 2023, the “Expert Consensus on the Process of in-Hospital Screening and Management of Viral Hepatitis E in China”

☆ Edited by Peiling Zhu.

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https://doi.org/10.1016/j.livres.2024.01.001

was introduced.[10] Compared with the aforementioned "Consensus on Prevention and Treatment of Hepatitis E", this consensus placed a greater emphasis on guiding healthcare institutions in coordinating efforts across various departments within the hospital. It aimed to effectively screen, diagnose, refer, treat, and manage patients with hepatitis E and to strengthen the ability of clinical departments, including nonhepatology specialties, to promptly identify individuals with HEV infection during routine medical activities.

In recent years, a wealth of research has emerged to shed new light on our understanding of HEV infection. However, the landscape of HEV research still suffers from significant gaps. The reliance on testing primarily among suspected patients hinders the accurate assessment of the disease burden. Additionally, the cost-effectiveness of routine HEV screening in specific cohorts, such as organ transplant recipients, remains uncertain.[11] Furthermore, insufficient fundamental research exists regarding HEV-related liver failure, chronic hepatitis E (CHE), and maternal infections, demanding safer antivirals and accessible vaccines. This article comprehensively reviews systemic clinical manifestations of HEV while stressing the urgency for pathogenesis research. It highlights potential novel therapeutic approaches and proposes hospital-based screening strategies to lower HEV incidence, enhance diagnoses, and improve patient outcomes.

2. Epidemiology

Hepatitis E infection has a global distribution, with a reported annual incidence of approximately 20 million, of which 3.3 million are symptomatic. In 2015, hepatitis E accounted for 44,000 deaths, representing 3.3% of viral hepatitis mortality.[12] HEV is a single-stranded RNA virus with eight genotypes. Genotypes 1–4 had been established to infect humans; genotypes 1 and 2 are restricted to humans, whereas genotypes 3 and 4 are zoonotic and are transmitted between humans and animals, such as pigs, deer, and shellfish. These genotypes are now understood to have distinct geographical patterns.[13] Genotypes 1 and 2 prevail in developing regions, with genotype 1 in India, Nepal, China, and North Africa and genotype 2 in Mexico and West Africa. Genotype 3 is widespread in developed countries across Europe, Oceania, the Americas, Japan, and Korea. Genotype 4 is endemic to China and Southeast Asia but has emerged in indigenous cases in Europe over the past decade.[14] In China, genotype 1 has historically been the predominant strain, but it has been surpassed by genotype 4 in recent years.[15]

Current evidence suggests that in developed regions, the seroprevalence of HEV is relatively low and varies within the same region. For instance, in Europe, the HEV seroprevalence exceeded 50% in the southwest of France but was only 10%–30% in northern France, the United Kingdom, and Germany.[16] In the United States (U.S.), the HEV seroprevalence was lower. Based on data from a population-based survey of the U.S. in 2009–2010, the national seroprevalence of anti-HEV immunoglobulin G (IgG) in the general population aged ≥6 years was only 6%; this may be attributed to the lower consumption of game and animal offal in the U.S., as well as the lack of Food and Drug Administration-approved tests to confirm HEV infection.[17] Conversely, developing regions in Asia and Africa were reported to have relatively high HEV seroprevalences. The seroprevalence of anti-HEV reached 50% in India and was close to 80% in Egypt, where HEV was most prevalent.[18,19] Another study indicated that the seroprevalence of anti-HEV in pregnant women in Egypt was up to 84.3%. Poor sanitation, contamination of the water supply, and high population density may contribute to the high prevalence.[20] Unlike other regions, Egypt was reported to have a rare incidence of severe liver damage in pregnant women with HEV infection; the mechanisms behind this observation remain unclear. In China, regional variations in HEV seroprevalence have been documented: the seroprevalence was higher in Guangxi (43.0%) and Yunnan (39.9%) than in the eastern regions (17.2%).[21–23] From 2004 to 2021, the reported hepatitis E incidence per 100,000 people in China increased from 1.27 to 1.85 and peaked at 2.10 in 2017.[24]

In 2020, the World Health Organization estimated that one-third of the global population had been infected with HEV, based on seroprevalence data.[25] In fact, the limited awareness of hepatitis E among healthcare providers might have resulted in some patients with elevated alanine aminotransferase (ALT) not undergoing proactive screening for HEV. Currently, screening for HEV relies on anti-HEV IgG and IgM, with IgM positivity serving as an indicator of recent infection and being applied for initial screening, despite its relatively low sensitivity. In a study in Egypt on 15 patients with positive serum HEV RNA, an enzyme-linked immunosorbent assay for serum HEV IgM yielded a sensitivity and specificity of 26.7% and 85.7%, respectively.[26] HEV RNA testing to confirm HEV infection is not widely adopted because of the lack of standardization and the significant variability in sensitivity across different laboratories. Therefore, the epidemiology and health burden of hepatitis E is likely underestimated.

3. Clinical manifestations

Most HEV infections in humans are asymptomatic, with only 19.8% of infected adults exhibiting symptoms.[27] The most common presentation is acute viral hepatitis, although immunocompromised patients may develop chronic infection. Elderly individuals, pregnant women, and those with underlying liver diseases tend to experience more severe manifestations that often progress to fulminant hepatitis. Moreover, HEV can affect extrahepatic tissues. The clinical manifestations of HEV infection are shown in Fig. 1.

3.1. Acute hepatitis E

The incubation period of HEV is 2–10 weeks (mean, 5–6 weeks). Acute hepatitis E (AHE) is typically self-limited, with most patients experiencing anicteric hepatitis, although some develop jaundice or pruritus. Elevations in ALT, alkaline phosphatase, gamma-glutamyl transferase, and total bilirubin are also common.[28] Immunocompromised patients often have relatively mild symptoms and lower ALT and total bilirubin levels.[29,30] In rare cases, AHE was reported to progress to ALF, which was more prone with HEV genotypes 1 and 2 than with genotypes 3 and 4.[31] In one study, 6.7% of patients with HEV developed liver failure (LF).[32] Another study revealed that the 28-day and 90-day mortality rates for HEV genotype 4-related LF were 12.86% and 30.36%, respectively.[33] In a study conducted in India, the mortality rate of HEV-associated ALF was 44.9%, which was lower than that of the other ALF etiologies.[34] Furthermore, elderly individuals had a relatively high risk of symptomatic infection or ALF.[35]

Liver biopsies from patients with HEV RNA-confirmed AHE exhibited the typical histopathologic features, including cholestatic patterns and, in some cases, confluent necrosis in zone 3. Analysis of the live infiltrating lymphocyte subtypes indicated a predominance of $CD8^+$ cytotoxic T lymphocytes. HEV-induced acute hepatitis was suggested to share similarities with acute hepatitis secondary to HAV and HBV, in which the liver damage is caused by the immune response rather than the virus itself.[36] The study by Wu *et al.*[37] revealed significantly higher levels of T helper (Th) lymphocytes (i.e., $CD3^+$ and $CD4^+$), interferon-gamma (IFN-γ), and interleukin (IL)

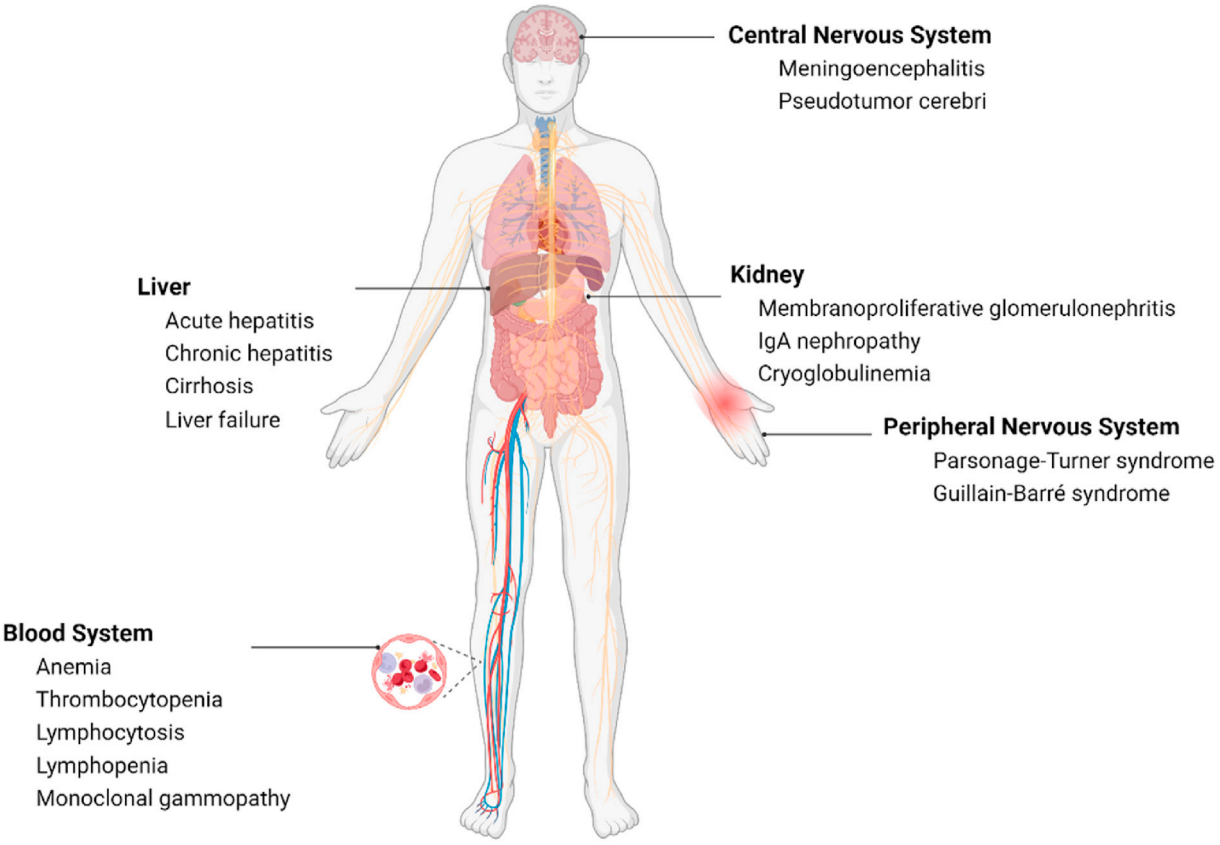

Fig. 1. The clinical manifestations of hepatitis E virus infection.

-10 in patients with AHE than in healthy individuals. The notably lower IFN-γ and higher IL-4 in patients with HEV-ALF than in patients with AHE indicated a potential association between IFN-γ and the prognosis of HEV-ALF and suggested that a Th2 bias in patients with HEV-ALF contributed to the onset and severity of AHE. The dose-dependent inhibitory effect of IFN-lambda (λ)-3, which is induced during the acute phase of HEV infection, on HEV replication *in vitro* implied its role in the innate immune response of the host and its protective action against HEV.[38]

3.2. Chronic hepatitis E

Chronic hepatitis E (CHE) is characterized by the detection of HEV RNA for over 3 months.[39] Most patients with CHE are asymptomatic or have mild symptoms, which are often accompanied by elevated transaminases. In rare cases, patients may continuously test negative for anti-HEV IgM and IgG, thereby, necessitating HEV RNA or antigen detection for diagnosis.[40] CHE predominantly occurs in immunocompromised populations, especially among organ transplant recipients. In addition, CHE has been reported to occur in persons living with human immunodeficiency virus, individuals undergoing chemotherapy for malignancies, patients with rheumatic disease, and even those with coronavirus disease 2019 (COVID-19).[41–44] Genotypes 3 and 4 are responsible for most CHE cases.[45] Among solid organ transplant recipients, 56.8%–65.9% of cases progress to chronic hepatitis following HEV infection.[39,40,44] However, it should be borne in mind that immunosuppression is not the sole factor contributing to the chronicity of HEV; in fact, a case of CHE in an immunocompetent patient has been reported.[46] Severely immunocompromised cases may progress to cirrhosis sooner.[43] Interestingly, a study by Liu *et al.*[47] on 55 immunocompetent patients with CHE did not observe the development of cirrhosis or hepatocellular carcinoma for 4–14 years. The heterogeneity in outcomes may arise from the distinct mechanisms of chronicity between typical patients with hepatitis E and those with compromised immune function.

The precise mechanisms underlying the chronicity of HEV infection remain unclear. Some studies have suggested a correlation between the absence of HEV-specific T-cell responses and the development of CHE.[48–50] In this regard, $CD8^+$ lymphocytes have been shown to play a direct role in early viral clearance, and under immunosuppressed conditions, chronic antigenic stimulation may lead to the exhaustion of $CD8^+$ lymphocytes. Reducing immunosuppressants and/or ribavirin treatment can reactivate T lymphocytes.[49,50] Notably, the use of T lymphocyte-suppressing agents, such as tacrolimus, was shown to be an independent predictor of CHE development.[40] Moreover, T cells contribute to viral control by producing IFN-γ.[48] Transcriptomic analysis of whole blood from kidney transplant recipients with CHE revealed the upregulation of 30 genes, including 25 IFN-stimulated genes. The association of increased gene expressions of *IFIT1*, *IFI44L*, *RSAD2*, *EPSTI1*, and *ISG15* with persistent HEV infection was validated by quantitative real-time polymerase chain reaction (qRT-PCR).[51] Nonetheless, further research is warranted to elucidate the roles of cellular immune responses and IFN-stimulated genes in chronic HEV infection.

3.3. HEV infection in pregnant women

HEV infection during pregnancy typically has clinical manifestations that are similar with those in the general population, with the majority of cases being asymptomatic. However, owing to physiologic and immunologic changes, pregnant women infected with HEV have a risk of developing LF, especially during late pregnancy. A study from India revealed that pregnant women comprised 57.9% of

patients with HEV-ALF.[34] The mortality rates among pregnant women infected with HEV can be as high as 20.0%–31.1%.[52,53] Pregnant women with genotypes 1 and 2 are more prone to severe diseases and have a relatively high mortality rate. However, studies on the association between genotypes 3 and 4 infections and severity in pregnant women are few.[54] Moreover, it should be borne in mind that mother-to-child transmission has a crucial impact, with rates ranging from 23.3% to 50.0%.[55] HEV infection has been established to result in adverse pregnancy outcomes, including fetal distress, fetal death, preterm birth, pathological neonatal jaundice, and low birth weight infants.[55,56] In the studies conducted in two genotype 4-endemic regions, 38.50%–42.99% of infected pregnant women had adverse pregnancy outcomes.[57,58]

Several factors that contribute to systemic immunosuppression increase the risk of severe disease in pregnant women. These factors encompass hormonal changes; micronutrient deficiencies; folate deficiency; oxidative stress; and the potential involvement of placental and trophoblast cell cytokines, such as transforming growth factor-beta, IL-4, and IL-10.[54,58] In pregnant rhesus macaques (Macaca mulatta), impaired IFN-stimulated gene expression and suppressed innate immune response have been reported to facilitate HEV replication and result in adverse pregnancy outcomes.[59] In a study that used the decidua basalis and fetal placenta to model HEV infection *ex vivo* at the maternal-fetal interface, replication of genotype 1 was found to be more efficient, compared with that of genotype 3, by subverting the IFN signaling pathway. This resulted in the generation of more infectious progeny virions, which altered the local cellular cytokine microenvironment and induced more severe tissue damage.[60] Autophagy appears to offer a protective effect against liver diseases.[61] Yang *et al.*[62] used a pregnant ICR mice model infected with HEV to demonstrate that autophagy flux inhibition of placental trophoblast cells might play a vital role in the pregnancy disorders induced by HEV infection. HEV-infected placentas have been reported to exhibit significantly increased levels of $CD45^+$ lymphocytes, $F4/80^+$ macrophages, apoptosis, and autophagosome activation, all of which can lead to placental fibrosis and calcification and the severe inflammatory responses that directly impact fetal development and pregnancy outcomes.[57]

3.4. HEV infection in patients with underlying liver disease

The interaction between chronic liver disease (CLD) and AHE significantly influences the clinical presentations and outcomes. A Meta-analysis has shown that HEV infection can exacerbate the conditions and increase the risks of LF and death in patients with CLD.[63] The reported incidence of LF among patients with CLD and HEV coinfection was approximately 35.8%, with a mortality rate of 14.3%.[63] Moreover, liver cirrhosis was identified as an independent predictor of the development of LF.[63] In patients with cirrhosis secondary to hepatitis B, HEV superinfection was found to be a risk factor for decompensation and acute-on-chronic LF (ACLF).[64,65] Although HEV is a common trigger for ACLF, it was reported to have a higher survival rate and fewer complications, compared with ACLF induced by alcohol or unidentified causes, possibly because of the spontaneous clearance of HEV.[66,67] Conversely, CLD can worsen the conditions of patients with AHE. Compared with individuals who have uncomplicated AHE, those with AHE complicated by CLD were more susceptible to complications, such as ascites and peritonitis, and had a significantly higher incidence of LF (22.3% *vs.* 12.1%).[68,69]

3.5. Extrahepatic manifestations

Although the exact pathogenesis remains unclear, HEV infection can affect extrahepatic organs (see Fig. 1) and lead to neurologic manifestations, kidney damage, and hematologic alterations. Neurologic symptoms are the most frequently reported extrahepatic manifestations and were reported to occur in 16.5% and 30.4% of patients with acute HEV infection in France and Switzerland, respectively.[70,71] The most commonly observed neurologic conditions are Parsonage-Turner syndrome and Guillain-Barré syndrome, followed by meningoencephalitis, neuropathic pain, and painless sensory disorders.[72] Patients with neurologic symptoms typically tend to be younger, often without jaundice, display mild transaminitis, and have normal immune function.[70,71,73] The predominant genotype is genotype 3 in approximately 90%, followed by genotype 1.[72,74] The widely thought association between the different genotypes and neurotropism has led to the concept of quasispecies and neurotropic variants, as proposed by Abravanel *et al.*[75] The ability of HEV infection to affect the blood-brain barrier by infecting the brain microvascular endothelial cells and astrocytes potentially contributes to its neuroinvasive mechanism.[76–79] However, the specific mechanisms behind HEV invasion of the nervous system remain unclear and require further exploration, including investigations on genotypes, gene expression, viral variations, and biological processes.

Current evidence showed that in regions where genotype 3 is prevalent, serum creatinine levels were significantly higher in patients with AHE than in patients with acute hepatitis A.[80] In Scotland, the rate of acute kidney injury among 511 cases of hepatitis E was 8.6%.[81] In another study on patients with glomerulonephritis, the anti-HEV IgG positivity rate (60.5%) was notably higher, compared with that in healthy control groups (25.0%).[82] Further research suggested that membranoproliferative glomerulonephritis and IgA nephropathy were extrahepatic manifestations of HEV.[44] Although most of the reported cases of HEV-related glomerulonephritis were associated with cryoglobulinemia, the clinical significance remains unclear.[83–85] HEV can efficiently replicate in renal tubular epithelial cells *in vitro*. The immune mechanisms of HEV-induced kidney disease may involve interactions between immune cells and renal epithelial cells, IFN-γ/chemokine pathways, and IL-18.[85]

A minority of patients with hepatitis E may experience hematologic derangements, including anemia, thrombocytopenia, lymphocytosis or lymphopenia, and monoclonal gammopathy of undetermined significance. However, the absence of a consistent association between these changes and clinical consequences may be attributed to the continuous viral replication in human monocytes, macrophages, and bone marrow-derived macrophages.[73,86–88]

4. Management and treatment of viral hepatitis E

4.1. Enhancing in-hospital screening and management of patients with hepatitis E

The management and treatment of viral hepatitis E have been a subject of increasing concern, especially in cases of delayed diagnosis and treatment because of inadequate screening. This issue is particularly critical for specific patient populations, including the elderly, individuals with underlying liver diseases, and organ transplant recipients, who are at risk of developing severe outcomes, such as cirrhosis and LF. In 2023, the “Expert Consensus on the Process of In-Hospital Screening and Management of Viral Hepatitis E in China” was released with the primary objectives of mitigating misdiagnosis and underdiagnosis of viral hepatitis E and prioritizing the identification of affected individuals for appropriate disease management.[10] According to the consensus, HEV screening is recommended for the following groups: (1) Individuals with symptoms of acute hepatitis; (2) Those with unexplained CLDs; (3) Immunosuppressed individuals with persistent liver enzyme

abnormalities; (4) Individuals with unexplained neurologic symptoms, such as Guillain-Barré syndrome and viral encephalitis, and unexplained hematologic, renal, autoimmune, and pancreatic diseases; (5) Cases that need to be differentiated from other liver diseases, such as hepatitis A, drug-induced liver injury, and autoimmune liver diseases; and (6) those with abnormal liver enzymes after blood transfusion.

In clinical practice, the diagnosis, consultation, referral, and treatment of viral hepatitis E necessitate close collaboration among various departments, including hepatology, infectious diseases, neurology, transplant medicine, nephrology, laboratory, information technology, and medical administration. Hepatology and infectious disease specialists assume the responsibilities of screening high-risk populations, offering consultations, conducting pretreatment assessments of HEV-infected individuals, and managing the treatment and follow-up of eligible patients. Other clinical departments, such as neurology, transplant medicine, and nephrology, are tasked to perform HEV screening of suspicious cases and initiate consultations or referrals to hepatology or infectious disease specialists when deemed necessary. The information technology department plays a crucial role in establishing and maintaining an early warning system of HEV IgM antibody and HEV RNA positivity. This system involves routine data collection and summarization, reporting to the hospital-acquired infection control and medical administration departments, and provision of feedback to clinical departments. The medical administration department oversees the coordination of training programs for healthcare professionals and supervises the activities of the various departments involved in the screening and management of hepatitis E within the hospital. The hospital-based screening and management protocol for hepatitis E is depicted in Fig. 2.[10]

4.2. Treatment of AHE

Given that AHE typically resolves spontaneously without antiviral therapy in most cases, the primary treatment approach for AHE should focus on symptomatic and supportive care, including adequate rest, appropriate nutritional intake, and the use of medications to mitigate hepatitis and alleviate bile stasis. Medications containing glycyrrhizic acid agents, S-adenosylmethionine, and ursodeoxycholic acid are typically used for this patient population.[89] For high-risk groups such as pregnant women or the elderly with AHE, the primary treatment is still supportive care. Moreover, regular close monitoring is crucial, and an artificial liver support system can be considered in cases prone to severe disease.[9]

4.3. Treatment of hepatitis E-induced LF

In cases of AHE progressing to LF, particularly in pregnant women, the elderly, and individuals with CLDs, aggressive symptomatic and supportive treatment is crucial and may involve an artificial liver support system and liver transplantation if necessary.[90] Although ribavirin treatment has been reported to lead to HEV clearance in some cases of ACLF, further large-scale studies or high-level randomized controlled trials are needed to confirm its efficacy in cases of HEV-related LF (HEV-LF).[91] Because of its potential teratogenic effects, ribavirin is not recommended in pregnant patients with severe hepatitis. Steroids have been shown to potentially slow disease progression in some patients with HEV-LF.[5] Furthermore, steroid therapy has yielded favorable outcomes in some HEV-ACLF cases, although these patients were suspected of having concurrent autoimmune hepatitis.[92] Therefore, the efficacy of steroid therapy in HEV-LF remains controversial.

4.4. Treatment of CHE

The European Association for the Study of the Liver (EASL) recommended ribavirin, pegylated IFN-α (pegIFN-α), or combination therapy as the standard treatment for CHE, although the optimal dosing and duration remain uncertain.[39] In solid organ transplant recipients, in whom the risk of CHE is high, the reported sustained virologic response (SVR) rates were 32%, 78%, and 85% after treatment with immunosuppression reduction, ribavirin, and pegIFN-α, respectively.[93] A multicenter study on ribavirin monotherapy at a median dose of 600 mg/day for posttransplant chronic HEV revealed a 78% (46/59) SVR rate after 3 months; however, 10 patients experienced HEV recurrence after discontinuing ribavirin.[94] In another study, restarting ribavirin in relapsed patients was found to increase the SVR.[95] Extending ribavirin in patients with persistent fecal HEV RNA at the end of a 3-month therapy may prevent relapse.[96] A high baseline lymphocyte count has been associated with SVR, although treatment failure may be secondary to viral genome mutations.[94,96–99]

The currently available evidence is inadequate to establish the safety and efficacy of pegIFN-α for the treatment of CHE. PegIFN-α has successfully treated a limited number of liver transplant recipients with concomitant chronic HEV infection.[100,101] However, given the high risk of graft rejection after transplantation, the use of pegIFN-α for chronic HEV infection in liver or kidney transplant recipients is advised with caution. Further research is warranted to establish the therapeutic potential of pegIFN-α in this patient population.

4.5. Emerging drugs for CHE

Because of the drawbacks of conventional treatment options, the optimal antiviral therapy for HEV remains controversial. The past few years have witnessed a burgeoning interest in novel antiviral drugs (Table 1). The use of sofosbuvir as an alternative to ribavirin remains a subject of debate. Although *in vitro* and *in vivo* experiments have demonstrated a synergistic antiviral effect of a sofosbuvir and ribavirin combination, mixed clinical outcomes have been reported; some studies reported rapid HEV suppression, whereas others found limited efficacy.[102,103] Monotherapy with sofosbuvir has not consistently led to HEV clearance in CHE.[93,104,105] Sofosbuvir/ledipasvir, in combination with ribavirin, has shown promising antiviral activity against persistent HEV infection, as demonstrated by the undetectable HEV RNA in blood and stool after an 8-week regimen in a case that previously failed ribavirin and pegIFN-α therapy.[106]

Silvestrol, which is a natural compound from *Aglaia foveolata*, has been identified as an inhibitor of DEAD-box RNA helicase eukaryotic initiation factor 4A (eIF4A), was confirmed as a pangenotypic HEV replication inhibitor *in vitro*, and exhibited synergistic effects with ribavirin. *In vivo* experiments demonstrated a rapid reduction in HEV RNA levels in mice feces following treatment.[107] Azithromycin, which is a macrolide antibiotic that is widely used for bacterial and chlamydial infections, inhibits genotypes 1 and 3 HEV replication and viral protein expression *in vitro*. Because of its easy accessibility and safety, azithromycin holds promise as a therapeutic option for HEV infection, particularly in resource-limited regions.[108] High-throughput screening, which targeted human hepatocytes harboring an HEV replicon, has identified inhibitors of heat shock protein (HSP90). Compared with the traditional antiviral drugs, such as ribavirin and IFN-α, HSP90 inhibition exhibited superior inhibitory effects on HEV replication *in vitro*.[109] Animal experiments further validated its safety and efficacy.[109] Ritonavir is another agent that has been shown to inhibit HEV growth in cultured cells by blocking HEV internalization and has a synergistic effect with ribavirin.[110]

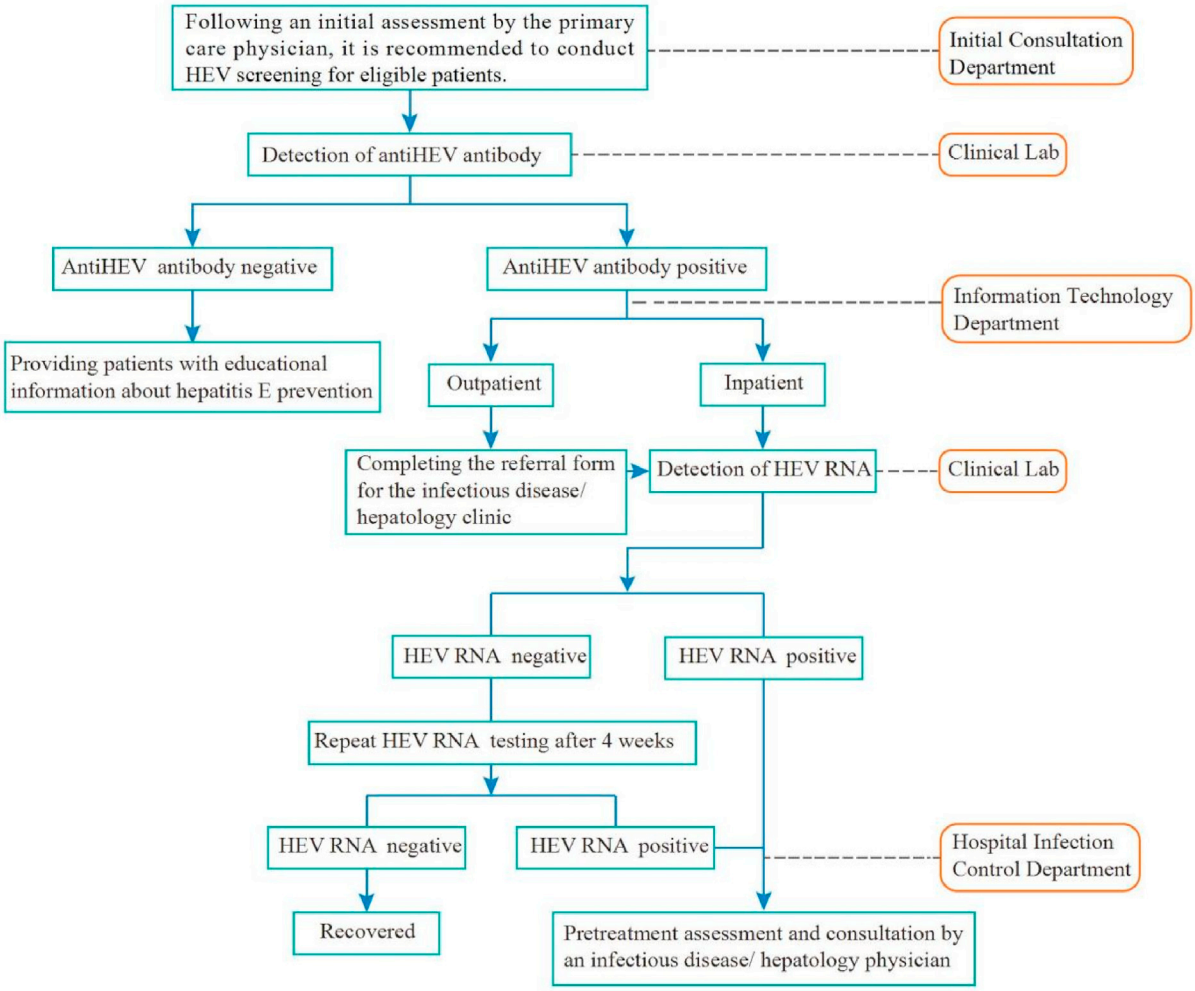

Fig. 2. The hospital-based screening and management protocol for hepatitis E. Abrreviations: HEV, hepatitis E virus; RNA, ribonucleic acid.

Overall, these emerging therapies offer potential strategies for the treatment of HEV infection. In addition, gene and T cell therapies hold promise for future research.[111–113] Further investigations and clinical trials are needed to establish the safety, efficacy, and broader applicability of these options in diverse patient populations.

5. Prevention

5.1. Control sources of infection

Asymptomatic HEV carriers and individuals with viral hepatitis E have been identified as the most common transmission sources. To mitigate viral transmission, strengthening the screening for HEV infection, prompt identification of infectious sources, and implementation of corresponding management measures that encompass home or hospital isolation and treatment of patients with AHE for up to 3 weeks after symptom onset are essential. Home isolation is recommended for asymptomatic HEV carriers. Antiviral treatment is advisable for patients with CHE to expedite virus elimination. Rigorous disinfection of the feces and excreta of patients is imperative, and suspected cases and close contacts should undergo medical observation for 4–6 weeks. The above-suggested quarantine periods are based on the time of infected persons excreting the virus and the average incubation period.[12]

5.2. Disrupting transmission pathways

The fecal-oral route is the most common mode of HEV transmission, which commonly occurs through contaminated water and food.[127,128] Genotypes 3 and 4 can induce foodborne transmission through animal hosts, such as pigs. A notable outbreak of HEV infection in France involved 17 individuals who consumed undercooked pork liver.[129] Consequently, enhancing water and sanitation management, improving environmental hygiene, and promoting good personal hygiene practices are critical. Preventing the consumption of undercooked animal organs, meat products, and shellfish and separating utensils for raw and cooked foods are essential measures to prevent foodborne transmission.[130,131]

In addition, transmission of HEV through blood transfusions has been documented in several countries.[132–134] A Meta-analysis on Chinese blood donors revealed prevalence rates of 29.2%, 1.1%, 0.1%, and 0.1% for HEV IgG, HEV IgM, HEV RNA, and HEV antigen, respectively.[135] However, it is worth noting that this study focused on screening for HEV RNA only among those blood donors who tested positive for HEV IgG or IgM. Conversely, a French study identified 22 blood donors who tested negative for HEV IgG and IgM but tested positive for HEV RNA.[136] Therefore, the prevalence of HEV RNA among Chinese blood donors might have been underestimated in the Meta-analysis. Currently, most countries do not

Table 1
Potential therapies under investigation for treating HEV infection.

Medications (Refs)	Prospective mechanisms	Research phases	Outcomes
Sofosbuvir[103,105,114]	Viral RNA-dependent RNA polymerase inhibitor	Clinical trial phase	Sofosbuvir alone may not clear hepatitis E virus (HEV) RNA.
Interferon-lambda (IFN-λ)[115]	Immunomodulatory	Preclinical testing phase	In 8 out of 9 mice, a 0.3 mg/kg dose of pegIFN-λ eliminated HEV antigen and RNA from the liver.
Brequinar[116]	Blocking pyrimidine nucleotide biosynthesis	Cellular experimentation phase	Brequinar exhibited effectiveness even against the G1634R mutation.
Homoharringtonine[116]	Undefined	Cellular experimentation phase	Homoharringtonine exhibited effectiveness even against the G1634R mutation.
Mycophenolic acid (MPA)[117–119]	Targeting the later steps of the purine synthesis pathway	Cellular experimentation phase	MPA exhibits antiviral activity *in vitro* experiments.
Gemcitabine[120]	Triggering IFN-like response through signal transducer and activator of transcription 1 (STAT1) phosphorylation	Cellular experimentation phase	The antiviral effect was confirmed in a range of cell culture models with genotype 1 and 3 HEV strains.
Silvestrol[107,121]	Inhibiting the release of HEV infectious viral particles	Preclinical testing phase	Silvestrol exhibited a swift decline in HEV RNA levels in mice feces post-treatment.
Azithromycin[108,122]	Anti-inflammatory and immunomodulatory properties	Cellular experimentation phase	Azithromycin inhibits HEV replication and viral protein expression in multiple cell culture models with genotype 1 and 3 strains.
Inhibitors of heat shock protein 90 (iHSP90)[109]	Targeting proteostasis of the HEV replicase	Preclinical testing phase	The iHSP90 was found to offer a secure, effective approach, capable of averting HEV-induced liver damage.
Ritonavir[106,122]	Blocking HEV internalization	Cellular experimentation phase	In combination with ribavirin, it notably enhanced HEV growth inhibition compared to ribavirin alone.
T cell therapy[111,113]	Killing HEV-infected target cells	Cellular experimentation phase	T-cell receptors (TCRs) directed at distinct $CD8^+$ T cell epitopes of HEV were evaluated for their immune characteristics.
RNA interference (RNAi)[112]	Down-regulating HEV replication	Cellular experimentation phase	The combined approach of RNAi and adeno-associated virus (AAV) vector-based gene therapy may suppress HEV replication.
Isocotoin[123]	Interference with HSP90	Cellular experimentation phase	Isocotoin inhibits HEV replication through interference with HSP90.
Zinc[124,125]	Inhibiting the activity of viral RNA-dependent RNA polymerase (RdRp)	Cellular experimentation phase	Zinc salts dose-dependently inhibited replication of genotype 1 and 3 HEV replicons.
Monoclonal antibody (mAb)[126]	Neutralizing HEV	Preclinical testing phase	The mAb 8G12 exhibits protective, neutralizing abilities. It may be utilized for preventing HEV.

routinely screen blood donors for HEV because of the perceived low transfusion transmission risk, based on existing evidence, and the high screening cost.[137] Selective screening strategies have been adopted in regions that have a relatively high risk of transfusion transmission. In China, serum HEV RNA or HEV antigen testing is recommended for blood donors with a high risk of infection (*e.g.,* livestock breeders, travelers from endemic areas, and food service personnel), and those who test positive are prohibited from donating blood.[9]

As mentioned above, mother-to-child transmission of HEV infection occurs not infrequently. However, due to the safety limitations of antiviral drugs for pregnancy, prevention relies on protecting women prior to conception.

5.3. Protecting susceptible populations

In the absence of prior immunity, individuals are generally susceptible to HEV infection. The high-risk populations for HEV acquisition include livestock handlers, food service workers, travelers from endemic areas, and those in crowded living quarters, such as boarding school students and military personnel. Research has indicated that elderly individuals, pregnant women, and individuals with underlying CLDs (*e.g.,* chronic hepatitis B and alcoholic liver disease) were more likely to develop severe illness following HEV infection.[35,61,138,139] Therefore, vaccination against hepatitis E to confer protective antibodies is a crucial preventive measure for these susceptible populations.[9]

The recombinant hepatitis E vaccine (*Escherichia coli*) was developed in China and is the sole globally licensed hepatitis E vaccine. It is suitable for susceptible individuals aged ≥16 years and is typically administered in three doses at 0, 1, and 6 months. Phase III clinical trials have demonstrated that the hepatitis E vaccine provided up to 100% protection 1 year after completing the full vaccination course.[140] Subsequent studies have indicated that 4.5 years after vaccination, the protective efficacy against HEV infection remained at 86.8%.[141] Furthermore, the vaccine is safe, with no reports of serious adverse reactions during vaccination, even among individuals aged ≥65 years and hepatitis B carriers.[142,143] Therefore, hepatitis E vaccination of individuals with chronic hepatitis B infection and elderly patients is safe and feasible. At present, hepatitis E vaccination is not recommended for pregnant women because of limited safety data. In a phase III clinical trial for a cervical cancer vaccine, the control group received the hepatitis E vaccine; after a follow-up period of 5.5 years, post-analysis did not reveal any potential hepatitis E vaccine-associated risks to the pregnant woman or the fetus.[144] Furthermore, coadministration of the hepatitis E and hepatitis B vaccines was reported to be safe and effective.[145]

6. Summary and prospects

Although HEV infection typically follows an acute and self-limited course, certain populations may experience more complex outcomes. Notably, elderly individuals, pregnant women, and patients with underlying CLDs are susceptible to LF upon infection. Moreover, organ transplant recipients and immunocompromised individuals are at risk of CHE or cirrhosis. Therefore, in these specific populations, emphasis on HEV screening is crucial for timely diagnosis. For CHE, timely antiviral treatment, in addition to symptomatic support, should be administered to expedite viral clearance and enhance prognosis. Moreover, hepatitis E vaccination of high-risk and vulnerable populations has been proven to be an effective preventive measure. As mentioned above, the existing screening for HEV is inadequate, and the anti-HEV test exhibits low sensitivity. The likely underestimation of the actual incidence and prevalence of HEV infection constitutes a major limitation of this study.

In May 2023, the China Hepatitis E Prevention and Treatment Alliance was established through the collaborative efforts of the Third Affiliated Hospital of Sun Yat-sen University and the Guangdong Provincial Preventive Medicine Association. This alliance, while spearheading efforts in China, also signifies a crucial step towards addressing global concerns regarding hepatitis E. By leveraging the expertise and resources of leading medical institutions and infectious disease experts, including the Third Affiliated Hospital of Sun Yat-sen University, this initiative aims not only to establish a nationwide hepatitis E database and research platform but also to contribute valuable insights and strategies that can be adopted globally. By sharing knowledge, enhancing screening methods, developing effective management strategies, and advocating for HEV vaccination, these efforts will not only aim to control hepatitis E within China but also serve as a model for global hepatitis E prevention and treatment.

Authors' contributions

Qiumin Luo and Jia Chen contributed equally to this work and should be considered co-first authors. Qiumin Luo: Writing - original draft, Writing - review & editing. Jia Chen: Writing - original draft. Yeqiong Zhang: Writing - review & editing. Wenxiong Xu: Supervision, Writing - review & editing. Ying Liu: Conceptualization, Writing - review & editing. Chan Xie: Project administration. Liang Peng: Conceptualization, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by grants from the Natural Science Foundation of China (No.82070611), Natural Science Foundation of Guangdong Province (2020A1515010317), Guangdong Basic and Applied Basic Research Foundation (No. 21202104030000608 and 2021A1515220029), Guangzhou Science and Technology Plan Projects (No. 202102010204 and 2023B03J1287), Guangzhou Science and Technology Program Key Projects (No. 2023B01J1007), Sun Yat-sen University Clinical Research 5010 Program (No. 2020007 and 2018009), Transformation of Scientific and Technological Achievements Project of Sun Yat-sen University (No. 82000-18843236), and the Five-Year Plan of the Third Affiliated Hospital of Sun Yat-sen University (No.K00006 and P02421).

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