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From discovery to treatment: tracing the path of hepatitis E virus

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Abstract

The hepatitis E virus (HEV) is a major cause of acute viral hepatitis worldwide. HEV is classified into eight genotypes, labeled HEV-1 through HEV-8. Genotypes 1 and 2 exclusively infect humans, while genotypes 3, 4, and 7 can infect both humans and animals. In contrast, genotypes 5, 6, and 8 are restricted to infecting animals. While most individuals with a strong immune system experience a self-limiting infection, those who are immunosuppressed may develop chronic hepatitis. Pregnant women are particularly vulnerable to severe illness and mortality due to HEV infection. In addition to liver-related complications, HEV can also cause extrahepatic manifestations, including neurological disorders. The immune response is vital in determining the outcome of HEV infection. Deficiencies in T cells, NK cells, and antibody responses are linked to poor prognosis. Interestingly, HEV itself contains microRNAs that regulate its replication and modify the host's antiviral response. Diagnosis of HEV infection involves the detection of HEV RNA and anti-HEV IgM/IgG antibodies. Supportive care is the mainstay of treatment for acute infection, while chronic HEV infection may be cleared with the use of ribavirin and pegylated interferon. Prevention remains the best approach against HEV, focusing on sanitation infrastructure improvements and vaccination, with one vaccine already licensed in China. This comprehensive review provides insights into the spread, genotypes, prevalence, and clinical effects of HEV. Furthermore, it emphasizes the need for further research and attention to HEV, particularly in cases of acute hepatitis, especially among solid-organ transplant recipients.

Keywords HEV, Prevalence, Transmission, Pathogenesis, Treatment

Introduction

As an enteric RNA virus, HEV can cause both disease outbreaks and sporadic cases. This virus belongs to the *Hepeviridae* family and is characterized as a single-stranded, positive-sense RNA virus. Contamination of the water supply is the main cause of virus outbreaks, although there are evidence suggests that the virus may also spread through person-to-person transmission. After a significant hepatitis outbreak in Kashmir in 1978, it was initially established as a distinct infectious agent. The virus was subsequently found in the fecal specimens of Soviet military recruits posted in Afghanistan in 1981 [1–3]. Human-infecting HEV genotypes can be found in

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the species *Paslahepevirus balayani* and *Rocahepevirus ratti* [4]. HEV consists of two major species: mammalian HEV, which leads to acute hepatitis in humans and is harbored by pigs and possibly other animals, and avian HEV, accountable for a condition known as big liver and spleen disease in chickens [5, 6]. HEV RNA becomes detectable in blood and stool roughly three weeks after infection. Viremia typically persists for three to six weeks, while the virus continues to be shed in stool for about four to six weeks [7]. Typically, the incubation period of HEV infection ranges from 2 to 6 weeks [8]. Increasing age and living in low socioeconomic conditions are contributing risk factors for HEV infection [9].

A comprehensive study estimated the worldwide anti-HEV IgG seroprevalence at 12.47%, the pooled anti-HEV IgM seroprevalence at 1.47%, and the pooled prevalence of HEV RNA-positive in the general population at 0.20% [10]. In the overall population, the mortality rate varies from 0.5 to 4%. However, for pregnant women infected with HEV, the mortality rate escalates to as high as 30% [11]. In immunocompromised individuals, this infection can potentially become a chronic and significant medical issue, particularly for those who have undergone solid organ transplants as well as for patients with HIV, leukemia, and lymphoma [12]. According to a systematic review and meta-analysis, the prevalence of HEV infection among organ transplant recipients ranges from 6 to 29.6%, while among HIV-positive patients, it ranges from 3.5 to 19.4% [13]. The occurrence of HEV infection differs across various global regions, primarily due to distinct genotypes [14]. HEV has eight different genotypes, but only five of them are linked to human diseases and are designated as HEV-1 through HEV-4 and HEV-7 [15]. HEV-1 and HEV-2 are prevalent in developing nations like those in Africa, Asia, and Mexico, while HEV-3 and HEV-4 are more prevalent in developed countries. Genotypes 1 and 2 are typically linked to human infection, often resulting in outbreaks in regions with inadequate sanitation. Genotypes 3 and 4 are typically transmitted through consuming undercooked meat or potentially via contact with infected animals. HEV strains originating from animals such as rabbits, pigs, camels, and rats possess zoonotic potential [16, 17]. In endemic region, HEV primarily transferred via the fecal-oral route, often via the pollution of drinking water [5]. Other modes of transmission, such as contaminated food, maternal-fetal (vertical transmission), and modes involving injection, are less frequent [18]. Remarkably, the age-specific seroprevalence patterns of HEV differ significantly from those of HAV, despite both viruses sharing similar transmission routes in regions where these diseases are prevalent [19].

This comprehensive review explores the complexities of mammalian HEV, highlighting its transmission routes, various genotypes, global prevalence patterns, and the range of clinical manifestations it can cause. Emphasizing the critical need for expanded research efforts, particularly in the domain of acute hepatitis, the text underscores the importance of heightened scrutiny, especially within vulnerable populations such as recipients of solid-organ transplants. By deepening our understanding of these aspects, we aim to pave the way for more effective strategies for the management and prevention of this infectious pathogen.

Evolutionary history

In 2000, phylogenetic studies on four different HEV strains and a re-evaluation of conserved regions in the capsid, helicase, and polymerase showed that HEV should not be classified in the *Caliciviridae* family. Instead, it was repositioned into an unassigned clade with an uncertain taxonomic status, although it exhibited a closer relationship to the *Togaviridae* family [20]. Within the "alpha-like" major groupings, this ultimately clarified the virus's classification, resolving its placement within both the "Picorna-like" upper-level groupings and the "alpha-like" supergroup. With the increasing availability of sequences, it became increasingly evident that HEV was significantly differentiated from various viral genera and lineages. Consequently, it was designated as its genus (*Hepevirus*) by 2004 and later as its distinct family (*Hepeviridae*) in 2009 [21, 22]. In 2014, the classification of *Hepeviridae* underwent a reassessment, resulting in the creation of two new genera: *Orthohepevirus* and *Piscihepevirus* [23] (Fig. 1).

Capsid proteins of the hepatitis virus are crucial for its classification, serving as key distinguishing features [24]. Despite an in-depth examination of the non-structural protein-encoding region, the source of the HEV capsid remained inconclusive, as the *Benyviridae* family comprises non-enveloped rod-shaped plant viruses, while HEV capsids exhibit a T=3 icosahedral structure, comprise approximately 180 copies of the capsid protein [25, 26]. Icosahedral capsids are characterized by a triangulation number such as T1, T3, T4, etc., indicating identical equilateral triangles constructed by subunits [27]. Surprisingly, it wasn't until 2011 that it was discovered that the HEV capsid protein had its closest structural resemblance to capsids found in members of the Astroviridae family, which infect vertebrates [28]. *Astroviruses*, akin to HEV, possess a T=3 icosahedral capsid structure. However, they are affiliated with the "Picorna-like" supergroup of viruses. Presently, the enigma of HEV's origin persists, as the non-structural protein-encoding region is categorized within the "alpha-like" supergroup, as opposed to the structural region [25].

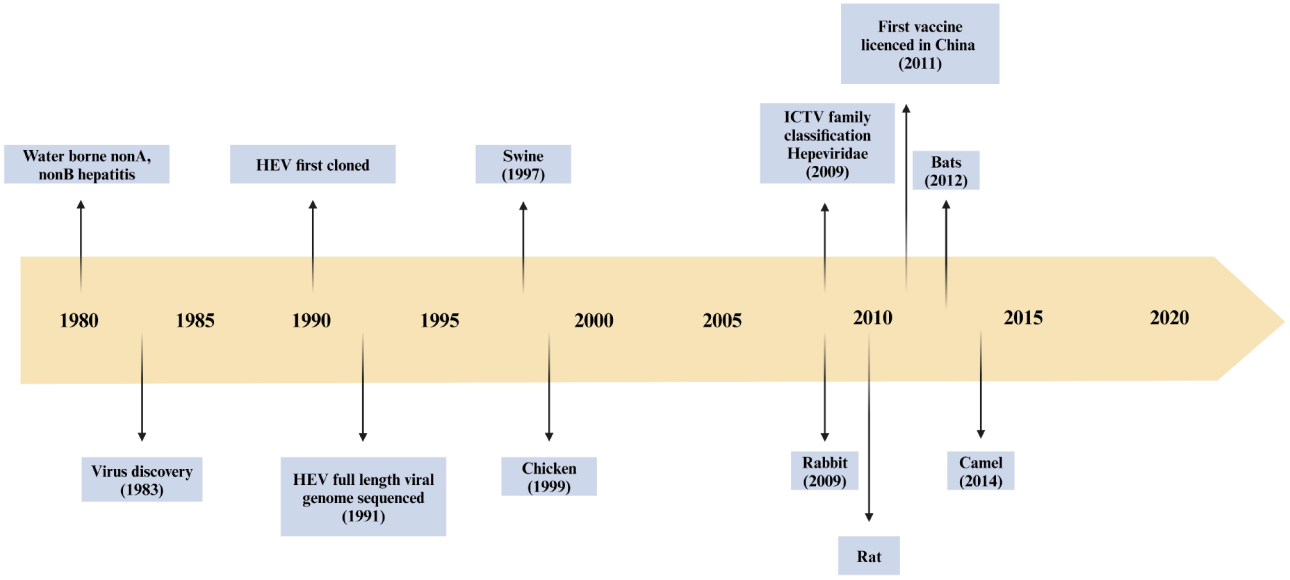

Fig. 1 A timeline chronology of key advancements in the field of hepatitis E virus [6, 177–184]

HEV's taxonomy

HEV belongs to the family *Hepeviridae*, which is categorized into two main subfamilies: *Orthohepevirinae* (encompassing four genera) and *Parahepevirinae* (only one genus: *Piscihepevirus*) based on international committee on taxonomy of viruses (ICTV) report in 2022 [29, 30]. Whitin the *Orthohepevirinae* subfamily, genera *Paslahepevirus* and *Rocahepevirus* can infect humans, wild and domestic mammals, while *Chirohepevirus* affects bats and *Avihepevirus* infects birds [30]. *Paslahepevirus* includes two species: *P. balayani* and *P. alci* (specific to moose). *P. balayani*, formerly known as *Orthohepevirus A*, infects humans and various mammals. It has 8 distinct genotypes, with genotypes 1–4 causing significant human disease. Genotypes 1 and 2 lead to large epidemics in developing countries, while zoonotic infections with genotypes 3 and 4 cause sporadic and clustered cases of HEV [31, 32].

Virion structure and genome organization

HEV has a genome consisting of positive-sense, single-stranded RNA, approximately 7.2 kb in size. This RNA genome features a 7-methylguanosine RNA cap at the 5′ terminus and a polyadenylated tail at the 3′ end [33]. The viral genetic material usually contains three open reading frames (ORFs), specifically known as ORF1, ORF2, and ORF3. However, a fourth ORF (ORF4), which can be found in ORF1, is exclusive to genotype 1 (G-1 HEV) strains and ORF4-specific antibodies are present in G-1 HEV case serum [34]. ORF1 extends about 5 kb in length and is located at the 5′ end of the genome, while ORF2 is around 2 kb and is positioned at the 3′ end. Notably ORF3 consists of 372 bases, with its 5′ end sharing an overlap of merely 4 nucleotides with ORF1 and its 3′ end overlapping with ORF2 by 331 nucleotides [35, 36]. As well, ORF1 represents a substantial polyprotein harboring numerous functional domains crucial for virus replication. On the contrary, ORF2 and ORF3 originate from a 2.2 sub-genomic RNA generated during virus replication, fulfilling functions in virus assembly and egress, respectively [37]. In HEV-infected cells, the quantity of sub-genomic RNA copies is notably greater than that of their genomic RNA equivalents [37] (Fig. 2). ORF2 is crucial for HEV assembly, facilitating the packaging and folding of viral RNA and the formation of viral particles. Strategies include disrupting ORF2's binding to RNA elements at the 5′ end of the genomic RNA and targeting ORF2 oligomerization to form the capsid, both of which could be hopeful approaches for antiviral drug development. Alternatively, ORF3 facilitates viral particle release by connecting assembled particles to the ESCRT (endosomal sorting complexes required for transport) pathway through its attachment to the ESCRT component Tsg101 (tumor susceptibility gene 101) [38]. Furthermore, the ORF4 protein interacts with viral helicase, RNA-dependent RNA polymerase (RdRp), X, eukaryotic elongation factor 1 isoform-1 (eEF1α1), and tubulinβ, forming a protein complex. ORF4 and eEF1α1 together boost viral RdRp activity. In addition, it was reported that a proteasome-resistant ORF4 mutant greatly increased HEV replication [34].

Epidemiology

Five genotypes of HEV have been identified that can cause harm. Among these genotypes, genotype 1 and genotype 2 exclusively affect humans. Genotype 3 and

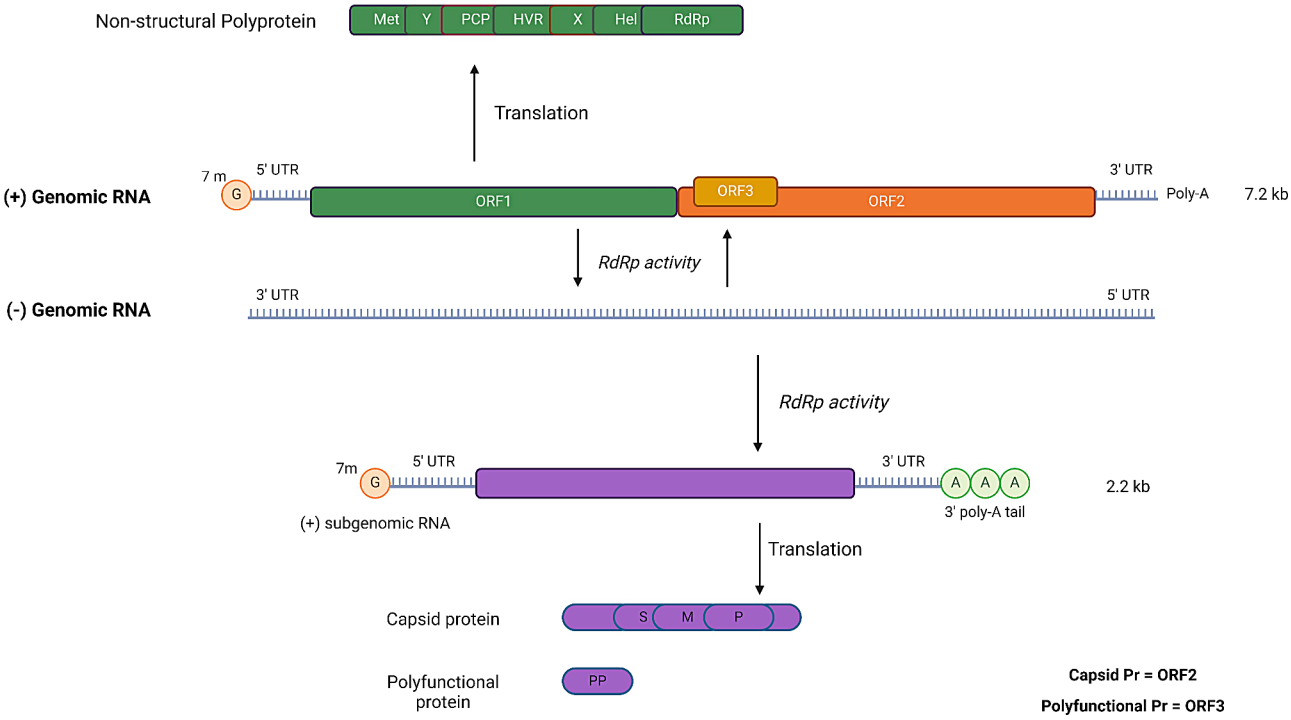

Fig. 2 Hepatitis E virus genome: The genome organization of the Hepatitis E Virus (HEV) involves a single-stranded positive-sense RNA molecule, approximately 7.2 kilobases in length. At its 5′ end, the RNA molecule begins with a 7-methylguanosine RNA cap, while at the 3′ terminus, it is polyadenylated. Notably, the HEV genome consists of three consistently conserved open reading frames (ORFs) present in all identified HEV strains: ORF1, ORF2, and ORF3. ORF1 is responsible for encoding nonstructural polyproteins, which contain various functional domains including methyltransferase (Met), X domain, helicase (Hel), hypervariable region (HVR), RNA-dependent RNA polymerase (RdRp), Y domain, and papain-like cysteine protease (PCP). ORF2 encodes the structural capsid protein, which comprises P, S, and M domains. The capsid protein is essential for viral assembly and its interaction with the immune system of the host. ORF3 contains a highly conserved PxxP motif and encodes a small protein that has been demonstrated in vitro to bind with various proteins involved in cellular signal transduction [185–194]

genotype 4 are associated with animal reservoirs, specifically found in wild boars, deer, swine, and rabbits [39, 40]. Recently, a new genotype, genotype 7, has been discovered, which is primarily found in camels. There has been a documented case of human infection with this genotype, involving an individual who owned camels and had previously undergone a liver transplant in the United Arab Emirates [41]. Genotype 1 strains of HEV have been identified in various regions, including China, Pakistan, Nepal, the Indian subcontinent, Afghanistan, Bangladesh, and several sub-Saharan African countries. In contrast, genotype 2 strains are prevalent in the Central African Republic, Chad, Nigeria, Mexico, and Sudan. Genotype 3 strains have been found in Central and Southern Japan, as well as in the United States, other North American countries, Europe, Australia, and New Zealand. Moreover, genotype 4 is known to exist in northern Japan, China, India, and several European countries, including France and Germany. It is important to note that genotype 7 has only been detected in the United Arab Emirates, and there is limited research available regarding its geographic distribution [42, 43].

HEV genotype 1 strain-induced outbreaks are commonly associated with the transmission of the virus through contaminated water sources. India has experienced recurring outbreaks since the initial outbreak in Delhi in 1955. These outbreaks have affected hundreds or even thousands of individuals, demonstrating a significant impact observed during the period from 1975 to 1994 [42]. This outbreak affected over 200 villages with a total population of 600,000. It resulted in 20,083 cases of jaundice and 600 deaths within a seven-week period. Pregnant women, in all three trimesters, were more frequently infected with HEV compared to men and non-pregnant women aged 15–45 years [18, 44]. Another significant epidemic occurred between 1986 and 1988, leaving a lasting impact on the affected region. During this period, there were approximately 120,000 reported cases of HEV infection. This epidemic claimed the lives of 765 individuals, with 51 of them being pregnant women [42]. The most extensive outbreak of HEV in India occurred from December 1990 to April 1991 in Kanpur. This outbreak had a significant impact, with a staggering 79,000 reported cases of clinical hepatitis [45]. Indeed, HEV outbreaks have been documented in various Asian

countries, including Uzbekistan, Indonesia, Japan, Vietnam, Iraq, Pakistan, Bangladesh, Nepal, Myanmar, China, and Turkmenistan [46].

Moreover, in the United States, individuals of African descent seem to have a reduced occurrence of HEV infection. Data from the national health and nutrition examination survey (NHANES) indicate that the prevalence of anti-HEV IgG was 14.5% among non-Hispanic blacks, 22.1% among non-Hispanic whites, and 20.3% among Mexican-Americans [47]. In non-Hispanic black individuals, research has shown that the presence of specific gene polymorphisms within the apolipoprotein E gene (APOE) is associated with lower anti-HEV IgG seroprevalence. The APOE gene plays a role in regulating lipoprotein metabolism. Among individuals with these gene polymorphisms, specifically the APOE ε4 allele, there was significantly lower seropositivity for HEV compared to those with the APOE ε2 allele [48]. In South Africa, where genotype 1 of the virus has persisted, the occurrence of anti-HEV IgG was discovered to be less common among black blood donors when compared to white or mixed-race donors. This disparity suggests that there may be variations in HEV exposure and immune responses among different racial and ethnic groups in South Africa [49].

Transmission

HEV causes widespread outbreaks of viral hepatitis transmitted through contaminated water and is the leading cause of sporadic cases of acute hepatitis and severe liver failure in these regions [50]. Transmission to humans from various species, including pigs, rabbits, deer, camels, and rats, has been well-documented for HEV strains. This typically occurs by eating raw or undercooked meat from infected animals or through direct contact with infected animals [51].

HEV is predominantly spread by the fecal-oral pathway [50]. Epidemics have a shared point of origin when the epidemic curve is markedly condensed, usually spanning approximately six to eight weeks due to contamination [18]. Studies have demonstrated that localities that consume different water supplies for drinking, particularly safeguarded well water, both before and during epidemics, do not experience the disease [18]. Epidemics can stem from the pollution of river water utilized for drinking, sewage disposal, washing, and bathing. Typically, outbreaks in these environments tend to happen in the winter months when water levels drop, leading to a rise in water contamination due to higher concentrations of contaminants [50]. Groundwater, crops, and waterways can all be subject to contamination. The act of openly in backyards and open fields can act as an extra origin of fecal pollution for groundwater, crops, and water bodies [18, 52].

The transmission route of sporadic diseases triggered by HEV-1 and HEV-2 is also currently being studied [18]. The transmission of sporadic HEV infection within families was a rare incidence. Human infections are typically contracted through three primary pathways: direct contact with infected animals, zoonotic foodborne consumption, and environmental contamination caused by the runoff of animal waste. The spread of HEV-3 and HEV-4 via food-borne zoonotic routes has also been proposed [53]. Wild boars, sika deer, and domestic pigs play a part in the cross-infection of HEV [4]. Consuming partially cooked flesh or liver (considered a culinary delicacy in numerous nations) might be the cause of autochthonous (locally acquired) cases and outbreaks of HEV [54]. A commonly observed method of HEV transmission is the consumption of raw liver from grocery stores or Corsican figatelli sausage in Europe [55]. These livers and sausages frequently contain live HEV. Work-related contact with domestic pig farms, manure, and sewage is a notable risk for HEV infections in multiple regions [56–59]. It was reported that swine veterinarians had a 1.9 times higher likelihood of being seropositive for HEV compared to non-swine veterinarians [60]. Additionally, environmental contamination can result from pig slurry through various routes. Employing pig slurry as fertilizer for pastures can result in the contamination of agricultural produce such as raspberries, strawberries, and various vegetables commonly used in salads [61, 62]. Run-off from outdoor pig farms can contaminate coastal waters [63, 64], affecting marine life, such as fish and shellfish [65].

Tropism

Despite its main focus on the liver, HEV has exhibited the ability to replicate in various tissues, resulting in extrahepatic effects like neurological symptoms, myositis, renal and hematologic complications in HEV-infected individuals [66, 67]. Through experimental infections of animals with HEV, researchers have detected negative-strand viral RNA, a sign of continuous viral reproduction. This replication isn't limited to the liver; it is also present in the pig's intestinal tract, colon, and lymph nodes [68]. Similarly, rabbit models have shown negative-strand RNA intermediates in the liver, kidney, small intestine, spleen, and stomach [69].

As well, patients with HEV, whether in acute or chronic cases have presented neurological manifestations, yet the actual prevalence and the underlying pathogenic mechanisms are not definitively established [8]. Given that HEV is disseminated through the fecal-oral transmission route, it is most probable that the primary site for the virus's initial replication is the gastrointestinal system. From there, the virus can infiltrate the bloodstream and impact other organs [70, 71]. Furthermore, the association between HEV and kidney disorders is indicated by

renal complications [72, 73]. The recent confirmation of this link is based on the discovery of HEV in urine samples from individuals with both acute and chronic virus infections, as well as in monkeys. Furthermore, immunohistochemical evidence has revealed the existence of afflicted cells within the kidneys of these animals [74].

Overall, although HEV is primarily associated with liver infections, its ability to replicate in various tissues highlights its broader impact on human health. Ongoing research into the prevalence and mechanisms of these complications is crucial for developing targeted interventions and improving patient outcomes.

Clinical features

The clinical features of HEV infection resemble those of other hepatitis viruses and include a broad spectrum of symptoms. The prevailing form of illness is acute icteric hepatitis, usually commencing with several days of flu-like symptoms, such as fever, chills, abdominal discomfort, loss of appetite, queasiness, emesis, and diarrhea. Additional symptoms may encompass pale or clay-colored stools, darkened urine, joint pain, asthenia, and a temporary macular skin rash. Subsequently, these initial symptoms are succeeded by the development of jaundice, marked by the darkening of urine and lightening of stool color. Itchiness may also manifest. Fever and other preliminary symptoms typically wane quickly once jaundice sets in [75]. At times, HEV infection can manifest entirely without symptoms and go unnoticed. The precise frequencies of asymptomatic infection and anicteric hepatitis remain unknown but are thought to be more common than icteric disease [75–77]. Laboratory tests reveal elevated levels of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, and alkaline phosphatase [78]. Serum aminotransferase and bilirubin levels typically commence their normalization within 6 weeks [77].

A minority of patients may encounter severe variants of the condition, including fulminant or subacute hepatic failure [77]. Pregnant women, particularly those in the second and third trimesters, are more susceptible to the virus during outbreaks and have a higher risk of complications. Additionally, HEV-infected pregnant women may witness a greater incidence of miscarriages, stillbirths, and deaths among newborns [79–83]. Severe liver damage can result in sub-massive or massive necrosis, causing the collapse of liver tissue [75, 79, 84, 85].

Other complications associated with HEV

Hepatitis E infection has been linked to a diverse range of extra-hepatic manifestations, primarily affecting the neurological, renal, cardiac, and hematological systems [86] (Fig. 3). Neurological manifestations, increasingly recognized as complications of HEV infection, are the most frequent extrahepatic symptoms. Multiple neurological disorders have been reported in Europe (74%) and the Southeast Asia Region (SEAR), particularly in Bangladesh, India, and France (15%). Guillain-Barré syndrome (37%) and Neuralgic amyotrophy (39%) are the most common neurological conditions linked to HEV infection [87]. According to the systematic review by Rawla et al., neuralgic amyotrophy was observed in 102 out of 179 patients (56.98%), while Guillain-Barré syndrome was present in 36 out of 179 patients (20.11%) [88]. One patient was diagnosed with myasthenia gravis, and two others had poly-neuromyopathy. Additionally, six patients experienced mononeuritis multiplex, while five suffered from meningo-radiculitis and cerebral ischemia. Transverse myelitis was found in one patient, peripheral neuropathy in three patients, and vestibular neuritis in one patient. Lastly, one patient was affected by myositis [88]. According to the results of case report experiment, a renal transplant recipient experienced encephalopathy, unsteady walking, Lhermitte's sign, difficulty emptying the bladder, and peripheral sensory nerve damage as a result of long-term HEV infection [89]. These findings highlight the potential involvement of the nervous and musculoskeletal systems in HEV infections, emphasizing the need for healthcare professionals to be vigilant in recognizing and monitoring these disorders in infected patients for appropriate management and treatment.

A study was conducted to report the extra-hepatic manifestations of hepatitis E virus through a retrospective review of data from 106 cases of autochthonous hepatitis E (105 acute and 1 chronic) [90]. Eight cases (7.5%) presented with neurological syndromes, including brachial neuritis, Guillain-Barré syndrome, peripheral neuropathy, neuromyopathy, and vestibular neuritis. One patient had a cardiac arrhythmia, twelve patients (11.3%) had thrombocytopenia, fourteen (13.2%) had lymphocytosis, and eight (7.5%) had lymphopenia, none of which had any clinical consequences. Moreover, monoclonal gammopathy was documented in seventeen cases (26%) [90].

Additionally, in other studies, a 32-year-old male with acute HEV infection was reported to have leukocytosis [91]. Another case involved a 48-year-old male who experienced massive hemolysis, leading to renal failure, also associated with acute HEV infection [92]. Long QT syndrome (LQTS) and Torsades de Pointe (TdPe) (a specific type of ventricular tachycardia(were observed in one case involving a 62-year-old woman with acute HEV infection [93]. The observation of this unusual case highlights the importance of our awareness and understanding of the mechanisms behind LQTS, which will aid in identifying at-risk patients and minimizing their exposure to risk factors.

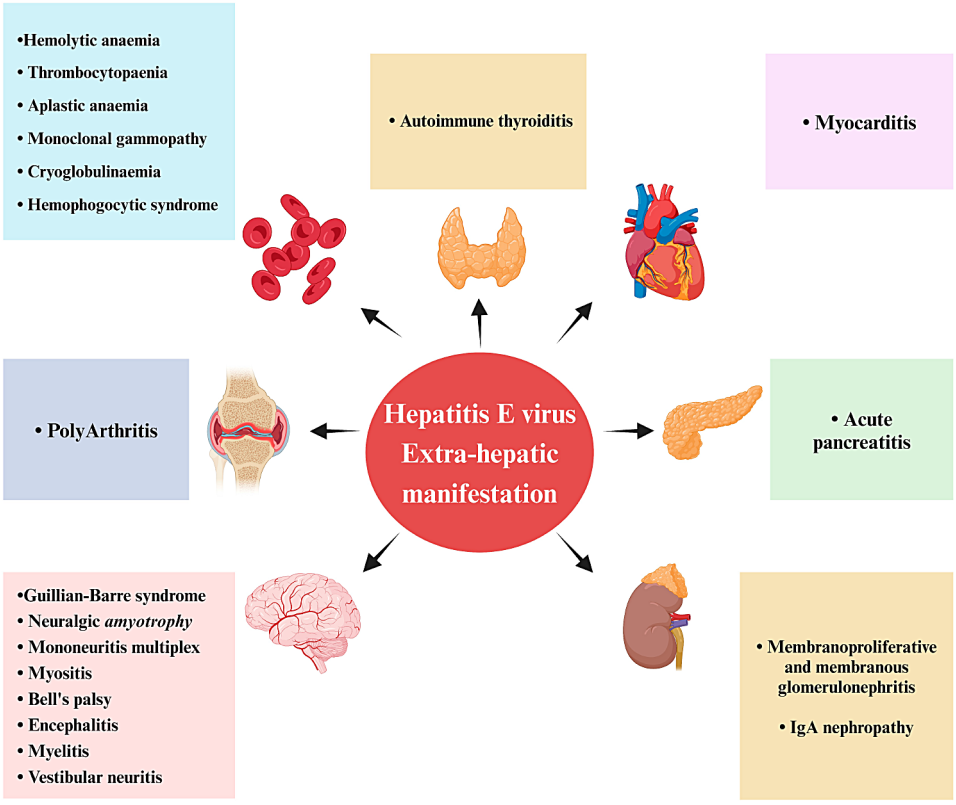

Fig. 3 The extra-hepatic manifestations of HEV infection can be depicted as follows: HEV is associated with myocarditis and acute pancreatitis, affecting the heart and pancreas respectively. Neurological and hematological symptoms include Guillain-Barré syndrome, Bell's palsy, neuralgic amyotrophy, thrombocytopenia, hemolytic anemia, and aplastic anemia. Additionally, skeletal-related manifestations of HEV infection can result in polyarthritis [73, 79, 86, 90, 93, 195–208]

The occurrence of acute pancreatitis due to HEV infection is uncommon. Somani et al. describe a case where severe acute pancreatitis developed in a 35-year-old man with jaundice lasting one week. His serum tested positive for IgM anti-HEV and negative for hepatitis A, B, and C viruses. Despite undergoing hemodialysis and blood transfusion, the patient experienced refractory hypotension and did not respond to inotropic medications. His condition rapidly deteriorated, leading to a fatal outcome. This case illustrates that hepatitis E virus infection can lead to severe acute pancreatitis accompanied by multiorgan failure [94].

These results indicate that a range of extra-hepatic manifestations can occur with hepatitis E. However, it's important to mention that most of these disorders were observed in isolated cases or limited numbers of patients. Further investigations are needed to enhance our knowledge of the pathogenesis, clinical characteristics, and optimal management strategies for HEV-related digestive system disorders.

Vulnerability to HEV infection

Susceptibility to HEV infection is influenced by various factors. In nations where the disease is widespread and where transmission primarily occurs through the fecal/oral route, the availability of safe public water supplies and effective waste management systems is essential [95]. While race does not appear to influence HEV infection, there is a notable geographical bias [96]. Tropical and subtropical countries with poor socioeconomic and hygienic conditions are more prone to HEV outbreaks. Asia, Africa, and Mexico have experienced epidemics, while Latin America, industrialized areas, and certain European countries have not reported outbreaks except for Mexico [97–101]. Bolivia, Chile, Cuba, and Mexico have endemic HEV [96]. Second, a sex-related bias is observed in HEV infection, with males being at higher risk of developing clinical hepatitis in contrast to females [96]. The gender distribution among adults varies from an equal 1:1 ratio to a 3:1 ratio, favoring males [96]. The causes for this bias are not well understood, but they may be linked to occupational and social roles. However, children with clinical HEV do not show a sex bias [96, 99].

Third, age is a factor in HEV infection rates and clinical disease. During HEV epidemics, individuals aged

15 to 40 have the highest infection and clinical disease rates. Children generally have lower infection rates and are less likely to be affected by clinical HEV compared to adults [102, 103]. Studies in India and Vietnam indicate that children under 10 have a lower prevalence of HEV, although acute HEV can still occur in children, albeit rarely [96].

Fourth, pregnant women are especially at risk of developing severe illness if they contract HEV. Pregnant women affected by HEV displayed pooled Case Fatality Rates (CFRs) of 20.8% [104]. Pregnant women infected with the virus are at a higher risk of developing fulminant hepatic failure (FHF) and experiencing adverse outcomes such as abortion, premature delivery, or neonatal death. Several factors contribute to the heightened susceptibility and seriousness of HEV infection among pregnant women [80].

Hormonal and immunological changes throughout pregnancy could influence the seriousness of HEV infection, even though there is a lack of supporting data. Limited access to adequate medical care and nutrition in developing countries further contributes to higher maternal morbidity and mortality associated with HEV [105]. The compromised immune system of pregnant women, combined with factors like malaria, parasitic infections, and other viral and bacterial infections that are widespread in developing countries, weaken their immune response, making them more susceptible to HEV infection [105, 106]. Therefore, those who live in tropical and subtropical areas with poor socioeconomic and hygienic circumstances, as well as men, people in their 15–40 s, and pregnant women are susceptible to HEV infection [96].

Immune responses

HEV infection can become chronic in immunocompromised cases (e.g. HIV cases, recipients of organ transplants, hematologic malignant conditions) [107–109]. Studies show reduced CD2, CD3, and CD4 lymphocytes in transplant recipients who develop chronic HEV compared to those who resolve the infection [107]. This suggests that compromised T-cell responses in immunocompromised individuals can hinder the elimination of the virus, leading to a persistent HEV infection [110]. Research have shown that it is the immune response, as opposed to direct harm to hepatocytes by the virus, that likely underlies the expression of HEV symptoms, such as self-limiting acute viral hepatitis (AVH) and acute liver failure (ALF) [111]. The concurrent appearance of icteric symptoms, an increase in antibodies, and a reduction in viral load support this idea [112]. In a study on HEV-induced acute hepatitis, elevated levels of anti-HEV IgM and IgG antibodies discovered. Individuals experiencing liver failure showed increased levels of gamma interferon (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin-2 (IL-2), and IL-10 compared to those with self-limiting acute hepatitis. Remarkably, HEV RNA was present in cases of AVH but not in individuals with liver failure. Given that most ALF patients developed encephalopathy and underwent testing within a fortnight of symptom onset, and patients with AVH were sampled about 14 days after symptom onset, the absence of HEV RNA in liver failure cases is unlikely to be solely attributed to the time between disease onset and sampling. These findings suggest that both Th1- and Th2-type immune responses may contribute in the development of liver failure in symptomatic HEV patients [113].

NK and T-cells are crucial in the immune response to HEV infection. A study on acute HEV infection compared to healthy individuals, observed that HEV patients exhibited reduced percentages of CD3+/CD69+/IFN-γ and CD3+/CD69+/TNF-α, along with elevated proportions of $CD4^+$ cells. Interestingly, the quantities of CD69+/IL-4 cells and CD8+cells showed no significant difference between HEV patients and healthy individuals. It is suggested that the increase in CD4+cells in patients may signal an augmentation in the population of NK cells [114]. A study on acute HEV patients revealed reduced proportions of NK and NKT cells among MCs in HEV patients compared to controls. However, there was a significantly higher proportion of activated NK cells in patients. The decrease in the total count of NK and NKT cells in PBMCs (peripheral blood mononuclear cells) could result from the specific accumulation or apoptosis of these cells in the livers of infected individuals. It is suggested that the decreased presence of NK cells in pregnant women may contribute to their increased vulnerability to severe HEV, as it diminishes their capacity to eliminate the virus from the liver [115].

The proliferation of CD4+T cells producing IFN- γ and TNF-α in HEV patients also contributes to restricting HEV replication and assisting in the resolution of the infection. The increase in disease severity has an inverse correlation with the expansion of T cells producing cytokines specific to the antigen. Individuals experiencing disease exhibited diminished proliferation of CD4+T cells when stimulated by pORF3, leading to decreased levels of IFN-γ and TNF-α production in contrast to those with mild disease. As these cytokines are recognized for their role in regulating viral replication, the absence of an increase in HEV-specific T cells producing cytokines in patients with fulminant HEV might lead to immune system failure in controlling HEV replication, resulting in more extensive liver injury. Recent research has supported this idea, as it reveals higher levels of HEV-RNA in the bloodstream of patients with fulminant HEV, in contrast to individuals with uncomplicated disease [116]. TNF-α not only contributes to hepatocyte death but

also plays a role in liver tissue regeneration. Studies have shown that the TNF-α-mediated nuclear factor (NF)-kB pathway plays a role in the process of liver regeneration, a vital process for recovering liver function post-injury. As a result, a less robust TNF-α reaction in fulminant HEV might obstruct the recovery procedure [117–119].

Most patients become anti-HEV IgG positive over time, but the duration of IgG persistence remains unknown due to variations in sensitivity among different enzyme-linked immunosorbent assay (ELISA) assays. Nevertheless, in India, anti-HEV IgG can be identified for a minimum of 14 years after the outbreak [120]. Patients with uncomplicated HEV had a higher anti-HEV IgG-secreting cells compared to healthy controls [119]. The count of these cells was notably greater in individuals with fulminant HEV when compared to those with uncomplicated disease. B cells producing antigen-specific IgG were assessed by stimulating PBMCs with polyclonal agents. These findings represent the complete population of HEV-specific memory B cells, offering an indirect indication of antigen-specific IgG levels after HEV exposure. The link between memory B-cells and illness severity suggests these cells and anti-HEV antibodies may cause liver damage in HEV cases [119].

MicroRNA (miRNAs)

With a high degree of conservation, microRNAs (miRNAs) are classified as small non-coding RNAs and make up approximately 1% of the human genome. They possess the capacity to interact with approximately 60% of messenger RNAs (mRNAs) [121]. Besides viral transcripts, HEV is also capable of producing diverse miRNAs. The investigation of these miRNAs has predominantly hinged on predictive models, which are then confirmed through experimental validation using either in vivo or in vitro infection models. The lack of a suitable infectious model for HEV, characterized by slow replication in cell-cultured systems, has been a significant challenge in this research [122]. Nine potential HEV-miRNAs for HEV-1 have been revealed through predictive computational modeling, known as HEV-MD1, -MD2, -MD3, -MD31, -MD35, -MD39, -MR9, -MR10 and, -MR25 [123]. It has been proposed that the potential target sites for these HEV-miRNAs can be found at both the 3'-end and 5'-end of human mRNA. It is predicted that these HEV-miRNAs will specifically interact with genes involved in lipid and nitrogen metabolism, transmembrane transport, cellular differentiation, membrane organization, chromosome organization, and cell-cell signaling [123]. HEV is present in a state where it is enveloped within the liquid above cell cultures that are infected, as well as in the blood of individuals who have acute HEV infection. This finding implies that the virus might utilize these miRNAs to facilitate the process of envelopment and dissemination of its offspring within the host [26]. For instance, there have been forecasts suggesting that HEV-MD2 plays a role in controlling the synthesis of cyclin G-associated kinase (GAK), a pivotal element in clathrin trafficking and receptor signaling [123, 124].

Until now, the primary miRNAs that have been thoroughly studied for their impact on HEV replication are miR-122 and miR-214 [125, 126]. The gene encoding miR-122 is located on chromosome 18 within the human genome [127]. The miRNA identified as the most abundant in the human liver has been extensively studied for its involvement in cholesterol metabolism, liver cell differentiation, and the development of liver diseases such as hepatocellular carcinoma triggered by HCV and HBV [128, 129]. The interaction between miRNA-122 and the virus has a significant impact on viral replication. Specifically, the direct complementarity between miRNA-122 and a specific binding site on the viral genome, usually found in the RdRp region of the ORF1 gene, enhances viral replication [126]. Research has highlighted differences in the expression levels of certain miRNAs in HEV RNA-positive individuals when compared to negative blood donors. Specifically, these miRNAs include miR-1285, 151-3p, 302b, 526b, 520b, 627-5p, 628-3p, and 365 [130]. Furthermore, pregnant women with acute self-limiting HEV-1 infection exhibited a distinct expression pattern when compared to non-pregnant women. The presence of miR-188, 365a, 190b, 365b, 374c, 450a-1, 450b, 4482, 450a-2, 616, 2115, 580, 504, 3117, 4772, and 5690 was identified, enabling differentiation between acute infection, self-limiting acute infection, and acute liver failure [131](Table 1).

Diagnosis

HEV diagnosis is achievable using direct or indirect testing techniques. Direct diagnosis involves the measurement of HEV RNA in blood or stool samples, while indirect diagnosis is based on identifying the host's immune response to HEV infection [73]. The diagnosis often involves employing nucleic acid amplification techniques (NATs) to analyze HEV RNA in biological specimens like stools, serum, and liver biopsy [133]. Direct methods identify viral particles, proteins, or nucleic acids in the samples by RT-PCR and immune-electron microscopy. Moreover, indirect tests have elevated sensitivity than anti-HEV IgM and IgG [134].

Optimal diagnosis of acute HEV infection is achieved by combining serological testing and NAT assays [135]. Indirect diagnosis involves the display of IgM and IgG anti-HEV antibodies in the serum using ELISA. The presence of IgM antibodies indicates acute infection and becoming detectable four days after jaundice begins [133]. Enzyme immunoassays rely on detection of anti-HEV antibodies or HEV capsid antigen. However, HEV

Table 1 MicroRNAs encoded by Hepatitis E Virus (HEV)

Name	Coding region	Binding site	Effects on host physiology	Identification method	Length (nt)	Reference
HEV-MD1	ORF1 (MeT domain)	INCA1	Affects Cell Proliferation, Membrane Organization, and Transmembrane Transport	In silico (Computational Modeling)	22	[123, 132]
HEV-MD2	ORF1 (MeT domain)	GAK	Cellular component assembly, Vesicle-Mediated Transport, Alters Membrane Organization, Inhibits Production of Cyclin G-Associated Kinase	In silico (Computational Modeling)	22	[123, 132]
HEV-MD3	ORF1 (Y domain)	KDM4B	Affects Nitrogen Compound Metabolism, Alters Chromosome Organization	In silico (Computational Modeling)	22	[123, 132]
HEV-MD31	ORF1 (RdRp domain)	ADAMTS16	Cytoskeleton-dependent intracellular transport, Impairs Vesicle-Mediated Transport, Silences ADAMTS16 Gene Expression (can lead to fetal loss and pre-term labor)	In silico (Computational Modeling)	21	[123, 132]
HEV-MD35	ORF1 (RdRp domain)	CCDC34	Signal transduction	In silico (Computational Modeling)	22	[123, 132]
HEV-MD39	ORF2	LRRC8A	Sulfur compound metabolism, Cell proliferation, Catabolism	In silico (Computational Modeling)	22	[123, 132]
HEV-MR9	ORF1 (PCP domain)	FKRP	Affects Cell Differentiation, Impairs Protein Maturation	In silico (Computational Modeling)	22	[123, 132]
HEV-MR10	ORF1 (PCP domain)	MMAB	Suppresses MMAB gene, Nitrogen compound metabolism, and Transmembrane Transport	In silico (Computational Modeling)	22	[123, 132]
HEV-MR25	ORF1 (RdRp domain)	PNPLA6	Affects Lipid Metabolism, Impairs Cell-Cell Signaling, Disrupts Transmembrane Transport	In silico (Computational Modeling)	21	[123, 132]
HEV-miR-A26	ORF1 (MeT domain)	IFN- β	Inhibits IFN-β generation	Animal Infection, Cell Transfection	22	[132]

antigen can remain for months after ribavirin clears HEV RNA, suggesting it doesn't indicate infectious virions, thus its diagnostic role is unclear [3]. Anti-HEV IgM levels reach their peak at clinical presentation and remain relatively high for about 8 weeks, but subsequently decline rapidly. On the other hand, HEV IgG levels increase after the onset of symptoms, peak at approximately 4 weeks, and are retained at a high level for over a year [135].

The "gold standard" for confirming acute HEV infection is by identifying HEV RNA in biological samples like serum and feces [134, 135]. HEV RNA is detectable in fecal samples from the onset of symptoms and for up to six weeks thereafter, as well as in serum for four weeks from the start of the illness. Nevertheless, the accuracy of molecular tests for detecting HEV RNA depends on early patient presentation, timely sample collection, and appropriate transport and processing. Since viral RNA quantities may be minimal, and the timeframe for detecting HEV can be limited, the lack of detectable viral RNA does not necessarily indicate the absence of HEV infection [133, 136]. In most of the commercially accessible tests for detecting HEV RNA, the NAT technique is used. This technique comprises reverse transcriptase-polymerase chain reaction (RT-PCR), real-time PCR, and the loop-mediated isothermal amplification assay [137, 138].

In conclusion, the diagnosis of HEV involves a combination of direct and indirect testing methods. Direct tests detect HEV RNA, while indirect tests measure the immune response through the identification of specific antibodies. Detecting HEV RNA in biological samples is considered the gold standard for confirming acute HEV infection. Nevertheless, it's essential to take into account the limitations and the timing of these diagnostic approaches [133, 135, 139].

Treatment

Since the HEV infection is may self-limiting, most patients do not require specific treatment. Hospitalization in an intensive care unit is imperative for individuals suffering from acute or acute-on-chronic liver failure. Interventions to address cerebral edema must be implemented, and there may be a need for liver transplantation [5]. At present, there are no approved medications for HEV treatment, but patients receive broad-spectrum antiviral drugs, such as PegIFN2alpha and ribavirin [140].

Ribavirin is given orally twice a day, starting with a daily dose of 600 to 1000 mg, which varies based on the patient's hemoglobin level and comorbidities. If the hemoglobin level decreases or patients experience symptoms related to anemia, the dosage is decreased. Typically, the intended treatment duration for chronic HEV is 5 months, based on earlier reports suggesting that a shorter treatment period of 3 months could lead to viral relapse [141]. A 3-month treatment regimen of pegylated interferon therapy (weekly dose of 135 μg) was administered to a kidney transplant patient under hemodialysis with chronic HEV infection and successfully attained sustained viral response [142]. In the case of solid organ transplant (SOT) patients with chronic infection, the

initial approach to treatment involves reducing immunosuppressive therapy, specifically medications that affect T-cell function. If HEV is not successfully cleared, the next step is administering ribavirin as the sole therapy [143].

Pegylated-interferon-α has proven effective in the treatment of certain liver transplant recipients, and a hemodialysis patient managed to achieve HEV clearance after a three-month treatment regimen. Nevertheless, it is generally not recommended to use interferon for individuals who have undergone kidney, pancreas, heart, or lung transplants. This is because interferon can activate the immune system and enhance the risk of acute rejection [144, 145].

Treatment failure

A systematic review and meta-analysis on chronic HEV cases (395 cases) reported a 78% sustained virological response (SVR) with ribavirin administration. Rapid virological response (RVR) was achieved by 25%, while relapse was observed in 18% of cases. Second ribavirin treatment caused a 76% SVR [146]. Although ribavirin is the key treatment for HEV infection, examination of the evolutionary changes within the HEV population inside a host showed that ribavirin efficacy could be compromised and cause treatment failures [147]. HEV genome alterations were observed, particularly during ribavirin monotherapy in infected patients [148]. In a chronically HEV-infected patient who failed ribavirin treatment due to a fully resistant phenotype, the Y1320H, K1383N, and G1634R mutations in the viral RdRp were linked to ribavirin resistance. In vitro investigation showed that the Y1320H and G1634R mutations and the hypervariable region insertion increased viral replication [149]. In line with previous studies, research confirmed that the Y1320H mutation increases viral replication during acute HEV-3ra infection in rabbits [150]. However, study on solid-organ transplant cases with chronic HEV yielded divergent results, asserting that the presence of the 1634R variant at the onset of ribavirin treatment does not confer complete resistance to ribavirin. Among 63 patients, 42 achieved SVR while 21 did not, with the 1634R variant detected in 36.5% (23/63) of cases. The 1634R variant was found in 31% of baseline plasma samples of SVR cases and in 47.6% of non-SVR cases. This mutation did not affect the initial drop in viral RNA, and a second extended ribavirin treatment resulted in SVR in 70% of the non-SVR patients, despite the mutation [151]. In the context of HEV genetic heterogeneity induced by ribavirin, Meister et al. reported that the single-nucleotide variant (SNV) in ORF2 of HEV caused by ribavirin, generates defective HEV particles that act as immune decoys. The SNV of HEV ORF2 resulted in smaller, non-infectious particles, capable of interfering with antibody neutralization. This variant may act as an immune decoy despite its loss of infectiousness [152].

Vaccines

Given HEV's global spread and its potential to cause large outbreaks in low-income countries, there is an urgent need for a widely available HEV vaccine [153]. Initial findings from the inaugural human trial carried out at the Walter Reed Army Institute of Research in the US recommended that the recombinant HEV (rHEV) vaccine was both safe and immunogenic. The vaccine consists of polypeptide from insect cells (Sf9) infected with recombinant baculoviruses encompassing a ORF2 of HEV from a 1987 outbreak in Sargodha, Pakistan [154]. The rHEV vaccine was evaluated in 1,794 healthy adults from Nepal who were vulnerable to HEV infection, in 3 doses (at months 0, 1, and 6). The vaccine had an efficacy rate of 95.5% [155].

Several potential HEV vaccines are presently under development. Nevertheless, Hecolin® is the sole licensed vaccine accessible in China since 2012. It consists of a recombinant truncated ORF2 protein HEV239 (aa368-606) that includes 23 nm VLPs which expressed in *Escherichia coli* [156]. It has undergone multiple clinical trials involving the application of three doses at intervals of 0, 1, and 6 months. In the phase III clinical study that included 48,693 in vaccine group and 48,663 in placebo group ranging from 16 to 65 years of age, it was proven that this vaccine is effective and few and mild side effects related to it were reported [157]. A recent clinical trial showed Hecolin's safety and immunogenicity, with all participants seroconverting after one month and maintaining IgG responses through six months [158].

In addition to Hecolin, several candidate vaccines for HEV are presently in development, and they primarily focus on the ORF2 structural capsid protein, which envelops the viral particles [156]. Multiple expression systems are utilized during the advancement of these vaccines [159, 160]. A limited number of vaccines are currently in development to offer combined protection against two separate pathogens: hepatitis E and A including HE vaccine HEVp179 and inactivated HA vaccine [161]. Nonetheless, only a single vaccine for HEV has obtained licensing for use in China [162]. Further investigation is needed to establish its effectiveness in populations at high risk, particularly pregnant women, utilizing fast-tracked vaccine schedules that are appropriate for circumstances involving an outbreak [163].

Development of new drug

Ribavirin clears the HEV just in 80% of treated patients and, like pegylated interferon-alpha, is unsuitable for use in pregnancy, underscoring the urgent need for alternative therapies [164]. Sofosbuvir is a prodrug that

undergoes triphosphorylation within cells and functions as an analogue of the uridine nucleotide [165]. It is a candidate for HEV treatment that showed inconclusive efficacy [164]. Dao Thi et al. reported that Sofosbuvir could hinder the replication of G3-HEV in subgenomic replicon systems and full-length infectious clones and pairing Sofosbuvir with Ribavirin enhances the antiviral impact [166]. However, a Phase II pilot study on 9 patients indicated that using Sofosbuvir alone doesn't successfully eliminate HEV RNA in patients suffering from chronic HEV and exhibited just a modest anti-HEV efficacy [167]. Moreover, André et al. found that a single amino acid change (A1343V) in the ORF1 region of HEV may reduce the effectiveness of sofosbuvir treatment in 8 out of 9 patients [168]. In the context of screening leading drug repurposing, Guo et al. identified vidofludimus calcium and pyrazofurin as new HEV treatments. Both drugs effectively suppress HEV replication in human primary liver organoids, reducing the pyrimidine nucleotide pool, enhancing the antiviral effects of IFN-α against HEV, and successfully inhibiting HEV mutants (Y1320H, G1634R) associated with ribavirin treatment failure [169]. The nucleoside analogue 2'-C-methylcytidine effectively blocked HEV replication and maintained its potency over long-term use. Nevertheless, combining it with Ribavirin has counterproductive effects [170]. NITD008 is an adenosine nucleoside analogue that acts as an RdRp inhibitor and could be HEV treatment. It showed less effectiveness in cells derived from neurons compared to those from hepatoma [171]. In another study, favipiravir (polymerase inhibitor), when used together with sofosbuvir, had an additive impact against HEV and inhibited HEV RNA copies by nearly 90% [172]. Efforts to discover alternative treatments for cases where ribavirin is ineffective will persist.

Control measures

The prevention of HEV infections can be accomplished through primary approaches such as access to clean drinking water, managing human waste properly, promoting good personal hygiene practices and generating immunity via vaccination [5]. In developed nations, prevention is a more intricate process due to multiple routes of infection that are not fully understood. However, there are several recommended approaches It is recommended to cook meat products thoroughly, follow proper handling procedures for raw meat. As well, vaccination against HEV has become a realistic possibility [173].

To avoid HEV infection, safeguarding water supplies, and appropriate removal of human feces is of utmost importance. In outbreak settings, it's essential to adhere to strict sanitation protocols, boiling and chlorination of water. Enhancements in the storage, treatment, and distribution of drinking water, along with improved community sanitation and sewage control, can contribute to a reduction in HEV transmission. In high-risk communities, promoting knowledge about personal and environmental hygiene for better health is equally significant. Surveillance for HEV can aid in early outbreak identification and recommendation of prophylactic measures. Chlorination water supplies and boiling importing drinking water during suspected HEV epidemics are additional preventive measures [5, 174]. However, it is important to note that there have been instances where the introduction of chlorine into the water distribution system during an HEV epidemic, such as the one in Darfur, Sudan in 2004, was found to be insufficient to preventing new infections [175]. Travelers to endemic regions should implement habits like staying away from untreated drinking water, avoiding iced beverages of unknown quality, and refraining from consuming raw shellfish, fruits, or vegetables. Vaccines for HEV are obtainable in China, but they lack FDA endorsement and research on immunoglobulin prophylaxis for HEV prevention is controversial [83, 176].

Future perspectives

Hepatitis E is a public health concern, especially in developing countries with poor sanitation. In the context of HEV diagnosis, HEV RNA is present in the blood and stool for a relatively short period, making timely PCR testing crucial for accurate detection. Additionally, diagnosing HEV in transplant patients using serological methods can be challenging due to the effects of immunosuppressive drugs. Improved diagnostic capabilities and increased awareness about this infection will likely lead to better detection and reporting of HEV cases. The HEV vaccine (Hecolin) is currently available, and ongoing research aims to expand vaccination availability globally. Hecolin is administered in a three-dose schedule, providing longer duration of immunity and higher efficacy. However, in developing countries with poor sanitation where HEV is endemic, adhering to a multi-dose schedule can be challenging. These regions often face limited access to healthcare facilities, logistical difficulties, and increased costs related to vaccine storage, transportation, and administration. Developing a single-dose vaccine with long-term immunity and high efficacy could overcome these obstacles and significantly aid in eradicating the virus in the future. Research into antiviral treatments specifically targeting HEV is ongoing. Future breakthroughs could offer effective treatment options for those infected, particularly immunocompromised individuals or patients who have not responded to ribavirin treatment. Enhanced management protocols for HEV, especially during pregnancy and for patients with chronic infections, could improve outcomes. Improved sanitation and access to clean water in developing countries will

be crucial in reducing HEV transmission. Understanding the genotypic variability and pathogenesis of HEV will aid in developing targeted interventions and treatments. Research on zoonotic transmission of HEV from animals to humans can lead to better control measures in both agricultural and food industries. However, despite advancements, complete eradication of HEV faces challenges due to its zoonotic nature and the need for widespread vaccine coverage and improved global sanitation.

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