

## Hepatitis E virus infection: Epidemiology and treatment implications

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### Abstract

Hepatitis E virus (HEV) infection is now established as an emerging enteric viral hepatitis. Standard treatments in acute and chronic hepatitis E remain to be established. This study undertakes a review of the epidemiology, treatment implication and vaccine prevention from published literature. HEV infection is a worldwide public health problem and can cause acute and chronic hepatitis E. HEV genotypes 1 and 2 are primarily found in developing countries due to waterborne transmission, while the zoonotic potential of genotypes 3 and 4 affects mostly industrialized countries. An awareness of HEV transmission through blood donation, especially in the immunocompromised and solid organ transplant patients, merits an effective anti-viral therapy. There are currently no clear indications for the treatment of acute hepatitis E. Despite concerns for side effects, ribavirin monotherapy or in combination with pegylated

interferon alpha for at least 3 mo appeared to show significant efficacy in the treatment of chronic hepatitis E. However, there are no available treatment options for specific patient population groups, such as women who are pregnant. Vaccination and screening of HEV in blood donors are currently a global priority in managing infection. New strategies for the treatment and control of hepatitis E are required for both acute and chronic infections, such as prophylactic use of medications, controlling large outbreaks, and finding acceptable antiviral therapy for pregnant women and other patient groups for whom the current options of treatment are not viable.

**Key words:** Treatments; Blood donors; Adverse effects; Vaccination; Pegylated-interferon; Ribavirin; Hepatitis E

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**Core tip:** Hepatitis E virus (HEV) infection affects individuals in both industrialized and developing countries and can cause acute and chronic hepatitis E. HEV genotypes 1 and 2 are primarily found in developing countries due to waterborne transmission, while the zoonotic potential of genotypes 3 and 4 affects mostly industrialized countries. An awareness of HEV transmission through blood donation, especially in the immunocompromised and solid organ transplant patients, merits an effective anti-viral therapy. The current treatment for HEV infection involving ribavirin and pegylated interferon- $\alpha$  therapy has shown limited efficacy. Although not widely used, an HEV vaccine is available for immunization in China.

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## INTRODUCTION

Hepatitis E infection is now regarded as a major cause of fecal-orally transmitted non-A, non-B hepatitis. Hepatitis E virus (HEV) is a non-enveloped, single-stranded RNA virus that contains three open reading frames (ORFs) that encode structural and non-structural proteins<sup>[1]</sup>. There are 4 major HEV genotypes (1, 2, 3 and 4). Symptomatic HEV infections produce varying clinical presentations depending on the HEV genotypes. Fulminant hepatic failures are caused mainly by genotype 1, while chronic infections have been observed only with genotype 3 thus far<sup>[2]</sup>. Recent reports of sporadic cases from developed countries in Europe and in the United States resulted from HEV genotype 3, which is zoonotic<sup>[3]</sup>. In a 2015 survey on the seroprevalence and

risk factors for HEV infection among slaughterhouse workers in South Korea, the seropositive rate for HEV IgG was 33.5%<sup>[4]</sup>. Another report from Thailand in 2014 found that HEV strains identified from acute symptomatic hepatitis E infections were all genotype 3f, which was genetically closely related to a strain isolated in swine<sup>[5]</sup>.

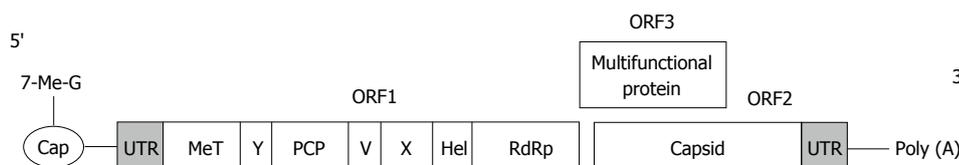
The clinical course of HEV infection among pregnant women is known to be more severe and often led to fulminant hepatic failure and death in up to 20%-25%, specifically in those living in developing countries<sup>[6]</sup>. The mortality rate has been found to be higher during the 2<sup>nd</sup> and the 3<sup>rd</sup> trimester<sup>[7]</sup>. However, underlying factors influencing high mortality during pregnancy are poorly understood.

Studies in chimpanzees to examine HEV and hepatitis C virus (HCV) infection revealed that HEV showed a lower frequency and a shorter duration of differentially expressed genes compared to HCV in intrahepatic transcriptome analysis. This suggests that HEV may be more susceptible to the innate immunity induced by interferon alpha<sup>[8]</sup>. However, HEV showed suppression of interferon alpha signaling *in vitro*<sup>[9]</sup>.

## MOLECULAR VIROLOGY OF HEV

HEV belongs to the family *Hepeviridae*<sup>[10]</sup>. It is a small non-enveloped virus 27-34 nm in diameter. The single-stranded positive-sense RNA genome of HEV is approximately 7.2 kb, 7-methylguanine capped at the 5' terminus, and polyadenylated at the 3' terminus<sup>[11]</sup>. Both ends of the genome consist of short 5' and 3' untranslated regions, which fold into stem-loop structures and are approximately 58 and 68 nucleotides, respectively<sup>[12]</sup>. The viral genome contains 3 open reading frames (ORF)<sup>[10,13]</sup>. ORF1 encodes a 1693 amino acid non-structural polyprotein including: Methyltransferase (MeT), which catalyses the capping of viral RNA; a papain like cysteine protease (PCP) with presumed post-translational protein processing; a helicase (Hel), which supports MeT by catalyzing the first step of RNA capping; an RNA-dependent RNA polymerase (RdRp) required for the synthesis of the genomic RNA; and several uncharacterized domains such as X or Macro, Y and V domain<sup>[1,12]</sup>. ORF2 located near the 3' end encodes 599 to 660 amino acids capsid protein<sup>[1,10]</sup>. It is involved in virion assembly, cell attachment, and immunogenicity. ORF3, which overlaps ORF2, encodes a protein of 114 amino acids shown to be associated with subcellular localization and virion morphogenesis<sup>[11,14]</sup> (Figure 1).

Replication steps in the HEV life cycle are not easily elucidated due to lack of a suitable cell culture system. However, proposed replication cycle commences with the viral attachment to the surface of target cells (hepatocyte) and binding to the unknown receptor(s). Next, the virus penetrates, uncoats, and releases the genomic RNA. Translation of the nonstructural proteins occurs in the cytoplasm. RdRp synthesizes the negative-sense intermediate RNA from the positive-sense genome, which subsequently acts as a template for



**Figure 1** Schematic representation of hepatitis E virus genome<sup>[1,12,14]</sup>. ORF: Open reading frame; UTR: Untranslated region; MeT: Methyltransferase; PCP: A papain like cysteine protease; Hel: Helicase.

the synthesis of subgenomic RNA and the full-length positive-sense transcripts. The subgenomic RNA is then translated into ORF2 and ORF3 proteins, which facilitates viral assembly and optimizes the host cell environment for viral replication<sup>[11,12]</sup>. The mechanism of viral egress from the host cells remains unclear<sup>[15,16]</sup>.

## IMMUNE RESPONSES IN HEV INFECTION

Investigation of host immune responses against virus infection are essential to understand host immunity and for vaccine development. Several studies have examined the host immune responses following HEV infection and the roles of immune components responsible for causing liver damage as a consequence of HEV infection. Although the mechanisms of hepatic injury enhanced by the host immune responses to HEV infection are still unclear<sup>[17-19]</sup>, we review here the available literatures on HEV infection and how it affects host immunity and induction of liver injury.

Once HEV enters the body, viral clearance involves recruitment of immune cells against infection. These cells recognize HEV in the early stages through pattern recognition receptors. HEV components are then detected by toll-like receptors and retinoic acid-inducible gene- I like receptors. Subsequent recruitment of adapter proteins MyD88 and TRIF mediate interferon regulatory transcription factor 3 (IRF3) and nuclear factor  $\kappa$ B (NF- $\kappa$ B) to produce type I interferons and pro-inflammatory cytokines vital to antiviral response<sup>[20]</sup>.

Type I interferons are cytokines, which play important roles in innate immunity against virus infection. Interferon-inducible genes are up-regulated in HEV infected PLC/PRF/5 cells. Replication of HEV in this cell type was inhibited when cells were treated with interferon (IFN)- $\alpha$ 2b<sup>[21]</sup>. A549 cells infected with HEV genotype 3 showed inhibition of IFN- $\alpha$  induced the signal transducer and activator of transcription 1 (STAT1) phosphorylation. Additionally, HEV ORF3 protein enhances IFN- $\beta$  production induced by poly (I:C), a double-stranded RNA analogue<sup>[22]</sup>. HEV ORF3 was also shown to bind STAT1 resulting in inhibition of STAT1 phosphorylation<sup>[9]</sup>. A study in hepatocyte cells demonstrated that HEV infection inhibited IFN- $\beta$  production induced by poly (I:C). Meanwhile, HEV ORF1 was identified as an IFN antagonist. It inhibited phosphorylation and ubiquitination of various proteins involving in interferon production such as IRF3, retinoic acid-inducible gene 1 and TANK-binding kinase 1<sup>[23]</sup>. ORF1 also activates the promoter activity of a chemokine,

chemokine (C-X-C motif) ligand 8<sup>[24]</sup>. These reports collectively demonstrated that HEV proteins are involved in the activation of host antiviral cytokines, although some viral components could also inhibit interferon signalling, which facilitate HEV evasion from the host innate immune defenses.

Natural killer (NK) cells and NKT cells are responsible for killing virus-infected cells. Comparison of the numbers and function of NK/NKT cells from HEV infected patients and healthy controls showed that the percentage of activated NK cells was higher in patients than in controls<sup>[18]</sup>. However, there was no difference in the target cell cytotoxicity of NK cells from both groups. A study of lymphocytes taken from liver biopsy demonstrated that CD56 cell counts were higher in HEV patients than in patients with hepatitis A, B and C virus infections<sup>[25]</sup>. This group also showed increased CD8<sup>+</sup> cells in liver failure cases caused by HEV and other viruses.

IFN- $\gamma$  is a cytokine responsible for activation of NK and T cell function. IFN- $\gamma$  expression was up-regulated in peripheral blood mononuclear cells (PBMCs) from HEV infected patients following HEV ORF2 stimulation<sup>[26]</sup>. In addition, PBMCs from acute viral hepatitis cases elicited higher responses to recombinant HEV ORF2 peptides than PBMCs from the liver failure group<sup>[27]</sup>. Studies in hepatocytes demonstrated that HEV ORF2 inhibited NF- $\kappa$ B activation<sup>[28]</sup>.

Besides the innate immune responses, the alteration of cell-mediated immune responses by HEV infection had also been reported. HEV infected patients had increased CD8<sup>+</sup> and CD4<sup>+</sup>CD8<sup>+</sup> cells compared with healthy individuals. In addition, proportion of IFN- $\gamma$  secreting cells in response to recombinant ORF2 and ORF3 were higher in patients than in controls. These data provided evidence of effector T cell responses induced by HEV components<sup>[29]</sup>.

The studies of clinical manifestations in patients with self-limited acute viral hepatitis and acute liver failure support the roles of immune responses in liver injury. HEV infected patients with acute liver failure had higher antibody titers and higher levels of cytokines such as tumor necrosis factor- $\alpha$ , IFN- $\gamma$ , interleukin-2 (IL-2) and IL-10. HEV RNA was detected in patients with self-limited acute hepatitis group but not in liver failure cases. This observation suggests that the immune responses rather than the virus are responsible for liver damage<sup>[30]</sup>.

For humoral immune response, the incubation period is around 15-60 d after infection<sup>[31]</sup>. IgM antibodies increase rapidly and then begin to subside after 3

mo<sup>[32,33]</sup>. Anti-HEV IgG antibodies start to increase when anti-HEV IgM is first detected and may persist for years<sup>[17,34,35]</sup>. Presently, the viral detection by serology tests has been developed for HEV. Examination of blood and stool of 10 patients with acute HEV infection can identify HEV RNA, but only for a short period<sup>[36]</sup>. Experimental infection in chimpanzee demonstrated that HEV RNA was detectable in blood around 22 d after inoculation. In human volunteer, HEV RNA could be detected in blood sooner than in feces<sup>[37]</sup>. Naturally acquired humoral immune response in the body not only increased rapidly after infection, but also afforded protect from infection during an outbreak<sup>[38]</sup>.

Regulatory T cells (Treg) and IL-10, components of the immune system which modulate immune response, were examined in acute hepatitis E patients, recovered individuals and healthy controls. Both percentage of Treg cells and IL-10 levels were higher in acute hepatitis patients than in recovered and healthy individual groups<sup>[39,40]</sup>, implicating a role for Treg in the immune response induction as a result of HEV infection.

The regulation of protection in the body involves a complex network of innate and adaptive immune response. Immune responses are shown to promote tissue injury in various infectious diseases. During viral infection, both innate and adaptive immune responses are elicited in order to eliminate pathogens. Even so, several viruses are able to evade eradication by the host immunity. Prolonged or hyper-immune responses to eradicate persistent infection, however, could result in tissue injury. Knowledge gained from HEV studies thus far have mostly relied on recombinant HEV proteins instead of viral infections due to the lack of an efficient cell culture system. Moreover, most HEV infections are self-limited. Future studies including patients presented with various degrees of clinical manifestations should allow better understanding of the immunity or immunopathology induced by HEV infection.

## EPIDEMIOLOGY OF HEV

HEV is a leading cause of hepatitis transmitted *via* fecal-oral route<sup>[41]</sup>. The first outbreak of HEV occurred in India around 1955-56, which affected as many as 29000 persons<sup>[42]</sup>. Other large outbreaks were reported in China, India, Somalia and Uganda<sup>[1]</sup>. Outbreaks were observed to occur after heavy rainfall and floods, which allowed contamination of human excreta with drinking water sources. Alternatively, outbreaks sometimes follow the dry summer season when water in the rivers or streams is reduced, resulting in increased concentration of fecal contamination in water<sup>[43]</sup>.

It is known that humans could be infected with all 4 HEV genotypes<sup>[44]</sup>. In developing countries where HEV is endemic (Indian subcontinent, Asia, Middle East and Africa)<sup>[11]</sup>, HEV genotypes 1 and 2 are common and restricted to human. In developed countries, these two genotypes were diagnosed only in persons who had recently traveled to highly endemic areas<sup>[45]</sup>. It is

estimated that 21.1 million people, or 71% of the world population, are infected with HEV genotypes 1 and 2. Furthermore, HEV infection results in approximately 3 million symptomatic acute cases each year and 70000 deaths worldwide<sup>[1,44,46]</sup>. Individuals could be infected with HEV genotypes 1 and 2 from drinking contaminated water<sup>[47]</sup>, and unfortunately people affected in large HEV outbreaks were found using water from a common source for cooking, drinking, and bathing. HEV RNA has also been detected in the sewage-contaminated water source. The limitation of inadequate public infrastructure may facilitate the spread of HEV infection, such as in refugee or military camps<sup>[43]</sup>. Areas affected by natural disasters such as earthquakes and monsoon storms are also at risk of HEV epidemic. Displaced populations with limited access to clean drinking water, lack of sanitary facilities, overburdened health-care infrastructure, and immunologically naive population lacking protective antibodies combined will increase the likelihood of HEV transmission<sup>[48]</sup>. Large outbreaks of HEV have occurred in Nepal, which in 2014 involved more than 10000 cases<sup>[49]</sup>.

HEV infection does not only affect developing countries. HEV genotypes 3 and 4 are autochthonous in several industrialized countries. Occasional foodborne outbreaks have occurred in Europe, North America, Japan and New Zealand from consuming undercooked meat contaminated with HEV<sup>[50-53]</sup>. HEV genotypes 3 and 4 are found in human and other animal species such as pig, wild boar, and shellfish<sup>[54-56]</sup>. Specifically, HEV genotype 3 is zoonotic in developed countries from reports in pig farmers, individuals who came into close contact with animal reservoir and who consumed raw meat or meat products from deer, wild boar, and pig. HEV RNA could also be detected in food products such as liver and sausage. Viral sequence extracted from uncooked meat or sausage were very similar (99.7%-100% identity) to sequences of virus recovered from HEV-infected patients. In addition, HEV genotype 4 infection could be detected in both human and swine in Eastern Asia and Europe<sup>[57,58]</sup>. These evidence supported foodborne zoonotic HEV transmission, which occurred from consuming infected meat<sup>[59-63]</sup>.

Several studies suggest that HEV genotypes 3 and 4 could be transmitted across multiple species. In animal models, pathogen-free pigs could be experimentally infected with human HEV genotypes 3 and 4. Furthermore, swine HEV genotypes 3 and 4 inoculated in rhesus monkey and chimpanzee resulted in seroconversion and virus shedding in feces. Anti-HEV IgG seroconversion in the pigs was observed within 2 wk. These experiments suggest that human HEV genotypes 3 and 4 could replicate in pigs and likely originated from swine<sup>[64]</sup>. In contrast, pigs inoculated with HEV genotypes 1 and 2 were not infected. This suggests that HEV genotypes 1 and 2 were host-restricted compared to genotypes 3 and 4<sup>[65]</sup>. Therefore, zoonotic transmission to humans is possible for HEV genotypes 3 and 4<sup>[65-67]</sup>. Other routes of transmission

**Table 1** Global prevalence of anti-hepatitis E virus IgG in different populations

Regions	Prevalence (%)	Ref.
Low-to-medium income		
Kashmir region	49.6	Khuroo <i>et al</i> <sup>[35]</sup>
India	23.8-28.7	Mathur <i>et al</i> <sup>[76]</sup>
Myanmar	32.0	Nakai <i>et al</i> <sup>[77]</sup>
Egypt	67.7	Stoszek <i>et al</i> <sup>[71]</sup>
Bangladesh	22.5	Labrique <i>et al</i> <sup>[78]</sup>
China	19.7	Dong <i>et al</i> <sup>[79]</sup>
Mexico	36.6	Alvarado-Esquivel <i>et al</i> <sup>[80]</sup>
Thailand	14.0	Gonwong <i>et al</i> <sup>[75]</sup>
Nigeria	42.7	Junaid <i>et al</i> <sup>[81]</sup>
Industrialized		
Germany	17.0	Wenzel <i>et al</i> <sup>[82]</sup>
United States	6.0	Teshale <i>et al</i> <sup>[83]</sup>

including HEV-infected blood transfusion, mother-to-child, person-to-person, and sexual intercourse were also documented but relatively uncommon<sup>[68-70]</sup>.

Seroprevalence of anti-HEV IgG varies in different parts of the world. In developing countries, positive anti-HEV IgG serology might reach as high as 70%<sup>[71]</sup>. Being male, having pet animals or frequent contact with animal reservoirs, residing in the endemic area, or consuming liver or other organ meats were highly associated with positive HEV serology. Veterinary and slaughterhouse workers also have high seropositive rates for anti-HEV IgG compared to individuals with no occupational exposure to swine<sup>[72,73]</sup>. In swine-dense areas, individuals were more likely to be HEV-seropositive compared to those living in areas with few pig farms<sup>[74,75]</sup>. The seroprevalence of anti-HEV IgG antibodies is shown in Table 1.

## CLINICAL MANIFESTATIONS AND DIAGNOSTIC CRITERIA

HEV infection produces wide-ranging clinical manifestations. Most cases of HEV-related acute viral hepatitis resolve within 1 to 2 mo. However, HEV sometimes leads to acute liver failure, chronic infection, or extrahepatic symptoms<sup>[17]</sup>. An acute hepatitis from HEV is indistinguishable from other forms of acute viral hepatitis and is usually asymptomatic or self-limiting in most individuals<sup>[34]</sup>. However, acute hepatitis E infection can be severe and prolonged among the immunocompromised and even healthy individuals<sup>[84]</sup>. Severe acute hepatitis E infections have been described in pregnant women, elderly men, and persons with pre-existing chronic liver disease<sup>[85-87]</sup>. Among people with the chronic liver disease, acute hepatitis E can adversely lead to acute-on-chronic liver failure<sup>[88]</sup>. Acute HEV infection with pronounced symptoms resulted in higher mortality rates of 1%-4% and up to 11%, compared to the mortality rates of acute HAV (1%) or HBV (1.5%) infection based on CDC viral hepatitis surveillance data (2010)<sup>[84]</sup>. Extrahepatic manifestations including pancreatitis, arthritis, aplastic anemia, and neurologic

complications have all been reported<sup>[11,89,90]</sup>.

Hepatitis E, especially genotype 3, is known to cause chronic infection among the immunocompromised, especially solid organ recipients. Recently, however, there are reports of chronic hepatitis E infection in elderly immunocompetent patients<sup>[91,92]</sup>. Diagnosis of acute hepatitis E infection is established in patients with clinically relevant symptoms of acute hepatitis with positive level of anti-HEV IgM or a level of anti-HEV IgG that is twice the baseline concomitant with detectable HEV RNA in the serum and/or stool<sup>[93]</sup>. Chronic hepatitis E is defined by the persistent increase in liver enzyme levels and polymerase chain reaction-detectable HEV in the serum and/or stool over 6 mo<sup>[94]</sup>.

## TREATMENT OF ACUTE HEPATITIS E

Currently, there is no indicated treatment of acute hepatitis E. Nevertheless, treatment with ribavirin showed significant clinical improvements by reducing the symptomatic period (Table 2). Considering the high mortality caused by acute hepatitis E in acute-on-chronic liver failure, ribavirin therapy provides significant benefits for those with poor prognosis or at high risk of fulminant liver failure such as underlying chronic liver disease. Moreover, a high percentage of immunosuppressed individuals [such as human immunodeficiency virus (HIV)-positive individuals or recipients of organ transplant] who eventually develop chronic hepatitis E necessitate early and effective treatment of acute hepatitis E<sup>[84,88,95-98]</sup>.

## TREATMENT OF CHRONIC HEPATITIS E

In a case-control study of solid-organ transplant recipients performed in France, 22 out of 38 individuals who tested positive for HEV genotype 3 (58%) developed chronic infection. Compared to the control group of 148 individuals who had no markers for HEV infection, one independent factor associated with HEV infection was the consumption of game meat (68% vs 47%, OR = 2.32)<sup>[3]</sup>. Moreover, a retrospective analysis of data from Europe and the United States found that among 85 recipients of solid organ transplants who had HEV infection, 56 patients (65.9%) developed chronic hepatitis E<sup>[94]</sup>. The main factor associated with developing chronicity assessed by multivariate analysis in this study was tacrolimus use for immune-suppression (OR = 1.87; 95%CI: 1.49-1.97). The reduction of immunosuppressive drugs, however, enabled HEV clearance in one-third of the individuals.

When reduction of immunosuppression is impossible or when clearing HEV by immunosuppression could not be achieved, 2 alternative therapies for chronic hepatitis E may be pursued: (1) Ribavirin monotherapy (dose 29-1200 mg/d, for 1-18 mo)<sup>[96,99,100]</sup>; and (2) Pegylated (Peg)-IFN- $\alpha$  for 3-12 mo<sup>[101,102]</sup>.

It was reported that among 59 patients with chronic HEV after solid organ transplantation, HEV clearance was observed in 95% of the patients at the end of

**Table 2** Recent evidences on the outcome of therapies against acute hepatitis E infection

Ref.	Type of study	Patient profile	HEV genotype	Ribavirin regimen	Results
Gerolami <i>et al</i> <sup>[84]</sup>	Case report	61-year-old man, 7 d after admission ALT 4565 IU/L	3	1200 mg/d for 21 d	At day 21 of treatment, ALT normalized, RNA almost undetectable
Péron <i>et al</i> <sup>[88]</sup>	Case report	79-year-old man with chronic liver disease, acute kidney failure	3f	200 mg/d for 3 mo	Serum HEV RNA negative at 1 mo therapy, stopped dialysis at 2 mo
		A patient with chronic liver disease	3f	1000 mg/d for 10 d	Viral load 4.07 log copies/mL declined to 2.54 log copies/mL at day 6, Hgb 12.6 g/dL declined to 11.6 g/dL at day 6 of treatment
Del Bello <i>et al</i> <sup>[95]</sup>	Case report	65-year-old man, liver transplant recipient Guillain-Barré syndrome with severe necrotizing myositis	3f	400 mg/d adapted to GFR (40 mL/min) for 3 mo	HEV RNA undetectable by day 15, progressive recovery of mobility
Pischke <i>et al</i> <sup>[96]</sup>	Case from prospective case series	42-year-old woman had traveled to Eritrea and acquired severe acute hepatitis E	1e	For 6 wk (dose: Undefined)	Rapidly improved liver function and cleared HEV
Robbins <i>et al</i> <sup>[97]</sup>	Case report	39-year-old man HIV (+) CD4 51/mm <sup>3</sup> prothrombin index 45%	3c	1200 mg/d (15 mg/kg per day) for 12 wk	Gradual normalization of LFT-HEV RNA decreased to < 100 copies/mL at 1 mo of treatment
Riveiro-Barciela <i>et al</i> <sup>[98]</sup>	Case report	68-year-old man with Waldenström's macroglobulinemia	3f	800 mg/d for 12 wk	Achieved SVR after 12 wk; no ribavirin-related side effect reported

LFT: Liver function test; ALT: Alanine transaminase; Hgb: Haemoglobin; GFR: Glomerular filtration rate; SVR: Sustained virological response; HIV: Human immunodeficiency virus; HEV: Hepatitis E virus.

ribavirin therapy and that 78% of the patients achieved sustained virologic response (defined by undetectable serum HEV RNA at least 6 mo after cessation of therapy). These patients received ribavirin for a median of 3 mo. Longer treatment duration allowed 4 patients who had recurrence to achieve sustained virologic response<sup>[100]</sup>. The mechanism that ribavirin acts against HEV is not clearly understood<sup>[103]</sup>. However, a recent study suggests that ribavirin exerts an antiviral effect against HEV by depleting intracellular guanosine 5'-triphosphate pools<sup>[104]</sup>. Further research on this mechanism as well as other possible mechanisms of action of ribavirin is to be revealed. Meanwhile, overall data showed that ribavirin provided therapeutic effect in the treatment of chronic hepatitis E with the only significant adverse effect being anemia (Table 3).

Treatment with Peg-IFN- $\alpha$  has been reported (Table 4). The duration of therapy ranged from 3 mo to 1 year. Most of the cases are from solid organ transplant recipients, all of them showed the favourable outcome in liver enzyme levels as well as viral RNA suppression. However, 2 out of 6 transplanted patients developed acute allograft rejection after 3-mo Peg-IFN therapy<sup>[101,109]</sup>.

The slight synergistic effect for ribavirin combined with Peg-IFN- $\alpha$  was observed in a recent study *in vitro*<sup>[104]</sup>. Successful combination therapy had also been reported for a chronic HEV infection in an HIV-positive patient<sup>[110]</sup>. Decreasing the ribavirin dosage may help reduce anemia and other treatment-associated side effects<sup>[111]</sup>.

## HEPATITIS E VACCINE

Current data demonstrated that immunity acquired

from infection or vaccination can protect individuals from symptomatic hepatitis E. In a large cohort study, the risk of infection was highest among the baseline seronegative placebo group participants (2.04%). The risks of HEV infection in population with pre-existing immunity or vaccine-induced immunity were significantly reduced to 0.52% and 0.30%, respectively<sup>[112]</sup>. Two recombinant hepatitis E vaccines developed from HEV genotype 1, by Glaxo SmithKline and Xiamen Innovax Biotech, have had short-term efficacy in clinical trials<sup>[113,114]</sup>. The latter vaccine, commercially available as Hecolin, has been in use in China since 2012. Its long-term efficacy was 86.8% during the 4.5-year follow-up period<sup>[93]</sup>. Estimated long-term persistence of anti-HEV IgG from hepatitis E vaccine is predicted to be from 8 years to nearly life-long based on mathematical assumptions<sup>[115]</sup>. The only currently licensed hepatitis E vaccine (Hecolin) is approved for use in China in those aged 16-65 years available in prefilled syringe for intramuscular injection at 0, 1, and 6 mo. Expansion of vaccine coverage to other HEV endemic country is necessary and might significant decrease burden of the disease<sup>[85]</sup>. In addition to improved personal hygiene, sanitation, and health education, vaccination might play a crucial role in the future prevention and control of HEV infection.

## HEV IN BLOOD DONORS: CLINICAL IMPLICATIONS

Experiments involving the transfusion of blood plasma from anti-HEV IgM positive and anti-HEV IgG negative blood donors to rhesus monkey demonstrated that the

**Table 3 Treatment of chronic hepatitis E virus with ribavirin regimen**

Ref.	Type of study	Patient profile	Ribavirin regimen	Result	Adverse effects
Kamar <i>et al</i> <sup>[99]</sup>	Prospective case series	6 kidney transplant recipients, HEV RNA (+) for median of 36.5 mo	600-800 mg/d for 3 mo adapted to GFR, Hgb	SVR in 4/6 patients; relapse in 2/6; AST, ALT normalized all	Anemia led to blood transfusion and RBV dose reduction in 2/6 patients
Mallet <i>et al</i> <sup>[105]</sup>	Case report	A kidney and pancreas transplanted man, a woman with idiopathic CD4 <sup>+</sup> T lymphocytopenia	12 mg/kg daily for 12 wk	Both cleared HEV after 4 wk of treatment and remained undetectable, LFT normalized	Anemia in 1 <sup>st</sup> patient led to Ribavirin dose reduction to 200 mg/d
Pischke <i>et al</i> <sup>[96]</sup>	Prospective case series	Organ transplant recipients 11 subjects	600-1000 mg/d for 5 mo, dose reduction according to Hgb or anemia	9/11 showed SVR	Anemia, the mean Hgb decline was 3.4 g/dL (range 0-7.9 g/dL)
Neukam <i>et al</i> <sup>[106]</sup>	Case report	2 HIV (+) male with liver cirrhosis with severe immunosuppression	Oral ribavirin 1200 mg/d (case 1) 1000 mg/d (case 2) for 24 wk	LFT normalized-Liver stiffness improved HEV RNA was detected after the end of treatment in both patients	-
Giordani <i>et al</i> <sup>[107]</sup>	Case report	60-year-old man with lymphocytic leukemia	1000 mg/d in 2 doses (400 and 600 mg), for 3 mo	HEV cleared and sustained over 6 mo after therapy	Mild anemia (Hgb 10.5 mg/dL)
Kamar <i>et al</i> <sup>[100]</sup>	Retrospective, multicentre case series	37 kidney, 10 liver, 5 heart, 5 kidneys and pancreas, and 2 lung transplant recipients with chronic HEV	Median dose of 600 mg/d (range 29-1200), for a median of 3 mo (range 1-18 mo)	At the end of the therapy, 95% cleared HEV, 18% recurred after cessation of therapy is stopped, 78% showed SVR	Anemia required dose reduction (29%); use of erythropoietin (54%); required blood transfusion (12%)

LFT: Liver function test; AST: Aspartate aminotransferase; ALT: Alanine transaminase; SVR: Sustained virological response; Hgb: Haemoglobin; GFR: Glomerular filtration rate; HEV: Hepatitis E virus; HIV: Human immunodeficiency virus.

**Table 4 Treatment of chronic hepatitis E virus with pegylated interferon- $\alpha$  therapy**

Ref.	Patient profile	Peg-IFN- $\alpha$ regimen	Result	Adverse effects
Kamar <i>et al</i> <sup>[101]</sup>	29-year-old man with liver transplantation	Peg-IFN- $\alpha$ -2a for 12 wk (135 $\mu$ g/wk)	Liver enzyme levels decreased. HEV RNA levels remained undetectable until week 12	At week 12, signs of acute humoral rejection in liver biopsy
	26-year-old man with liver transplantation	Peg-IFN- $\alpha$ -2a for 12 wk (135 $\mu$ g/wk)	HEV RNA levels undetectable by week 12; liver enzyme levels normalized by week 12	
	58-year-old man with liver transplantation liver cirrhosis from chronic HEV infection	Peg-IFN- $\alpha$ -2a for 12 wk (135 $\mu$ g/wk)	HEV RNA was redetected 2 wk after completion of treatment; Liver enzyme levels normalized by 3 mo of therapy	
Haagsma <i>et al</i> <sup>[102]</sup>	37-year-old woman with liver transplantation	Peg-IFN- $\alpha$ -2b for 52 wk (80 $\mu$ g/wk declined to 60 $\mu$ g/wk)	Serum HEV RNA sustained undetectable during 3 mo follow-up; serum liver enzyme became normalized	Leukopenia
	59-year-old man with liver transplantation	Peg-IFN- $\alpha$ -2b 150 $\mu$ g/wk, dose reduction due to leukopenia	HEV viral load and aminotransferases declined, but Peg-IFN discontinued from lack of further efficacy, HEV RNA level undetectable at 4 wk after the discontinuation of Peg-IFN and aminotransferase normalized	
Alric <i>et al</i> <sup>[108]</sup>	57-year-old man with hairy cell leukemia	Discontinued at week 16, Peg-IFN- $\alpha$ -2b 1 $\mu$ g/kg per week for 3 mo	Achieved a complete virologic response by week 4	
Kamar <i>et al</i> <sup>[109]</sup>	24-year-old man with kidney transplantation, kidney failure from chronic HEV infection	3-mo Peg-IFN- $\alpha$ -2a 135 $\mu$ g/wk	Serum RNA undetectable after 5 mo, SVR for 6 mo after treatment	Acute rejection of the kidney allograft by month 3 of Peg-IFN therapy

Peg-IFN: Pegylated interferon; SVR: Sustained virological response; HEV: Hepatitis E virus.

virus was transmissible<sup>[116]</sup>. Therefore, many developed countries are now focused on studying the prevalence of viral transmission from blood donation<sup>[117-124]</sup> (Table 5). The demand for pathogen-free blood and blood components is highly needed for hospital patients and individuals requiring continuous blood transfusion (*e.g.*, thalassemia patients). Thus, these patients are at-risk for being infected with HEV from donated blood. The development of screening methods for detecting

HEV in donated blood involves both serology test and nucleic acid test. Novel techniques are being developed to increase the efficiency and sensitivity to identify HEV rapidly even at low viral concentration<sup>[125-127]</sup>. Many countries are aware of the necessity to screen the blood supply for HEV among blood donors and have begun to implement diagnostic tests for HEV. For example, Japan has started monitoring for HEV by comparing the increase in the alanine aminotransferase as a biomarker

**Table 5** Incidence of detectable hepatitis E virus in blood donors (hepatitis E virus-RNA)

Year of study	Countries	Technique used for detection	No. of tests	Ratio of positive detections	Ref.
2005	China	Real-time fluorescence RT-PCR	10741	1:1094	Ren <i>et al</i> <sup>[117]</sup>
2011	England	PCR	42000	1:7000	Ijaz <i>et al</i> <sup>[118]</sup>
2011	German	Real-time RT-PCR	18100	1:4525	Baylis <i>et al</i> <sup>[119]</sup>
2011	Sweden	Real-time RT-PCR	95835	1:7986	Baylis <i>et al</i> <sup>[119]</sup>
2011	United States	Real-time RT-PCR	51075	None detected	Baylis <i>et al</i> <sup>[119]</sup>
2011	German	Real-time RT-PCR	16125	1:1241	Vollmer <i>et al</i> <sup>[120]</sup>
2011-2012	The Netherlands	Real-time PCR	45415	1:2672	Slot <i>et al</i> <sup>[121]</sup>
2012-2013	England	RT-PCR	225000	1:2848	Hewitt <i>et al</i> <sup>[122]</sup>
2012	France	RT-PCR	53234	1:2218	Gallian <i>et al</i> <sup>[123]</sup>
2013	Spain	Transcription-mediated amplification assay	9998	1:3333	Sauleda <i>et al</i> <sup>[124]</sup>

RT-PCR: Reverse transcription-polymerase chain reaction.

in the surveillance of HEV<sup>[128]</sup>. Germany is looking for a new approach to detecting HEV to find alternative ways to blood screening test<sup>[120]</sup>. Other countries have also implemented screening test but only focus on the suspected cases<sup>[129]</sup>. In Thailand, there were two reports on the incidence of HEV among blood donors. First, a study in 1996 reported the prevalence of HEV transmission among adults in different parts of Thailand, in which the studied population also included blood donors. The study found 9%-22% positive rates for anti-HEV IgG<sup>[130]</sup>. Another study found HEV seroprevalence around 8.7% among blood donors in 4 Northern provinces of Thailand<sup>[131]</sup>, which was similar to those in other countries (Table 5). Thus, HEV poses a significant public health problem especially in blood donation even if the prevalence and virulence of the disease are lower than other infections<sup>[132]</sup>.

## CHALLENGES IN THE TREATMENT OF HEPATITIS E

Although the recent reports of treatment of HEV infection are showing beneficial outcomes, there are still areas to be overcome in the treatment of HEV infection. First of all, as described by previous articles, there are known severe side effects of current regimen with Peg-IFN- $\alpha$  and ribavirin. For Peg-IFN- $\alpha$ , the severe side effects include influenza-like symptoms<sup>[133]</sup> and acute rejection of allografts for solid organ transplant recipients<sup>[101]</sup>. For ribavirin monotherapy, it has the side effect of severe hemolytic anemia, sometimes resulting in treatment failures probably caused by dose reduction<sup>[100,111]</sup>. Furthermore, both ribavirin and Peg-IFN- $\alpha$  cannot be administered in pregnancy. Also, ribavirin use requires close monitoring of hemoglobin levels and other hematological parameters that make it difficult to apply in developing countries<sup>[111]</sup>.

There has been a case report showing resolution of acute liver injury cause by hepatitis E with steroid use that was initially intended for immunosuppression<sup>[134]</sup>. Also, there have been reports of fulminant hepatic failure from HEV in women taking oral contraceptives<sup>[135]</sup>. Known that immunosuppression can cause persistent infection of hepatitis E, the relation between steroid hormone use

and the clinical course of hepatitis E is not clear as the immune pathogenesis of hepatitis E infection itself being not explained thoroughly<sup>[2]</sup>. The various manifestations of hepatitis E according to the potential immune and hormonal status including pregnancy need to be explored precisely in their relation and the pathogenesis for the future direction of developing treatment regimen of hepatitis E. Larger research for establishing appropriate standard treatment as well as supportive treatment and steroid use are still in need in order to minimize limitations and side effects of the current administration of ribavirin and Peg-IFN- $\alpha$  monotherapy, with appropriate vaccination for the high-risk populations for controlling epidemics in resource-limited settings, and for pregnant women living in developing countries where the acute infections are threatening extremely great number of women and new-borns.

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