Curr Treat Options Infect Dis (2020) 12:310–320
DOI 10.1007/s40506-020-00235-4

Hepatitis C (J Raybould, Section Editor)

A Review of the Diagnosis and Management of Hepatitis E

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Published online: 17 July 2020

This article is part of the Topical Collection on *Hepatitis C*

Keywords Hepatitis E virus · Ribavirin · Pregnancy · Viral hepatitis

Abstract

Purpose of review We aim to provide the readers an up-to-date knowledge of the structure, epidemiology, and transmission followed by a detailed discussion on testing, diagnostics and management of hepatitis E virus infection. We have also included a comprehensive review of hepatitis E in pregnancy.
Recent findings European Association for the Study of the Liver established clinical practice guidelines for testing and treatment of suspected hepatitis E virus infections in 2018. Evidence suggests chronic hepatitis E may follow a course similar to hepatitis B/C with progression to cirrhosis and possibly hepatocellular carcinoma in immunocompromised patients.
Summary Hepatitis E virus is the most common cause of acute viral hepatitis worldwide. A combination of serology and nucleic acid amplification testing is the recommended strategy for suspected patients. Ribavirin therapy for a period of 3 months is the drug of choice for severe acute hepatitis, acute-on chronic liver failure, and chronic infections from hepatitis E virus in immunocompromised patients who are unresponsive to decreased immunosuppression. PEGylated interferon α can be used for ribavirin-resistant liver transplant patients with chronic hepatitis E. Further research in therapeutic options is essential considering the stormy course of hepatitis E infection during pregnancy and teratogenicity of all available options.

Introduction

Hepatitis E virus (HEV) causes acute hepatitis and acute liver failure (ALF) and is the most common cause of acute viral hepatitis worldwide. It was discovered in the early 1980s when sera of patients

suspected of viral hepatitis during an outbreak in Kashmir province of India tested negative for hepatitis A and B [1, 2]. This enterically transmitted non-A non-B hepatitis virus was termed as hepatitis E virus, with "E" standing for its association with epidemics and enteric mode of transmission. The article aims to provide the readers with up-to-date knowledge and recent advances in the clinical aspects of hepatitis E virus infection focusing mainly on diagnostics and management options.

Structure of HEV

HEV is a member of the Orthohepevirus genus and belongs to the Hepeviridae family. It is a small, non-enveloped 27–34-nm diameter particle with an icosahedral capsid. The virus was first isolated in the 1980s, from stool suspension of HEV-infected patients, and the excreted form of HEV in stool was found to be non-enveloped [3, 4]. Recently, enveloped forms of the virus have been identified in the blood of patients during viremia [5]. The virus gets enveloped in the membrane obtained from the host cell [5]. The enveloped virus particles do not get neutralized by antibodies and help the virus survive in the host [4].

The virus genome is 7.2 kb, linear, single-stranded, positive-sense RNA, with a 7-methylguanine cap at 5′ end, 3 open reading frames, namely, *orf 1–3*, in between and a poly adenine tail at the other end. ORF 1 is responsible for encoding nonstructural proteins, responsible for RNA replication including RNA helicase and RNA-dependent RNA polymerase [6]. ORF2 encodes structural proteins responsible for viral capsid formation [6]. These structural proteins represent antigenic sites against which immune response can develop, hence are potential antigens for vaccine development [7, 8]. ORF3 protein is found in blood-borne enveloped HEV particles only, responsible for viral replication, survival, and extrusion from the host cell [6].

Epidemiology

HEV infection occurs throughout the world but predominantly is associated with waterborne outbreaks in Asia and Africa [9, 10]. There are seven genotypes of HEV, viz. HEV 1–7, but only a single serotype. HEV 1–4 are known to infect humans, while HEV 5–7 have animals as their host only. There are two different epidemiological patterns of HEV. HEV genotypes 1 and 2 cause outbreaks, mostly in hyperendemic regions of the world. Mostly young adults are affected, and the disease is particularly troublesome for pregnant women who develop a very severe form of the disease [11••]. Genotype 1 causes outbreaks in Asia (south, southeast, and central) and North Africa while genotype 2 is usually located in Mexico and western parts of Africa [12•]. Using epidemiological tools and mathematical models, it has been estimated that HEV 1 and HEV 2 cause together approximately 20.1 million (95% credible interval 2.8–37.0 million) cases in Asia and Africa, with acute hepatitis E accounting for 3.4 million cases [13]. HEV infection is also estimated to cause 70,000 deaths from acute liver failure and ~3000 stillbirths [13]. In the developed parts of the world, such as Europe, the USA, and some high-income areas in Asia, the infection is predominantly caused by HEV 3 [12•]. HEV 4 usually causes infection in China and Japan [14, 15].

Transmission

Outbreaks from genotype 1 and 2 occur through the fecal-oral route due to fecal contamination of drinking water [3, 10]. HEV 3 and HEV 4 cause only sporadic cases in less endemic parts of the world, mostly from direct or indirect animal contacts, and consumption of undercooked animal products [11••]. Undercooked or raw pork meat, liver, and infected cow's milk are some known sources of HEV infection in these regions [12•]. Though relatively less common, person to person transmission of HEV is also known. It occurs through transfusion of blood, blood products, solid organ transplant, and via vertical transmission [16•, 17, 18•]. Transfusion-transmitted HEV infection accounts for <1% of all HEV infections in the UK [12•]. Many other European nations, China, and Japan have reported cases of transfusion-transmitted HEV caused by genotypes 3 and 4 predominantly [19•, 20, 21]. Transfusion-transmitted HEV infection usually causes an asymptomatic or mild infection but may cause chronic infection in immunocompromised individuals [21]. Vertical transmission of HEV causes adverse effects on fetus including intrauterine demise or neonatal mortality. Khurro et al. first demonstrated evidence of vertical transmission in 5 out of 8 babies in mothers who developed HEV infection during the third trimester [22]. In another study, Kumar et al. demonstrated 100% transmission rates from HEV-infected mothers to fetus [23].

HEV testing

Who should be tested?

European Association for the Study of the Liver (EASL) recommends considering HEV infection as a cause of viral hepatitis and as an important differential diagnosis to drug-induced liver injury in all patients [24••]. Also, people with hepatitis returning from areas endemic to HEV genotype 1 and 2 should be tested. Certain population groups like pregnant women, immunocompromised-like malignancy, and people on immunosuppressants are at high risk for devastating liver disease from HEV infection. Hence, it is imperative to test them upon suspicion of viral hepatitis. EASL recommends testing for HEV during flares up of chronic liver disease and immunocompromised patients or blood recipients with abnormal LFTs [24••]. In many countries around the world, either universal screening of blood or targeted screening for the high-risk recipient is being done. EASL recommends screening blood donors for HEV by nucleic acid amplification testing (NAT) [24••]. Also, HEV has extrahepatic manifestations, including neurologic, renal, hematological, and pancreatic injury. EASL recommends testing for HEV as a causative agent for neuralgia amyotrophy and Guillain-Barre syndrome and suggested testing for encephalitis/myelitis [24••].

Diagnostic tests

Since the research work in the field of HEV infection picked up in the last 20 years, diagnostic testing for HEV infection has become more refined. However, it is still marred with a lack of commercial kits in many parts of the world, non-standardization of the diagnostics, and wide variability in the results achieved. In the USA, no testing kit has been licensed for commercial usage.

The diagnosis of HEV infection can be established through direct or indirect testing. The direct tests aim to detect either HEV ribonucleic acid (RNA) or viral capsid antigens in the blood. Since they detect parts of the viral particles itself, the specificity of these tests is usually high, but sensitivity is low. The indirect tests are based upon human immune response against HEV particles, i.e., anti-HEV antibodies. Hence, these tests usually have high sensitivity but low specificity. A summary of available tests for HEV infection is represented in Table 1.

Indirect tests

The indirect tests for HEV rely upon the human immune response to generate antibodies against antigenic proteins of HEV. The antigenic proteins used in the assays are recombinant ORF2 and/or ORF3 protein of viral capsid, from HEV 1 genotype [25]. Both IgM and IgG types of antibodies can be detected in these patients; however, the performances and validity of both assays are under question [26]. IgM anti-HEV antibodies develop nearly 4 weeks after the infection and can be detected in the sera for nearly 6 months, hence indicating an acute or recent infection from HEV. IgG antibodies usually also develop simultaneously with IgM antibodies early after the infection and last for years, indicating either a recent or past infection [27]. The utility of these assays is limited by their non-standardization and discordance between different kits. Sometimes, in a subset of the infected population, both IgM and IgG antibodies may be negative in HEV RNA-positive patients [4]. Also, these antibodies may wane with time, thus limiting their role for diagnostic and epidemiological purposes [28]. In a study by Abranavel et al., the specificity of IgM anti-HEV was ≥99.5% while the specificity of IgG anti-HEV was 89.5% and 97.8% for two different diagnostic kits [29]. The testing kits for the detection of IgM antibodies had a higher sensitivity of 80–90% in immunocompetent while it was lower among immunocompromised patients viz. 85–87.5% [29]. The sensitivity of IgG detection kits among immunocompetent patients was 80–90% while it fell dramatically to 15–45% in immunocompromised patients, rendering the test practically useless [29]. Also, there was no correlation between HEV RNA levels and IgG anti-HEV antibody levels [29]. The limits of detection of various anti-HEV IgG detection kits available commercially worldwide vary from 0.25 to 2.5 World Health Organization (WHO) units per ml. Using assays with a lower detection limit of 0.25 WHO units per ml gives a more elaborate estimation of the prevalence of HEV infection [30]. National Institute for Biological Standards and Control established the WHO reference reagent for HEV detection kit. Experts have suggested that waning anti-HEV IgG antibody levels after the natural course of disease or vaccination could pose a risk for reinfection [31].

Rapid, technically simpler, cheaper alternatives to serological or RNA-based tests have been gaining attention in recent times. Using IgM capture format, an immunochromatographic assay for detecting IgM anti-

Table 1. A summary of available tests for HEV infection

Test name	Time from infection to positive	Duration of clinical usefulness	Sensitivity	Specificity	Comments
Anti-HEV IgM	~4 weeks	6–9 months	Immunocompromised: 85–87.5% Immunocompetent: 80–90%	≥99.5%	Usually first test to be considered
Anti-HEV IgG	~4 weeks	years	Immunocompromised: 15–45% Immunocompetent: 80–90%	89–98%	Useful for seroepidemiological studies; not clinically useful
HEV Capsid	antigen	~2 weeks	4–5 weeks	88–99%	100%
Low cost and easy to perform; can be	considered for blood screening				
HEV RNA	~2 weeks	4–5 weeks	–	–	Gold standard test; useful in immunocompromised and seronegative patients

HEV antibodies have been developed (ASSURE® HEV IgM Rapid Test; MP Biomedical, Singapore) [32]. It has a sensitivity of 93% and specificity of 99.7%, established based upon data obtained from a study in Nepal and Indonesia (Genotype1) [32]. While, in another study, during a predominant genotype 3 infection in France, the kit showed sensitivity and specificity of 82% and 100% respectively [33].

Direct tests

HEV RNA

HEV RNA detection in blood or stool is the gold standard for the detection of HEV infection. It becomes detectable even before the patient becomes clinically symptomatic and may persist for nearly 4 weeks in the blood and 6 weeks in the feces [12•]. Most commercially available assays for detecting HEV RNA are based upon NAT. These NAT-based assays include reverse transcriptase polymerase chain reaction (RT-PCR), real-time PCR, and loop-mediated isothermal amplification assay [34, 35]. The real-time RT-PCR methods are more sensitive than nested RT-PCR methods [36]. These methods employ amplification of specific genome sequences mostly ORF3, followed by a nucleotide probe [37]. The limit of detection of available RNA probes is 7–80 IU/ml [35, 37]. Characterization of HEV genotypes or subgenotypes is mostly used for epidemiological purposes, and their clinical significance is yet to be determined. Even though it is the most specific method of establishing HEV infection, its utility is mostly limited by high cost, the requirement of specialized tools and expertise, and limited resources in areas with a high burden of the disease. Subject experts and gastroenterologists have suggested HEV RNA testing in the following clinical scenarios [4]:

1. Blood screening
2. Suspected chronic HEV infection with negative serology
3. Non-hepatic presentations to confirm infection
4. HEV infection diagnosis in immunocompromised patients, with negative serology
5. Monitoring response to antivirals
6. Before genotyping and for epidemiological purposes

Capsid antigen detection

Viral capsid antigen can be detected in the blood of those infected with HEV even before the patient becomes clinically symptomatic and persists for approximately 4 weeks. Testing for capsid antigen is technically less demanding and can be performed even without molecular detection laboratories. It can be detected using an indirect sandwich enzyme immunoassay, with an estimated sensitivity of 91% and specificity of 100% [38]. Studies have demonstrated waning levels of capsid antigen in blood of patients with HEV infection correlated with rising levels of anti-HEV antibodies [39]. Thus, it has a lower sensitivity for the detection of acute infection than HEV RNA and IgM anti-HEV [39]. However, ease of performing the diagnosis combined with a lower cost than RNA detection makes it an attractive option for blood screening and in early diagnosis of HEV infection.

Recommendations

Experts suggest testing for anti-HEV IgM initially for suspected HEV infection [12•]. A positive test suggests recent or active infection, after which HEV RNA analysis can be done for molecular characterization, while negative test results rule out the disease. The recommended algorithm differs slightly in immunocompromised patients considering the weakened immune response that develops in these patients. Patients who test negative for IgM anti-HEV should be tested for HEV RNA. Positive results for either HEV RNA or anti-HEV IgM confirms recent or active infection, but negative results for both the tests are required to rule out a disease. Also, since immunocompromised patients are at high risk of developing chronic HEV infection, HEV RNA testing in both blood and stools must be done to determine viral clearance before the patient is declared free from infection.

Treatment

Management of HEV infection depends upon its clinical presentation. The spectrum of clinical presentation ranges from asymptomatic infections through icteric and anicteric acute hepatitis to chronic hepatitis or liver failure. HEV infection is usually a self-limiting infection, and complete resolution is seen usually without any antiviral therapy. The management of icteric or anicteric viral hepatitis is mostly conservative and focuses on self-resolution of the disease. However, HEV may have a stormy course of disease in the form of ALF, more so in pregnant women. Interestingly, a study by Shalimar et al. has revealed HEV ALF to have lower rates of cerebral edema, infections, seizures, and mortality as compared to other causes of ALF [40].

In recent years, ribavirin has gained some spotlight in the treatment of HEV infection. Ribavirin, a prodrug, is a guanosine analog and when metabolized acts as a nucleotide analog to deplete intracellular guanosine triphosphate and, subsequently, RNA replication. It has also been postulated that ribavirin acts by inhibiting viral replication and has a role in immune modulation, increased expression of interferon stimulation genes, and mutagenesis [41, 42]. There have been reports of improvement in patients with severe acute hepatitis E with treatment with ribavirin [43, 44]. Hence, ribavirin therapy can be considered for severe acute hepatitis or acute-on chronic liver failure [24••]. Limited evidence with ribavirin suggests a rapid improvement in liver enzyme profile and a decline in HEV RNA levels in patients with HEV genotype 1 and 3 infections. However, its usage in patients with severe acute hepatitis E is based upon anecdotal evidence only.

The existence of chronic HEV infection was first reported in 2008 among solid organ transplant patients [45]. Chronic HEV infection is seen clinically in immunosuppressed patients especially with defective T cell response arm, including patients on immunosuppressant for organ transplants, HIV, and hematological malignancies [45–47]. Chronic HEV infection is defined as the detection of HEV RNA in blood or stools or any other body fluids for more than 6 months [11••]. Nearly, 10% of immunosuppressed chronic HEV-infected patients developed fibrosis and chronic liver disease within a few years [48, 49]. Recently, a case of hepatocellular carcinoma in a patient with HEV-associated cirrhosis has been described [50•].

The management of chronic HEV infection in immunocompromised requires careful assessment of risks and benefits. The first-line management option in such cases is to boost immune response either by reducing the dose of immunosuppressant or initiating antiretroviral therapy along with HEV RNA monthly monitoring for 3 months [12•]. This the preferred approach and is successful in nearly 33% of patients but must be balanced against the possibility of solid organ rejection [49]. In case the risks of reducing immunosuppressants outweigh the benefits, or the first-line option fails, oral ribavirin is the drug of choice, usually administered

initially for a period of 3 months. In a retrospective study analyzing the efficacy of ribavirin among 59 transplant patients with chronic hepatitis E, drug ribavirin administered in a median dose of ∼8.1 mg/kg for 3 months led to a sustained virological response in 78% patients [51]. Sustained virological response is defined as undetectable serum HEV RNA at 6 months after stopping ribavirin. A fall in HEV RNA ≥0.5 $\log_{10}$ copies/ml on day 7 of ribavirin is said to be a predictor of sustained virological response [52]. However, the study did not show any difference in sustained virological response between those treated for ≤3 months from those treated for >3 months [51]. Hence, patients with solid organ transplants who fail to clear HEV RNA within 3 months can be considered for ribavirin treatment. Moreover, the patients who relapsed exhibited sustained virological response after treatment with ribavirin for 6 more months [51]. Though the exact dose and duration of ribavirin therapy for chronic HEV infection is not defined, treatment courses of 3 to 6 months are typically used. Since chronic hepatitis E patients frequently suffer from anemia and kidney disease and ribavirin pharmacokinetics depend on kidney function, the dose and duration of the therapy must be adjusted according to hemoglobin and eGFR levels in these patients [53]. EASL recommends treating patients with chronic HEV and glomerular diseases with antivirals [24••]. Also, ribavirin resistance is now being reported with increasing frequency in patients with chronic hepatitis E due to G1634R mutation in RNA polymerase [54]. In an in vitro system, ribavirin shows a synergistic effect with mycophenolate, which is an inosine monophosphate dehydrogenase inhibitor in depreciating HEV RNA replicative machinery; however, no such evidence has been found in vivo till date [55].

Sofosbuvir, a nucleotide analog that brought revolutionary changes in the treatment of the hepatitis C virus, has been found to decrease genotype 3 HEV replication in vitro [56]. Valk et al. reported a case of chronic hepatitis E in an immunocompromised patient where sofosbuvir showed antiviral activity [57•]. Wezel et al. observed that sofosbuvir showed antiviral activity in chronic HEV-infected three solid organ transplant patients but failed to achieve sustained virological response [58].

Interferon α (IFNα) is another therapeutic option for chronic hepatitis E and has shown efficacy in achieving a sustained virological response in patients with liver transplants and hemodialysis [59–61]. However, IFNα is contraindicated in patients with transplant recipients due to the risk of acute rejection [62]. Limited evidence exists for the treatment of chronic HEV infection in HIV or hematological disease with IFNα, ribavirin, or both, which could form the template for further research and clinical trials to determine the dose, route, and efficacy of available treatment options. In a case report, corticosteroids were associated with biochemical recovery in patients with HEV infection and may prevent the progression of severe hepatitis to liver failure [63].

HEV in pregnancy

HEV infection in pregnancy caused by genotypes 1 and 2 in developing countries has been associated with poor fetal-maternal outcomes as compared to the relatively benign course of illness in the Western world where infections are more commonly caused by genotypes 3 and 4 [64•]. Data from our previous study shows HEV infection to have a higher incidence, severe and aggressive course of illness, and poor outcomes during pregnancy [65]. In pregnant women, HEV was the leading cause of acute viral hepatitis and acute liver failure accounting for 80.36% (442/550) and 73.38% (102/139) of cases, respectively. HEV-related liver infection accounted for 98/129 (75.96%) death cases, whereas non-HEV liver infection accounted for 31/129 (24.04%) death cases in comparison among pregnant women. The course of illness is worse if the infection is acquired in the third trimester of pregnancy [64•]. Maternal mortality varies from 15 to 25% for genotype 1 infection acquired in the third trimester [66]. Life-threatening complications of ALF viz. coagulopathy, DIC, encephalopathy, and cerebral edema can be seen in 70% of HEV-infected pregnant women [67]. An interesting study from Egypt showed high anti-HEV prevalence (84.3%) among pregnant women, but many of them never recalled an episode of viral hepatitis [68]. The differences in severity and prognosis in the different parts of the world could be accounted for by infections caused by different genotypes, differences in the rates of childhood infections, healthcare facility, and maternal nutritional state.

Fetal complications of HEV infection range from preterm delivery, intrauterine death, and poor infant survival rates [69, 70]. In a study from India, it was observed that 56% of infants born to HEV-infected mothers die in utero or soon after birth [10]. In another study, the authors observed that 15 to 50% of such infants die within a week of birth [70, 71]. In a study by Rayis et al., out of 39 pregnant women with HEV infection, there were 14 intrauterine deaths and 9 premature deliveries [72]. In a retrospective study by Banait

et al. among 42 pregnant women with HEV-induced ALF, 23 women could not survive [73]. Out of 42 women, 22 delivered with spontaneous delivery in 13 women and induction of labor in 9 women for intrauterine demise [73]. The study showed better outcomes in terms of survival among women with encephalopathy who delivered [73].

Currently, the management of HEV infection in pregnancy is mainly supportive. The use of ribavirin and PEGylated IFNα among pregnant women with HEV has not been explored due to the high risks of teratogenicity. In recent times, the increasing interest in sofosbuvir for HEV in pregnancy is something to look out for, since it is a pregnancy category B drug [64•]. Also, termination of pregnancy is useful in immunologically mediated liver failures in pregnancy such as HELLP syndrome and acute fatty liver of pregnancy (AFLP). Currently, there is no evidence of any therapeutic benefit of termination of pregnancy in HEV-induced ALF. EASL recommends treatment of HEV genotypes 1 and 2 infections during pregnancy in high-dependency units and prompt transfer to Liver Transplant Unit if liver failure develops [24••]. Liver transplant for HEV-induced ALF during pregnancy is rare, and outcome, complications, and timing of delivery in such a scenario remain unexplored.

HEV prevention

Since HEV infection is water and foodborne in hyperendemic and low endemic areas respectively, preventive strategies are focused on preventing water and food contamination. In hyperendemic areas of the world, preventive measures focus on improvement in drinking water quality via chlorination and sanitation hygiene. In low endemicity areas, safe food handling and thorough cooking are the cornerstones of preventing food-based transmission. Immunosuppressed and chronic liver disease patients are advised to refrain from eating raw, undercooked meat, and shellfish [24••]. It has been recommended to cook meat thoroughly at temperatures of 70 °C and above before consumption [24••].

There has been a considerable amount of research in the past 20 years in the field of HEV vaccination. One of the structural proteins, orf2, responsible for capsid formation, represents antigenic sites against which immune response can develop. Different strains of HEV share neutralizing epitopes on orf2 capsid proteins, thus providing cross-reactivity and potential antigens for vaccine development [8, 74]. The first HEV vaccine to be tested in randomized, double-blind, controlled, phase II trial among 2000 Nepalese men showed 95.5% protection during a median follow up of 804 days [75]. The vaccine contained a 56-kilo Dalton truncated (amino acid 112–607) *orf2* protein administered in three doses at 0–1–6 months [75]. The vaccine did not undergo further development. Another vaccine called HEV 239 (Hecolin®), tested in a double-blind, controlled, randomized phase III trial among 112,604 healthy men and women, is available commercially in China since 2012 [76]. The vaccine contains 26 k Dalton recombinant, truncated (amino acid 368–606) *orf2* protein, administered 30 μg intramuscularly at 0–1–6 months, and showed a protection rate of 95.5% after a year and cross-protection for HEV 1 and 4 [76]. Long-term follow up of the recruited subjects has shown the vaccine to be protective even after 4 years and safe in women [77]. However, the vaccine is not available in other countries. The 30th Global Advisory Committee on Vaccine Safety, WHO has recommended a phase IV trial of the vaccine and further data on its safety in special population groups including children and elderly [78]. Experts recommend selective vaccination against HEV in certain high-risk groups such as immunosuppressed population, persons with chronic liver disease, pregnant women in disease-endemic areas, travelers from low-endemicity areas to high-endemicity areas and general population in hyperendemic areas [11••].

Conclusions

Hepatitis E virus leads to outbreaks in developing countries and causes significant morbidity and mortality in immunocompromised and pregnant females. Our knowledge of HEV infection has increased dramatically over the past 20 years. A combination of serology and NAT is the recommended testing strategy for suspected patients. Further research into therapeutic options for

treating hepatitis E infection is the need of the hour. Oral ribavirin is the initial drug of choice for severe acute hepatitis, acute-on chronic liver failure, and chronic hepatitis E. PEGylated interferon α can be used for ribavirin-resistant liver transplant patients with chronic hepatitis E. However, no further treatment option is available for immunocompromised organ transplant patients who fail initial ribavirin therapy. Sofosbuvir shows promise as antiviral in immunocompromised patients with chronic hepatitis E, but more evidence would be needed before being considered as a reliable therapeutic option in ribavirin-resistant patients. There is no available treatment option for HEV infection during pregnancy, which takes a very stormy course sometimes. Our further focus should be on finding appropriate management options for HEV infection during pregnancy and for ribavirin-resistant infections.

Author's contribution

Premashis Kar: conceptualization, planning, literature search, manuscript drafting, revision and editing
Rahul Karna: literature search, manuscript drafting, revision and editing.

Compliance with ethical standards

Conflict of interest
Kar P declares that he has no conflict of interest. Karna R declares that he has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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