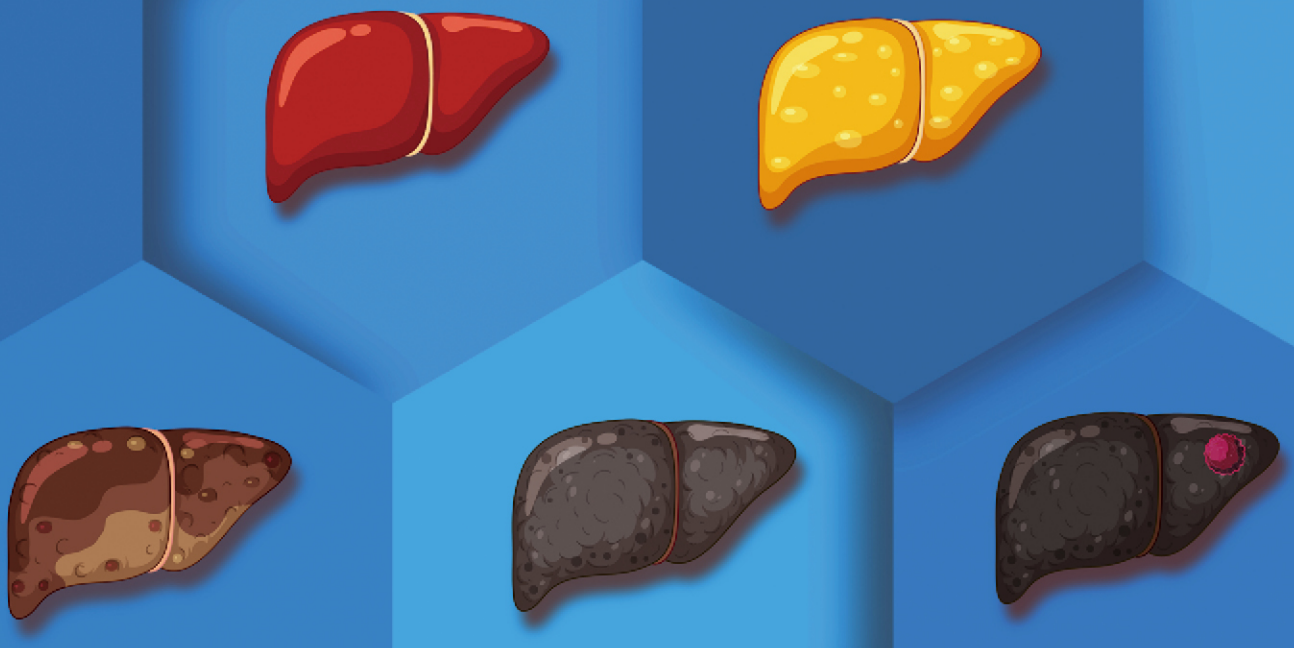
VOLUME 31 SUPPLEMENT February 2025
pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases



KASL 2025 MASLD clinical practice guidelines

Prognostication of MASLD

Epidemiology of MASLD

Precision medicine and MASH

Microbiome-centered therapies for MASLD

KASL

pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2024.0758
Clinical and Molecular Hepatology 2025;31(Suppl):S196-S204

Review

Hepatitis E as a trigger for acute-on-chronic liver failure

Maria Buti[1,2,3], Juan Carlos Ruiz-Cobo[1,2], Rafael Esteban[1], and Mar Riveiro-Barciela[1,2,3,4]

[1]Liver Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [2]Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; [3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain; [4]European Reference Network on Hepatological Diseases (ERN RARE-LIVER)

Acute hepatitis E virus (HEV) infection is typically self-limiting and has a favourable prognosis. However, certain populations such as patients with pre-existing chronic liver disease may experience severe manifestations, including progression to acute-on-chronic liver failure (ACLF). Among viral hepatitis types, hepatitis A, E, and B are major causes of ACLF. Active screening and early diagnosis of HEV infection in patients with cirrhosis, especially those who develop ACLF, can improve management and enable timely antiviral therapy. Preventive measures, including HEV vaccination for high-risk groups, could reduce the morbidity and mortality associated with hepatitis E. **(Clin Mol Hepatol 2025;31(Suppl):S196-S204)**

Keywords: Hepatitis E; Acute on chronic liver failure; Liver cirrhosis; Ribavirin; Vaccination

INTRODUCTION

Hepatitis E virus (HEV) is a major contributor to acute hepatitis worldwide. It is estimated to cause at least 20 million infections annually, leading to 3.4 million symptomatic cases and 70,000 deaths. This places a significant burden on health systems around the world.[1-3] While most acute hepatitis E cases are asymptomatic in healthy individuals, the infection can take a severe course in certain populations. Outbreaks of acute hepatitis E in low-income countries have been associated with cases of acute liver failure, with high morbidity and mortality rates, particularly among pregnant women.[2-4] In immunocompromised individuals, such as solid organ transplant recipients, acute HEV infection can progress to chronic infection with rapid development of cirrhosis.[2,3] Additionally, in chronic liver disease patients, HEV infection can lead to acute-on-chronic liver failure (ACLF).

In this review we aimed to focus on several aspects of acute HEV infection as a trigger for ACLF in patients with chronic liver disease, including its prevalence, mortality, diagnosis, pathogenesis, therapy, and prevention.

VIROLOGY

HEV belongs to the *Hepeviridae* family, a diverse group of viruses that infect mammals, birds, and fish. While HEV mainly targets the liver, it has also been found to infect other tissues, such as neuronal, kidney and placental tissue, which

Corresponding author : **Maria Buti**
Liver Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Paseo Valle Hebrón 119-129; Barcelona 08035, Barcelona, Spain
Tel: (+34) 932746559, E-mail: mariabutiferret@gmail.com
https://orcid.org/0000-0002-0732-3078

Editor: Hyung Joon Yim, Korea University, Korea

Received: Sep. 5, 2024 / **Revised:** Oct. 27, 2024 / **Accepted:** Nov. 7, 2024

helps explain some of its extrahepatic manifestations.

HEV is a single positive-stranded RNA virus, 7.2 kb in size. The viral particles have a diameter of 27 to 34 nm. The virions are non-enveloped in faeces and bile, while in blood they circulate in a membrane-associated, quasi-enveloped configuration. The genome consists of three open reading frames (ORFs) encased by noncoding regions, a 5' cap, and a poly-A tail. ORF1 encodes a non-structural polyprotein essential for viral replication, ORF2 encodes the viral capsid protein, and ORF3 is involved in the release of infectious virions from host cells.[3] HEV is divided into at least 8 different genotypes. HEV 1 to 4 mainly affect humans, HEV 5 and 6 are limited to wild boars, and HEV-7 and 8 infect dromedary and Bactrian camels. In rare cases, humans can be infected by HEV-7. Routes of transmission of the different HEV genotypes are summarized in Figure 1.

HEV genotypes show considerable variation in geographical distribution, modes of transmission, and disease progression. HEV-1 and HEV-2 are mainly spread through faecal-contaminated water, often due to incidents with water supply or natural disasters. These genotypes cause human disease in regions with inadequate sanitary infrastructure, such as parts of Asia (HEV-1), Africa (HEV-1 and HEV-2), and Mexico (HEV-2). In these areas, HEV is known to cause large outbreaks involving thousands or even tens of thousands of individuals, although sporadic cases also occur. Notably, no cases of chronic infection have been reported in relation to HEV-1 or HEV-2 (Fig. 1).

HEV-3 and HEV-4 infect mammalian species, particularly pigs and wild boars. Humans are mainly infected through foodborne zoonotic transmission after consuming undercooked or raw pork, game meat, or shellfish. HEV-3 is found worldwide, whereas HEV-4 is mainly limited to Southeast Asia, although it has also been detected in

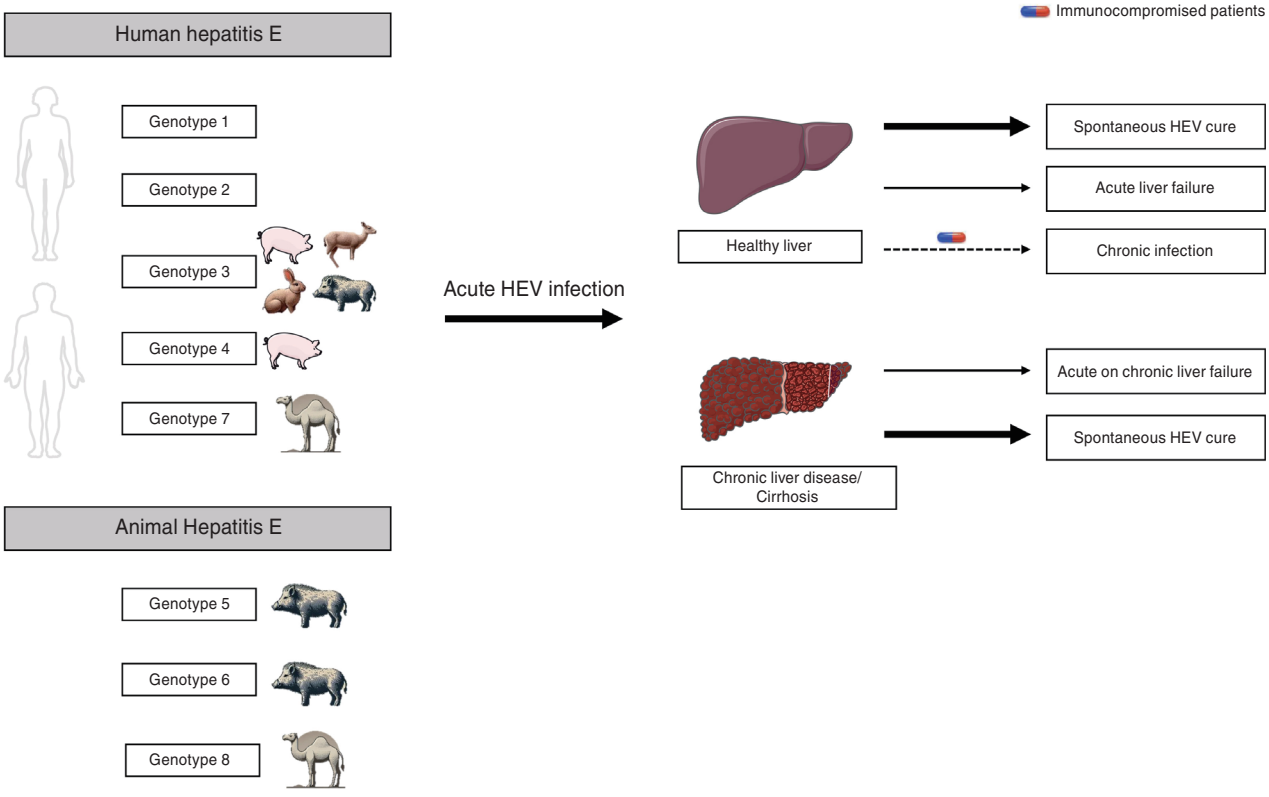


Figure 1. Hepatitis E hosts and type of infection according to genotype. HEV, hepatitis E virus.

Abbreviations:

ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; CLD, chronic liver disease; EASL-CLIF, European Association for the Study of the Liver Chronic Liver Failure; HAV, hepatitis A; HEV, hepatitis E virus; ICU, intensive care unit; IL, interleukin; IFN, interferon; OR, odds ratio; ORFs, open reading frames; TNF, tumor necrosis factor

European pigs. In humans, HEV-3 and HEV-4 cause sporadic cases of acute viral hepatitis in high- and middle-income countries, with fewer cases occurring in low-income countries.[5] Most sporadic acute hepatitis E cases have been reported in Europe, particularly in Southwest France and England.[3] Acute HEV infections related to HEV-3 and HEV-4 can progress to chronic hepatitis and liver cirrhosis, especially in organ transplant recipients and immunocompromised individuals. In addition, HEV-3 has been associated with a risk of inducing extrahepatic manifestations, particularly neurological symptoms.[6] In patients with chronic liver disease, HEV superinfection can progress to ACLF.[3]

HEV SUPERINFECTION AND MORTALITY IN PATIENTS WITH CHRONIC LIVER DISEASE

The first cases of HEV superinfection in patients with chronic liver disease (CLD) were reported by Hamid et al.[7] in Pakistan in 2002. These authors documented 4 cases of HEV superinfection in patients with compensated cirrhosis who developed severe liver decompensation, one of whom died. The diagnosis was based on the presence of IgG anti-HEV, but HEV RNA and genotype were not determined. Overall, 41 of 233 (17.5%) CLD patients tested positive for HEV antibodies. This study was the first to show that HEV superinfection in patients with underlying CLD can cause severe hepatic decompensation, leading to increased morbidity and mortality.

Subsequently, several studies from HEV-endemic regions in Asia and Africa reported HEV infection as a major cause of ACLF in patients with compensated cirrhosis.[8-24] The largest study, from China, included 188 patients with chronic hepatitis B infection. Among the total, 136 had HEV superinfection and 52 had hepatitis A virus (HAV) superinfection.[12] The HEV group experienced a larger percentage of complications (94.9% vs. 61.5%, $P<0.001$), and liver failure (39.7% vs. 11.5%, $P=0.002$) compared to the HAV group. Furthermore, mortality was significantly higher in the HEV group (33.8% vs. 1.9%, $P<0.001$), indicating that chronic hepatitis B patients with HEV superinfection face more severe liver disease and a poorer prognosis than those with HAV superinfection.

Another large Asian study, performed in India,[22] analysed 121 cases of ACLF. The precipitating cause of the condition was found to be HEV in 80 (61%) patients, HAV in 33 (27%), and a combination of both in 8 (6%). The underlying liver cirrhosis in these patients had several aetiologies, such as hepatitis B infection, alcohol consumption, Wilson's disease, hepatitis C infection, autoimmune disorders, Budd-Chiari syndrome, hemochromatosis, and cryptogenic origins. The 3-month mortality rate for the cohort was 45%. On multivariate analysis, grades 3 and 4 hepatic encephalopathy (odds ratio [OR] 32.1), hyponatremia (OR 9.2), and renal failure (OR 16.8) were significant predictors of 3-month mortality.

Neither of these studies conducted in Asia reported data on HEV genotype. However, the epidemiology of HEV is changing in certain countries like China, where the previously dominant HEV genotype 1 has become less common, while zoonotic genotypes 3 and 4 are now the most prevalent.[23] A recent retrospective study from Taiwan by Tseng et al.[20] in patients with chronic hepatitis B infection found a similar percentage of HEV superinfection regardless of liver damage: 10 (2.4%) of 414 patients with cirrhosis and 46 (2.1%) of 2,123 without cirrhosis. However, the 1-year mortality rate after HEV superinfection was higher in patients who developed cirrhosis during follow-up compared to those who did not (50% vs. 2.4%, $P=0.001$).[20] This is one of the few Asian studies reporting HEV genotype results. All patients were infected with HEV-4, in contrast to the presumed HEV-1 in previous Asian studies, which may have contributed to the lower ACLF rate.

In Europe, hepatitis E is primarily a zoonotic infection associated with swine and caused mainly by the HEV-3 strain. A prospective study at three United Kingdom centres and one in Toulouse (France) found that hepatitis E was present in a small percentage of patients with decompensated CLD. Among 343 such patients, 11 (3.2%) had acute HEV infection, with five patients infected by HEV-3.[18] Over a six-month follow-up, three of these patients died. The incidence of hepatitis E was higher in Toulouse than in the UK (7.9% vs 1.2%, $P=0.003$). Patients with CLD and acute hepatitis E were older (>50 years), predominantly male, and had elevated alanine aminotransferase levels. The main cause of liver disease was alcohol abuse. Mortality rates did not significantly differ between patients with and without hepatitis E infection, although the number of hepatitis E cases was relatively low.

In a retrospective study including 511 cases of acute

https://doi.org/10.3350/cmh.2024.0758

hepatitis E in Scotland, 58 patients (11%) had pre-existing cirrhosis, and there were 17 (3.3%) HEV-related deaths.[24] The two most important factors predicting mortality were haematological malignancy (OR 51.56; 95% CI 3.40–782.83; *P*=0.005) and cirrhosis (OR 41.85; 95% CI 2.85–594.16; *P*=0.006). The findings indicate that HEV causes a significant burden of inpatient admissions and deaths.

In the PREDICT study, a multicentre European study involving 1273 hospitalized patients with acute liver decompensation (no ACLF, n=1,071; ACLF, n=202), the primary precipitating factors were bacterial infection, severe alcoholic hepatitis, gastrointestinal bleeding, and toxic encephalopathy.[25] Only 16 cases of viral hepatitis or other viral infections (etiologic agent not shown) were reported as precipitating factors. The study found no significant difference in acute viral hepatitis rates between patients with ACLF (1.4%) and those without (1.2%), suggesting that viral hepatitis is a rare cause of ACLF in Europe.

ACUTE HEV SUPERINFECTION INCREASES MORTALITY IN PATIENTS WITH CIRRHOSIS REGARDLESS OF THE ACLF DEFINITION

Previous studies conducted in Asia found a 12-month mortality rate approaching 70% in HEV-infected patients with underlying CLD.[9] In this line, two small European studies reported that patients with locally acquired HEV infection and pre-existing CLD or alcohol abuse (3 patients in the UK and 7 in France) had an approximate mortality rate of 70%.[26,27] However, recent data from 11 patients with decompensated CLD in UK/France showed that only 3 (27%) died within 180 days of presentation.[18] The discrepancy in mortality could be attributed to differences in the definition of ACLF across studies, which vary in international guidelines due to differences in the precipitating events and underlying aetiology. According to the European Association for the Study of the Liver Chronic Liver Failure (EASL-CLIF) Consortium, ACLF is established based on failure of one of the six major organ systems: liver, kidney, brain, coagulation, circulation, and respiration.[28] In contrast, the Asian Pacific Association for the Study of the Liver (APASL) defines ACLF in patients with CLD as an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL) and coagulation dysfunction (international normalized ratio ≥1.5), complicated within 4 weeks by overt ascites and/or hepatic encephalopathy.[29] Table 1 shows a selection of studies on the rate and mortality related to hepatitis E virus infection as a trigger of acute-on-chronic liver failure, according to the geographical distribution.

Table 1. Selected studies on the rate and mortality related to hepatitis E virus infection as a trigger of acute-on-chronic liver failure, according to the geographical distribution

Country	Author, year	No of patients	Rate of ACLF triggered by HEV	Mortality of HEV-related ACLF
China[11,12]	Ke et al., 2006	107	75%	100%*
	Zhang et al., 2010	188	72%	34%
India[13,14]	Kumar and Saraswat, 2013†	763	4–66%	0–67%
	Gawande et al., 2019	208	7.2%	11.5%‖
Bangladesh[15]	Mahtab et al., 2009	69	22%	13%
Egypt[16]	El Sayed Zaki and Othman, 2011	100	13%	23%
France[17]	Haim-Boukobza et al., 2015§	84	3.6%	100%
France/United Kingdom[18]	Blasco-Perrin et al., 2015	343	3.2%	27%
Gambia[19]	Shimakawa et al., 2016	40	0%	-
Taiwan[20]	Tseng et al., 2020‡	414	NA	36%
Korea[21]	Choi et al., 2022**	22	31.8%	57.1%

ACLF, acute-on-chronic liver failure; HEV, hepatitis E virus; NA, not applicable.
*In the cohort from Ke et al. only fatal cases were included. †This reference includes data from 11 different studies carried out throughout India. ‡This cohort only included patients with underlying chronic hepatitis B. §Only patients with severe acute alcoholic hepatitis were included. ‖In this cohort mortality for all viral hepatitis was analysed altogether (HEV and hepatitis B reactivation). **In this cohort only patients with acute HEV were included.

A study by Choi et al.[21] illustrates how the ACLF definition can affect mortality rates. The study, involving 74 Korean patients with acute HEV infection, reported an overall 180-day mortality rate of 9.5%: 3.8% in patients without cirrhosis compared to 22.7% with cirrhosis (*P*=0.013), an approximately eightfold higher mortality risk in cirrhosis patients.[21] In a further analysis, the authors applied the EASL and APASL ACLF criteria to their results and compared the findings. The 180-day mortality rate was 57.1% following the EASL criteria and 28.6%, according to the APASL criteria. These values were higher than those observed in patients without ACLF or underlying liver disease, suggesting that deterioration of pre-existing liver status and the development of organ failure are both crucial factors influencing the prognosis of patients with acute HEV infection.[21]

SHOULD CLINICIANS ROUTINELY TEST PATIENTS WITH ACLF FOR HEPATITIS E?

The EASL guidelines recommend HEV testing for all patients with unexplained flares of chronic liver disease, those with ACLF, and immunosuppressed patients with unexplained abnormal liver function analyses. Recommended tests include anti-HEV IgM, anti-HEV IgG, and HEV RNA for patients with elevated liver enzymes, and HEV RNA for immunocompromised patients.[3] HEV testing rates are generally low, leading to frequent underdiagnoses of this infection.[30] In a recent study, a common finding was significantly higher aspartate aminotransferase (AST) levels in patients with HEV-related ACLF (median AST 2,818 U/L; range 1,176–8,611) compared to matched patients with severe alcoholic hepatitis. However, the number of cases included was very low.[29]

Histological damage is not a characteristic feature of ACLF. In a Swiss study of 5 patients who died in the context of HEV-related ACLF, histological analyses showed steatohepatitis on a background of cirrhosis, suggesting an alcoholic or non-alcoholic origin, with no specific signs of HEV infection. Two of these patients had been treated with corticosteroids due to an initial suspicion of alcoholic hepatitis based on the histopathological findings, showing that histopathology can be misleading.[31]

IMMUNE RESPONSES AND REGULATORY MECHANISMS OF HEPATITIS E-ASSOCIATED LIVER FAILURE

Previous research has shown that the host immune response, rather than the virus itself, is the primary driver of HEV-associated liver failure and ACLF.[32] When these conditions occur, a series of changes takes place in both the intrahepatic environment and extrahepatic microenvironment. The immune imbalance is attributed to alterations in the type and distribution of immune cells, particularly infiltrating macrophages and lymphocytes, within liver tissue. Immune cell counts are significantly higher in ACLF patients than in healthy individuals.[32] Although the pathogenesis of ACLF has not been fully elucidated, the differences in lymphocyte counts suggest that cellular immunity is involved in progression of the disease.

Cytotoxic T cells and elevated levels of proinflammatory cytokines and chemokines, such as interferon (IFN)-γ, tumour necrosis factor (TNF)-α, interleukin (IL)-10 and IL-18, have been linked to adverse outcomes in HEV patients.[33] The gene expression profile in liver tissue of HEV-infected individuals with liver failure shows considerable changes, with many upregulated and downregulated genes associated with immune function compared to healthy liver tissue. In patients with HEV-related ACLF, hepatic levels of proinflammatory cytokines (IFN-γ and TNF-α) are significantly higher than those in healthy individuals, while the expression of anti-inflammatory cytokines (IL-10) remain unchanged. This suggests that an imbalance between proinflammatory and anti-inflammatory cytokine expression may be a crucial factor in the immune response contributing to the pathogenesis of HEV-related ACLF.

Recent studies have identified inborn errors in type I interferon immunity among patients with symptomatic acute hepatitis E. This group showed significant enrichment in type I interferon response pathways, with 10 of 24 patients carrying a damaging variant in one of nine genes involved in this immune response. These genes encode intracellular viral sensors (IFIH1, DDX58, TLR3, POLR3B, POLR3C) or other molecules involved in the type I interferon response.[34] In contrast, no such enrichment was observed in patients with HEV-associated neurological manifestations or in healthy controls, highlighting the essential role of type I interferon in preventing symptomatic acute hepatitis E.

https://doi.org/10.3350/cmh.2024.0758

MANAGEMENT OF HEV-RELATED ACLF

The clinical management of ACLF is generally similar regardless of the etiological agent. It includes hospital admission, supportive care in the intensive care unit (ICU) to address hepatic and extrahepatic complications, support for failing organs, and measures to halt disease progression.[28,29] Early transplantation and priority on the transplant waiting list is often necessary to improve survival due to the high short-term mortality rate associated with ACLF.

Currently, there is no recommended treatment for acute hepatitis E in the EASL clinical practice guidelines, as most HEV infections clear spontaneously.[3] However, certain patients may progress to liver failure. Ribavirin has been suggested for patients with chronic hepatitis E, with therapy leading to rapid normalization of liver enzymes and undetectable HEV RNA within a few days.[3,35] Although very few case reports are available on ribavirin treatment for severe acute HEV infection or ACLF,[18,31] the rationale behind its use is that early therapy may shorten the disease course and reduce morbidity, as has been shown in the treatment of acute hepatitis caused by hepatitis B or C. However, due to the high short-term mortality of ACLF, the effectiveness of ribavirin in this situation is difficult to assess. In these cases, ribavirin is administered at a dose of 400 to 600 mg daily, with no new side effects reported.[3] Table 2 shows the cases reported treated with ribavirin.[6,24,31,35,36,37]

Corticosteroids have been used in individual cases of ACLF that were later retrospectively identified as being caused by HEV, as well as in some cases of acute liver failure where misinterpretation in the diagnosis occurred.[3,31] Steroid therapy has been associated with improved liver function in acute liver failure, but there is insufficient data on its effectiveness in ACLF. The current evidence does not suffice to support corticosteroid treatment in patients with acute liver failure due to HEV infection.

PREVENTION OF HEV INFECTION

Individuals at risk of severe acute or chronic HEV infection should avoid consuming foods that may harbour the virus such as undercooked meat from pigs, wild boar, deer, and shellfish. In several case-control studies, previous consumption of certain food products has been conclusively identified as a risk factor for HEV infection.[3]

In 2011, a vaccine against HEV was licensed in China. The vaccine is based on a protein containing 239 amino acids from the HEV ORF2 protein (aa 368–606) derived from HEV-1. It demonstrated a 97% efficacy for preventing symptomatic acute hepatitis E infection, with long-term protection confirmed during a 10-year follow-up. Vaccine-induced antibodies against HEV persisted for at least 8.5 years.[38,39] Although the vaccine was tested in China, where HEV genotype 4 is predominant, suggesting cross genotype efficacy, it does not provide sterilizing immunity, which means subclinical infections can still occur. The HEV-239 vaccine has not yet been prequalified by the World Health Organization, a necessary step for its introduction in low- and middle-income countries where the disease burden is highest.

Table 2. Studies reporting cases of HEV-related ACLF treated with Ribavirin

Country	Year	Number of cases	Aetiology of underlying cirrhosis	MELD (range)	RBV dosage (range, mg daily)	RBV duration (range, days)	Side effects/ discontinuation	Outcome
France[36]	2011	2	NA	NA	100–1,000	10–60	None/No	2 SVR
India[35]	2012	4	1 HBV 2 AIH 1 NA	NA	200–600	21–168	1 anaemia/1 (hematuria)	4 SVR
France[37]	2016	3	ARLD	NA	600–1,000	10–28	None/no	1 SVR; 2 deaths
Switzerland[6]	2018	2	NA	NA	NA	1 and 5	None/no	2 deaths
Scotland[24]	2020	4	ARLD	NA	NA	5–30	NA/NA	1 SVR; 3 deaths
Switzerland[31]	2021	4	ARLD	27-40	200–800	5–17	NA/NA	4 deaths*

AIH, autoimmune hepatitis; ARLD, alcohol related liver disease; HBE; hepatitis B virus; HEV, hepatitis E virus; NA, not available; SVR, sustained virological response.
*Only patients who died as consequences of HEV-related ACLF were included in this cohort.

Recently, in response to a hepatitis E outbreak in South Sudan, a vaccination campaign was launched to provide protection for women and girls of reproductive age, who are at the highest risk of death from the disease in case of acute liver failure development.[40] Since October 2022, 299 participants, including pregnant women, have been vaccinated, and the preliminary data suggest strong short-term coverage. Furthermore, the vaccine seems to be safe for use during pregnancy.[41]

However, the effectiveness and tolerability of the HEV vaccine has yet to be assessed in other populations at risk of severe infection, such as patients with chronic liver disease and immunosuppressed individuals, particularly those with solid organ transplants who are susceptible to chronic hepatitis and rapid progression to cirrhosis.[42] These populations appear to be ideal candidates, although the effectiveness of the vaccine may be lower in these cases, as was seen with other vaccines. There is an urgent need to test the hepatitis E vaccine in these groups to determine whether it can prevent or mitigate ACLF.

In summary, acute hepatitis E infection is a well-stablished cause of ACLF in patients with CLD, especially in areas where this infection is endemic. In case of ACLF development, supportive care in the ICU is crucial for supporting the failing organs and halting the disease progression. Besides, the majority of these patients may need early transplantation and priority on the transplant waiting list to improve their survival. Ribavirin treatment may be considered in cases of severe acute hepatitis or acute-on-chronic liver failure, though its efficacy and safety require further research.

Authors' Contributions

All authors contributed to the study design, literature review, drafting, and critical revision of the manuscript.

Conflicts of Interest

Maria Buti advisory board and/or speakers' bureau fees: AbbVie, Altimmune, Janssen, GlaxoSmithKline, Gilead and Roche; Grants: Gilead. Mar Riveiro-Barciela: advisory board and/or speakers' bureau fees: Bristol Myers Squibb, Gilead, GlaxoSmithKline; Grants: Gilead.

REFERENCES

1. Odenwald MA, Paul S. Viral hepatitis: Past, present, and future. World J Gastroenterol 2022;28:1405-1429.
2. Songtanin B, Molehin AJ, Brittan K, Manatsathit W, Nugent K. Hepatitis E virus infections: Epidemiology, genetic diversity, and clinical considerations. Viruses 2023;15:1389.
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatitis E virus infection. J Hepatol 2018;68:1256-1271.
4. Shalimar, Acharya SK. Hepatitis e and acute liver failure in pregnancy. J Clin Exp Hepatol 2013;3:213-224.
5. Colson P, Romanet P, Moal V, Borentain P, Purgus R, Benezech A, et al. Autochthonous infections with hepatitis E virus genotype 4, France. Emerg Infect Dis 2012;18:1361-1364.
6. Fraga M, Doerig C, Moulin H, Bihl F, Brunner F, Müllhaupt B, et al. Hepatitis E virus as a cause of acute hepatitis acquired in Switzerland. Liver Int 2018;38:619-626.
7. Hamid SS, Atiq M, Shehzad F, Yasmeen A, Nissa T, Salam A, et al. Hepatitis E virus superinfection in patients with chronic liver disease. Hepatology 2002;36:474-478.
8. Kumar M, Sharma BC, Sarin SK. Hepatitis E virus as an etiology of acute exacerbation of previously unrecognized asymptomatic patients with hepatitis B virus-related chronic liver disease. J Gastroenterol Hepatol 2008;23:883-887.
9. Qiu LX, Huang Y, Quan JL, Bi ZF, Zhong GH, Wang JY, et al. Prognosis of hepatitis E infection in patients with chronic liver disease: A meta-analysis. J Viral Hepat 2023;30:101-107.
10. Zhao H, Ye W, Yu X, Hu J, Zhang X, Yang M, et al. Hepatitis E virus superinfection impairs long-term outcome in hospitalized patients with hepatitis B virus-related decompensated liver cirrhosis. Ann Hepatol 2023;28:100878.
11. Zhang X, Ke W, Xie J, Zhao Z, Xie D, Gao Z. Comparison of effects of hepatitis E or A viral superinfection in patients with chronic hepatitis B. Hepatol Int 2010;4:615-620.
12. Ke WM, Li XJ, Yu LN, Lai J, Li XH, Gao ZL, et al. Etiological investigation of fatal liver failure during the course of chronic hepatitis B in southeast China. J Gastroenterol 2006;41:347-351.
13. Kumar A, Saraswat VA. Hepatitis E and acute-on-chronic liver failure. J Clin Exp Hepatol 2013;3:225-230.
14. Gawande A, Gupta GK, Gupta A, Wanjari SJ, Goel V, Rathore V, et al. Acute-on-chronic liver failure: Etiology of chronic and acute precipitating factors and their effect on mortality. J Clin Exp Hepatol 2019;9:699-703.

https://doi.org/10.3350/cmh.2024.0758

15. Mahtab MA, Rahman S, Khan M, Karim MF. Hepatitis E virus is a leading cause of acute-on-chronic liver disease: experience from a tertiary centre in Bangladesh. Hepatobiliary Pancreat Dis Int 2009;8:50-52.
16. El Sayed Zaki M, Othman W. Role of hepatitis E infection in acute on chronic liver failure in Egyptian patients. Liver Int 2011;31:1001-1005.
17. Haim-Boukobza S, Coilly A, Sebagh M, Bouamoud M, Antonini T, Roche B, et al. Hepatitis E infection in patients with severe acute alcoholic hepatitis. Liver Int 2015;35:870-875.
18. Blasco-Perrin H, Madden RG, Stanley A, Crossan C, Hunter JG, Vine L, et al. Hepatitis E virus in patients with decompensated chronic liver disease: a prospective UK/French study. Aliment Pharmacol Ther 2015;42:574-581.
19. Shimakawa Y, Njai HF, Takahashi K, Berg L, Ndow G, Jeng-Barry A, et al. Hepatitis E virus infection and acute-on-chronic liver failure in West Africa: a case-control study from The Gambia. Aliment Pharmacol Ther 2016;43:375-384.
20. Tseng TC, Liu CJ, Chang CT, Su TH, Yang WT, Tsai CH, et al. HEV superinfection accelerates disease progression in patients with chronic HBV infection and increases mortality in those with cirrhosis. J Hepatol 2020;72:1105-1111.
21. Choi JW, Son HJ, Lee SS, Jeon H, Cho JK, Kim HJ, et al. Acute hepatitis E virus superinfection increases mortality in patients with cirrhosis. BMC Infect Dis 2022;22:62.
22. Radha Krishna Y, Saraswat VA, Das K, Himanshu G, Yachha SK, Aggarwal R, et al. Clinical features and predictors of outcome in acute hepatitis A and hepatitis E virus hepatitis on cirrhosis. Liver Int 2009;29:392-398.
23. Kamar N, Bendall R, Legrand-Abravanel F, Xia NS, Ijaz S, Izopet J, et al. Hepatitis E. Lancet 2012;379:2477-2488.
24. Wallace SJ, Swann R, Donnelly M, Kemp L, Guaci J, Murray A, et al. Mortality and morbidity of locally acquired hepatitis E in the national Scottish cohort: a multicentre retrospective study. Aliment Pharmacol Ther 2020;51:974-986.
25. Trebicka J, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, et al. PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis. J Hepatol 2021;74:1097-1108.
26. Dalton HR, Hazeldine S, Banks M, Ijaz S, Bendall R. Locally acquired hepatitis E in chronic liver disease. Lancet 2007;369:1260.
27. Péron JM, Bureau C, Poirson H, Mansuy JM, Alric L, Selves J, et al. Fulminant liver failure from acute autochthonous hepatitis E in France: description of seven patients with acute hepatitis E and encephalopathy. J Viral Hepat 2007;14:298-303.
28. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on acute-on-chronic liver failure. J Hepatol 2023;79:461-491.
29. Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. Hepatol Int 2019;13:353-390.
30. Li P, Liu J, Li Y, Su J, Ma Z, Bramer WM, et al. The global epidemiology of hepatitis E virus infection: A systematic review and meta-analysis. Liver Int 2020;40:1516-1528.
31. Vieira Barbosa J, Müllhaupt B, Brunner F, Filipowicz Sinnreich M, Semela D, Montani M, et al. Autochthonous hepatitis E as a cause of acute-on-chronic liver failure and death: histopathology can be misleading but transaminases may provide a clue. Swiss Med Wkly 2021;151:w20502.
32. Chen C, Zhang SY, Chen L. Review of clinical characteristics, immune responses and regulatory mechanisms of hepatitis E-associated liver failure. World J Clin Cases 2022;10:6341-6348.
33. Krawczynski K, Meng XJ, Rybczynska J. Pathogenetic elements of hepatitis E and animal models of HEV infection. Virus Res 2011;161:78-83.
34. Saadat A, Gouttenoire J, Ripellino P, Semela D, Amar S, Frey BM, et al. Inborn errors of type I interferon immunity in patients with symptomatic acute hepatitis E. Hepatology 2024;79:1421-1431.
35. Goyal R, Kumar A, Panda SK, Paul SB, Acharya SK. Ribavirin therapy for hepatitis E virus-induced acute on chronic liver failure: a preliminary report. Antivir Ther 2012;17:1091-1096.
36. Péron JM, Dalton H, Izopet J, Kamar N. Acute autochthonous hepatitis E in western patients with underlying chronic liver disease: a role for ribavirin? J Hepatol 2011;54:1323-1324; author reply 1324-1325.
37. Péron JM, Abravanel F, Guillaume M, Gérolami R, Nana J, Anty R, et al. Treatment of autochthonous acute hepatitis E with short-term ribavirin: a multicenter retrospective study. Liver Int 2016;36:328-333.
38. Zhu FC, Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet 2010;376:895-902.
39. Huang S, Zhang X, Su Y, Zhuang C, Tang Z, Huang X, et al. Long-term efficacy of a recombinant hepatitis E vaccine in adults: 10-year results from a randomised, double-blind,

placebo-controlled, phase 3 trial. Lancet 2024;403:813-823.
40. Ciglenecki I, Rumunu J, Wamala JF, Nkemenang P, Duncker J, Nesbitt R, et al. The first reactive vaccination campaign against hepatitis E. Lancet Infect Dis 2022;22:1110-1111.
41. Nesbitt R, Asilaza V, Gitahi P, Nkemenang P, Haile M, Duncker J, et al. The first mass reactive vaccination campaign against hepatitis E in Bentiu, South Sudan: feasibility, vaccination coverage and two-dose vaccine effectiveness. J Hepatol 2023;78:S74-S75.
42. Peron JM, Larrue H, Izopet J, Buti M. The pressing need for a global HEV vaccine. J Hepatol 2023;79:876-880.

https://doi.org/10.3350/cmh.2024.0758