

Review

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Hepatitis A and E Viruses Are Important Etiologies of Acute Severe Hepatitis in Asia-Pacific Countries: A Narrative Review

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Review

Hepatitis A and E Viruses are Important Etiologies of Acute Severe Hepatitis in Asia–Pacific Countries: A Narrative Review

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Abstract: Background/Objectives: Acute-on-chronic liver failure (ACLF) and acute liver failure (ALF) are symptoms of acute severe hepatitis which can result in higher liver-related mortality without liver transplantation following acute hepatitis and acute liver injury in patients with and without chronic liver diseases, respectively. Hepatitis A and E viruses (HAV and HEV) infect humans through the fecal–oral route, causing acute hepatitis A and E. Hepatitis E also causes zoonosis, which causes chronic hepatitis E in immunocompromised hosts. These viruses replicate in hepatocytes and egress into blood and feces through the biliary tract system. Prevention and treatment of these viruses is a major health concern. **Methods:** This narrative review is the result of a traditional, nonsystematic review. **Discussion:** The Japan Agency for Medical Research and Development (AMED) HAV and HEV Study Group has recently published two guidelines for HAV and HEV infections. Medical researchers should highlight the importance of HAV and HEV infection, and share various guidelines so that patients infected with HAV and HEV are accurately diagnosed and treated. In Asia–Pacific countries, guidelines for hepatitis A and E to prevent progression to ALF and ACLF are required. **Conclusions:** It is important to develop and highlight specific treatment and preventive methods, including vaccines, for HAV/HEV. Medical researchers should notice that HAV and HEV infections still play roles in progression to acute severe hepatitis in Asia–Pacific countries.

Keywords: Asia; guideline; genotype; hepatitis A virus; hepatitis E virus; vaccine

1. Introduction

Acute acute-on-chronic liver failure (ACLF) and acute liver failure (ALF), are severe conditions which occur, respectively, in patients with or without chronic liver diseases/cirrhosis or cirrhosis. Both ACLF and ALF are associated with high mortality rates unless liver transplantation is performed [1–3].

Hepatitis A virus (HAV) infection causes acute hepatitis, occasionally leading to ALF and ACLF [4]. HAV also causes extrahepatic manifestations. Hepatitis E virus (HEV) infection causes acute hepatitis, including ALF and ACLF, chronic hepatitis (especially in compromised hosts), and various extrahepatic manifestations [5–7].

McSteen et al. reviewed the viral causes of ALF, along with diagnosis, treatment options and expected outcomes [8]. Although drug-induced liver injury, including acetaminophen (paracetamol) overdose, is the leading cause of ALF in Western countries [8–10], viral infection is a common cause of ALF in Asia–Pacific countries [11–14]. Viral infection is also one of the major causes of ACLF in Asia–Pacific countries [15–17].

Recently, it has become easier to treat patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection because of the development of nucleoside/nucleotide analogues [18–20] and direct-

acting antivirals (DAAs) [21], although there are several issues still be addressed in this area [22–24]. In this paper, we describe the roles played by HAV and HEV infection in ALF and ACLF. We also discuss the present situation regarding development of specific treatment and preventive methods, including vaccines, for HAV/HEV.

2. Methods

A traditional, nonsystematic literature review was carried out using PubMed for the purpose of this narrative review.

3. ALF AND ACLF

3.1. Definitions of acute severe hepatitis: ALF and ACLF

ALF, or fulminant hepatic failure, occurs in patients without pre-existing liver diseases. It is a life-threatening disease characterized by severe liver damage with coagulopathy, hepatic encephalopathy, and high mortality [25]. ALF is defined according to the time interval between the development of symptoms and onset of hepatic encephalopathy [25,26]. Trey and Davidson defined ALF as a condition in which there is development of hepatic encephalopathy within 8 weeks of the first symptoms of liver disease as fulminant hepatic failure [27].

O'Grady et al. classified cases in which hepatic encephalopathy developed within 7 days of the onset of jaundice as “hyperacute liver failure”, from 8 to 28 days as “acute liver failure”, and from 5 to 12 weeks as “subacute liver failure” [28]. Bernuau et al. defined cases in which hepatic encephalopathy developed within 2 weeks after the appearance of jaundice as “fulminant liver failure”. When hepatic encephalopathy developed within 2 weeks to 3 months, this was defined as “subfulminant liver failure” [29].

In Japan, patients showing 40% or less of the standardized prothrombin time value or having an INR of 1.5 or more caused by severe liver damage within 8 weeks of onset of symptoms are diagnosed as having ALF [30–32]. Gimson et al. defined patients in whom hepatic encephalopathy occurs between 8 and 24 weeks after the first symptoms of liver diseases as late-onset hepatic failure (LOHF) [33].

The Asia-Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC) for APASL ACLF Working Party defined ACLF as acute hepatic insult manifesting as jaundice and coagulopathy, leading to complications within 4 weeks, defined by ascites and/or encephalopathy, in patients with previously diagnosed or undiagnosed chronic liver disease associated with high mortality [1]. The European Association for the Study of the Liver (EASL)/Chronic Liver Failure (CLIF) defined ACLF as an acute deterioration of pre-existing chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure [34,35]. The North American Consortium For The Study Of End-Stage Liver Disease (NACSELD) defined ACLF as a syndrome characterized by acute deterioration in a patient with cirrhosis due to infection presenting with failure of two or more extrahepatic organs [36].

In Japan, ACLF has been defined as a patient with cirrhosis and a Child–Pugh score of 5–9 in which there is deterioration of liver function (serum bilirubin level equal to or more than 5.0 mg/dL and prothrombin time value equal to or less than 40% of the standardized values and/or international normalization rate equal to or more than 1.5) caused by severe liver damage developing within 28 days after acute insults (alcohol abuse, bacterial infection, gastrointestinal bleeding, or the exacerbation of underlying liver diseases) [37].

Thus, although there are various definitions, ACLF and ALF may be understood as severe forms of acute hepatitis in patients who may or may not suffer from chronic liver disease. As ALF and ACLF patients also have poor prognosis without liver transplantation, it is very important to diagnose their etiologic agents.

3.2. Causes of ALF and ACLF

It is now widely known that ALF is caused by various viral infections, drugs, autoimmune hepatitis, and other factors. The causes of ACLF are similar, but also include excess alcohol intake [1,8,25]. McSteen et al. presented a summary of viral causes of ALF, diagnostic approaches, treatment options and expected outcomes [8]. This showed that HAV, HBV, HCV, hepatitis delta virus (HDV), HEV, cytomegalovirus (CMV), Epstein–Barr virus (EBV), varicella zoster virus (VZV), parvovirus B19, herpes simplex virus (HSV), yellow fever (YF), dengue virus (DENV), and human adenovirus (HAdV) are all causes of ALF [8].

In Asian countries, reactivation of HBV as an acute hepatic insult is the leading cause of ACLF [1]. On the Indian subcontinent, superinfection with HEV is the other important infectious event in ACLF cases [1]. Among the noninfectious etiologies, alcoholic hepatitis is the major cause of acute deterioration, this being especially the case in Western countries [1].

For the present report, we focused on HAV and HEV infection as causes of ALF and ACLF.

4. HEPATITIS A VIRUS (HAV)

HAV is a nonenveloped RNA virus with a length of approximately 7.6 kb [4,8]. In general, HAV replicates mainly in the liver and is a noncytopathic virus. However, HAV virions are egressed nonlytically from HAV-infected hepatocytes into blood vessels and bile canaliculus as quasi-enveloped virions (eHAV) cloaked in host membranes similar to exosomes but lacking any HAV RNA genome-derived protein on the surface, so that eHAV efficiently enters cells [4,38,39]. eHAV is resistant to neutralizing antibodies; it is released across the canalicular membrane and stripped of membranes by bile acids acting as detergents within the proximal biliary canaliculus. A highly stable naked nonenveloped virion is thereby formed which is shed in feces and optimized for transmission [40,41].

4.1. Symptoms of HAV infection

In adults with acute HAV infection, jaundice, abdominal pain, appetite loss, nausea, vomiting, diarrhea, and hyperbilirubinemia peaking at 7–10 days after jaundice onset, are typically presented [4]. Adults with acute HAV infection present with higher fever than those with other types of acute viral hepatitis. Children with acute HAV infection are asymptomatic.

4.2. Diagnosis of hepatitis A

In general, diagnosis of hepatitis A is confirmed by a positive result for anti-HAV IgM antibodies [4]. Delayed anti-HAV IgM seroconversion as a positive result for anti-HAV IgM on a repeat test after an initially negative result was observed in 38 (6.4%) of 595 patients with acute HAV infection in a Korean outbreak [42]. If a patient with a negative result for anti-HAV IgM antibody is suspected of having hepatitis A, then testing for the anti-HAV IgM antibody should be repeatedly conducted during the 7 days following the first examination.

HAV is transmitted via the fecal–oral route through consumption of HAV-contaminated food and water, person-to-person contact, etc. [8,43–48]. Data from the Japanese National Epidemiological Surveillance of Infectious Diseases program demonstrated that about 68% of individuals aged 60 years and older had anti-HAV antibodies, but only 1.1% of those aged below 60 years old had immunity; thus, almost all individuals younger than 60 years of age were susceptible to HAV infection [49]. Thus, we should notice that it is possible that HAV outbreaks may occur in developed countries as well as developing countries. In Japan, we observed an outbreak of acute HAV infection between 2018 and 2020 [50–54].

4.3. Acute severe hepatitis A

It is estimated that ALF progression occurs in 0.1%–0.5% of patients with acute HAV infection [8]. A Japanese study showed that numbers of patients with fulminant hepatitis and/or ALF coma

type with hepatic encephalopathy of grade 2 or higher, and LOHF caused by HAV infection were 65 (6.4%)/698, 14 (2.9%)/487 and 103 (6.4%)/1603 patients with acute HAV infection who were seen between 1998 and 2003, between 2004 and 2009, and between 2010 and 2015, respectively [55], although the frequency of HAV infection is decreasing year by year.

In India, the most common cause for ALF was found to be HAV infection, this being recorded in 81(44.2%) of 183 cases [56]. Also in India, ACLF due to HAV infection was observed in 33 (27.2%) of 121 adult patients with cirrhosis [15]. In Indiana, in the United States, the mortality rate for HAV infection caused by illicit drug use was found to be 2% in the period from January 2017 to April 2019, with ALF being seen in 4% of cases and ACLF in 30% [57]. In Ontario, Canada, 938 cases of hepatitis A were recorded between January 1, 2015 and November 22, 2022 (an average rate 0.9 case per 100,000 population). Asymptomatic infection among children and youth may be an important contributor to local transmission of HAV [58].

In Nepal, 266 (92.7%) of 287 children with hepatitis in a tertiary care center were found to have hepatitis A. One child died due to complication, and the mortality rate was therefore one (0.38%) out of two hundred and sixty-six children with hepatitis [59]. In India, HAV infection has been shown to be the most common cause (42%) of ACLF in children [60]. There are various host, viral, and other factors associated with severe HAV diseases; these are described in a previous work by ourselves [4].

It is important to note that HAV infection causes ALF in 2%(95% CI: 1-3) and 27%(95% CI: 13-43) of cases, respectively, in countries where HAV vaccination is performed or not [14]. It has been reported that, after HAV infection, fecal shedding of HAV can last for months after resolution of symptoms, and that such patients could be an important source of further local transmission [61,62].

4.3. Vaccine, and challenges facing developers of anti-HAV drugs to prevent HAV infection

Although HAV vaccination faces several challenges which remain to be solved [63,64], the HAV vaccine is effective in preventing HAV infection. Nevertheless, it is also important that anti-HAV drugs be developed. Researchers have previously demonstrated the effectiveness of small interfering RNAs against HAV [65–67] and HAV 3C cysteine protease inhibitors [68,69]. The effectiveness of interferon-alfa [70–74], interferon-lambda-1 [75], interferon-gamma [76], ribavirin [77–79], amantadine [77,78,80–82] and favipiravir [83] as direct-acting antivirals (DAAs) against HAV or host-targeting agents (HTAs) has also been reported.

In previous works, we have also shown that JAK2 inhibitor AZD1480 [84], sirtuin inhibitor sirtinol [85], Japanese rice-koji miso [86,87], zinc chloride [88,89], zinc sulfate [90], and nicotinamide [91] inhibit HAV replication. La protein [92], GRP78 (Bip) [90,93,94], mitogen-activated protein kinase 3 (MAP2K3) [89], and c-Jun [91] are all critical targets of anti HAV drugs.

A potential anti HAV 3C protease inhibitor, Z10325150, was identified in one molecular docking study [69]. Artificial intelligence and machine learning methods could support the development of anti-HAV drugs [69,95]. It is important to develop and disseminate HAV vaccines with lower costs and greater efficacy, and to develop antivirals against HAV infection [4]. Useful recommendations and guidelines for prevention of HAV infection have been produced in the United States [96,97], as well as in Asia-Pacific countries [4]. However, further studies are still needed in this area.

In summary, the above review highlights the viral features of HAV, the present situation regarding HAV infection in representative countries of the Asia-Pacific area, and the development of anti-HAV drugs. It is important for medical researchers to be aware of the role of HAV as one of the causes of ALF and ACLF.

5. HEPATITIS E VIRUS (HEV)

As HEV infection can potentially lead to ALF and ACLF, causing death or a need for liver transplantation, the prevention and treatment of HEV infection can be seen as a major health concern [8]. HEV infects humans through the fecal–oral route, causing acute hepatitis E. Hepatitis E also causes zoonosis, and HEV causes chronic infection in immunocompromised hosts [5–8].

The mammalian HEV genome is a single-stranded, positive-sense RNA with a length of approximately 7.2 kb [5,8]. HEV also exists in two distinct particle forms. HEV particles present in the bile and shed in the feces are classified as the membrane-unassociated form (nonenveloped HEV [neHEV]); those in the bloodstream as well as cell culture supernatants are classified as the membrane-associated form (quasi-enveloped HEV [eHEV]) [5]. eHEV is coated with a lipid membrane which resembles the lipid membrane of exosomes [98]. HEV replicates in hepatocytes [99].

5.1. HEV genotypes and clinical manifestations

The various strains of the Hepeviridae family are classified as HEV-1 to HEV-8 within the species *Paslahepevirus balayani* [5,100]. HEV-1 and HEV-2 infect only humans, and are related to HEV outbreaks in developing countries [101]. In addition, acute HEV infection may lead to a greater incidence of ALF in pregnant women, compared with nonpregnant women and men, in developing countries [8,102]. This may depend on HEV genotypes. HEV-3 and HEV-4 cause zoonosis, resulting in sporadic and autochthonous HEV infection in developed countries [101]. HEV-3 and HEV-4 are also major causes of chronic HEV infection in immunocompromised hosts and elderly persons [5,103]. In Japan, several studies have found HEV-4 in fulminant hepatitis E, rather than HEV-3 [104–106]. HEV-5 and HEV-6 have also been found in wild boars in Japan [5]. In addition, HEV-7 and HEV-8 have been identified in dromedary camels in the Middle East, and in Bactrian camels in China and Mongolia, respectively [5].

5.2. Symptoms of HEV infection

Acute HEV infection rarely presents clinical symptoms in children [5]. In adults with symptoms (such as flu-like myalgia, arthralgia, weakness, vomiting, jaundice, itching, uncolored stools, and dark urine), incubation periods range from 2 to 9 weeks [5].

5.3. Acute severe hepatitis E

A systematic review and meta-analysis demonstrated that the pooled HEV-attributable proportion of viral-related ALF (n=1312) was 40.0% (95% CI: 0.28-0.52), 30.0% (95% CI: 0.18-0.44), and 61.0% (95% CI: 0.49-0.72) among nonpregnant participants in India, China, and Bangladesh, respectively. However, a rate of 71.0% (95% CI: 0.62-0.79) was recorded among 676 Indian pregnant females [13]. The prevalence of HEV-ALF in HEV-infected nonpregnant individuals was found to be 28.0% (95% CI: 0.20–0.37) and 10.0% (95% CI: 0.01–0.28) in India and China, respectively, and it was 34% (95% CI: 0.27–0.42) in Indian pregnant females with HEV infection [13]. In India, the overall mortality of HEV-ALF was estimated to be 32.0% (95% CI: 0.23-0.42) and 64.0% (95% CI: 0.50-0.77), among nonpregnant and pregnant participants, respectively. Among Chinese nonpregnant participants, overall mortality was 23.0% (95% CI: 0.14-0.34) [13]. The incubation period of HEV-ALF and factors leading to its progression were found to be 2-9 weeks and not known, respectively, by the authors of [107], who also reported that the transplant-free survival rate of HEV-ALF was 55.1% [107].

In one hospital in Germany, approximately 10% to 15% of patients with ALF had evidence for HEV infection [108]. The prevalence of HEV-ALF has been relatively rare in viral ALF cases in the United States and Japan [109–111]. In Japan, when hepatitis occurs as a result of consumption of undercooked or grilled pork, wild boar meat, or offal (including pig liver and intestines), HEV infection should be considered [5]. The routes of HEV infection have not completely been elucidated yet.

After the approval by Japan's Health Insurance System of anti-HEV immunoglobulin A (IgA) antibody as a laboratory diagnostic tool for hepatitis E in 2011 [112], the number of hepatitis E cases has increased. As HEV-3 and HEV-4 may infect through transfusion, universal nucleic acid amplification testing blood-donor screening started in 2020 to prevent transfusion-transmitted HEV infection, revealing that asymptomatic indigenous HEV infection also exists in Japan [5]. HEV plays

a role in the pathogenesis of non-A, non-B, and non-C ALF in developed countries such as Japan. Further studies are needed in this area; however, a positive test for HEV RNA is now established as the gold standard for diagnosis of HEV infection [5].

In India, ACLF due to HEV infection was observed in 74 (61.2%)/121 adult patients with cirrhosis [15]. HEV-ACLF has lower mortality [113]. In Bangladesh, positive tests for acute HEV infection were obtained in 21.7% (15/69) of ACLF patients [114]. In China, patients infected with HEV-4 were found to be at high risk of developing ALF or ACLF [115]. Typical histopathological features of viral hepatitis may be absent in HEV-ACLF [116]. Thus, HEV infection is a trigger of ACLF [117–120].

Host factors (older age and genetic factors), viral factors (viral load, HEV genotype, nucleotide mutations in HEV RNA genomes) and other factors (coinfection with HIV, presence of chronic liver disease, existence of metabolic disease) have been identified as factors influencing the severity of HEV infection [5].

5.4. Vaccine, and challenges facing developers of anti-HEV drugs to prevent HEV infection

In Japan, a HEV vaccine which could prevent the spread of HEV is still under development [6]. In China, HEV 239 (Hecolin) has been shown to be well tolerated and effective in the prevention of hepatitis E [121–124]. Outside China, successful clinical trials of HEV 239 have also been reported from Bangladesh [123,125], the United States [124] and South Sudan [126,127].

Ribavirin treatment is recommended in cases of severe acute hepatitis E or acute-on-chronic liver failure (Table 1) [6,8]. Japan’s Health Insurance System has not yet approved the use of ribavirin as a drug for the treatment of HEV infection [5]. Ribavirin is a contraindication for pregnant patients, patients with anemia, and patients with renal dysfunction. The development of more effective and safer drugs and spread of vaccination for HEV infection is still needed [125].

Table 1. Distribution of hepatitis E virus genotypes; availability of treatments.

Countries	HEV genotypes	Specific treatment
European countries	HEV-3, HEV-4	Reduced immunosuppression/ribavirin
India	HEV-1	Urgent liver transplantation for acute liver failure
Japan	HEV-3, HEV-4	Off-label ribavirin
Mainland China	HEV-1, HEV-4	Ribavirin
North African countries	HEV-1, HEV-2	Various
Mexico, West African countries	HEV-2	Various

HEV – hepatitis E virus.

Several research reports about anti-HEV drugs have been published. Nishiyama et al. reported that type III interferons (interferon λ 1-3) could suppress HEV replication [128]. In another study, 2'-C-methylcytidine (2CMC)/ribavirin was found to exhibit a synergic effect against HEV replication [129]. Azithromycin and ritonavir were shown to strongly inhibit HEV replication in vitro by the authors of [130]. The pan-cathepsin inhibitor K11777 has also been shown to suppress HEV infection [131]. Further studies are needed.

Gu et al. reported a wide variation in the quality of guidelines and primary recommendations regarding HEV, further stating that because the evidence supporting the primary recommendations is currently of insufficient quality, guideline developers and researchers should address these issues when updating and applying guidelines for the diagnosis and treatment of HEV infection [7]. We agree with their opinions to some extent.

In European countries and in the United States, several HEV guidelines have been published concerning diagnosis, treatment and transplantation for both adults and children [6, 132-136]. Domestic HEV guidelines have also been published in China and India [7]. The Japan Agency for

Medical Research and Development (AMED) HAV and HEV Study Group has recently published two guidelines for HAV and HEV infections [4,5]. These reports will aid diagnosis and treatment of acute and chronic HEV infection, and help to prevent the progression of ALF and ACLF [4,5,7,8].

Chronic progression of HEV infection is observed in immunocompromised patients and extrahepatic manifestation may be complicated, including prolonged hepatitis, glomerulonephritis and cryoglobulinemia, hematological disorders, neuromuscular complications, etc. In the control of HEV infection, HTAs as well as DAA may be useful in disrupting host-HEV interactions by modulating host cell pathways that are related to the viral replication [137]. It was recently reported that serum-exosome-derived argininosuccinate synthase 1 and aldehyde dehydrogenase 1 family member A1 could effectively predict occurrence and prognosis, respectively, of HEV-ALF [138,139]. The Chinese consortium for the Study of Hepatitis E has reported important findings of HEV research [138–143]. Researchers from India also have greatly contributed to hepatitis E research [144–155]. Extremely careful attention also should be paid to these matters.

In summary, we have described the viral feature of HEV, the present situation regarding HEV infection in representative countries of Asia-Pacific area, and the development of anti-HEV drugs and HEV vaccines. It is important for medical researchers to notice the role of HEV as one of the causes of ALF and ACLF. Clinical features of HEV infection depend on HEV genotypes.

The different roles played by HAV and HEV in both ALF and ACLF are shown in Table 2. Differences among recommendations for hepatitis E virus diagnosis, treatment, and prevention produced by the World Health Organization (WHO), EASL and AMED, Japan are shown in Table 3) [5,6,156]. These three sets of recommendations do not describe HEV vaccinations.

Table 2. Different roles of hepatitis A and E viruses in acute severe hepatitis.

Items	ALF	ACLF
Background of liver	No liver diseases Causes of chronic liver diseases	Chronic liver diseases, or cirrhosis
HAV	No	No
HEV	No	Yes
	Acute insults	
HAV	Yes	Yes
HEV	Yes	Yes

ALF—acute liver failure; ACLF—acute-on-chronic liver failure; HAV—hepatitis A virus; HEV—hepatitis E virus.

Table 3. Differences among recommendations for hepatitis E virus diagnosis, treatment, and prevention produced by WHO [156], EASL [6], and AMED HAV and HEV Study Group [5].

Items	WHO	EASL	AMED HAV and HEV Study Group
Diagnosis	HEV RNA, and anti-HEV IgM	HEV RNA, anti-HEV IgM, anti-HEV IgG and HEV antigen	Anti-HEV IgA; HEV RNA in feces and sera and HEV genotype
Treatment	No specific treatment for acute hepatitis E; hospitalization for fulminant hepatitis and symptomatic pregnant women; and Ribavirin for chronic hepatitis E	Ribavirin for severe acute hepatitis E, ACLF-E and chronic hepatitis E in solid organ transplant recipients; pegylated interferon- α plus ribavirin for liver transplant recipients	Off-label use of ribavirin should be considered in cases of chronic hepatitis E; off-label use of ribavirin may be considered in cases of severe acute hepatitis E, acute-on-chronic liver failure; liver transplant recipients with chronic hepatitis E without interferon intolerance or contraindication, or patients

			showing nonresponse to ribavirin, can be considered for treatment with pegylated interferon- α with or without ribavirin. In patients with HEV-ALF and hepatic encephalopathy, liver transplantation should be considered; high-flow continuous hemodiafiltration or on-line hemodiafiltration with or without plasma exchange can be performed until hepatic encephalopathy in HEV-ALF patients improves; and high-dose corticosteroid administration in the early stage of illness may be required in certain patients with severe hepatitis E. Further research for establishment of antiviral drugs is needed.
Prevention	Maintaining quality standards for public water supplies; establishing proper disposal systems for human feces; maintaining hygienic practices; and avoiding consumption of water and ice of unknown purity	Immunocompromised individuals and those with chronic liver diseases should avoid consumption of undercooked meat (pork, wild boar and venison) and shellfish; immunocompromised patients should consume meat only if it has been thoroughly cooked to temperatures of at least 70 °C.	Heating at a temperature of 95 °C for at least 10 min; HEV in pork/wild boar meat and entrails, including pig liver and intestines, should be completely devitalized by cooking for 10 min at a temperature close to 100 °C; and travelers to endemic and developing countries should avoid drinking untreated water and eating raw food.

WHO—World Health Organization; EASL—European Association for the Study of the Liver; AMED—Japan Agency for Medical Research and Development; HEV—hepatitis E virus; ACLF-E— acute-on-chronic liver failure caused by HEV infection.

6. Conclusions

HAV and HEV infections are important infections that cause severe liver diseases globally. Although there is variation in the quality of guidelines and primary recommendations are different across different regions, medical researchers should highlight important findings about HAV and HEV infections in Asia-Pacific countries.

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