Chronic hepatitis E in immunosuppressed patients: a comprehensive review of the literature

M. Philippart[1], T. Vanwolleghem[2,3], G. Dahlqvist[1]

(1) Service d'hepatogastroentérologie, Cliniques universitaires Saint-Luc, Brussels; (2) Department of Gastroenterology and Hepatology, Antwerp University Hospital, 2650 Antwerp, Belgium; (3)Viral Hepatitis Research Group, Laboratory for Experimental Medicine and Pediatrics, Faculty of Medicine and Health Sciences, University of Antwerp, Belgium.

Abstract

Hepatitis E virus (HEV) is the commonest cause of acute viral hepatitis in Western countries, especially genotypes 3 and 4.

Chronic cases are reported in immunosuppressed patients, which includes patients who have undergone solid organ or stem cell transplantation, patients who are being treated for cancer or autoimmune diseases.

Chronic HEV can eventually lead to liver fibrosis, and exceptional cases requiring liver transplantation for decompensated liver cirrhosis have been reported.

The mechanisms leading to chronic HEV and its incidence in the immunosuppressed population is still unclear due to the paucity of well-designed prospective studies.

According to studies conducted in various European countries, the HEV seroprevalence in immunocompromised patients ranges up to 40% and HEV RNA viremic prevalence between 0,5 to 2%.

In this review, we provide a description of the epidemiology, risk factors and natural history of chronic HEV in relation to various types of underlying immunosuppressive conditions and discuss the different treatment options available. (Acta gastroenterol belg., **2025,** 88**, 323-332).**

Keywords: Hepatitis E, chronic, immunosuppression, transplantation.

Introduction

Hepatitis E virus (HEV) was originally identified in developing countries during the early 1980s, primarily known to cause acute hepatitis through waterborne contamination. However, it has since been established that HEV is also prevalent in high-income countries such as countries from the European Union and the United-States (1).

Initially, HEV was only known as a cause of acute infections in humans. However, in 2008, Kamar et al. described in France the first eight cases of chronic HEV infection among recipients of solid organ transplants, all infected with genotype 3 virus, pointing towards a zoonotic source of infection (2). Since then, cases of chronic hepatitis E with genotype 3 or 4 have been described worldwide, leading in certain cases to cirrhosis, decompensation and death or liver transplantation.

Several immunosuppressive conditions are associated with chronic HEV. These conditions include patients receiving immunosuppressive regimens for a solid organ transplant (SOT), patients with solid or hematological cancers receiving chemotherapy and/or immunotherapy, individuals living with HIV and low CD4 count, and patients with auto-immune diseases receiving immunosuppressive or immunomodulatory therapies (3).

Hepatitis E Virus and mode of transmission

HEV is an RNA virus that belongs to the Hepeviridae family and has eight genotypes (HEV 1 to HEV 8) with 36 subtypes (4). Five genotypes (HEV-1-4 and HEV-7) have been shown to infect humans. HEV-1 and HEV-2 are mainly found in developing countries, infecting only humans and transmitted via fecal-oral contamination. HEV-3 and HEV-4 are zoonotic and can be found in animals such as pigs, wild boars, deers, rabbits, camels, goats, and cattle. HEV-5 and HEV-6 are exclusively found in wild boars, while HEV-7 and HEV-8 are identified in camels, with only a few cases of HEV-7 infections reported in humans who consumed camel milk (3,5). A few cases of HEV infections have also been reported to be transmitted through blood transfusion (6,7).

HEV is now the most-common cause of acute viral hepatitis in humans world-wide, and genotype 3 accounts for the majority of infections in Europe (8). In Belgium, HEV-3 is the predominant circulating genotype, with sporadic occurrences of HEV-1 and HEV-4. HEV 3 subtypes can be classified in three major clades: abchijklm (HEV-3.1), efg (HEV-3.2), and ra (HEV-3.3). Until 2015, subtype 3f was the prevailing subtype identified in Belgium, but in 2016 and 2017, subtype 3c emerged as the most frequently identified subtype (9,10).

Chronic HEV among immunocompromised patients know a geographical spread in European countries most belonging to HEV-3.1 clade, whereas genotype 4 is the predominant chronic HEV genotype in Asian countries. Only two isolated case reports of chronic infection with genotype 1 have been published to date, and no chronic infections with genotype 2 have been documented (11,12).

Instances of HEV-3 outbreaks have been linked to the intake of pork products, particularly those involving undercooked pork liver or sausages (13).

In Belgium, Sciensano examined the HEV RNA

Correspondence to: Prof Géraldine Dahlqvist, Phone +32(0)27642857; Fax +32(0)27648927

Email: geraldine.dahlqvist@saintluc.uclouvain.be
Submission date: 24/08/2023
Acceptance date: 10/10/2025

positivity rate in pork meat products commonly found in supermarkets to evaluate the HEV consumer exposure.

31% of the ready-to-eat (RTE) pork meat products was tested positive for HEV RNA.

Specifically, HEV RNA was found in 65 % of the pork liver patés, 15 % of raw dried hams and 0 % of raw dried sausages. Samples in which sequencing was carried out all revealed the 3c , subtype (clade HEV-3.1). Although it is not currently possible to differentiate between infectious and damaged viral particles, Sciensano concludes by advising immunocompromised patients to avoid pork liver products, especially if these are RTE (14). HEV genotype 3 and 4 have also been detected in various types of environmental water, in waste and drinking water in Europe. A recent systematic review and meta analysis assessed the occurrence of hepatitis E virus (HEV) RNA in different water environments worldwide, with a strong representation of European data. Overall pooled prevalence of HEV RNA in water was 9.8 % (95 % CI 6.4–13.7 %). By water type, pooled prevalence was approximately 15.1 % in untreated wastewater, 7.4 % in surface water, 4.7 % in drinking water, and 3.8 % in treated wastewater. Genotyping was reported in about 37 % of studies; HEV genotype 3 predominated, with smaller contributions of genotype 1 and rare reports of genotype 4.

However, it is important to note that RT-PCR and real-time PCR assays are able to detect only viral genome fragments, which does not necessarily confirm infectivity, and there was considerable heterogeneity in sampling, concentration, and detection methods (15).

In the case of patients who have undergone a solid organ transplant, a particular route of contamination that has been described in case reports is infection via the graft. In such instances, a rapid evolution to liver cirrhosis after liver transplantation with a HEV infected liver graft has been reported, which raises the question of testing donors for HEV before transplantation (16). A recent review has addressed this issue. Currently, there is no recommendation for universal screening of tissue/organ donors for HEV (17).

Diagnosis of HEV infection and definition of chronic HEV

The incubation period for HEV typically lasts from 15 to 60 days. Approximately three weeks after infection, HEV RNA becomes detectable in both blood and stool. IgM antibodies emerge first, followed shortly by IgG antibodies.

In the case of acute infection, viremia persists for about three to six weeks and the IgM do not usually remain in the blood for more than three to four months (but may persist for up to a year). In contrast, the IgG response is enduring (5).

Chronic HEV infection has been defined by EASL (European Association for the Study of the Liver) as a persistence of HEV replication (positive detection of anti-HEV IgM in serum and/or HEV RNA in serum or stool samples) for at least three months. Indeed, there is evidence to suggest that, except in very few cases, no natural HEV clearance occurred between three to six months post-infection. It's important to know that, in patients with associated immunodeficiencies, anti-HEV antibodies can be undetectable given the possibility of a low humoral immune response against HEV. For these patients, diagnosis can only be made with nucleic acid amplification technique-based detection of viral RNA in blood and/or stool samples (3,5,18).

Clinical manifestations of chronic HEV infection

Intrahepatic manifestations

HEV acute infection is asymptomatic in most cases, with normal or mildly elevated liver tests. Symptoms of acute hepatitis are observed in less than 5% of cases, and acute liver failure is an exceptionally rare outcome (1).

After being infected with HEV, immunosuppressed patients can have a resolving hepatitis or on the contrary develop chronic hepatitis. The majority of patients with chronic HEV are asymptomatic and present with persistent mild to moderate abnormalities of liver function tests, but normal liver tests do not exclude the diagnosis (5). Diagnosis of chronic HEV is sometimes tricky because it can be confused with drug induce liver injury (DILI) or mild graft rejection, in the case of liver transplantation.

Roughly two thirds of immunocompromised patients develop a chronic HEV infection after exposure, even though studies vary widely. In 2011, a retrospective multicenter study analyzed data from 85 recipients

Table 1. — **Practical recommandations for immunosuppressed patients.**

Recommendations
Avoid consumption of undercooked or raw pork, wild boar, and game meat, as well as products containing raw pork liver (e.g., certain sausages).
Cook all meat products thoroughly (≥71 °C core temperature).
Wash fruits and vegetables carefully and peel when possible, especially if eaten raw.
Be cautious with untreated or potentially contaminated drinking water, particularly when traveling to endemic areas.
Reinforce standard food hygiene measures (hand washing, separate raw and cooked food preparation areas).

of solid organ transplants who were infected with HEV found that 65.9% of HEV infections in solid organ transplant recipients became chronic (19). In 2013, Zhou et al. did a literature review comprising 12 studies mainly in Europe, including 5050 SOT. 99 patients (1.96%) were HEV RNA positive and 64 of these 99 patients developed chronic HEV (20). However, prospective studies showed that progression towards chronicity is much less than previously stated. For example, a per-protocol analysis in Sweden systematically screened all patients regardless of their liver tests prior to liver transplantation and up to one year after liver transplantation. None of the seven patients with detectable HEV RNA evolved towards chronicity. It is worth mentioning that some immunocompromised patients do not have antibody responses despite HEV infections, so studies that only look for HEV RNA upon the detection of anti-HEV IgM or ALT flares are likely to underestimate the prevalence of silent and self-limited infections (21).

Although advanced fibrosis has been described in some patients affected by chronic HEV (19,22), the fibrosis progression of chronic HEV is not well understood because most reports are cross-sectional cohorts or post-hoc analyses of dramatic cases presenting with cirrhosis after a previous SOT. In 2021, a systematic analysis of HEV histology and its association with clinical parameters has been made. They analyzed 52 liver samples from 41 patients with HEV-3 for 33 histopathologic features. 56% of patients where immunocompromised, 12% had pre-existing liver disease and 44% had no known immunosuppression. They identified three histopathologic clusters (C1–C3), separated according to immune status and pre-existing liver disease, suggesting three groups with distinct histopathologies. C1 comprised mostly patients with pre-existing liver disease and the histology mainly reflected the respective liver disease without additional signs of hepatitis, C2 comprised mostly immunocompetent patients with histology mainly displaying florid hepatitis and C3 comprised mostly immunocompromised patients with histology mainly displaying smoldering hepatitis (23).

Several animal models have been used to improve the characterization of this disease and its evolution. Cao et al. had previously devised a pig model of chronic HEV infection by treating them with an immunosuppressive regimen including cyclosporine, azathioprine, and prednisolone. Pigs showed abnormal liver tests and persistent shedding of HEV into feces. Nevertheless, this model differed from chronic hepatitis E in humans as there were no observable liver lesions (24). Recently, a new pig model of chronic hepatitis E has been developed with a tacrolimus-based regimen and an optimization of the immunosuppressive treatment through a blood concentration monitoring. This is the first animal model displaying a combination of persistent HEV RNA with liver inflammation and fibrosis, which could lead to a better understanding of the pathophysiology underlying the development of fibrosis and help in finding targets for future anti-viral treatments (25).

Other viral hepatitis such as HBV or HCV are well-established as leading causes of hepatocellular carcinoma (HCC). In this context, recent epidemiological and clinical investigations have brought forward the notion that hepatitis E virus infections might play a role as a contributing factor in hepatocellular carcinoma. However, preliminary data suggest that HEV-driven hepatic carcinogenesis is uncommon, as there is only one clinical case report of HEV-related cirrhosis complicated with HCC. Additional studies are expected (26). Table 2 summarizes the differential diagnosis to consider when faced with elevated liver enzymes in immunosuppressed patients.

Extra-hepatic manifestation

HEV can also cause extra-hepatic manifestations. A variety of neurological injuries have been reported in connection with HEV infection, such as Guillain-

Table 2. — **Approach to Elevated Liver Enzymes in Immunosuppressed Patients: Key Diagnostic Work-up.**

Differential diagnosis	Lab tests
Chronic HEV infection	HEV RNA (serum and stool); anti-HEV IgM/IgG (may be negative in immunosuppressed)
Graft rejection (post-LT/KT/HT/LuT)	Graft biopsy; donor-specific antibodies
CMV reactivation (± other herpesviruses)	CMV PCR (blood); CMV antibodies
Drug-induced liver injury (DILI)	Medication review; liver biopsy
HBV or HCV reactivation	HBsAg, anti-HBc, HBV DNA; anti-HCV, HCV RNA
Biliary obstruction	Abdominal ultrasound ± Doppler; MRCP
Autoimmune hepatitis flare/overlap	ANA, SMA, IgG; liver biopsy
Ischemic/congestive hepatopathy	Clinical context, liver biopsy

HEV: Hepatitis E virus, Hb : hemoglobin, RNA: Ribonucleic acid. MRCP: Magnetic Resonance, Cholangiopancreatography, CMV : Cytomegalovirus, HBV : Hepatitis B virus, HCV : Hepatitis C virus, ANA : Antinuclear Antibody, SMA: Smooth Muscle Antibody.

Barré syndrome, neuralgic amyotrophy, myelitis, and encephalitis. Most of documented cases occur in immunocompetent individuals, but instances of neurological injuries may also manifest in the context of chronic infection with HEV genotype 3 (27). Cases of membranoproliferative and membranous glomerulonephritis have also been reported among immunocompetent as well as immunosuppressed patients (28,29). Other extra-hepatic manifestations include acute pancreatitis and cryoglobulinemia (5).

Risk factors for the severity of HEV infections

Viral factors

Several factors have been studied to find a correlation with the severity of the clinical presentation of HEV. Several studies with a few numbers of HEV-3/HEV-4 cases have suggested that genotype 4 is more virulent than genotype 3 (30, 31). Micas et al. compared in 2021 clinical and biological data from 27 cases of HEV-4 acute infections matched for age and gender with 54 cases of HEV-3 acute infections, both groups being immunocompetent patients in Belgium or France. They showed that HEV-4 infected patients had significant higher alanine aminotransferase (ALT) values. The two groups had similar numbers of severe hepatitis cases. Two deaths were recorded among HEV-4 infected patients while none among HEV-3 infected patients, but multivariate analysis did not confirm a significative difference (32).

In Belgium HEV-3 is the most common, and the most represented subtypes are HEV 3c et HEV 3f. A Belgian and a French team have already suggested that patients infected with HEV-3c were at lower risk of hospitalization compared to those infected with HEV-3f, but there were potential confounding factors (33,34). A recent study managed to examine the role of viral and host factors on disease presentation of all laboratory confirmed HEV infections reported by the Belgian National Reference Centre during 8 years. By clustering them by clades, they revealed a significant association between viral clade and the severity of HEV genotype 3 disease, regardless of established host risk factors. Specifically, symptomatic patients infected with a clade-HEV-3.2 (efg) virus were linked to increased rates of hospitalization, higher peak serum bilirubin levels and more pronounced histopathology (35).

Host factors

The variability in clinical disease presentations can also be influenced by a combination of host factors. The host factors identified so far in acute HEV hepatitis are male gender, age over 50 years, preexisting liver conditions, and compromised immune status. Additionally, diabetes mellitus and alcohol consumption are recognized as other risk factors, likely associated with underlying chronic liver disease (23,36).

The immunosuppressed status of the patients is the most important host-related risk factor for the development of chronic HEV. In SOT, tacrolimus use has been shown to be one of the main predictive risk factors for chronic HEV infection (19).

Pathophysiology of chronic HEV

Evidence from clinical and experimental studies indicates that the dysfunction of various components of the immune system, such as innate immunity, T-cell function, and antibody response, likely contributes to the development of chronic HEV infection. According to Kemming et al., individuals with persistent HEV infection exhibited a diminished and declining CD8+ T cell response, showing signs of exhaustion. However, they observed that reducing immunosuppression and/or administering ribavirin treatment results in an improvement in the proliferation of HEV-specific CD8+ T cells and an increase in IFN-γ production. These changes were accompanied by viral clearance (37). Immunosuppressive medications also modulate and reduce the immune response acting on different targets, linking their use to the occurrence of chronic HEV infections. The association between chronicity and the universal use of immunosuppressants has been extensively documented (38). However, due to the limited number of patients with chronic HEV, it is challenging to analyze the effects of different immunosuppressants separately. In vitro models showed no significant effect of steroids on HEV replication but calcineurin inhibitors seems to stimulate HEV replication. On the other hand, this in vitro model showed that ribavirin and mycophenolic acid have a synergistic effect against HEV (39). As the in vitro concentrations of the tested immunosuppressants are often outside clinical ranges, it is crucial to combine clinical and experimental approaches to improve our understanding of how various immunosuppressants impact chronic HEV in vivo (3).

Specificity according to the underlying disease

Solid organ transplanted recipients

Liver transplantation (LT)

In 2020, Buescher et al. made a literature review based on two different databases (Scopus and PubMed) and selected studies assessed on their methodological quality according to the Joanna Briggs Institute's well-established critical appraisal tool for prevalence studies (40). They analyzed the HEV seroprevalence (n= 4915) and prevalence of HEV RNA (n=5821) liver transplanted patients. The HEV seroprevalence was 27,4% (95% CI 18.33 - 38.86) and the HEV RNA positivity is 0.95% (95% CI 0.56 - 1.63) (41).

Only a limited number of studies have prospectively monitored patients for HEV infection during the peri-transplant period.

As mentioned before, a prospective analysis has been conducted in Sweden by Frankal et al. They investigated the HEV-seroprevalence and the viremic prevalence and incidence of HEV infections among LT recipients between 2013 and 2015 by repeated serological and HEV RNA determinations during the pre- and post-LT period (Three and twelve months post LT). Of the 109 patients, before transplantation, they found a HEV seroprevalence of 13% and one patient was tested positive for HEV RNA before LT. Three others were tested HEV RNA positive at the 3-month post-LT follow-up, and other three were tested HEV RNA positive at the 12-month follow-up. Half of the patients with HEV RNA had normal liver tests at diagnosis. Besides, five patients acquired anti-HEV antibodies during the study period but without detectable HEV RNA. Importantly and unlike the reported chronicity rates from retrospective cohort studies, all the patients from the Swedish study cleared the infection without any treatment, and subsequent follow-up tests showed undetectable HEV RNA in serum (21).

Another prospective study conducted in Thailand, where genotype 3 is the commonest HEV genotype, followed 91 cases for up to one year post liver transplant without clinical evidence of HEV-related hepatitis at inclusion. The HEV seroprevalence was 52.7% at study initiation. HEV RNA was detected in 7 patients during the 12-month study period. In these 7 cases, HEV RNA was detected in serum exclusively (n=4), feces exclusively (n=2) and 1 patient had HEV RNA in both compartments. Only three of the seven patients had positive anti-HEV antibodies. Six of the seven patients were asymptomatic with normal transaminase levels. Two of them became chronically infected. Clearly, the HEV seroprevalence does not correlate with the presence of HEV RNA in the serum or feces and hence is not a preferred diagnostic test.

It appears that by carrying out systematic screening, more HEV RNA positive patients with normal liver tests can be detected, which do not necessarily lead to chronic HEV infections. The presence of HEV RNA must be confirmed three months later to diagnose a chronic infection, and as observed it will develop in less than half of the RNA positive patients. In addition, the absence of HEV antibodies does not exclude HEV infection.

Kidney transplantation (KT)

Kidney transplant recipients (KT) are a vulnerable group at risk for infections due to their life-long need for strong immunosuppressive therapy.

In the literature review made by Buescher et al., the data from around 8000 KT recipients around the world were analyzed. The HEV seroprevalence is 33.94% (95% CI 23.97- 45.56), with positive HEV RNA in 1.17% of cases (95% CI 0.68-2.00) (41).

In the literature, two cases of HEV transmission via renal grafts coming from one single donor have been described (42). Another case resulted in a fatal decompensated cirrhosis five years after KT (43).

It has been suggested that HEV infection can be a trigger for kidney rejection. Wasuwanich et al. in 2022 compared the evolution of 9 KT who showed evidence of recent post-transplant HEV infection (positive HEV RNA in post-transplant sera or in feces) with 45 HEV negative KT controls. Patients with evidence of post-transplantation HEV infection demonstrated a more frequent and earlier kidney graft rejection compared to controls (8/9 vs 21/45; HR = 3,23, IC 95 %: 1,19-8,79; 17,4 months vs 30,8 months; p = 0,029. However, the study sample was very small, the data are retrospective and the 9 KT patients with post-transplant HEV infection were registered as “high-risk” (broadly sensitized to HLA and/or receipt of an HLA or ABO incompatible transplant) (44).

More studies with larger sample sizes are needed to evaluate the impact of HEV infection on the kidney graft.

In our experience in two tertiary hospitals in Belgium, HEV seroprevalence is similar in KT compared with other SOT, but the prevalence of HEV RNA is higher in kidney transplant patients in view of the more intense immunosuppression.

Heart transplantation (HT)

In the meta-analysis by Buescher et al., the highest rates of HEV seroprevalence among SOT patient was observed in HT recipients (36.5% (95%CI 20.24-56.63)), while the HEV RNA positivity was 1.30% (95%CI 0.52-3.23) (41). Some studies suggest that this high rate of HEV seroprevalence in HT recipients may be partly explained by their greater need for blood product transfusions (22).

One major prospective study in HT patients has been conducted in 2012. Pischke et al. screened 274 HT patients from Germany for one year, for anti-HEV antibodies (IgG) and HEV RNA. They found a HEV seroprevalence at 11.3%, which was significantly higher than a group a healthy control ($p < 0.001$). Four patients were identified with HEV RNA and developed chronic HEV post transplantation (1,5%). Fifteen patients developed anti-HEV antibodies after transplantation but cleared the infection without developing chronic HEV (22).

Lung transplantation

The first prospective study in lung transplanted patients was conducted in Sweden in 2015. 62 patients were observed during the first year after lung transplantation and were analyzed for HEV seroprevalence (IgG and IgM) at 12 months after transplantation, with subsequent HEV RNA confirmatory testing. At one year follow up, 13% had positive anti-HEV antibodies but none of them had positive HEV RNA (45). However, as described earlier, patients can be HEV RNA positive despite HEV seronegativity. These patients could therefore

have been missed in this prospective protocol. Several retrospective studies evaluated the seroprevalence in lung transplanted patients (46). They were all included in the meta-analysis by Buescher et al., showing that lung transplant recipients had the second highest seroprevalence (32.5%), after heart transplant patients, and the highest rates of HEV RNA positivity (2.1%) (41).

Rheumatological disease

Prior to 2015, there was limited knowledge regarding the frequency of acute and chronic HEV infection among individuals with inflammatory rheumatic diseases. From January 2010 to August 2013, a retrospective multicenter study was conducted in France to investigate HEV cases among patients known to have inflammatory rheumatism and followed by approximately 2400 physicians. The study identified 23 patients with HEV infection, all having inflammatory arthritis and being treated with immunosuppressants. None of them progressed to chronic infection. However, immediately after the diagnosis of the HEV infection, immunosuppressants were discontinued in 20 patients and ribavirin was initiated in additional 5 of them, thereby minimizing the risk of chronicity (47).

To clarify the risk of chronic HEV infection in this specific population, a retrospective multicentric European cohort study was conducted, including data of all cases of HEV infection diagnosed between April 2014 and April 2016. This study involved 7 rheumatology and internal medicine centers in Germany, Italy, the United Kingdom, the Netherlands, and France. Twenty-one patients were identified as having a HEV infection, that persisted for over 12 weeks in 7 patients (33.3%) and over 24 weeks in 5 patients (24%). Except for one patient who was lost to follow-up, all the patients cleared their HEV infection, including 15 patients (71%) who recovered after discontinuing immunosuppressive treatment and/or received ribavirin therapy (48).

Other cases of chronic HEV infections in patients with immunological/rheumatological diseases were described in the literature as case reports in strongly immunosuppressed patients (49, 50). No systematic data are available on the seroprevalence in this heterogeneous population.

Hematological diseases

There have been limited reports on chronicity rates of HEV infections in patients with hematological malignancies, coming mostly from small case series or cross-sectional retrospective analyses on biobanked serum samples.

Recently, a systematic review and meta-analysis was conducted to assess the prevalence of HEV infection in hematopoietic stem cell transplant (HSCT) recipients. The final analysis encompassed 1,977 patients from nine studies, with follow-up periods extending up to 40 months. The combined prevalence of positive HEV-RNA was calculated to be 3.0% (95% CI 2.3% to 4.0%), while the combined prevalence of positive HEV-IgG was determined to be 10.3% (95% CI 4.5% to 21.8%).

HEV-associated morbidity and mortality in a broader range of hematological diseases has been explored further in a recent retrospective cohort study across 11 European centers between April 2014 and March 2017. Participating centers retrospectively included a total of 50 patients who had been identified with HEV RNA. The prevalent underlying hematological malignancy included aggressive non-Hodgkin lymphoma (NHL) (34%), indolent NHL (iNHL) (24%), and acute leukemia (36%). Among the patients, twenty-one (42%) had undergone allogeneic hematopoietic stem cell transplantation (alloHSCT). Hepatitis E was associated with mortality in 8 patients, of which 4 experienced death-related to liver decompensation. Reducing immunosuppressive treatment was linked to mortality in two patients. In summary, this retrospective study highlights that HEV was related to liver-related mortality and that ribavirin should be initiated early because of the risk of reducing the immunosuppressive treatment in these patients (51).

The high HEV associated mortality has been confirmed by a retrospective observational study among European Society for Blood and Marrow Transplantation (EBMT) centers. They identified 34 cases of HEV infection among patients followed for a stem cell transplant in 12 centers from 6 countries (20 with an acute and 14 with a chronic infection). For 3 patients, HEV was considered the cause of death.

Importantly, HEV infection can alter cancer treatment plans, including delaying hematopoietic stem cell transplantation and decreasing cancer-free survival (51-53).

Cancer

Only few data are available concerning HEV infection in patients treated for solid tumors. In a tertiary care cancer center in the United States, HEV serology was screened for in oncologic patients considered at risk for complications of a HEV infection (if they had pre-existing hepatitis B virus infection, hepatitis C virus infection, or acute elevation of liver enzyme levels). Among the 405 patients screened, 63 showed anti-HEV antibodies, of which 41 had been diagnosed with a solid tumor. However, the only 2 patients with HEV RNA were being treated for a hematological malignancy (54). Further studies therefore need to be conducted to evaluate the risk of chronic HEV in solid tumor patients.

HIV

Research investigating HEV seroprevalence among individuals living with HIV has been conducted across all continents. Higher HEV seroprevalences were found in Africa and Asia, with most countries reporting rates exceeding 40%. In continental European Union countries, the rates were lower, ranging between 10-

20%. Finally, in South and North America and Oceania, the seroprevalence rates were even lower, with less than 10% of HIV+ individuals testing positive for anti-HEV antibodies. The prevalence of chronic HEV infection among HIV-infected patients is relatively low, ranging from 0 and 0.5% (55).

The first cases of chronic HEV in HIV-infected patients were reported in 2011 (56).

Those HIV patients with a CD4 count below 200/mm3 , corresponding to a severely immunocompromised status, are at higher risk for chronic viremia. HIV patients with restored CD4 counts generally clear HEV spontaneously, although exceptions have been reported. Ingiliz et al. described one case report where cirrhosis was discovered in a HIV patient with a normal CD4 count, the etiology of which turned out to be chronic HEV acquired during periods of immunodeficiency that persisted despite normalization of the CD4 count (57).

Immunocompetent patients

In very rare instances chronic HEV has been observed in presumed immunocompetent patients(58-60). Although one patient had an underlying cirrhosis, known to impact innate cellular immune responses. Other subtle deficiencies in adaptive or innate immune responses, that require thorough molecular immunological testing, might be involved in these cases as well.

Treatment options

According to the 2018 EASL guidelines, the management of chronic HEV infection should follow a stepwise and patient-specific strategy. This approach has been resumed in Figure 1.

Reduction of immunosuppression:

In SOT patient, the initial therapeutic option for managing chronically infected transplant recipients is to reduce the dosage of immunosuppressive medications, if possible, which can result in sustained viral clearance in approximately one-third of cases (5). However, reduction of immunosuppressive drugs is not possible in all patients, especially regarding the risk of an acute post-transplant rejection or recurrence of hematological disease. Indeed, in the series of hematologic patients described by von Felden et al., reduction of immunosuppression was associated with mortality in 2 patients (51). A recent systematic review and meta-analysis showed that viral clearance was achieved in 32% of patient after reduction of immunosuppressive medication. However, the effectiveness of reducing immunosuppressive doses may be overestimated due to the limited reporting on its efficacy in a minority of studies (61).

Antiviral Therapy with Ribavirin (RBV)

If reduction of immunosuppression is not possible or if the viral clearance is not achieved, ribavirin (RBV) as monotherapy can be administered. Ribavirin exerts direct antiviral effects through inhibition of inosine monophosphate dehydrogenase and induction of lethal mutagenesis. In addition, it enhances type I and II interferon signaling, promotes Th1-polarized T cell responses, and modulates cytokine production, thereby supporting immune-mediated clearance of hepatitis E virus. These complementary mechanisms explain its high rate of sustained viral clearance (62, 63).

Several studies involving SOT have reported that RBV monotherapy can result in sustained virological

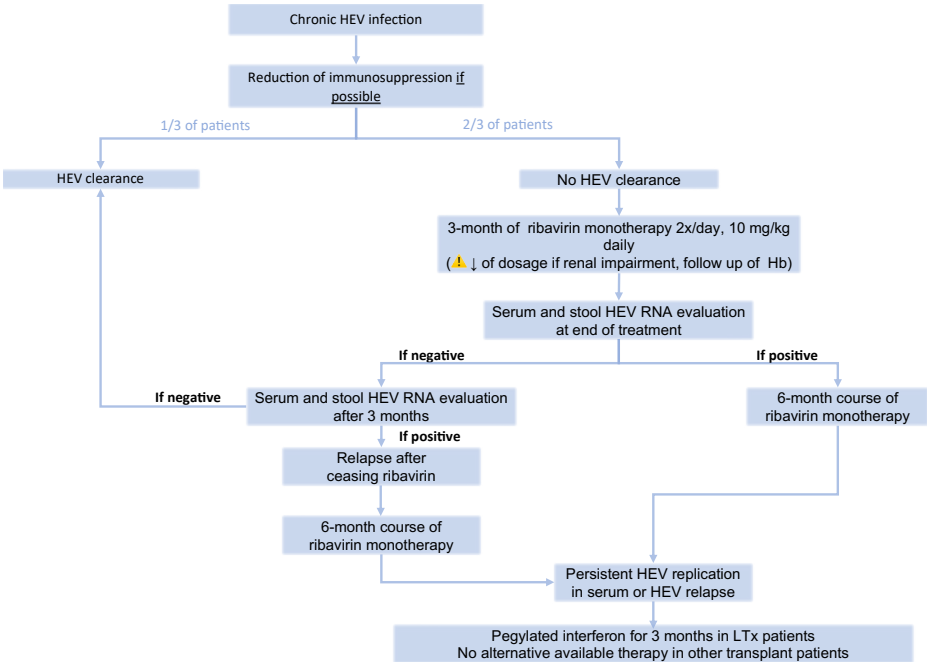

Figure 1. — Stepwise strategy for chronic HEV infection treatment. HEV: Hepatitis E virus, Hb:hemoglobin, RNA: Ribonucleic acid, LTx: liver transplanted.

response (SVR) in up to 80% of patients (64). Unfortunately, up until now no randomized controlled trial or prospective study has established the optimal RBV dose and treatment duration. Retrospective case series apply dosages ranging from 200mg/day to 1200mg/day for different durations ranging from 1 to 18 months. The standard treatment protocol recommended by EASL is a median dose of 600 mg per day for 3 months, but prospective validation is required (5). Practically, a twice daily weight-adjusted dosing totalling10 mg/kg daily is recommended, followed by dosage adjustment based on tolerance, toxicity and possibly therapeutic drug monitoring (65). The most frequent side effect of ribavirin is profound hemolytic anemia , due to extensive accumulation in erythrocytes, necessitating multiple transfusions and erythropoietin injections in over half of the patients (66). It is teratogenic and therefore contra-indicated during pregnancy. Hyperuricemia and skin reactions have been reported as well. In addition, its renal clearance and long half-life of 300 hours complicates dosing in patients with impaired renal function, as is often seen in SOT.

In this context, a retrospective multicentric study explored the relationship between RBV plasma levels and both virologic response and anemia in transplant recipients, taking into account renal function. They showed no correlation between the RBV dose and RBV plasma concentrations at steady state and no association between RBV plasma levels and SVR. They defined a RBV therapeutic range of 1.8-2.3 mg/L to avoid toxicity. However, RBV therapeutic drug monitoring is not available in every center.

In practice, they recommend reducing the dose by 25% in case of a glomerular filtration rate (eGFR) between 30 and 50 mL/min per 1.73m2 and by 50% in case of eGFR between 10 and 30 mL/min per 1.73m2. The hemoglobin level should be regularly monitored and if the concentration of hemoglobin decreases by over 15%, it is recommended to consider reducing the dosage or even stopping the treatment for 2 weeks and then restart at half the initial dose (65).

Following the withdrawal of ribavirin-based medications from the Belgian market, the National Institute for Health and Disability Insurance has taken the initiative of including ribavirin in chapter IVbis for certain indications for which there are no reimbursable therapeutic alternatives in Belgium. Imported ribavirin from Germany can therefore be reimbursed under certain specific conditions.

The presence of HEV-RNA in the feces and serum should be evaluated at end of treatment and twelve weeks after completing treatment to confirm eradication and prevent potential relapses. In cases where HEV RNA is undetectable in the serum but still present in the stools at the end of a three months treatment course, the risk of relapse is high, and prolonged treatment may be necessary to achieve sustained viral clearance (67).

Patients who experience a relapse after completing 3 months of therapy may benefit from extended treatment (6 months or longer), which has been shown to improve the likelihood of SVR (64,66).

Other medications

Pegylated-interferon-α has been promising in treating chronic hepatitis E in a limited number of cases, including liver transplant recipients and a patient undergoing hemodialysis, who achieved HEV clearance following a three-month course of therapy. However, interferon therapy should be used with caution in SOT recipients due to its immunomodulatory effects, which can increase the risk of acute rejection in these patients (68, 69)

For the patients who remain viremic, a prospective trial has been performed with sofosbuvir, which was initially shown to inhibit HEV in in vitro models. However, none of the 9 treated patients achieved SVR (70).

Given the potentially severe complications caused by chronic HEV infections, a preventive approach could be cost-effective. Dietary adaptation is essential to lower the risk of HEV infection at the individual level, especially in immunosuppressed individuals. Patients should be advised to cook meat properly, to avoid pork-derived products if they receive immunosuppressive treatment or are immunosuppressed. Furthermore, to prevent the risk of blood-borne transmission, systematic HEV screening in the blood donors could be considered, depending on the seroprevalence in each country.

What about vaccination

Finally, based on recombinant technology of a HEV genotype 1 strain the HEV 239-vaccine, to prevent HEV infection has been developed in China by Zhu et al, showing adequate protection against acute HEV-1 and HEV-4 infections (71). However, several important questions remain before this vaccine can be advocated to prevent chronic HEV infections. Specifically, the seroconversion rate and duration of humoral responses in the context of immunocompromised patients are unknown. It is also unclear whether the vaccine offers protection against a HEV-3 infection. Finally, some natural and experimental HEV breakthrough infections have been reported despite measurable anti-HEV antibodies, that were related to the avidity of the humoral response (66). Given the omnipresence of HEV in the European food chain resulting in a spontaneous seroconversion during lifetime in up to 25% of persons, it is doubtful whether such a vaccine would be cost-effectiveness. Therefore, it is too early to recommend a HEV vaccine strategy to prevent chronic HEV infections.

Conclusion and prospects for future research

While most cases of acute HEV infection resolve on their own and require only symptomatic care, chronic disease can be fatal. Certain populations, such as SOT

recipients and individuals with HIV or rheumatological conditions, are at particular risk for chronic HEV infection. In immunosuppressed individuals, an increase in liver enzymes should prompt immediate serological testing and HEV RNA detection, as these patients may not mount a sufficient immune response. More prospective studies on the real HEV infection prevalence in this population are needed. In transplanted patients, cases of HEV transmission via the graft raises the question of systematic graft screening for HEV. Moreover, preventing strategies should be developed, first insisting on dietary adaptations, on screening for HEV in blood donors and on evaluating the efficacy and cost-effectiveness of a vaccination strategy in this specific population.

Further clinical research is essential to develop safe and effective treatments for chronic HEV and improve outcomes for immunosuppressed individuals worldwide.

Declarations

Conflict of interests: The authors do not have any conflict of interest.

References

1. Adlhoch, C., Avellon, A., Baylis, S. A., Ciccaglione, A. R., Couturier, E., de Sousa, R., *et al*. Hepatitis E virus: Assessment of the epidemiological situation in humans in Europe, 2014/15. *J Clin Virol*. 2016;82:9-16.
2. Kamar, N., Selves, J., Mansuy, J. M., Ouezzani, L., Peron, J. M., Guitard, J., *et al*. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med*. 2008;358:811-7.
3. Ma, Z., de Man, R. A., Kamar, N., Pan, Q. Chronic hepatitis E: Advancing research and patient care. *J Hepatol*. 2022;77:1109-23.
4. Smith, D. B., Izopet, J., Nicot, F., Simmonds, P., Jameel, S., Meng, X. J., *et al.* Update: proposed reference sequences for subtypes of hepatitis E virus (species Orthohepevirus A). *J Gen Virol*. 2020;101:692-8.
5. European Association for the Study of the Liver. Electronic address, E. E. E., European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatitis E virus infection. *J Hepatol*. 2018;68:1256-71.
6. Gallian, P., Pouchol, E., Djoudi, R., Lhomme, S., Mouna, L., Gross, S., *t al.* Transfusion-Transmitted Hepatitis E Virus Infection in France. *Transfus Med Rev*. 2019;33:146-53.
7. Westholter, D., Hiller, J., Denzer, U., Polywka, S., Ayuk, F., Rybczynski, M., e*t al.* HEV-positive blood donations represent a relevant infection risk for immunosuppressed recipients. *J Hepatol*. 2018;69:36-42.
8. Lapa, D., Capobianchi, M. R., Garbuglia, A. R. Epidemiology of Hepatitis E Virus in European Countries. *Int J Mol Sci*. 2015;16:25711-43.
9. Suin, V., Klamer, S. E., Hutse, V., Wautier, M., Jacques, M., Abady, M., *et al.* Epidemiology and genotype 3 subtype dynamics of hepatitis E virus in Belgium, 2010 to 2017. *Euro Surveill*. 2019;24.
10. Nicot, F., Dimeglio, C., Migueres, M., Jeanne, N., Latour, J., Abravanel, F., e*t al.* Classification of the Zoonotic Hepatitis E Virus Genotype 3 Into Distinct Subgenotypes. *Front Microbiol*. 2020;11:634430.
11 Rathi, S., Duseja, A., Thakur, V., Ratho, R. K., Singh, M. P., Taneja, S., e*t al.* Chronic Hepatitis E With Genotype 1—Masquerading as Allograft Rejection After Liver Transplantation. *J Clin Exp Hepatol*. 2021;11:400-3.
12. Robins, A. E. M., Bowden, D. J., Gelson, W. T. H. Chronic genotype 1 hepatitis E infection from immunosuppression for ileo-colonic Crohn's disease. *Oxf Med Case Reports*. 2018;2018:omy059.
13. Di Cola, G., Fantilli, A. C., Pisano, M. B., Re, V. E. Foodborne transmission of hepatitis A and hepatitis E viruses: A literature review. *Int J Food Microbiol*. 2021;338:108986.
14. Locus, T., Lambrecht, E., Peeters, M., Suin, V., Verhaegen, B., Van Hoorde, K., e*t al.* Hepatitis E virus in pork meat products and exposure assessment in Belgium. *Int J Food Microbiol*. 2023;397:110198.
15. Takuissu, G. R., Kenmoe, S., Ndip, L., Ebogo-Belobo, J. T., Kengne-Nde, C., Mbaga, D. S., e*t al.* Hepatitis E Virus in Water Environments: A Systematic Review and Meta-analysis. *Food Environ Virol*. 2022;14:223-35.
16. Schlosser, B., Stein, A., Neuhaus, R., Pahl, S., Ramez, B., Kruger, D. H., e*t al.* Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient. *J Hepatol*. 2012;56:500-2.
17. Villalba, R., Mirabet, V. Risk assessment of hepatitis E transmission through tissue allografts. *World J Gastrointest Pathophysiol*. 2022;13:50-8.
18. Kamar, N., Rostaing, L., Legrand-Abravanel, F., Izopet, J. How should hepatitis E virus infection be defined in organ-transplant recipients? *Am J Transplant*. 2013;13:1935-6.
19. Kamar, N., Garrouste, C., Haagsma, E. B., Garrigue, V., Pischke, S., Chauvet, C., e*t al.* Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. *Gastroenterology*. 2011;140:1481-9.
20. Zhou, X., de Man, R. A., de Knegt, R. J., Metselaar, H. J., Peppelenbosch, M. P., Pan, Q. Epidemiology and management of chronic hepatitis E infection in solid organ transplantation: a comprehensive literature review. *Rev Med Virol*. 2013;23:295-304.
21. Frankal, M., Skoglund, C., Castedal, M., Lagging, M., Norder, H. Hepatitis E Virus Infection, a Risk for Liver Transplant Recipients in Sweden. *Transplant Direct*. 2022;8:e1409.
22. Pischke, S., Stiefel, P., Franz, B., Bremer, B., Suneetha, P. V., Heim, A., e*t al.* Chronic hepatitis E in heart transplant recipients. *Am J Transplant*. 2012;12:3128-33.
23. Lenggenhager, D., Pawel, S., Honcharova-Biletska, H., Evert, K., Wenzel, J. J., Montani, M., e*t al.* The histologic presentation of hepatitis E reflects patients' immune status and pre-existing liver condition. *Mod Pathol*. 2021;34:233-48.
24. Cao, D., Cao, Q. M., Subramaniam, S., Yugo, D. M., Heffron, C. L., Rogers, A. J., e*t al.* Pig model mimicking chronic hepatitis E virus infection in immunocompromised patients to assess immune correlates during chronicity. *Proc Natl Acad Sci U S A*. 2017;114:6914-23.
25. Leon-Janampa, N., Caballero-Posadas, I., Barc, C., Darrouzain, F., Moreau, A., Guinoiseau, T., e*t al.* A pig model of chronic hepatitis E displaying persistent viremia and a downregulation of innate immune responses in the liver. *Hepatol Commun*. 2023;7.
26. Klohn, M., Schrader, J. A., Bruggemann, Y., Todt, D., Steinmann, E. Beyond the Usual Suspects: Hepatitis E Virus and Its Implications in Hepatocellular Carcinoma. *Cancers (Basel)*. 2021;13.
27. Dalton, H. R., Kamar, N., van Eijk, J. J., McLean, B. N., Cintas, P., Bendall, R. P., *et al.* Hepatitis E virus and neurological injury. *Nat Rev Neurol*. 2016;12:77-85.
28. Taton, B., Moreau, K., Lepreux, S., Bachelet, T., Trimoulet, P., de Ledinghen, V., *et al.* Hepatitis E virus infection as a new probable cause of de novo membranous nephropathy after kidney transplantation. *Transpl Infect Dis*. 2013;15:E211-5.
29. Guinault, D., Ribes, D., Delas, A., Milongo, D., Abravanel, F., Puissant-Lubrano, B., *et al.* Hepatitis E Virus-Induced Cryoglobulinemic Glomerulonephritis in a Nonimmunocompromised Person. *Am J Kidney Dis*. 2016;67:660-3.
30. Ohnishi, S., Kang, J. H., Maekubo, H., Arakawa, T., Karino, Y., Toyota, J., *et al.* Comparison of clinical features of acute hepatitis caused by hepatitis E virus (HEV) genotypes 3 and 4 in Sapporo, Japan. *Hepatol Res*. 2006;36:301-7.
31. Jeblaoui, A., Haim-Boukobza, S., Marchadier, E., Mokhtari, C., Roque-Afonso, A. M. Genotype 4 hepatitis E virus in France: an autochthonous infection with a more severe presentation. *Clin Infect Dis*. 2013;57:e122-6.
32. Micas, F., Suin, V., Peron, J. M., Scholtes, C., Tuaillon, E., Vanwolleghem, T., *et al*. Analyses of Clinical and Biological Data for French and Belgian Immunocompetent Patients Infected With Hepatitis E Virus Genotypes 4 and 3. *Front Microbiol*. 2021;12:645020.
33. Subissi, L., Peeters, M., Lamoral, S., Klamer, S., Suin, V., Van Gucht, S. Subtype-specific differences in the risk of hospitalisation among patients infected with hepatitis E virus genotype 3 in Belgium, 2010–2018. *Epidemiol Infect*. 2019;147:e224.
34. Abravanel, F., Dimeglio, C., Castanier, M., Peron, J. M., Kamar, N., Lhomme, S., *et al.* Does HEV-3 subtype play a role in the severity of acute hepatitis E? *Liver Int*. 2020;40:333-7.
35. Peeters, M., Schenk, J., De Somer, T., Roskams, T., Locus, T., Klamer, S., *et al.* Viral clade is associated with severity of symptomatic genotype 3 hepatitis E virus infections in Belgium, 2010–2018. *J Hepatol*. 2023;78:67-77.
36. Dalton, H. R., Bendall, R. P., Rashid, M., Ellis, V., Ali, R., Ramnarace, R., *et al.* Host risk factors and autochthonous hepatitis E infection. *Eur J Gastroenterol Hepatol*. 2011;23:1200-5.
37. Kemming, J., Gundlach, S., Panning, M., Huzly, D., Huang, J., Lütgehetmann, M., *et al.* Mechanisms of CD8+ T-cell failure in chronic hepatitis E virus infection. *J Hepatol*. 2022;77:978-90.
38. Wang, Y., Metselaar, H. J., Peppelenbosch, M. P., Pan, Q. Chronic hepatitis E

in solid-organ transplantation: the key implications of immunosuppressants. *Curr Opin Infect Dis*. 2014;27:303-8.
39. Wang, Y., Zhou, X., Debing, Y., Chen, K., van der Laan, L. J., Neyts, J., *et al.* Calcineurin inhibitors stimulate and mycophenolic acid inhibits replication of hepatitis E virus. *Gastroenterology*. 2014;146:1775-83.
40. JBI Institute. Critical Appraisal Checklist for Prevalence Studies. 2016.
41. Buescher, G., Ozga, A. K., Lorenz, E., Pischke, S., May, J., Addo, M. M., *et al.* Hepatitis E seroprevalence and viremia rate in immunocompromised patients: a systematic review and meta-analysis. *Liver Int*. 2021;41:449-55.
42. Pourbaix, A., Ouali, N., Soussan, P., Roque Afonso, A. M., Peraldi, M. N., Rondeau, E., *et al.* Evidence of hepatitis E virus transmission by renal graft. *Transpl Infect Dis*. 2017;19.
43. Schiller, D., Schoefl, R., Holzmann, H. Fatal acute liver failure in a kidney-transplant recipient. *Gastroenterology*. 2014;146:36, 325.
44. Wasuwanich, P., Sirisreetreerux, P., Ingviya, T., Kraus, E. S., Brennan, D. C., Sue, P. K., *et al.* Hepatitis E virus infection and rejection in kidney transplant recipients. *Transpl Immunol*. 2022;70:101517.
45. Magnusson, J., Norder, H., Riise, G. C., Andersson, L. M., Brittain-Long, R., Westin, J. Incidence of Hepatitis E Antibodies in Swedish Lung Transplant Recipients. *Transplant Proc*. 2015;47:1972-6.
46. Riezebos-Brilman, A., Puchhammer-Stöckl, E., van der Weide, H. Y., Haagsma, E. B., Jaksch, P., Bejvl, I., *et al.* Chronic hepatitis E infection in lung transplant recipients. *J Heart Lung Transplant*. 2013;32:341-6.
47. Bauer, H., Luxembourger, C., Gottenberg, J. E., Fournier, S., Abravanel, F., Cantagrel, A., *et al.* Outcome of hepatitis E virus infection in patients with inflammatory arthritides treated with immunosuppressants: a French retrospective multicenter study. *Medicine (Baltimore)*. 2015;94:e675.
48. Pischke, S., Peron, J. M., von Wulffen, M., von Felden, J., Honer zu Siederdissen, C., Fournier, S., *et al.* Chronic Hepatitis E in Rheumatology and Internal Medicine Patients: A Retrospective Multicenter European Cohort Study. *Viruses*. 2019;11.
49. van Bijnen, S. T., Ledeboer, M., Martens, H. A. Chronic hepatitis E in a patient with rheumatoid arthritis treated with adalimumab and methotrexate. *Rheumatology (Oxford)*. 2017;56:497-8.
50. Fraticelli, P., Bagnarelli, P., Tarantino, G., Martino, G. P., Benfaremo, D., Nobili, L., *et al.* Chronic hepatitis E in a patient treated with rituximab and mycophenolate mofetil for Sjogren's syndrome. *Rheumatology (Oxford)*. 2016;55:2275-7.
51. Von Felden, J., Alric, L., Pischke, S., Aitken, C., Schabe, S., Spengler, U., *et al.* The burden of hepatitis E among patients with haematological malignancies: A retrospective European cohort study. *J Hepatol*. 2019;71:465-72.
52. Mikulska, M., Penack, O., Wendel, L., Knelange, N., Cornelissen, J. J., Blijlevens, N., *et al.* HEV infection in stem cell transplant recipients-retrospective study of EBMT Infectious Diseases Working Party. *Bone Marrow Transplant*. 2022;57:167-75.
53. Ghandili, S., Lindhauer, C., Pischke, S., zur Wiesch, J. S., von Kroge, P. H., Polywka, S., *et al.* Clinical features of hepatitis E infections in patients with hematologic disorders. *Haematologica*. 2022;107:2870-83.
54. Chiu, C. Y., Zhang, H. C., Westin, J., Hosing, C., Torres, H. A. Hepatitis E Virus Infection in Cancer Patients. *Transplant Cell Ther*. 2022;28:788 e1-e5.
55. Rivero-Juarez, A., Lopez-Lopez, P., Frias, M., Rivero, A. Hepatitis E Infection in HIV-Infected Patients. *Front Microbiol*. 2019;10:1425.
56. Kenfak-Foguena, A., Schoni-Affolter, F., Burgisser, P., Witteck, A., Darling, K. E., Kovari, H., *et al.* Hepatitis E Virus seroprevalence and chronic infections in patients with HIV, Switzerland. *Emerg Infect Dis*. 2011;17:1074-8.
57. Ingiliz, P., Mayr, C., Obermeier, M., Herbst, H., Polywka, S., Pischke, S. Persisting hepatitis E virus infection leading to liver cirrhosis despite recovery of the immune system in an HIV-infected patient. *Clin Res Hepatol Gastroenterol*. 2016;40:e23-e5.
58. Loyrion, E., Trouve-Buisson, T., Pouzol, P., Larrat, S., Decaens, T., Payen, J. F. Hepatitis E Virus Infection after Platelet Transfusion in an Immunocompetent Trauma Patient. *Emerg Infect Dis*. 2017;23:146-7.
59. Grewal, P., Kamili, S., Motamed, D. Chronic hepatitis E in an immunocompetent patient: a case report. *Hepatology*. 2014;59:347-8.
60. Wang, Y., Liu, S., Pan, Q., Zhao, J. Chronic hepatitis E in an immunocompetent patient. *Clin Res Hepatol Gastroenterol*. 2020;44:e66-e8.
61. Gorris, M., van der Lecq, B. M., van Erpecum, K. J., de Bruijne, J. Treatment for chronic hepatitis E virus infection: A systematic review and meta-analysis. *J Viral Hepat*. 2021;28:454-63.
62. Debing, Y., Emerson, S. U., Wang, Y., Pan, Q., Balzarini, J., Dallmeier, K., *et al.* Ribavirin inhibits in vitro hepatitis E virus replication through depletion of cellular GTP pools and is moderately synergistic with alpha interferon. *Antimicrob Agents Chemother*. 2014;58:267-73.
63. Beaucourt, S., Vignuzzi, M. Ribavirin: a drug active against many viruses with multiple effects on virus replication and propagation. Molecular basis of ribavirin resistance. *Curr Opin Virol*. 2014;8:10-5.
64. Kamar, N., Abravanel, F., Behrendt, P., Hofmann, J., Pageaux, G. P., Barbet, C., *et al.* Ribavirin for Hepatitis E Virus Infection After Organ Transplantation: A Large European Retrospective Multicenter Study. *Clin Infect Dis*. 2020;71:1204-11.
65. Mulder, M. B., de Man, R. A., Kamar, N., Durmaz, G., de Bruijne, J., Vanwolleghem, T., *et al.* Determining the therapeutic range for ribavirin in transplant recipients with chronic hepatitis E virus infection. *J Viral Hepat*. 2021;28:431-5.
66. Kamar, N., Izopet, J., Tripon, S., Bismuth, M., Hillaire, S., Dumortier, J., *et al.* Ribavirin for chronic hepatitis E virus infection in transplant recipients. *N Engl J Med*. 2014;370:1111-20.
67. Abravanel, F., Lhomme, S., Rostaing, L., Kamar, N., Izopet, J. Protracted fecal shedding of HEV during ribavirin therapy predicts treatment relapse. *Clin Infect Dis*. 2015;60:96-9.
68. Kamar, N., Rostaing, L., Abravanel, F., Garrouste, C., Esposito, L., Cardeau-Desangles, I., *et al.* Pegylated interferon-alpha for treating chronic hepatitis E virus infection after liver transplantation. *Clin Infect Dis*. 2010;50:e30-3.
69. Kamar, N., Abravanel, F., Garrouste, C., Cardeau-Desangles, I., Mansuy, J. M., Weclawiak, H., *et al.* Three-month pegylated interferon-alpha-2a therapy for chronic hepatitis E virus infection in a haemodialysis patient. *Nephrol Dial Transplant*. 2010;25:2792-5.
70. Cornberg, M., Pischke, S., Muller, T., Behrendt, P., Piecha, F., Benckert, J., *et al.* Sofosbuvir monotherapy fails to achieve HEV RNA elimination in patients with chronic hepatitis E - The HepNet SofE pilot study. *J Hepatol*. 2020;73:696-9.
71. Zhu, F. C., Zhang, J., Zhang, X. F., Zhou, C., Wang, Z. Z., Huang, S. J., *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.