REVIEW

Hepatitis E Infection in Liver Transplant Recipients

Alberto Unzueta[1] **and Jorge Rakela**[2]
[1]*Division of Hospital Internal Medicine, Mayo Clinic, Phoenix, AZ;* [2]*Division of Hepatology, Mayo Clinic, Phoenix, AZ*

Hepatitis E virus (HEV) infection (genotype 3) has been described in developed countries as a cause of chronic hepatitis in recipients of solid organ transplantation (SOT), with the first cases reported in 2008. Immunosuppression seems to play a major role in the pathogenesis of chronic infections. The current gold standard for the diagnosis of HEV infection is the detection of HEV RNA in serum, stools, or both. In liver transplant recipients, HEV infection is considered an uncommon disease; however, a high index of suspicion is needed for patients with graft hepatitis of an unclear etiology. Liver transplant recipients seem more likely to develop chronic HEV after an acute infection, and there is accelerated progression to advanced fibrosis and cirrhosis. A decrease in immunosuppression is considered the first line of treatment, and pegylated interferon can be considered the second line of treatment for liver transplant recipients. At the present time, there are not enough data to recommend treatment with ribavirin for adult liver transplant recipients, although this has been tried in other SOT populations. ***Liver Transpl 20:15-24, 2014***. © **2013 AASLD.**

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Hepatitis E virus (HEV) is a small, single-stranded, nonenveloped RNA virus. It is classified as the single member of the Hepeviridae family (genus *Hepevirus*). The virus has 3 overlapping open reading frames (ORF). ORF1 encodes for nonstructural proteins (methyl transferase, cysteine protease, helicase, and HEV RNA polymerase) required for viral replication, ORF2 encodes the structural capsid protein, and ORF3 encodes a small protein also involved in HEV replication that is likely released from virally infected cells.[1-3]

There are 4 genotypes (HEV1-HEV4) that are part of a single serotype.[1] HEV1 and HEV2 are found only in humans, with the main mechanism of transmission being fecal-oral from contaminated water sources. Asian and African strains are part of HEV1, whereas Mexican and African strains are part of HEV2. HEV3 and HEV4 can infect humans, pigs, and other mammals. Locally acquired or autochthonous infections have been described in developing and developed countries.[4,5] HEV3 has a worldwide distribution, whereas HEV4 has been reported in Japan and China.[6-8] A hyperendemic area of HEV3 is localized in southwest France in the Toulouse area.[9] Zoonotic transmission has been confirmed for HEV3 and HEV4 on the basis of phylogenetic analyses of HEV subgenotypes found in humans and animals in the same geographic area. HEV3 and HEV4 are primarily swine viruses that are transmitted to humans by direct contact or by the ingestion of infected meat, with humans acting as accidental hosts.[10]

EPIDEMIOLOGY OF HEPATITIS E VIRUS

The epidemiology of HEV varies with the genotype and the affected population. In developing countries, acute HEV has been described in epidemics of acute hepatitis associated with transmission through fecal-contaminated water as well as sporadic cases.[6] The seroprevalence ranges from 30% to 80%, with the majority of waterborne epidemics affecting young

Abbreviations: AHR, acute humoral rejection; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; HEV, hepatitis E virus; IgG, immunoglobulin G; IgM, immunoglobulin M; MMF, mycophenolate mofetil; ORF, open reading frame; PCR, polymerase chain reaction; PEG-IFN, pegylated interferon; RT-PCR, reverse-transcription polymerase chain reaction; SOT, solid organ transplantation; SVR, sustained virological response.

Address reprint requests to Jorge Rakela, M.D., Division of Hepatology, Mayo Clinic, 5777 East Mayo Boulevard, Phoenix, AZ 85054. Telephone: 480-301-6120; FAX: 480-301-7017; E-mail: rakela.jorge@mayo.edu

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male adults with a mortality rate ranging from 0.2% to 5%.[11] However, a high mortality rate (up to 25%) has mainly been reported for pregnant women.[6,12]

HEV3 and HEV4 affect humans and other mammals and are the main sources of HEV infections for sporadic cases in developing countries.[13,14] Locally acquired infections (autochthonous) have been associated with zoonotic transmission via the ingestion of pork or game meat from infected animals, but many cases do not seem to have an evident source of infection.[15,16]

Several autochthonous acute HEV hepatitis cases have been reported in Europe, Japan, New Zealand, and the United States.[6] In the United States, the annual incidence of HEV-associated acute hepatitis is 0.7%, and the reported seroprevalence is 21%[17]; however, reported cases with acute or chronic infections have been very rare.[18] The seroprevalence in other developed countries has been reported to be less than 5%, but there is significant variability in the sensitivity of the diagnostic tests.[6,19] In the hyperendemic area of southwest France, the incidence of HEV per year among solid organ transplantation (SOT) patients is 3.2% with serum HEV RNA detection used as a diagnostic tool.[20]

A study performed with laboratory samples sent to the Centers for Disease Control and Prevention from patients with non-A/non-B hepatitis evaluated the seroprevalence of HEV from 2005 to 2012: 26 of 154 subjects (17%) tested positive for HEV, which was diagnosed by the detection of anti-HEV immunoglobulin M (IgM) and immunoglobulin G (IgG) in serum or by the detection of HEV RNA in serum or stool samples.[21] Seven cases (27%) were organ transplant recipients [liver (2), kidney (3), kidney/pancreas (1) and heart/lung (1)]. None of the SOT patients had a history of travel outside the United States, and they had autochthonous HEV3. The serological assays for detecting anti-HEV IgM and IgG had a diagnostic sensitivity and specificity of 98% and 95.2%, respectively (Diagnostic Systems, Saronno, Italy). Reverse-transcription polymerase chain reaction (RT-PCR) for HEV RNA was used to test serum and stool samples.[21] As previously reported for SOT patients with HEV, patients were anicteric.[22]

A prospective study from Italy evaluated the prevalence of HEV among 651 hospitalized patients with acute non-A/non-B/non-C hepatitis. The prevalence of acute infections was 20.6% (n = 134) among patients who were positive for anti-HEV IgM and IgG; in this group, 71.6% (n = 96) were HEV RNA–positive in serum, and 84.6% were HEV RNA–positive in stools.[23] Most of the patients (81.3%) were immigrants to Italy who presented with the disease after they had traveled from areas endemic for HEV3; 16.4% had autochthonous HEV1 infections. All patients had self-limited disease with a short period to the clearance of HEV viremia from serum and stools.

HEV RNA was detected in 17 of 45,415 Dutch blood donations screened from 2011 to 2012.[24] In the same study, the seroprevalence of IgG antibodies to HEV according to an IgG enzyme immunoassay (Wantai, Beijing, China) in 5239 Dutch blood donors was 26.7% [n = 1401, 95% confidence interval (CI) = 25.6%-28%]. Other studies that used the same assay found a seroprevalence in blood donors of 16% in the southwest of the United Kingdom[13] and 53% in southwest France.[9] The transmission of HEV through blood transfusions is a potential source of infection for SOT recipients; however, because of the low prevalence of HEV RNA viremia in the general blood donor population, the routine screening of blood donors may not be cost-effective.

DIAGNOSIS OF HEPATITIS E VIRUS

The diagnosis of HEV is based on the detection of IgM and IgG antibodies; however, the sensitivity and the specificity are variable and depend on the commercial assay employed.[25,26] Nucleic acid amplification techniques for the detection of HEV RNA include RT-PCR and real-time RT-PCR.[27,28] HEV RNA detection has been considered the diagnostic test for SOT because seroconversion to anti-HEV antibodies is delayed or may not occur at all in these patients. The World Health Organization has recently developed an international standard using an HEV3b strain for reporting HEV RNA concentrations that should decrease interassay variability.[29]

A study comparing the performance of 8 commercial HEV-specific enzyme-linked immunosorbent assays (ELISAs) for the detection of serum antibodies for IgM and IgG with the World Health Organization anti-HEV antibody reference standard found that current commercial anti-HEV ELISAs have high sensitivity and specificity for diagnosing HEV3 infections.[30]

The performance of commercial diagnostic tests for HEV may vary. A published case report[31] illustrates the importance of a false-negative test for a liver transplant recipient who had a negative commercial test result. Later, the patient was confirmed to be positive by anti-HEV IgM and IgG assays and HEV RNA detection performed at the Centers for Disease Control and Prevention several months later.

Testing for HEV serology and anti-HEV IgM and IgG with commercially available kits and for HEV RNA via RT-PCR with in-house methodologies only for research use is conducted at the laboratory of the Division of Viral Hepatitis of the Centers for Disease Control and Prevention.[32] Physicians interested in submitting a patient's sample for testing will need to contact the laboratory for prior approval. A standardized questionnaire that includes demographic, laboratory, and clinical data is required to be submitted along with the test.[33] The use of the in-house RT-PCR assay methodology enabled the CDC laboratory to achieve perfect detection scores in an international evaluation of 20 laboratories conducting HEV RNA testing.[34]

HEPATITIS E VIRUS MISDIAGNOSED AS DRUG-INDUCED LIVER INJURY

In patients with drug-induced liver injury, an acute HEV infection needs to be considered in the differential diagnosis.[35] A study from the Drug-Induced Liver

TABLE 1. Characteristics of Chronic HEV Infections in Liver Transplant Recipients

Study (Year)	Country	Liver Transplant Recipients (n)	Prevalence [n (%) or n/N (%)]*	Outcome
Kamar et al.[43] (2008)	France	86	9 (10.5)†	Three patients had a chronic infection.
Haagsma et al.[44] (2008) Haagsma et al.[53] (2009)	The Netherlands	285	9/285 (3%)‡§	Two patients had chronic HEV: one had mild hepatitis, and the other developed cirrhosis and underwent retransplantation with HEV recurrence afterward.
Pischke et al.[45] (2010)	Germany	226	10 (4.4)†	Three liver transplant patients were positive for HEV RNA: 2 had a chronic infection, and 1 had advanced liver fibrosis 22 months after being diagnosed with acute infection.
Buti et al.[46] (2010)	Spain	82	3/108 (2.7)‖¶	There were no cases of chronic infection.
Legrand-Abravanel et al.[20] (2011)	France	171	22 (12.9)#	Sixteen of 34 patients (47%) had a chronic infection (this series combined patients with liver and kidney transplants).
Kamar et al.[47] (2011)	Multicenter	26**	63/78 (80.8)††	Twenty-three of 26 liver transplant recipients with an HEV infection (88%) developed chronic hepatitis.
Halac et al.[48] (2012)	Canada	80‡‡	22 (27.5)§§	One patient with chronic HEV developed cirrhosis; the same patient had 2 different HEV strains (possible zoonotic reinfection).

*Anti-HEV ELISAs for IgG were used.
†Abbott Laboratories (Abbott Park, IL).
‡Three patients (1%) acquired HEV hepatitis after liver transplantation.
§Genelabs Diagnostics, Inc. (Redwood City, CA).
‖This series combined 82 liver transplant recipients, 21 kidney transplant recipients, and 5 dual-organ recipients.
¶Biokit (Barcelona, Spain).
#Adaltis Ingen (Paris, France).
**These liver transplant patients had HEV infections (HEV RNA was found by PCR in 100% of the patients).
††SOT patients with HEV infections (including all types of SOT).
‡‡Pediatric patients.
§§Feldan Bio (Quebec, Canada).

Injury Network in the United States showed that 3% of patients (9/318) who were initially diagnosed with drug-induced liver injury had acute HEV.[36] Another study from the United Kingdom reported that 13% of patients (6/47) with a diagnosis of drug-induced liver injury had evidence of acute HEV.[37]

CHRONIC LIVER DISEASE AND HEPATITIS E VIRUS

The mortality rate for patients with chronic liver disease and superimposed acute HEV1 is significant. A study from India reported a 70% mortality rate for patients with cirrhosis during a 12-month period.[38] In another case series, 6 of 9 patients with chronic liver disease and acute HEV died.[39] The fatality rate associated with HEV3 in several studies has ranged from 7.5% to 10.8%; in most of these cases, the patients had associated chronic liver disease.[40] This observation is not dissimilar from the high fatality rate associated with acute hepatitis A and B among patients with chronic liver disease.[41,42]

HEPATITIS E VIRUS INFECTION IN LIVER TRANSPLANT RECIPIENTS

HEV was considered a well-established, worldwide etiology of acute hepatitis; there were no reports of

chronic disease associated with this viral infection until the first reports of chronic hepatitis were reported in the south of France by Kamar et al.[43] in 2008 (Table 1). In that study, 14 SOT patients (3 liver transplant recipients, 9 kidney transplant recipients, and 2 combined kidney-pancreas transplant recipients) had an acute HEV infection documented by HEV RNA in serum. Eight patients (57%) developed chronic hepatitis, which was defined by persistently elevated serum aminotransferases, HEV RNA in serum, and histological features of chronic hepatitis on liver biopsy. All 3 liver transplant recipients with acute HEV developed chronic HEV. Two of these patients had an increase in the Metavir fibrosis score after a follow-up of 15 to 16 months. The 8 SOT patients had a significantly shorter time from transplantation to the diagnosis of chronic hepatitis and lower total leukocyte, $CD2^+$, $CD3^+$, $CD4^+$, and platelet counts. Among the 14 patients with acute HEV, 7 (50%) had symptoms, which consisted of fatigue, arthralgias, and myalgias. All cases were autochthonous and associated with HEV3.

Haagsma et al.[44] reported 2 liver transplant recipients who developed chronic HEV and, subsequently, cirrhosis. The diagnosis was made after a retrospective analysis of serum samples with the identification of HEV antibodies and HEV RNA. Both patients underwent retransplantation, and one of them had a recurrence of chronic hepatitis 10 months after retransplantation that improved after a reduction of immunosuppression. One of these cases associated with an acute HEV infection likely acquired the infection during travel to the Caribbean. Both cases were secondary to HEV3.

Progression from chronic HEV to cirrhosis in a short period of time has been described in kidney transplant patients.[49,50] In a report of 2 cases, cirrhosis developed 22 and 38 months after the acute phase of the infection.[49]

The prevalence of HEV IgG antibodies in SOT recipients seems no higher than the prevalence in the general population, so the risk of infection is low.[46,51,52] However, liver transplant patients have an increased risk of chronic infection and the development of cirrhosis when they acquire this infection after transplantation and receive immunosuppression.

The prevalence of HEV infection in liver transplant patients has been described in a study from the Netherlands.[53] HEV infection markers, which included HEV RNA and HEV IgM and IgG antibodies (ELISA with confirmatory immunoblotting), were assessed in 285 patients who underwent liver transplantation. The prevalence of HEV after liver transplantation was 1%. Six patients (2.1%) had evidence of a pretransplant HEV infection according to a retrospective analysis of frozen serum samples of HEV IgG antibodies, and 1 patient developed a chronic HEV infection and was positive for HEV RNA without HEV antibodies after transplantation. This patient suffered mild hepatitis 2 to 5 years after liver transplantation; this was confirmed by HEV RNA, anti-HEV IgM and IgG, elevated serum aminotransferases, and compatible histology.

When SOT recipients are infected acutely with HEV, they may become long-term carriers of HEV. Patients usually remain positive for HEV RNA for several years before the virus is cleared, and they become IgG anti-HEV–positive.[51]

Transmission from a graft with an occult HEV infection was documented in a case report of a 73-year-old male who received an HEV-infected liver.[54] Before transplantation, recipient and donor serum samples were negative for HEV antibodies and HEV RNA; however, HEV RNA was found in high concentrations in the donor liver tissue. The recipient had evidence of an infection (anti-HEV IgG and IgM and HEV RNA) 150 days after liver transplantation and developed cirrhosis within 15 months. A phylogenetic analysis confirmed that the HEV3 strains were concordant between the donor and the recipient.

The reported prevalence of graft hepatitis among liver transplant patients with liver enzyme abnormalities has ranged from 5% in a northern German population[45] to 10% in southern France.[43]

A study from a single center in northern Germany evaluated the prevalence of HEV antibodies in liver transplant patients (n = 226), nontransplant patients with chronic liver disease (n = 129), and healthy subjects (n = 108).[45] The patients with liver transplants were also tested for serum HEV RNA. The liver transplant patients were divided into 2 groups, one with graft hepatitis and one without graft hepatitis, which was defined by an elevation of liver enzymes. Three patients in the group with liver enzyme elevations were HEV RNA–positive, and 2 patients developed chronic HEV3. One of these patients developed significant fibrosis in a short period of time (22 months after liver transplantation). The prevalence of anti-HEV IgG antibodies was 4.4% among liver transplant patients, 3% among nontransplant patients with chronic liver disease, and 1% among healthy controls. Among liver transplant patients with liver enzyme abnormalities, seroconversion to anti-HEV developed 4 months after the detection of serum HEV RNA, and there was clinical evidence of acute hepatitis 5 to 7 months after liver transplantation. The study evaluated reverse zoonotic transmission through the infection of 5 pigs via exposure to serum from a patient with an HEV infection. There was histological evidence of hepatic inflammation, and HEV RNA was found in different organs of the animals.

A study from Spain assessed the prevalence of anti-HEV IgG antibodies in liver and kidney transplant recipients with elevated aminotransferases.[46] The study included 82 liver transplant recipients, 21 kidney transplant recipients, and 5 dual-organ recipients. The authors found anti-HEV IgG antibodies in 3 of the 82 liver transplant recipients (3.6%). These patients were initially negative for anti-HEV IgM and HEV RNA. A follow-up after 6 months confirmed the presence of anti-HEV IgG antibodies, but the patients were negative for anti-HEV IgM and HEV RNA; this ruled out acute and ongoing HEV infections.

A study from France evaluated HEV infections in 700 SOT recipients (529 kidney transplant recipients and

171 liver transplant recipients).[20] Pretransplant antibodies against HEV (IgG and IgM) were detected in 77 of the 529 kidney transplant recipients (14.5%) and in 22 of the 171 liver transplant recipients (12.9%); the yearly pretransplant seroprevalence of anti-HEV ranged from 8.7% to 16.3%. The incidence of HEV infection for SOT patients was 3.2 cases per 100 person-years (95% CI = 2.06-4.13 cases per 100 person-years). Among liver transplant recipients, the incidence was 4.8 cases per 100 person-years (95% CI = 2.2-7.4 cases per 100 person-years), and this was higher than the incidence among kidney transplant recipients (2.7 cases per 100 person-years, 95% CI = 1.52-3.68 100 person-years, $P = 0.09$). Thirty-four patients had an HEV infection, and 16 developed a chronic infection (47%) with detectable serum HEV RNA for more than 6 months. None of the 18 patients whose viremia was cleared during the acute infection experienced reactivation or reinfection. Independent risk factors for HEV infection in a multivariate analysis were liver transplantation and a younger age (<52 years) at transplant.

In a retrospective analysis of 17 centers in Europe and the United States, 85 SOT patients with HEV infections were evaluated.[47] Fifty-six patients (65.9%) developed a chronic HEV infection, and these patients included 46% of the liver transplant recipients. In a univariate analysis, liver transplantation (versus no liver transplantation) was associated with chronic HEV infections, and tacrolimus (versus cyclosporine A; odds ratio = 1.87, 95% CI = 1.49-1.97, $P = 0.004$) and a low platelet count at the time of the HEV diagnosis (odds ratio = 1.02, 95% CI = 1.001-1.1, $P = 0.04$) were independent predictive factors associated with chronic HEV.

PATHOGENESIS OF CHRONIC HEPATITIS E VIRUS INFECTION

Patients with chronic HEV have impaired HEV-specific T cell responses: the proliferation and cytokine production of $CD4^+$ and $CD8^+$ T cells are absent in comparison with healthy controls.[55] These specific T cell responses have been reestablished in vitro after the blocking of programmed death 1 or cytotoxic T lymphocyte antigen 4 pathways.[55]

Decreased levels of serum interleukin-1 receptor antagonist and soluble serum interleukin-2 receptor have been documented in SOT patients with chronic HEV infections.[56] High serum levels of chemokines involved in leukocyte recruitment to the liver during acute HEV infections, a diminished inflammatory response, and increased HEV genetic heterogeneity (quasispecies) have been associated with chronic infections.[56]

DEFINITION OF CHRONIC HEPATITIS E VIRUS INFECTION IN SOLID ORGAN TRANSPLANTATION

Kamar et al.[57] proposed a new definition for chronic HEV infection in patients with HEV viremia persisting for more than 3 months. Previously, evidence of an ongoing HEV infection (which was characterized by the detection of HEV RNA in serum or stools) for more than 6 months was the requirement for establishing the diagnosis of a chronic HEV infection.[43] The change in the criteria for chronic HEV infections was established after they studied a cohort of 77 SOT patients in France who were diagnosed with an HEV infection between 2004 and 2012. HEV RNA by RT-PCR confirmed the HEV infections, and the patients were followed up at months 1 and 3 and then every 3 months until their viremia was cleared.[57] Sixty-nine patients were analyzed, and 59.4% (41/69) developed a chronic infection, with HEV RNA present for at least 6 months. They observed that all the patients whose serum became HEV RNA–negative had cleared the virus at 3 months.

CHRONIC HEPATITIS E VIRUS IN PEDIATRIC LIVER TRANSPLANT RECIPIENTS

A group from Montreal, Canada evaluated 80 children who underwent liver transplantation.[48] They compared 2 groups: one with normal aminotransferases (n = 66) and another group with increased serum aminotransferases that also had histological evidence of chronic hepatitis (n = 14). HEV RNA RT-PCR was performed, and antibody titers for IgG and IgM by ELISA were measured. In the group with elevated aminotransferases, 36% were positive for anti-HEV IgG antibodies before transplantation, and 86% were after liver transplantation. In the group with normal aminotransferases, 15% of the children were anti-HEV–positive during the follow-up. One patient developed anti-HEV IgG and IgM 8 years after liver transplantation and also developed cirrhosis during a period of 10 years. The phylogenetic analysis demonstrated 2 different HEV3 strains detected with a 3-year difference, and this raised the possibility of a zoonotic reinfection. The group with abnormal aminotransferases also had a trend of increased liver fibrosis on liver biopsy.

TREATMENT OF CHRONIC HEPATITIS E VIRUS IN LIVER TRANSPLANT RECIPIENTS

Lower $CD4^+$ cell counts have been found in solid organ recipients with chronic HEV,[43] and decreasing the doses of immunosuppressive drugs that are aimed at T cells (mainly calcineurin inhibitors) has been proposed as a way of promoting clearance of the virus[58] (Fig. 1).

The interferon-α signal pathways (signal transducer and activator of transcription 1) linked to phosphorylation play an important role in the control of viral replication. In vitro studies using cell lines infected with HEV (A549) have demonstrated a role of HEV in the inhibition of the signal transducer and activator of transcription 1 phosphorylation pathway and a

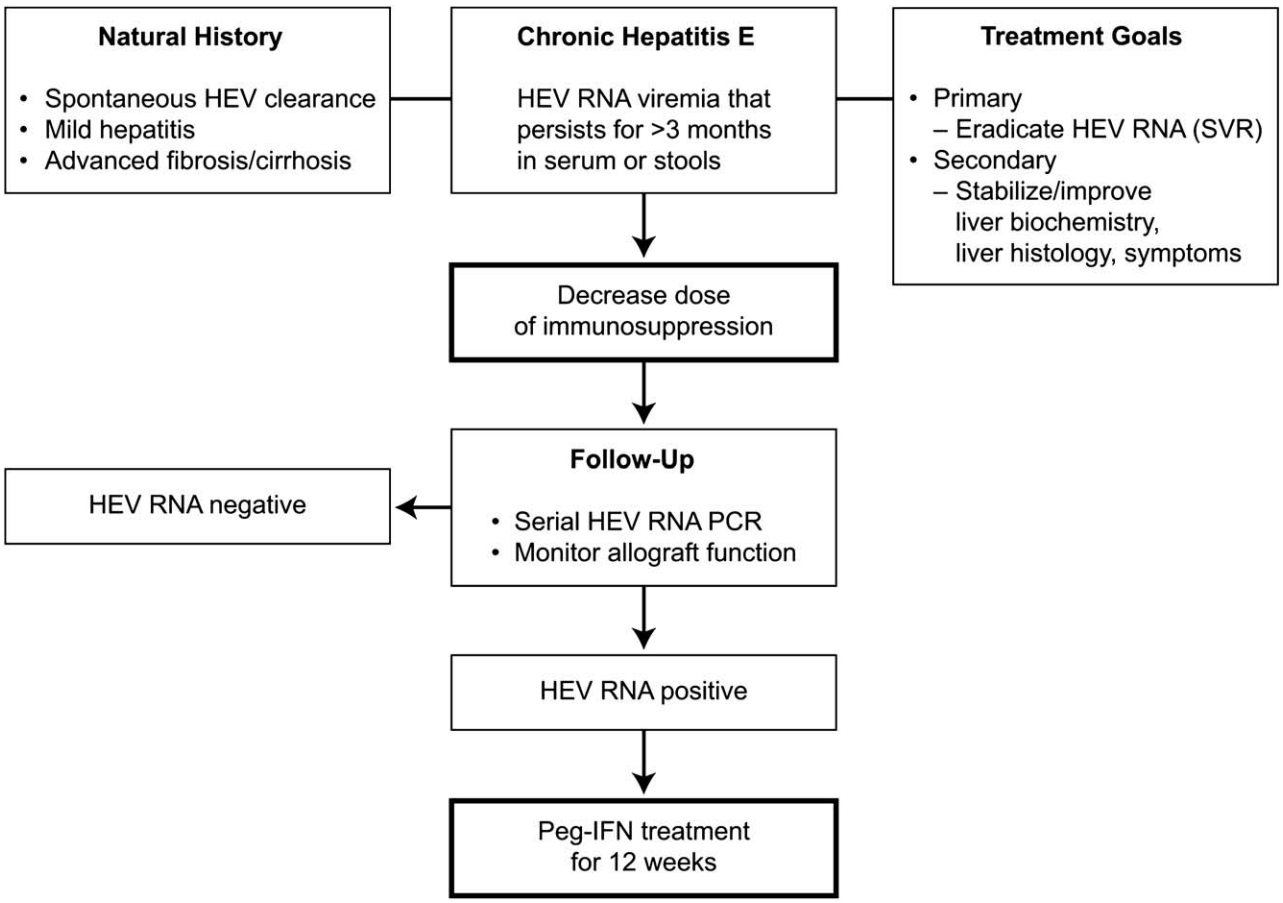

Figure 1. Algorithm for the evaluation and treatment of chronic HEV infections in liver transplant recipients.

decrease in interferon-α–stimulated gene expression, which could decrease the antiviral effect of interferon.[59]

Pegylated interferon-α2a (PEG-IFNα2a) has been used as monotherapy for liver transplant recipients developing chronic HEV[60] (Table 2). Three patients received 3 months of therapy with PEG-IFNα2a and two had a virological response at 24 and 20 weeks after completion of treatment. One experienced acute rejection after the completion of the treatment, and another had a relapse of the HEV infection. Treatment with interferon has been considered a possible risk for inducing acute rejection in liver transplant recipients and is contraindicated in kidney transplant patients because of the increase in acute rejection.[60]

A group from the Netherlands treated 2 liver transplant recipients with chronic HEV with PEG-IFNα2b.[61] One patient was treated for 1 year with normalization of liver tests and a complete virological response at week 20. The other patient had no evidence of a virological response, and interferon was stopped at week 16; however, after the immunosuppression dose was decreased, there was a normalization of liver tests, and the patient's serum became HEV RNA–negative.

The use of ribavirin in the treatment of a kidney-pancreas transplant recipient and a patient with idiopathic $CD4^+$ T lymphocytopenia and chronic HEV was associated with the normalization of liver function tests and the resolution of viremia after 4 weeks of treatment with a ribavirin dose of 12 mg/kg.[64]

A study from France evaluated ribavirin monotherapy in 6 kidney transplant patients who were HEV RNA–positive. The patients received treatment for 6 months: 4 patients had a sustained virological response (SVR), and 2 patients had a viral relapse after the completion of their ribavirin treatment.[65]

Ribavirin was used to treat an immunocompetent patient with severe acute HEV3.[66] The patient received ribavirin (1200 mg/day) for 21 days, and there were significant improvements in liver test abnormalities, histology, and HEV RNA levels.

A prospective study from Germany evaluated 33 SOT recipients with posttransplant HEV from 2008 to 2012; 15 of the 33 patients (45%) had HEV RNA with elevated alanine aminotransferase levels for more than 2 months (prolonged HEV viremia).[62] A reduction of immunosuppression cleared HEV viremia in 3 of the 15 patients with prolonged HEV viremia. Nine of 11 patients who received ribavirin became HEV RNA–negative after 3 to 6 weeks (median = 5 weeks); none of these patients had a recurrent HEV infection after they stopped the treatment. The administered dose of ribavirin was 600 to 1000 mg daily.

TABLE 2. Treatment of Chronic HEV Infections in Liver Transplant Recipients

Study (Year)	Patients (n)	Age (Years)	Sex	Immunosuppression	Treatment	Outcome
Kamar et al.[60] (2010)	3	29	Male	Tacrolimus MMF	1. Reduction of tacrolimus dose (trough level = 2-4 ng/mL) 2. PEG-IFNα2a for 12 weeks (stopped because of AHR)	No response to reduction of immunosuppression. AHR, SVR 24 weeks after completion of PEG-IFN and AHR treatment
		26	Male	Cyclosporine A MMF (2 g/day)	1. Reduction of MMF dose from 2 to 1 g/day 2. PEG-IFNα2a (for eradication of HEV before possible retransplantation)	SVR at 20 weeks after completion of PEG-IFN treatment
		58	Male	Tacrolimus	1. Reduction of immunosuppression tacrolimus dose (trough level = 4-6 ng/mL) 2. PEG-IFNα2a for 3 months	HEV recurrence 2 weeks after completion of PEG-IFN treatment
Haagsma et al.[61] (2010)	2	37	Female	Prednisolone (10 mg daily) Azathioprine (100 mg daily) Cyclosporine (75 mg twice daily; trough level = 150-200 ng/mL)	1. Reduction of immunosuppression, discontinuation of azathioprine, and cyclosporine trough levels of 100-150 ng/L 2. PEG-IFNα2b for 52 weeks	SVR at 20 weeks of PEG-IFNα2b treatment
		59	Male	Tacrolimus (trough level = 10-15 μg/L)	1. Reduction of tacrolimus level to 8-10 μg/L 2. PEG-IFNα2b 3. Further reduction of tacrolimus level	Discontinuation of PEG-IFNα2b after 16 weeks because of lack of response SVR 4 weeks after cessation of PEG-IFN
Pischke et al.[62] (2013)	2	34	Male	Tacrolimus MMF Prednisolone	Reduction of immunosuppression	SVR at 3 months
		40	Male	Cyclosporine MMF Prednisolone	Reduction of immunosuppression	SVR at 30 months
Junge et al.[63] (2013)	1*	10	Male	Tacrolimus MMF Prednisolone	1. Reduction of immunosuppression 2. Ribavirin for 6 months	HEV RNA–negative from 42 days after initiation of ribavirin with SVR

NOTE: All patients had HEV3.
*Pediatric liver transplant recipient.

Ten of 468 adult lung transplant recipients tested positive for HEV RNA (incidence = 2.1%).[67] Eight patients developed a chronic HEV infection (RT-PCR–positive for more than 6 months), and 2 patients were treated with ribavirin (400 mg twice daily) for 4 months and experienced clearance of HEV RNA after 2 months as well as normalization of aminotransferases. For lung, heart, and kidney transplant patients, treatment with interferon is contraindicated because of the high risk of rejection; ribavirin could be an option as the first line of treatment for such patients with chronic HEV infections.[64,67,68]

A reduction in immunosuppression may not be as safe for lung and heart transplant recipients as it is for liver transplant recipients.[62,68] Ribavirin monotherapy in kidney,[65] heart,[68,69] and lung transplant recipients[67] with chronic HEV infections seems to be well tolerated and safe and to be able to induce an SVR; however, the optimal dose and duration of the treatment need to be confirmed in further studies.

CONCLUSIONS

HEV infection is an uncommon cause of chronic hepatitis in immunosuppressed patients and has been documented in SOT recipients. The accelerated progression to increased fibrosis, cirrhosis, and graft failure in patients with chronic HEV is particularly relevant for liver transplant recipients. Until now, all reported cases have been secondary to HEV3. The gold standard for the diagnosis of acute or chronic HEV in SOT recipients is based on the detection of HEV RNA in serum and/or stools by RT-PCR. HEV infection needs to be considered in the differential diagnosis of patients with graft hepatitis of an unclear etiology. Limited data indicate that a reduction in immunosuppression is the first step in the management of patients with chronic HEV infections, and in the case of liver transplant recipients, PEG-IFN could be beneficial.

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