Published in final edited form as:

J Viral Hepat. 2019 April ; 26(4): 414–421. doi:10.1111/jvh.13059.

Clinical features and determinants of chronicity in hepatitis E virus infection

Shivakumar Narayanan¹, Ameer Abutaleb^{1,2}, Kenneth E. Sherman³, and Shyam Kottilil¹

¹Division of Clinical Care and Research, Institute of Human Virology, University of Maryland, Baltimore, Maryland ²Division of Gastroenterology & Hepatology, University of Maryland, Baltimore, Maryland ³Division of Digestive Diseases, University of Cincinnati, Cincinnati, Ohio

Summary

Hepatitis E virus (HEV) has traditionally been associated with an acute, self-limiting hepatitis and is not known to have any chronic sequelae. HEV genotypes 1 and 2, which are human pathogens, have been associated with this self-limiting presentation, in both sporadic and epidemic settings. HEV genotype 3, which is zoonotically transmitted, is increasingly being reported as a cause of chronic infection in immunocompromised patients. These include patients with solid organ transplants, patients receiving chemotherapy for haematologic malignancies and patients infected with HIV. Chronic infection is associated with rapidly progressing liver disease and extrahepatic manifestations including neurologic disorders. We review the clinical manifestations of chronic HEV infection and discuss factors determining persistence and chronicity of HEV.

Keywords

chronic HEV; genotype 3; hepatitis E virus

1 | INTRODUCTION

Hepatitis E virus (HEV) is one of the most common causes of acute hepatitis and jaundice in adults in the world.¹ Over the past 10 years, there has been increased recognition of HEV in the developed world, including its sporadic transmission as a zoonosis, extrahepatic manifestations of HEV and identification of chronic HEV. In this review, we evaluate the determinants of chronicity and persistence of HEV infection.

2 | THE VIRUS

Hepatitis E virus is a positive-stranded RNA virus belonging to the genus *Orthohepevirus* in the *Hepeviridae* family. It is a zoonotic disease and up to 8 genotypes have been described in the animal kingdom. So far, at least 4 genotypes have been shown to infect humans: HEV-1

Correspondence Shyamasundaran Kottilil, Division of Clinical Care and Research, Institute of Human Virology, University of Maryland, Baltimore, MD. skottilil@ihv.umaryland.edu.

CONFLICT OF INTEREST

None.

through HEV-4. More recently, camelid HEV genotype 7 has been shown to infect humans as well.²

The 7.2 kb HEV genome encodes three open reading frames (ORF) which are translated into (a) the ORF1 polyprotein, representing the viral replicase; (b) the ORF2 protein, corresponding to the viral capsid; and (c) the ORF3 protein, involved in viral replication and release (Figure 1). A cap-independent ORF-4 has been identified in HEV-1 only. The ORF4 product stimulates viral RNA-dependent RNA polymerase (RdRp), activity to promote viral replication.

Hepatitis E virus genotypes 1 and 2 are human viruses associated with self-limiting, enterically transmitted illness in sporadic and large water-borne epidemics, though fulminant liver disease with high mortality does occur in specific populations like internally displaced persons and pregnant women. HEV genotypes 3 and 4 are primarily swine viruses that infect humans as accidental hosts. These cause sporadic autochthonous (locally acquired) infection.³ Acquisition is thought to be by consumption of wild or domestic swine, game meat, but also from water contamination by feral pigs or run-off from pig farms. There is cross-neutralization among the four mammalian HEV strains and they all belong to one serotype.

More than two-thirds of patients who get infected with HEV-3 or HEV-4 in the developed world are asymptomatic or mildly symptomatic and may not develop clinically apparent jaundice. A small proportion will develop an acute autochthonous infection which is self-limiting, and they may be undiagnosed or misdiagnosed, sometimes as drug-induced liver injury.⁴ In patients with underlying chronic liver disease and alcoholism, it can cause severe hepatitis and liver failure.³

The diagnosis of acute hepatitis E is driven by clinical suspicion, with appropriate testing, since there is a lack of reliable standardized assays and great variability in test performance. Both positive and negative IgM anti-HEV assay test results should be confirmed with either a second assay and testing for HEV RNA in serum or stool.

3 | CHRONIC HEV INFECTION

A diagnosis of chronic hepatitis is considered when persisting HEV replication, documented as detectable HEV RNA in serum or stool, is identifiable for 3–6 months after original infection.^{5,6}

Chronic HEV infection is almost exclusively reported in immuno-suppressed patients. This group includes patients with solid organ transplantation (SOT),⁵ patients on chemotherapy for haematologic malignancies,⁷ patients infected with HIV⁸ and patients with rheumatologic conditions receiving immunomodulatory drugs.⁹ Chronic HEV in the SOT population is almost exclusively attributable to genotype 3 infection. Indeed, chronic infection is not documented with HEV-1 and HEV-2. It is exceedingly rare with HEV-4.¹⁰ Extrahepatic disease in the setting of chronic infection is also reported with HEV-3 infection.¹¹

3.1 | Chronic HEV in the solid organ transplant population

Kamar et al., in a study of 85 patients with chronic HEV in 17 transplant centres across Europe and North America, showed that almost 66% of SOT patients who contract HEV developed chronic infection and 10% progressed to cirrhosis (16% of those with chronic hepatitis).^{5,6}

Unlike HBV, this phenomenon is not a reactivation process in an anti-HEV seropositive host.¹² It has rarely been transmitted via liver allograft from a donor with occult infection.¹³ A case report of transmission through kidney allograft has been recently reported.¹⁴ It is thought that consumption of game meat, pork products and mussels causes HEV infection post-transplant which then progresses differently than course of infection in an immunocompetent host. Transfusion-transmitted HEV was thought to be low though this may be due to underreporting.

Incidence and seroprevalence of HEV in the SOT population are difficult to estimate accurately, due to a lack of commercially available HEV RNA assays and the significant variability of home-brew PCR tests.

Most patients with chronic HEV infection in the SOT population are asymptomatic, with only 32% of patients reporting symptoms.⁵ Liver enzyme elevation in acute cases is much lower than that reported in immunocompetent hosts in the range of 300s IU/L for alanine transaminase (ALT) levels in contrast to levels of 3000–5000 IU/L for nontransplant patients. This may be misinterpreted as a drug-related liver injury as mentioned above. When chronicity is established, lower levels of serum transaminases prevail. Seroconversion may be delayed or may not occur at all, and thus, RNA testing is recommended. Only 34% clear HEV spontaneously and the remaining go on to develop chronic hepatitis E. Progression to liver fibrosis occurs in 10%–15% and may occur much more rapidly, sometimes within 2–3 years.⁶ This occurs regardless of the type of allograft and in nonliver-transplanted hosts as well.¹⁵ When serial biopsies were done on chronically infected patients, a significant number had increase in their fibrosis scores within 2 years and 20% developed cirrhosis within 5 years.¹⁶

3.2 | Chronic HEV in patients with haematologic malignancies

There are sparse case reports of acute and chronic HEV in patients with haematological malignancies receiving chemotherapy. It has been reported in patients being treated for B- and T-cell lymphoma, chronic myelomonocytic leukaemia and untreated hairy cell leukaemia. In the stem cell transplant population, the prevalence of HEV may mirror the prevalence in the general population ranging from 5.8% to 32% when more sensitive assays for IgG (Wantai test) are used.¹⁷

In a larger retrospective analysis of chronic HEV in allogeneic hematopoietic stem cell transplant (alloHSCT) patients, 8 out of 328 (2.4%) were HEV RNA positive post-transplant. Five patients developed chronic hepatitis and four died. Of note, some of these patients were misdiagnosed as hepatic graft vs host disease (GVHD).¹⁸ Clinical manifestations are similar to the SOT population, though sparser numbers preclude specific

characterization. Development of cirrhosis within 2 years of infection has been described in a paediatric marrow transplant patient.¹⁹

3.3 | Chronic HEV infection in HIV

The prevalence of HEV infection in patients with HIV varies and may mirror baseline regional differences and test characteristics of assay used. Very few HEV RNA-positive cases have been documented <0.5% in one series.⁸ It is possible that patients with advanced HIV/AIDS may be seronegative, and immune reconstitution with seroconversion and clinical hepatitis has been documented in a HIV-positive patient who started antiretroviral therapy.²⁰ Most are genotype 3 and a third had chronic hepatitis. HEV-related cirrhosis has been very sparsely documented.²¹ Patients with CD4 counts <200 cells/mm³ tended to have persistent hepatitis while those with higher counts cleared infection. Chronic HEV infections in HIV-positive individuals have been associated with quick progression to cirrhosis.²² The higher prevalence of anti-HEV antibody in HIV-positive cirrhotic patients has led to suggestion to screen for HEV in cases of cryptogenic cirrhosis in HIV-positive individuals.

4 | DETERMINANTS OF CHRONICITY

4.1 | Virus factors

Hepatitis E virus causing chronic disease is predominantly HEV-3. HEV-1 and HEV-2 have not been associated with chronicity. Chronic infection with HEV-4 is reported but again extremely rare.¹⁰

The host adaptability and hence specificity and zoonotic potential of HEV viruses are probably variable. HEV-1 and HEV-2 are thought to be human adapted and more virulent.³ Genotype 3 is less adapted to human infection, and the spectrum of clinical disease caused by HEV-3 is quite variable—genotype 3f seems to produce more clinically apparent disease than genotype 3c.²³ Mutations within the helicase gene seem to produce clusters of HEV-3 associated with more virulence and clinically severe acute cases.²⁴ It may be possible that for less virulent, less host-adapted strains, the host immune system is unable to clear acute infection which establishes chronicity.

RNA viruses exist as quasispecies. Recent studies have shown that greater quasispecies diversification (intersample variability within the same individual) as measured by nucleotide sequence entropy and genetic distances of the region within the ORF-2 has been associated with the development of chronic infection.²⁵ However, the exact nature of HEV quasispecies in chronic patients is still not extensively studied.

Reinfection by 2 different strains of HEV subgenotypes and infection by 2 different subtypes of genotype 3 (3c and 3e) have been documented to occur by zoonotic transmission in SOT patients.²⁶ Similarly, reinfection with 2 different genotypes has been documented (HEV-3 and HEV-4, both swine viruses) in an otherwise healthy male.²⁷

The HEV virus is also unique among human hepatitis viruses in that short human-sequence inserts have been identified in HEV RNA in a HIV-infected patient with chronic neurologic symptoms. It is possible recombinant viruses may have different tissue tropism,

pathogenicity and replicative fitness.²⁸ So far, in human studies, tropism of HEV has been demonstrated for central nervous system, liver, kidney and placenta.

Hepatitis E virus like other viruses has mechanisms of evading innate immunity (downregulating interferon responses through ORF-3 protein interaction with the pathway for induction of IFN- α stimulated genes—see Figure 2) and adaptive immunity (viral escape by mutation of epitopes or glycosylation of surface proteins), or induction of T-cell exhaustion.

Hepatitis E virus strains in serum samples can replicate efficiently despite the coexistence of HEV antibodies. >90% of HEV particles in the circulation exist as free virions not complexed with immunoglobulins.²⁹ Recent studies suggest that virus secreted into the bloodstream is associated with the ORF3 protein and wrapped by cellular membranes, while virus secreted into the bile is nonenveloped. HEV being cloaked in host cell membrane may result in nonspecific uptake by different cell types.³⁰ Similarities between the membrane-associated HEV particles and exosomes may be important in facilitating entry of HEV into immunologically privileged sites such as the central nervous system.³¹

Hepatitis E virus RNA and antigen have been demonstrated in urine of monkeys infected with HEV and in the presence of pathologic abnormalities of chronic infection noted on renal biopsy specimens.³²

5 | HOST FACTORS

In HEV infection, innate immunity may have a role in clearing infection, as in other hepatotropic viruses by killing virus-infected cells. Cell-mediated immune responses cause infiltration of hepatocytes by cytotoxic T cells and inhibition of viral replication by cytokines and may be responsible for the clinical acute disease. Humoral immunity, either from prior infection or immunization, seems to protect against at least clinical disease caused by subsequent infection.

5.1 | Innate immunity

Innate immune response may play a more robust role in HEV clearance than adaptive immunity. This is suggested on DNA microarray transcriptome analysis on serial liver biopsies which show host response to hepatitis C infection being more robust in the magnitude and number of differentially expressed genes compared to HEV infection.³³

In acute viral hepatitis, the onset of icteric symptoms coinciding with rise in antibodies and decline in viral load indicates the role of the immune system in pathogenesis. High titres of proinflammatory interleukin-2 (IL-2), IL-10, tumour necrosis factor alfa (TNF- α) and gamma interferon (IFN- γ) have been found in cases of acute liver failure from HEV-induced acute hepatitis.³⁴ Selective accumulation and apoptosis of NK (CD3⁻/CD56⁺) and NKT (CD3⁺/CD56⁺) cell populations in the liver may secrete more IFN- γ and contribute to cytolysis in acute icteric hepatitis E. Indeed, lower NK cell counts and activity in pregnant women may explain their inability to clear virus and possibly greater susceptibility to acute HEV.³⁵

Within the SOT population, higher levels of IL-1 receptor agonist (IL-1Ra) and TNF- α concentrations were seen in those who cleared infection than in those who developed chronic HEV in this population. IL-1Ra stimulates type III IFN by plasmacytoid dendritic cells which is an antiviral and may help clear virus. TNF- α recruits and activates macrophages, NK and T cells.

Certain TNF- α and IFN- γ gene promoter polymorphisms, which seem to be associated with higher cytokine production, seem to be associated with higher susceptibility for HEV infections (-308-AA in promoter region) or severe symptomatic disease (TNF-1031CC and IFN-874TT).³⁶ HEV ORF-3 inhibits TNF α -induced nuclear factor-kappa B signalling.³⁷ Therapy with TNF- α inhibitors for rheumatologic conditions has been associated with HEV infection.⁹ Though most of these have been acute infections, chronic HEV has been described, despite anti-HEV T-cell responses being preserved, with use of these agents.

5.2 | Cell-mediated immunity

Cell-mediated immune responses may also be important in clearing HEV as suggested by higher IFN- γ -secreting cells among PBMCs of convalescent IgG anti-HEV-positive patients when stimulated with pooled ORF2 peptides and measured by enzyme-linked immunosorbent spot (ELISPOT) assay.³⁸ HEV-specific T-cell responses generated during acute disease predominantly target ORF2, but they contract in magnitude and polyfunctionality few months after acute infection. Patients with acute liver failure from hepatitis E seem to have increased infiltration of liver by CD8⁺ cytotoxic T cells besides NK cells as described above.³⁹ CD4⁺/CD25⁺/FoxP3⁺ and CD4⁺/CD 25⁻/FoxP3⁺ regulatory T cells were also found in higher frequencies along with higher levels of IL-10 in acute hepatitis E as compared to controls.⁴⁰

In the solid organ transplant population, total counts of CD2, CD3 and CD4 T cells were significantly lower in patients with chronic HEV than patients who resolved their acute hepatitis.⁵ HEV-specific T-cell responses are detectable in the majority of anti-HEV-positive organ transplant recipients receiving immunosuppressive medications. However, the strength of T-cell responses was much weaker in when assessed by ELISPOT IFN- γ release assays and T-cell proliferation assays.⁴¹ The concentration of soluble interleukin-2 receptor (sIL-2R), which is a marker of T-cell activation, was higher in a group of SOT patients with HEV infection who cleared the virus than in those whose infection became chronic. This also correlated with elevation of transaminases in this group.²⁶ HEV-specific T-cell responses could be restored in vitro by blocking co-inhibitory receptors programmed death ligand-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). In vitro models indicate anti-HEV-positive/HEV RNA-negative patients have higher IFN- γ and macrophage inflammatory protein-1 β (MIP-1 β) secretion indicating a T helper cell type 1 (Th1) response, whereas patients with chronic HEV infection show increased secretion of IL-10 indicating a T helper cell type 2 (Th2) response.⁴¹

The worse outcomes in pregnant women infected with HEV-1 in outbreaks may also be related in part to the virulence of this strain, but also to the epidemiologic context of these outbreaks (famine, malnutrition and their effect on immunity), and the immune-suppressed state of pregnancy. A Th 2 bias has been suggested as possibly contributing to poor

clearance and more severe disease with advancing pregnancy. Chronic hepatitis E in pregnancy is not described and may be epiphenomenal, given temporary nature of immune perturbation in pregnancy. Indeed, spontaneous clearance of chronic HEV in a pregnant kidney transplant patient is described and was thought to be related to changes in pharmacokinetics of calcineurin inhibitor due to volume expansion in pregnancy and resultant restoration of HEV-specific T-cell responses.⁴²

There is some evidence that HEV-specific T-cell responses may overlap between genotypes, just like there is cross-reactivity of neutralizing antibodies.⁴¹

Though Kamar et al⁵ showed a greater likelihood of chronicity in patients taking tacrolimus as compared to cyclosporine, chronic HEV has been documented in patients on a variety of immunosuppressive regimens including other T-cell inhibitors like corticosteroids, or mammalian target of rapamycin inhibitors like everolimus, B-cell modulating agents like rituximab or even agents like TNF- α modulating agents, methotrexate, or other drugs or their combinations.

Cyclosporine A and high concentrations of tacrolimus promoted replication of HEV in a dose-dependent manner through cyclophilins in subgenomic and infectious HEV replication models. Mycophenolic acid inhibited replication in this model by depletion of cellular guanosine nucleotides.⁴³ In support of this is the study which showed that clearance of chronic HEV after heart transplantation was more common in regimens containing mycophenolic acid mofetil, though numbers in this study were too small to draw conclusions. mTOR inhibitors like rapamycin and everolimus promoted HEV replication.⁴⁴

5.3 | Role of humoral responses

Humoral immunity in HEV from resolved infection or vaccination is thought to protect against subsequent clinical infection by the development of neutralizing antibodies against the 660 amino acid capsid encoded by ORF2. Clinical trials of candidate HEV vaccines in China and Nepal have demonstrated vaccine efficacy against preventing clinical illness of 79%–88%.^{45,46} Notably, vaccination produced higher antibody titres than prior natural infection and protection is supposed to be across genotypes. While vaccination may decrease risk of severe hepatitis, subclinical disease may occur in recipients.⁴⁵ Immunity from natural infection may wane over time, as reflected by decreasing titres of IgG, which may predispose to reinfection with related strains.⁴⁷

Neurologic problems are likely caused by cross-reactive cellular or antibody responses to viral epitopes targeting self-antigens, and kidney injury may involve deposition of immune complexes formed between viral antigens and antibodies. Cases of anti-GM1/anti-GM2 antibody-positive Guillain-Barré syndrome, in the setting of HEV infection, have been reported illustrating the theory of molecular mimicry.⁴⁸

6 | TREATMENT OF CHRONIC HEV

Most published data about treatment of chronic HEV have been from case series and reports in the SOT population.

Reduction of immunosuppression is a successful mode of therapy to clear HEV—almost 32% of patients with chronic HEV achieved viral clearance after immunosuppressive therapy was reduced.⁵ Indeed, in a group of SOT patients, HEV-infected patients who cleared the virus had lower trough levels of tacrolimus and daily steroid doses than those who did not. This group also had a lower proportion of patients who received induction immunosuppression and had higher circulating levels of CD3 and CD4 cells.¹⁶ When HEV is not cleared, antiviral therapy can be tried. Both PEGylated interferon and ribavirin are effective in treating chronic HEV. As interferon increases risk of transplant rejection, especially in kidney, heart and lung transplantation, ribavirin monotherapy is preferred. PEG-IFN- α -2a/2b have been used for durations of 3–12 months in HEV-infected liver transplant recipients in individual case reports. If IFN is used, then antirejection therapy would need to be optimized to avoid rejection.

Ribavirin monotherapy is used more widely to treat HEV as it does not increase rejection risk. It can also be used concomitantly in patients whose immunosuppression cannot be decreased. Ribavirin is converted to active metabolite ribavirin 5'-monophosphate which is a competitive inhibitor of the cellular inosine monophosphate dehydrogenase (IMPDH). This depletes intracellular guanosine triphosphate (GTP) pools which affects RNA virus replication and may be the main mechanism of action of ribavirin.⁴⁹ Other proposed mechanisms of action of ribavirin as an antiviral have included modulation of hepatic IFN-stimulated genes (ISG) expression, immunomodulation of T-cell response and effect as a virus mutagen. These mechanisms could also be putatively operative in its action as an antiviral in HEV. The optimal duration of IFN or ribavirin therapy is not known, but 3-month courses have been used most commonly. In a multicentre case series of 59 HEV-infected patients with SOT, ribavirin monotherapy, at a median dose of 600 mg/d achieved sustained virologic response (SVR), defined as undetectable serum HEV RNA at least 6 months after cessation of antivirals, in 78% of treated patients.⁵⁰ SVR with a 3-month course was predicted by viral clearance at 1 month on therapy, with those not having this early response responding to longer courses of ribavirin with better SVR rates. Other predictors of SVR in different studies include a lower lymphocyte count at initiation of ribavirin therapy and decrease in HEV RNA concentration of more than 0.5 log copies/mL within the first week after initiating ribavirin therapy. Some studies have indicated that faecal shedding of HEV in ribavirin-treated SOT patients is a risk factor for relapse after standard course therapy and monitoring this may be considered especially in relapsed patients on longer courses of therapy. Anaemia was the main side effect and needed ribavirin dose reduction 29%, erythropoietin administration in 54% and transfusion in 12% of treated patients.⁵⁰

Patients with HIV and chronic HEV have been treated variously with ribavirin, pegylated interferon or combinations with successful outcome. The effect of antiviral therapy on extrahepatic manifestations of HEV has been variable. Though it cleared HEV, its effect on clinical CNS disease was variable, while renal outcomes were more favourable.¹¹

In patients with liver transplant, renal transplant patients with allograft dysfunction or dialysis patients who have chronic hepatitis E, treatment of hepatitis E with PEGylated Interferon or Ribavirin with a goal of achievement of SVR may be appropriate before consideration for retransplantation, as HEV may recur after retransplantation leading to

chronic liver disease. Indeed, treatment of patients with fulminant hepatic failure from hepatitis E with ribavirin may even abrogate the need for a liver transplant.

7 | CONCLUSION

In summary, chronic HEV infection is documented in patients with immunocompromised states, including organ/hematopoietic transplantation and advanced HIV infection (Figure 3). The exact mechanism(s) involved in HEV persistence in these patients is not completely understood; however, greater HEV quasispecies diversity, as well as impaired innate and adaptive immune responses, seems to play a major role in the development of chronic HEV infection. It remains unclear whether HEV genotype or the epidemiologic differences between infections with different genotypes influences the outcome of acute infection and the risk of progression to chronicity. Future research should be focused on defining the epidemiology of chronic HEV infection and delineating the mechanisms that aid HEV persistence.

Acknowledgments

Funding information

KES, Grant/Award Number: 1R01KD108363; NIH, Grant/Award Number: R01DK108362

Abbreviations:

ALT	alanine transaminase
GTP	guanosine triphosphate
GVHD	graft vs host disease
HEV	hepatitis E virus
IMPDH	inosine monophosphate dehydrogenase
ISG	IFN-stimulated genes
ORF	open reading frames
SOT	solid organ transplantation
SVR	sustained virologic response.

REFERENCES

1. Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. *N Engl J Med* 2012;367(13):1237–1244. [PubMed: 23013075]
2. Lee GH, Tan BH, Teo EC, Lim SG, Dan YY, Wee A, et al. Chronic infection with camelid hepatitis E virus in a liver transplant recipient who regularly consumes camel meat and milk. *Gastroenterology* 2016;150(2):355–7.e3. [PubMed: 26551551]
3. Dalton HR, Bendall R, Ijaz S, Banks M. Hepatitis E: an emerging infection in developed countries. *Lancet Infect Dis* 2008;8(11):698–709. [PubMed: 18992406]

4. Dalton HR, Fellows HJ, Stableforth W, Joseph M, Thuraiajah PH, Warshow U, et al. The role of hepatitis E virus testing in drug-induced liver injury. *Aliment Pharmacol Ther* 2007;26(10):1429–1435. [PubMed: 17850420]
5. Kamar N, Selves J, Mansuy JM, Ouezzani L, Peron JM, Guitard J, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med* 2008;358(8):811–817. [PubMed: 18287603]
6. Kamar N, Garrouste C, Haagsma EB, Garrigue V, Pischke S, Chauvet C, et al. Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. *Gastroenterology* 2011;140(5):1481–1489. [PubMed: 21354150]
7. Tavitian S, Peron JM, Huynh A, Mansuy JM, Ysebaert L, Huguet F, et al. Hepatitis E virus excretion can be prolonged in patients with hematological malignancies. *J Clin Virol* 2010;49(2):141–144. [PubMed: 20678959]
8. Kaba M, Richet H, Ravaut I, Moreau J, Poizot-Martin I, Motte A, et al. Hepatitis E virus infection in patients infected with the human immunodeficiency virus. *J Med Virol* 2011;83(10):1704–1716. [PubMed: 21837786]
9. Bauer H, Luxembourger C, Gottenberg JE, 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(14):e675. [PubMed: 25860212]
10. Geng Y, Zhang H, Huang W, J Harrison T, Geng K, Li Z, et al. Persistent hepatitis e virus genotype 4 infection in a child with acute lymphoblastic leukemia. *Hepat Mon* 2014;14(1):e15618. [PubMed: 24596581]
11. Kamar N, Bendall RP, Peron JM, Cintas P, Prudhomme L, Mansuy JM, et al. Hepatitis E virus and neurologic disorders. *Emerg Infect Dis* 2011;17(2):173–179. [PubMed: 21291585]
12. Legrand-Abravanel F, Kamar N, Sandres-Saune K, Lhomme S, Mansuy JM, Muscari F, et al. Hepatitis E virus infection without reactivation in solid-organ transplant recipients, France. *Emerg Infect Dis* 2011;17(1):30–37. [PubMed: 21192851]
13. Schlosser B, Stein A, Neuhaus R, Pahl S, Ramez B, Kruger DH, et al. Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient. *J Hepatol* 2012;56(2):500–502. [PubMed: 21798217]
14. Pourbaix A, Ouali N, Soussan P, Roque Afonso AM, Peraldi MN, Rondeau E, et al. Evidence of hepatitis E virus transmission by renal graft. *Transpl Infect Dis* 2017;19:e12624 10.1111/tid.12624
15. Kamar N, Mansuy JM, Cointault O, Selves J, Abravanel F, Danjoux M, et al. Hepatitis E virus-related cirrhosis in kidney- and kidney-pancreas-transplant recipients. *Am J Transplant* 2008;8(8):1744–1748. [PubMed: 18557740]
16. Kamar N, Abravanel F, Selves J, Garrouste C, Esposito L, Lavyssiere L, et al. Influence of immunosuppressive therapy on the natural history of genotype 3 hepatitis-E virus infection after organ transplantation. *Transplantation* 2010;89(3):353–360. [PubMed: 20145528]
17. Koenecke C, Pischke S, Heim A, Raggub L, Bremer B, Raupach R, et al. Chronic hepatitis E in hematopoietic stem cell transplant patients in a low-endemic country? *Transpl Infect Dis* 2012;14(1):103–106. [PubMed: 22212560]
18. Versluis J, Pas SD, Agteresch HJ, de Man RA, Maaskant J, Schipper ME, et al. Hepatitis E virus: an underestimated opportunistic pathogen in recipients of allogeneic hematopoietic stem cell transplantation. *Blood* 2013;122(6):1079–1086. [PubMed: 23794068]
19. Halac U, Beland K, Lapierre P, Patey N, Ward P, Brassard J, et al. Cirrhosis due to chronic hepatitis E infection in a child post-bone marrow transplant. *J Pediatr* 2012;160(5):871–4.e1. [PubMed: 22341950]
20. Andersson MI, Preiser W, Maponga TG, Heys I, Taljaard JJ, van Rensburg C, et al. Immune reconstitution hepatitis E: a neglected complication of antiretroviral therapy in Africa? *AIDS* 2013;27(3):487–489. [PubMed: 23291543]
21. Dalton HR, Bendall RP, Keane FE, Tedder RS, Ijaz S. Persistent carriage of hepatitis E virus in patients with HIV infection. *N Engl J Med* 2009;361(10):1025–1027. [PubMed: 19726781]

22. Neukam K, Barreiro P, Macias J, Avellon A, Cifuentes C, Martin-Carbonero L, et al. Chronic hepatitis E in HIV patients: rapid progression to cirrhosis and response to oral ribavirin. *Clin Infect Dis* 2013;57(3):465–468. [PubMed: 23575198]
23. Renou C, Pariente A, Cadranel JF, Nicand E, Pavio N. Clinically silent forms may partly explain the rarity of acute cases of autochthonous genotype 3c hepatitis E infection in France. *J Clin Virol* 2011;51(2):139–141. [PubMed: 21435944]
24. Takahashi K, Okamoto H, Abe N, Kawakami M, Matsuda H, Mochida S, et al. Virulent strain of hepatitis E virus genotype 3, Japan. *Emerg Infect Dis* 2009;15(5):704–709. [PubMed: 19402955]
25. Lhomme S, Abravanel F, Dubois M, Sandres-Saune K, Rostaing L, Kamar N, et al. Hepatitis E virus quasispecies and the outcome of acute hepatitis E in solid-organ transplant patients. *J Virol* 2012;86(18):10006–10014. [PubMed: 22761386]
26. Moal V, Gerolami R, Colson P. First human case of co-infection with two different subtypes of hepatitis E virus. *Intervirology* 2012;55(6):484–487. [PubMed: 22398950]
27. Takahashi M, Nishizawa T, Yoshikawa A, Sato S, Isoda N, Ido K, et al. Identification of two distinct genotypes of hepatitis E virus in a Japanese patient with acute hepatitis who had not travelled abroad. *J Gen Virol* 2002;83(Pt 8):1931–1940. [PubMed: 12124457]
28. Shukla P, Nguyen HT, Torian U, Engle RE, Faulk K, Dalton HR, et al. Cross-species infections of cultured cells by hepatitis E virus and discovery of an infectious virus-host recombinant. *Proc Natl Acad Sci USA* 2011;108(6):2438–2443. [PubMed: 21262830]
29. Takahashi M, Tanaka T, Takahashi H, Hoshino Y, Nagashima S, Jirintai S, et al. Hepatitis E Virus (HEV) strains in serum samples can replicate efficiently in cultured cells despite the coexistence of HEV antibodies: characterization of HEV virions in blood circulation. *J Clin Microbiol* 2010;48(4):1112–1125. [PubMed: 20107086]
30. Feng Z, Lemon SM. Peek-a-boo: membrane hijacking and the pathogenesis of viral hepatitis. *Trends Microbiol* 2014;22(2):59–64. [PubMed: 24268716]
31. Nagashima S, Jirintai S, Takahashi M, Kobayashi T, Tanggis, Nishizawa T, et al. Hepatitis E virus egress depends on the exosomal pathway, with secretory exosomes derived from multivesicular bodies. *J Gen Virol* 2014;10:2166–2175.
32. Geng Y, Zhao C, Huang W, Harrison TJ, Zhang H, Geng K, et al. Detection and assessment of infectivity of hepatitis E virus in urine. *J Hepatol* 2016;64(1):37–43. [PubMed: 26362822]
33. Yu C, Boon D, McDonald SL, Myers TG, Tomioka K, Nguyen H, et al. Pathogenesis of hepatitis E virus and hepatitis C virus in chimpanzees: similarities and differences. *J Virol* 2010;84(21):11264–11278. [PubMed: 20739520]
34. Saravanabalaji S, Tripathy AS, Dhoot RR, Chadha MS, Kakrani AL, Arankalle VA. Viral load, antibody titers and recombinant open reading frame 2 protein-induced TH1/TH2 cytokines and cellular immune responses in self-limiting and fulminant hepatitis e. *Intervirology* 2009;52(2):78–85. [PubMed: 19401616]
35. Srivastava R, Aggarwal R, Bhagat MR, Chowdhury A, Naik S. Alterations in natural killer cells and natural killer T cells during acute viral hepatitis E. *J Viral Hepat* 2008;15(12):910–916. [PubMed: 18673427]
36. Mishra N, Arankalle VA. Association of polymorphisms in the promoter regions of TNF-alpha (–308) with susceptibility to hepatitis E virus and TNF-alpha (–1031) and IFN-gamma (+874) genes with clinical outcome of hepatitis E infection in India. *J Hepatol* 2011;55(6):1227–1234. [PubMed: 21703188]
37. Xu J, Wu F, Tian D, Wang J, Zheng Z, Xia N. Open reading frame 3 of genotype 1 hepatitis E virus inhibits nuclear factor-kappa B signaling induced by tumor necrosis factor-alpha in human A549 lung epithelial cells. *PLoS ONE* 2014;9(6):e100787. [PubMed: 24959724]
38. Shata MT, Barrett A, Shire NJ, Abdelwahab SF, Sobhy M, Daef E, et al. Characterization of hepatitis E-specific cell-mediated immune response using IFN-gamma ELISPOT assay. *J Immunol Methods* 2007;328(1–2):152–161. [PubMed: 17905301]
39. Prabhu SB, Gupta P, Durgapal H, Rath S, Gupta SD, Acharya SK, et al. Study of cellular immune response against Hepatitis E virus (HEV). *J Viral Hepat* 2011;18(8):587–594. [PubMed: 20579277]

40. Tripathy AS, Das R, Rathod SB, Gurav YK, Arankalle VA. Peripheral T regulatory cells and cytokines in hepatitis E infection. *Eur J Clin Microbiol Infect Dis* 2012;31(2):179–184. [PubMed: 21598072]
41. Suneetha PV, Pischke S, Schlaphoff V, Grabowski J, Fytli P, Gronert A, et al. Hepatitis E virus (HEV)-specific T-cell responses are associated with control of HEV infection. *Hepatology* 2012;55(3):695–708. [PubMed: 22006345]
42. Mallet V, Le Mener S, Roque-Afonso AM, Tsatsaris V, Mamzer MF. Chronic hepatitis E infection cured by pregnancy. *J Clin Virol* 2013;58(4):745–747. [PubMed: 24140032]
43. Wang Y, Zhou X, Debing Y, Chen K, Van Der Laan LJ, Neyts J, et al. Calcineurin inhibitors stimulate and mycophenolic acid inhibits replication of hepatitis E virus. *Gastroenterology* 2014;146(7):1775–1783. [PubMed: 24582714]
44. Zhou X, Wang Y, Metselaar HJ, Janssen HL, Peppelenbosch MP, Pan Q. Rapamycin and everolimus facilitate hepatitis E virus replication: revealing a basal defense mechanism of PI3K-PKB-mTOR pathway. *J Hepatol* 2014;61(4):746–754. [PubMed: 24859454]
45. Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ, Yao X, et al. Protection against hepatitis E virus infection by naturally acquired and vaccine-induced immunity. *Clin Microbiol Infect* 2014;20(6):O397–O405. [PubMed: 24118636]
46. Shrestha MP, Scott RM, Joshi DM, Mammen MP, Jr, Thapa GB, Thapa N, et al. Safety and efficacy of a recombinant hepatitis E vaccine. *N Engl J Med* 2007;356(9):895–903. [PubMed: 17329696]
47. Huang W, Zhang H, Harrison TJ, Lang S, Huang G, Wang Y. Crossprotection of hepatitis E virus genotypes 1 and 4 in rhesus macaques. *J Med Virol* 2008;80:824–832. [PubMed: 18360896]
48. Maurissen I, Jeurissen A, Strauven T, Sprengers D, De Schepper B. First case of anti-ganglioside GM1-positive Guillain-Barre syndrome due to hepatitis E virus infection. *Infection* 2012;40(3):323–326. [PubMed: 21877179]
49. Paeshuyse J, Dallmeier K, Neyts J. Ribavirin for the treatment of chronic hepatitis C virus infection: a review of the proposed mechanisms of action. *Curr Opin Virol* 2011;1(6):590–598. [PubMed: 22440916]
50. 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(12):1111–1120. [PubMed: 24645943]

FIGURE 1.

Hepatitis E virus genome. The flanking 5' methylguanylate cap and 3' poly A tail enclose 3 open reading frames. ORF-1 functional domains include methyltransferase, cysteine protease, RNA helicase and RNA-dependent RNA polymerase domains. Subgenomic ORF-2 encodes for capsid protein and overlapping ORF-3 protein is involved in viral packaging

FIGURE 2.

HEV infection leads to the expression of IFN and other proinflammatory cytokines through activation of interferon regulatory factor 3 (IRF3) and nuclear factor κ B (NF κ B) pathways. IFNs induce IFN-stimulated genes through the JAK/STAT pathway. ORF-3 binding to STAT-1 restricts phosphorylation and the downstream activation of ISG expression, while at same time enhancing IFN- α production by interacting with the RIG-1 receptor. With permission from Debing, Moradpur et al. *J Hepatol* 2016; 65(1):200–212. RIG-1, retinoic acid-inducible gene; TBK-1, TANK-binding kinase

FIGURE 3.

Natural course of HEV infection and its correlation with immune status and response.

Genotypes 1, 2 and 4 usually cause acute self-limited disease as well as fulminant disease in the immunocompetent host. Genotype 3 causes both acute disease as the other genotypes and chronic disease in the immunocompromised host. ALF, acute liver failure