Acute and Persistent Hepatitis E Virus Genotype 3 and 4 Infection: Clinical Features, Pathogenesis, and Treatment

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Hepatitis E virus (HEV) genotype (gt)3 and 4 infections are prevalent in industrialized and high-income countries. Although most HEV gt3 and gt4 infections are clinically silent, acute infection may be symptomatic in some patients. In persons with underlying liver disease and in elderly men, HEV infections may present as acute or acute-on-chronic liver failure. Chronic hepatitis may develop in immunosuppressed individuals, including transplant recipients, human immunodeficiency virus (HIV)-infected patients, and persons with hematologic malignancy undergoing chemotherapy, and may progress to life-threatening liver cirrhosis. Extrahepatic manifestations of infection may include neurological and renal disease. Although there is no approved specific therapy for the treatment of acute or chronic HEV gt3 or gt4 infection, off-label use of ribavirin appears to be capable of eliminating chronic HEV infection, and may reduce disease severity in patients suffering from acute liver failure.

Early studies suggested that hepatitis E virus (HEV) was largely limited to underdeveloped regions of the world, mainly South, Central, and Southeast Asia, Africa, the Middle East, and Mexico, and only rarely caused sporadic, usually imported, infections in industrialized, high-income countries. In the absence of fulminant disease, HEV infection was also considered to be self-limited without the potential for persistence and chronic hepatitis. However, within the last two decades, these assessments have changed. Indeed, infection with genotype (gt)3 or gt4 HEV is now known to be prevalent in many economically advanced countries, and chronic gt3 HEV infection has been recognized

in immunosuppressed patients (Kamar et al. 2008; Dalton et al. 2009).

HEV infections in developing countries are generally caused by gt1 and gt2 HEV, at times in association with large, waterborne outbreaks of disease. In contrast, gt3 and gt4 HEV are prevalent in high-income countries. Zoonotic transmission, predominantly from infected swine via consumption of poorly cooked or raw pork, is generally considered to be the major source of HEV gt3 and gt4 infection (Wedemeyer et al. 2012; see Dalton and Izopet 2018). The prevalence of infection can be estimated from the frequency with which HEV RNA-positivity is found among blood donors (Table 1). A few

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Table 1. HEV prevalence in blood donors

Country	Method	Samples	Results	References
Ghana	Individual testing	239	0/239	Meldal et al. 2013
United States	Individual testing	1939	0/1939	Xu et al. 2013
Canada	Pools of 48/100	13.993	0/13.993	Fearon et al. 2017
Australia	Pools of 6	74.131	1/74.131	Hoad et al. 2017
United States	Pools of 96	128.020	1/32.005	Roth et al. 2017
United States	Individual testing	18.829	1/9500	Stramer 2014
Germany	Pools of 96	18.100	1/4525	Baylis et al. 2012
Spain	Individual testing	9.998	1/3333	Sauleda et al. 2014
United Kingdom	Pools of 24	225.000	1/2850	Hewitt et al. 2014
France	Pools of 96	53.234	1/2218	Gallian et al. 2014
The Netherlands	Pools of 96/192	59.474	1/1440	Hogema et al. 2016
Germany	Pools of 48	16.000	1/1250	Vollmer et al. 2012

larger studies have identified HEV RNA in up to 0.037% of blood donations (Hewitt et al. 2014), although other studies have not identified positive donors (Xu et al. 2011; Meldal et al. 2013; Fearon et al. 2017). This could be related to differences in cohort sizes.

HEV infection has specific clinical and epidemiological features that differ depending on the underlying genotype of the infecting virus. For example, high mortality rates have been reported in women with acute HEV gt1 or gt2 infection during pregnancy (Acharya et al. 1996; Bhatia et al. 2008; Aggarwal and Jameel 2011), whereas there is no apparent increased risk of mortality if pregnant women are infected by gt3 or gt4 virus.

This review aims to summarize the clinical course, pathogenesis, and treatment options for acute and chronic gt3 and gt4 HEV infection in immunocompetent and immunosuppressed individuals.

PATHOGENESIS OF ACUTE AND CHRONIC HEV gt3 AND gt4 INFECTIONS

Most HEV gt3 and gt4 infections in immunocompetent individuals are self-limited and result only in clinically silent seroconversion. Less than 2% of those infected are symptomatic (Wedemeyer and Pischke 2011; Rein et al. 2012). The viral and host-related factors that influence the severity of HEV infections have yet to be determined (Fig. 1). Much of what is known of

the pathogenesis of these infections comes from studies of nonhuman primates (see Cullen and Lemon 2018; Lanford et al. 2018).

Infection with gt3 or gt4 HEV can be considered to involve three distinct temporal phases, including an incubation period, an acute phase, and a recovery phase. Viral replication is evident within the liver by about 7 days after exposure to the virus. The percentage of infected hepatocytes is unknown, but HEV RNA can be detected in the serum a few days before symptoms of hepatitis. Serum alanine aminotransferase (ALT) levels increase with the onset of symptoms, with ALT and serum HEV RNA levels peaking about 4 to 8 weeks after infection. In nonimmunosuppressed patients, viral replication persists for a few weeks in association with fecal virus shedding. HEV RNA continues to be shed in the stool for a few weeks after becoming undetectable in the serum (Aggarwal et al. 2000). The nature of immunity subsequent to clearance of the infection is not well known.

In contrast to such self-limited infections, viral RNA can remain detectable in the serum and stools for prolonged periods in patients with compromised immune systems (Kamar et al. 2008; Legrand-Abravanel et al. 2010). HEV infection can result in chronic hepatitis in such patients, defined by persistence of virus replication and hepatic inflammation for >3–6 months. Whether acute HEV infection resolves without sequelae or progresses into chronic hepatitis seems to be related primarily to the host's im-

Figure 1. Possible clinical outcomes of genotype (gt)3/4 hepatitis E virus (HEV) infections.

mune response (Fig. 1) (Suneetha et al. 2012; Abravanel et al. 2016). Indeed, chronic HEV infection has been only described in immunosuppressed patients. A decrease in the HEV-specific T-cell response has been reported in transplant recipients who develop chronic versus resolving HEV infections (Suneetha et al. 2012). Cell culture studies suggest that the virus is noncytopathic, but the mechanism(s) responsible for liver injury in either acutely or persistently infected patients are poorly understood.

Infection with HEV gt3 and gt4 can also cause fulminant hepatitis, but pregnant women do not appear to be at increased risk for this, as they are with gt1 HEV. gt3 HEV has also been associated with extrahepatic manifestations of disease, including both neurological and kidney injury as described below (Kamar et al. 2012a; Pischke et al. 2017). Preliminary evidence for extrahepatic replication of the virus has been obtained in animals and humans based on immunohistochemical detection of HEV antigen and/or detection of negative-strand HEV RNA within the gastrointestinal tract (Williams et al.

2001; Izopet et al. 2012), placenta (Bose et al. 2014), central nervous system (Drave et al. 2016), and kidney (Geng et al. 2016). However, the pathogenic mechanisms responsible for extrahepatic disease remain ill-defined (Fig. 2).

CLINICAL COURSE OF ACUTE HEV INFECTION IN OTHERWISE HEALTHY INDIVIDUALS

As indicated above, HEV gt3 or gt4 infections vary widely in severity, from clinically silent to fulminant hepatitis (Fig. 1). In immunocompetent patients, HEV infection leads to symptomatic hepatitis in <2% of cases (Zhu et al. 2010; Wedemeyer and Pischke 2011). The incubation period in immunocompetent individuals ranges from 21 to 56 days, with a mean of 40 days (Wedemeyer et al. 2012).

There are no symptoms that specifically differentiate acute HEV infection from other causes of viral hepatitis. Similar to acute hepatitis A, a short prodromal phase with nonspecific symptoms, including a flu-like syndrome of myalgia,

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Figure 2. Potential extrahepatic manifestations of genotype (gt)3/4 HEV infection. (A) Extrahepatic disease manifestations reported in the context of acute HEV infection. Underlying mechanisms of pathogenesis are unclear but could involve either (B) virus replication in tissues other than the liver, or (C) collateral damage from immune responses to HEV infection in the liver including, for example, immune complex formation or molecular mimicry resulting in nerve injury. (From Pischke et al. 2017; adapted, with permission, from Elsevier © 2017.)

arthralgia, asthenia, nausea, and vomiting, is followed by more “liver-specific” symptoms and signs, such as jaundice, pruritus, clay-colored stools, and darkened urine. Serum ALT levels usually peak about 6 weeks after exposure (Wedemeyer et al. 2012). ALT elevations are usually higher than increases of aspartate aminotransferase (AST), and frequently accompanied by an increase in alkaline phosphatase, γ -glutamyl-transpeptidase (GGTP), and bilirubin. In contrast to HEV gt1 or gt2, HEV gt3 or gt4 do not appear to cause fatal infections with fulminant hepatitis in pregnant women (Lachish et al. 2015).

ACUTE HEV INFECTION IN THE ELDERLY AND IN THOSE WITH UNDERLYING CHRONIC LIVER DISEASE

In elderly patients and/or those with underlying liver disease, acute HEV infection may present as

acute-on-chronic hepatitis, leading to decompensated cirrhosis, fulminant hepatitis, and death. A recent Swiss study described 93 cases of primarily asymptomatic autochthonous HEV gt3 and gt4 infection, and found that male gender and older age were risk factors for symptomatic disease (Fraga et al. 2017). In another recent study investigating clinical characteristics and outcomes of acute sporadic HEV infection in China, underlying chronic liver disease was identified as a risk factor for a worse outcome and increased mortality (Zhang et al. 2017). The clinical course is similar to acute exacerbations of chronic hepatitis because of other causes (Blasco-Perrin et al. 2015). The risk of death may be as high as 70% in cases in which HEV infection is associated with severe acute-on-chronic hepatitis (Peron et al. 2007; Kumar and Saraswat 2013).

In a study centered in the United Kingdom and France, acute HEV infection was identified

in 3.2% of 343 patients with acute decompensated hepatitis (Blasco-Perrin et al. 2015). In contrast, no evidence of HEV infection was found in a cohort of 40 patients from Gambia with acute-on-chronic liver failure (Shimakawa et al. 2016). Acute hepatitis caused by HEV infection may be misdiagnosed as acute drug-induced liver injury or as autoimmune hepatitis. A study from the United States investigated 681 patients with acute liver failure caused by various factors and found HEV infection to be the cause in only 0.4% of cases (Fontana et al. 2016). In a British study of 47 suspected cases of drug-induced liver injury, 13% were actually caused by HEV infection (Dalton et al. 2007). Although it may be relatively uncommon, HEV infection should be considered in patients presenting with suspected drug-induced liver injury or an otherwise unexplained acute exacerbation of chronic hepatitis.

CHRONIC HEV INFECTION IN TRANSPLANT RECIPIENTS

Similar to otherwise healthy individuals, an incubation period of 50–60 days was observed before the onset of liver disease in several transplant recipients and immunosuppressed patients transfused with HEV-contaminated blood products (Pischke et al. 2016). Such patients are at risk for chronic HEV infection, which has been defined generally as the persistence of HEV RNA in serum and/or stool for periods longer than 3 to 6 months (Kamar et al. 2013). Chronic HEV infection was first reported in cohorts of European transplant recipients beginning in 2008 (Gerolami et al. 2008; Kamar et al. 2008; Haagsma et al. 2009; Pischke et al. 2010). Initially, 14 cases of acute HEV infection were reported among kidney- and liver-transplant recipients (Kamar et al. 2008). Eight of these patients developed persistent HEV infections with chronically elevated ALT and portal inflammatory infiltrates with mild piecemeal necrosis, progressing to histologically proven fibrosis within 12 months of infection.

How commonly acute HEV infection persists in transplant recipients is still debated, however. A multicenter retrospective European study showed that 66% of transplant recipients

with an overt acute HEV infection developed chronic hepatitis E (Kamar et al. 2011b). Because of the retrospective design of this study, however, some asymptomatic HEV infections may have been missed. Other studies that have focused on seroconversion rates among transplant recipients and have thus included both symptomatic and asymptomatic cases of HEV infection, have reported rates of progression to chronicity ranging from 21% to 50% (Legrand-Abravanel et al. 2011; Pischke et al. 2012, 2013).

The risk of chronic HEV infection in transplant recipients may depend on the specific immunosuppressive regimen, as well as the intensity of immunosuppression (Suneetha et al. 2012). The use of tacrolimus, rather than cyclosporine A, has been associated with an increased risk of chronic hepatitis (Kamar et al. 2011b), whereas the use of mycophenolic acid was associated with a lower likelihood of chronic hepatitis (Pischke et al. 2012). Interestingly, *in vitro* studies suggest that calcineurin inhibitors may stimulate HEV replication, whereas mycophenolic acid may inhibit it (Wang et al. 2014). A very low prevalence of chronic HEV infection was reported in a large cohort of Japanese liver transplant recipients, suggesting that there may be HEV subtype- or strain-specific differences, or host genetic factors that influence the likelihood of viral persistence (Inagaki et al. 2015; Pischke and Wedemeyer 2015). Despite the potential for persistent infection and chronic hepatitis, fulminant liver failure has not been reported in HEV-infected transplant recipients.

Nearly all cases of chronic HEV infection have been reported in patients infected with HEV gt3; only a few cases of HEV gt4 chronic infection have been reported (Geng et al. 2014, 2016). Recently, however, persistent HEV gt7 and gt8 infections (derived from camels) have been recognized in transplant recipients (Lee et al. 2016). No case of chronic HEV infection caused by gt1 or gt2 has been reported.

CHRONIC HEV INFECTIONS BEYOND SOLID-ORGAN TRANSPLANT RECIPIENTS

Chronic HEV infections have been described in patients infected with human immunodeficien-

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cy virus (HIV) infection (Dalton et al. 2009, 2013), mainly in those with impaired immune responses. In contrast to transplant recipients, however, several studies of HIV-infected patients report very low rates of chronic HEV infection, ranging from 0 to 0.003%. HEV infection may persist in HIV-infected patients despite improvements in immune status (Ingiliz et al. 2016). Chronic HEV infections have also been reported in patients with hematological malignancies receiving chemotherapy (Tamura et al. 2007; Geng et al. 2014), stem-cell transplant recipients (Versluis et al. 2013), and in others with underlying immunosuppression, including patients with systemic lupus erythematosus (SLE), granulomatosis, retroperitoneal fibrosis, or CD4 T-cell deficiency (Honer zu Siederdisen et al. 2014).

EXTRAEXTRINSIC HEPATIC MANIFESTATIONS OF HEV gt3 AND gt4 INFECTIONS

Although a number of extrahepatic manifestations have been reported in association with HEV infection over the past decade, causal pathophysiologic links with HEV remain poorly defined (Fig. 2). The best evidence for a causal association exists for the Guillain-Barré syndrome, neuralgic amyotrophy, glomerulonephritis, and cryoglobulinemia (Fig. 2) (Kamar et al. 2016). Pancreatitis, which has been observed in patients infected with gt1 and gt2 HEV, does not appear to be associated with gt3 or gt4 HEV infections (Kamar et al. 2012b).

Neurological Manifestations

Neurological findings have been reported frequently in association with acute or chronic HEV infection (Comont et al. 2013). These involve primarily the peripheral nervous system, and include neuralgic amyotrophy (NA), Guillain-Barré syndrome, Bell's palsy (seventh cranial nerve), and polyradiculopathy (Dalton et al. 2017). In a large study of 126 HEV-infected patients from France and Great Britain, more than 5% developed neurologic complications in the context of acute gt3 infection (Kamar et al. 2011a). In some cases, HEV RNA has been de-

tected in the cerebrospinal fluid (Comont et al. 2013).

A particularly strong association exists between gt3 HEV infection and NA, also known as Parsonage-Turner syndrome or brachial neuritis. This rare, postinfectious disorder of the brachial plexus presents clinically with the acute onset of severe shoulder and arm pain, followed by weakness and atrophy. A recent study of NA patients in Cornwall (United Kingdom) and the Netherlands showed that five of 47 (11%) had acute HEV gt3 infection (van Eijk et al. 2014). Another recent multicenter European study compared NA in subjects with (57 cases) or without (61 cases) evidence of HEV infection (van Eijk et al. 2017). Patients with HEV-associated NA had predominantly bilateral asymmetrical involvement of the brachial plexus (van Eijk et al. 2017). They were mostly anicteric.

Three case-control studies have confirmed a relationship between HEV infection and Guillain-Barré syndrome. HEV infection was diagnosed at the start of the neurological illness in 5%–11% of patients, which was a significantly more than in healthy controls (Geurtsvankessel et al. 2013; van den Berg et al. 2014; Fukae et al. 2016). In a recent cohort study, six of 73 (8%) patients with Guillain-Barré syndrome had evidence of HEV infection (Stevens et al. 2017).

The association between HEV and other neurological disorders is still under debate. In a recent large study of 464 patients who presented at emergency rooms with nontraumatic neurological symptoms, sera were tested for anti-HEV immunoglobulin (Ig)M and HEV RNA by reverse transcription polymerase chain reaction (RT-PCR) (Dalton et al. 2017). Seven patients tested positive for HEV RNA, and four additional patients that tested negative by RT-PCR had detectable anti-HEV IgM as a marker of acute HEV exposure. None of these patients were jaundiced. Those with evidence of HEV infection presented with various neurological findings, including NA ($n = 3$), cerebral ischemia or infarction ($n = 4$), seizure ($n = 2$), encephalitis ($n = 1$), and acute combined facial and vestibular neuropathy ($n = 1$) (Dalton et al. 2017).

In summary, it seems clear that HEV infection may be causally related to the development of some peripheral neurological diseases. The underlying mechanism(s), however, are unknown and open to speculation (Fig. 2C).

Renal Injury

There is growing evidence for an association of HEV infection with renal disease. In a cohort of 51 kidney and liver transplant recipients, the glomerular filtration rate was significantly decreased during acute and chronic phases of HEV infection (Kamar et al. 2012b). In addition, kidney biopsies from immunocompetent patients, as well as solid-organ transplant recipients, with either acute or chronic HEV infection have revealed membranoproliferative or membranous glomerulonephritis with or without cryoglobulinemia (Kamar et al. 2012b; Taton et al. 2013; Del Bello et al. 2015; Guinault et al. 2016). Relapses have also been reported in HEV-infected patients with IgA nephropathy (Kamar et al. 2012b). Mechanisms responsible for renal damage have not been studied in detail, but HEV RNA and HEV antigens have been detected in the urine of patients as well as in the urine of monkeys and rabbits infected with HEV (Geng et al. 2016; Wang et al. 2016a).

THERAPEUTIC APPROACHES FOR HEV INFECTION

Treatment of Acute HEV Infection

There is no approved pharmacological intervention for HEV infection. In most cases of acute HEV infection, no treatment is required as the disease usually takes a self-limiting and moderate course. In single case reports involving immunocompetent patients with serious liver disease, ribavirin has been suggested to ameliorate HEV-associated acute or acute-on-chronic liver failure (Gerolami et al. 2011; Peron et al. 2011; Goyal et al. 2012). Unfortunately, no large double-blind, placebo-controlled study has evaluated the efficacy of ribavirin in this setting.

Treatment of Chronic HEV gt3 and gt4 Infections

Treatment of chronic HEV infection has been studied mainly in transplant recipients receiving immunosuppressive therapies. Because the strength of the host immune response seems to determine the risk for persistence and disease progression, reducing immunosuppression, especially limiting drugs that target T cells, is considered to be the first-line therapeutic option (Kamar et al. 2010b, 2011b). This approach is supported by the fact that tacrolimus trough levels were significantly lower in patients who cleared a chronic HEV infection compared to those who remained viremic (Kamar et al. 2010b). A reduction in immunosuppression allowed HEV clearance in up to one-third of patients who were chronically infected (Kamar et al. 2010b, 2011b). Antiviral therapy should be considered in the remaining patients.

Treatment with pegylated interferon α for 3 or 12 months has resulted in a sustained virological response (SVR) in liver transplant recipients with persistent HEV infection (Haagsma et al. 2010; Kamar et al. 2010a). In addition, a number of studies suggest that ribavirin may be effective therapy for chronic HEV infection in solid-organ transplant recipients (Kamar et al. 2010c, 2014; Mallet et al. 2010; Pischke et al. 2013; Riezebos-Brilman et al. 2013). In a few patients with hematological malignancies receiving chemotherapy and in HIV-infected patients, treatment with pegylated interferon alone, ribavirin alone, or a combination of both has been successful (Alric et al. 2010, 2011; Dalton et al. 2011; Hajji et al. 2013; Neukam et al. 2013; Tavitian et al. 2015).

In a retrospective multicenter study of 59 transplant recipients, ribavirin treatment resulted in an SVR of 78% (Kamar et al. 2014). The median duration of ribavirin therapy was 3 (range 1–18) months. Patients who relapsed were retreated for longer periods (6 months) with an increase in the overall SVR to 90% (Kamar et al. 2014). No difference in SVR was observed between patients who received ribavirin for 3 months or less initially versus those who received it for more than 3 months (Kamar et al.

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2014). However, the optimal duration of ribavirin therapy remains unclear, and rigorously controlled clinical trial data remain lacking.

The mechanism of action of ribavirin against HEV is not fully understood. It has been suggested that ribavirin inhibits HEV replication by depleting cellular pools of guanosine triphosphate (Debing et al. 2014a). Ribavirin is an inhibitor of cellular inosine monophosphate dehydrogenase (IMPDH); mycophenolic acid is also an IMPDH inhibitor and it has been suggested to both prevent HEV persistence in vivo (Pischke et al. 2012) and inhibit HEV replication in vitro (Debing et al. 2014a), especially when combined with ribavirin. In another study of transplant recipients, however, mycophenolic acid did not alter the response to ribavirin therapy (Kamar et al. 2015).

Ribavirin has also been suggested to exert its broad antiviral effects by acting as an RNA mutagen, leading to disruption of viral replication by error catastrophe (Crotty et al. 2001). Consistent with this, studies in treated patients indicate ribavirin induces mutagenesis of the HEV genome (Todt et al. 2016). Next-generation sequencing identified several mutations in the HEV RNA, including a G1634R substitution in the polymerase coding region that appeared to enhance the replicative capacity of the virus in cell culture and may have provided some level of resistance to ribavirin (Debing et al. 2014b, 2016). Ribavirin treatment promoted emergence of the G1634R variant along with a reversible increase in genetic heterogeneity of the virus (Debing et al. 2014b, 2016; Lhomme et al. 2014; Todt et al. 2016). The role of specific HEV variants and their impact on HEV treatment outcomes is uncertain (Lhomme et al. 2012; Debing et al. 2016). Whereas emergence of the G1634 mutation has been associated with treatment failure (Debing et al. 2014b; Todt et al. 2016), its presence does not confer absolute resistance (Lhomme et al. 2015).

An increased lymphocyte count at the initiation of therapy was a positive predictive factor for SVR in patients treated by ribavirin (Kamar et al. 2014), as was a rapid decrease in the serum viral load in association with treatment (Kamar et al. 2010b, 2015). Persistent HEV shedding at

the end of therapy was associated with an increased risk of relapse after cessation of ribavirin therapy (Abravanel et al. 2015).

Preliminary in vitro data show that the nucleoside analog sofosbuvir inhibits gt3 HEV replication, and that its antiviral effects are additive with those of ribavirin (Dao Thi et al. 2016). However, its antiviral activity against HEV is modest compared to its effect of hepatitis C virus, making it of questionable usefulness clinically (Wang et al. 2016b). Combined therapy with sofosbuvir and ribavirin showed promise in treating a patient who did not clear infection with ribavirin (van der Valk et al. 2017), but the role of sofosbuvir in treating HEV infection remains unclear (Kamar et al. 2017).

In vitro studies with HEV RNA replicons show that zinc salts block HEV replication by inhibiting the activity of the viral RNA-dependent RNA polymerase (Kaushik et al. 2017). This observation is of interest as patients with HEV infection may have zinc deficiency (Kolachi et al. 2011), suggesting a possible novel avenue for antiviral intervention.

CONCLUDING REMARKS

Our understanding of the epidemiology, clinical course, and treatment of HEV gt3 and gt4 infections has improved over the last decade. In most cases, infection is asymptomatic. Nevertheless, in specific populations, such as patients who are immunosuppressed, have underlying chronic liver disease, or who are elderly, an HEV infection can cause severe and/or chronic hepatitis. Infection can also be associated with extrahepatic manifestations involving the peripheral nervous system and kidney. A number of studies suggest ribavirin may be effective antiviral therapy in patients with persistent infection. Because of the high prevalence of HEV gt3 (and gt4) in well-developed, industrialized countries, the diagnosis of HEV infection should be considered as a part of a standard work-up for patients presenting with unexplained increases of serum liver enzyme levels. Patients presenting with Parsonage–Turner or Guillain–Barré syndrome should also be screened for HEV, even if liver enzyme levels are within the normal range.

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