ORIGINAL ARTICLE

Chronic Hepatitis E Virus Infection in Liver Transplant Recipients

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Hepatitis E virus (HEV) infection is known to run a self-limiting course. Sporadic cases of acute hepatitis due to infection with HEV genotype 3, present in pig populations, are increasingly recognized. Zoonotic transmission seems infrequent. The entity of unexplained chronic hepatitis after liver transplantation has been recognized. Detection of HEV in 2 liver transplant recipients triggered a review of these cases. Freeze-stored sera were available for retrospective analysis. HEV antibodies were determined. For virus detection and identification, a fragment of the gene encoding the major capsid protein (open reading frame 2) was amplified by reverse-transcription polymerase chain reaction and sequenced to identify the genotype. Two months after liver transplantation, case A developed unexplained chronic hepatitis, which developed into cirrhosis. Retransplantation followed 7 years later, after which chronic hepatitis recurred. In retrospect, HEV RNA was present in serum 3 weeks after the first transplantation and remained present afterwards. HEV RNA was also present in retransplant liver tissue. HEV antibodies appeared late after retransplantation. Case B developed unexplained chronic hepatitis 7 years after transplantation. Retransplantation was needed 5 years later, after which no signs of hepatitis recurred. In retrospect, the period of chronic hepatitis up to the retransplantation coincided with HEV RNA in serum. In case B, antibodies developed, the viral load was much lower than in case A, and the virus seemed to be cleared after retransplantation. Genotyping in both cases revealed 2 unique strains of genotype 3. In conclusion, chronic HEV infection may develop in immunosuppressed patients, who may then serve as long-term carriers of the virus. We hypothesize that HEV may be the cause of chronic hepatitis in liver transplant recipients. *Liver Transpl 14:547-553, 2008.* © 2008 AASLD.

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The enterically transmitted human hepatitis E virus (HEV) has long been known as a major cause of acute hepatitis E in developing countries, with occasional travel-related cases in developed countries.[1] However, following the discovery of a new lineage of HEV (genotype 3) in the mid 1990s, sporadic cases of acute hepatitis due to infection with this genotype have been increasingly recognized.[2,3] Since their discovery, genotype 3 HEV strains have been detected in pig populations worldwide, with very high prevalence in commercially held pigs.[1,4] Studies looking at risk factors of endemic HEV cases in Europe have failed to show evidence for direct zoonotic transmission resulting from contact with pigs, although this has been documented elsewhere.[5-9] HEV infection has been documented in other animal species, and transmission via contaminated water and food has been described.[1,6] In addition, persons with HEV infection go through a viremic

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; CT, point at which the fluorescence crosses a certain threshold in real-time polymerase chain reaction; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; IgG, immunoglobulin G; IgM, immunoglobulin M; neg, negative; OLT, orthotopic liver transplantation; PCR, polymerase chain reaction; pos, positive.

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phase, which results in the potential of blood-borne spread of the infection.[10,11] Therefore, studies are ongoing to understand the epidemiology and modes of transmission of HEV.

In general, HEV infection runs a self-limiting symptomatic or asymptomatic course with acute hepatitis. Most genotype 3 HEV infections detected in recent studies have been mild cases, and this indicates that the high prevalence of the virus in commercially held pigs may not be a problem for human health.[7-9] Fulminant hepatitis may occur, however, especially in pregnant women or in persons with underlying liver disease.[12,13] A recent retrospective screening of sera from patients with unresolved hepatitis in Japan provided a first indication of possible chronic hepatitis in a patient with T-cell lymphoma with a follow-up of 6 months.[14]

Here, we report 2 liver transplant recipients who acquired chronic HEV infection. In both patients, chronic hepatitis developed into cirrhosis. After retransplantation, HEV infection recurred in 1 patient.

PATIENTS AND METHODS

Recent diagnosis of HEV infection in a liver transplant recipient with chronic liver disease triggered a full review of this case and of an earlier case in whom HEV infection was suspected but could not be proven at the time. The presence of freeze-stored sera allowed for a retrospective trace-back for HEV infection history.

Diagnostic Work-Up of HEV

Serological diagnosis of HEV was done by the assaying of sera for the presence of anti-HEV immunoglobulin M (IgM) and immunoglobulin G (IgG) with commercially available methods (Genelabs Diagnostics, Inc., California) with confirmatory testing by immunoblot (Mikrogen GmbH, Neuried, Germany). Cutoff values for the assays were defined for testing in a low-endemic setting as described.[15] A combination of enzyme-linked immunosorbent assay (ELISA) screening and confirmatory testing by immunoblot gave specificities of 96% and 99% for IgM and IgG, respectively. Sensitivity was 100% for IgG detection but somewhat lower (88%) for IgM following genotype 3 infection in the combined test regime.[15]

In addition, serum samples were tested for the presence of viral RNA. For virus detection and identification, a fragment of 148 base pairs of the gene encoding the major capsid protein (open reading frame 2) was amplified by reverse-transcription polymerase chain reaction and then sequenced to identify the genotype. For viral load estimation, the fold differences in the CT values (that is, the points at which the fluorescence crosses a certain threshold in real-time polymerase chain reaction) of the cases were compared with those of a reference sample run in parallel in every polymerase chain reaction assay, a doubling being assumed for every point increase in CT (expressed as $2^{\Delta CT}$).

RESULTS

Case A

Medical History

Case A, a female patient, was transplanted on February 12, 1999 for end-stage hepatitis B cirrhosis at the age of 30 years. For prevention of recurrent hepatitis B virus (HBV) infection, hepatitis B immunoglobulins were given intravenously on a regular base, and lamivudine (100 mg) was added in the second year after transplantation. Immunosuppression consisted at first of prednisolone and tacrolimus and, after 1 year, of monotherapy tacrolimus. Two months after transplantation, from April 12, 1999 onward, liver tests became increasingly abnormal (on April 12: aspartate aminotransferase (AST) 88 U/L, alanine aminotransferase (ALT) 182 U/L, and bilirubin 29 μmol/L). Liver biopsy showed a mild portal and lobular hepatitis. Serum HBV DNA and hepatitis C virus (HCV) RNA were negative. No other possible cause for the liver abnormalities was found, but the patient was not tested for HEV infection. Since then, liver enzymes remained elevated; repeated serum HBV DNA, hepatitis D virus (HDV) RNA, and HCV RNA tests remained negative. Liver biopsies at 1, 3, and 4 years after transplantation showed persistent hepatitis and development to cirrhosis. The 3-year biopsy was also tested for HBV DNA, which again was negative. After the fourth year, in April 2003, the patient suffered from diarrhea, and the diagnosis of ulcerative colitis was made. At that time, it was hypothesized that the chronic hepatitis might be autoimmune hepatitis, although immunoglobulin levels were not elevated, and anti-nuclear antibodies were absent. Immunosuppression was changed from monotherapy tacrolimus to a combination of prednisolone, azathioprine, and cyclosporine. In addition, mesalazine was given for the colitis. The colitis responded well to therapy, but liver enzymes showed only a slight improvement for a few months. Decompensated cirrhosis with increasing jaundice and ascites developed in 2005. Variceal bleeding occurred in January 2006. At that time, the patient was on the retransplant waiting list after an extensive re-evaluation that did not reveal active viral infections [HBV, HDV, HCV, Epstein-Barr virus (EBV), and cytomegalovirus (CMV)], but again, HEV was not tested. Retransplantation followed in February 2006, 7 years after the first transplant. Pathology of the removed liver showed mild hepatitis, cirrhosis, and negative immunohistochemistry for HBV. Prevention of recurrent HBV infection with hepatitis B immunoglobulins given intravenously and lamivudine (100 mg) continued. Immunosuppression consisted of prednisolone and cyclosporine. After 6 weeks, a rise in liver enzymes was noticed, and the liver biopsy showed again mild hepatitis of unknown origin but no signs of rejection. A month later, liver tests were normal again. An exacerbation of ulcerative colitis occurred in July and September 2006, for which extra prednisolone courses were given, and azathioprine was added in September. Overall, immunosuppression was kept relatively high.

TABLE 1. Course of Hepatitis E Parameters in Case A

Date (Sera If Not Otherwise Stated)	ELISA		Blot Score		
	IgG	**IgM**	**IgG**	**IgM**	PCR
19-02-1997	neg	neg	Not done	Not done	Not done
OLT: 12 Feb 1999					
15-2-1999	neg	neg	neg	neg	neg
8-3-1999	neg	neg	neg	neg	**pos**
12-4-1999	neg	neg	neg	neg	**pos**
3-8-1999	neg	neg	neg	neg	**pos**
9-2-2000	neg	neg	neg	neg	**pos**
26-2-2001	neg	neg	neg	neg	**pos**
4-2-2002	neg	neg	neg	neg	**pos**
18-2-2003	**pos**	neg	neg	neg	**pos**
23-2-2004	neg	neg	neg	neg	**pos**
4-3-2005	neg	neg	neg	neg	**pos**
20-2-2006	neg	neg	neg	neg	**pos**
Re-OLT: 22-2-2006					
10-4-2006	neg	neg	neg	neg	**pos**
28-4-2006	neg	neg	neg	neg	**pos**
18-9-2006	neg	neg	neg	neg	**pos**
8-2-2007	neg	neg	neg	neg	**pos**
Liver biopsy: 12-02-2007					**pos**
16-4-2007	neg	neg	neg	neg	**pos**
Feces: 4-5-2007					**pos**
3-5-2007	neg	neg	neg	neg	**pos**
9-7-2007	neg	neg	neg	neg	**pos**
24-9-2007	**pos**	**pos**	Borderline	**pos**	**pos**

NOTE: First and second liver transplant dates are also listed.
Abbreviations: ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IgM, immunoglobulin M; neg, negative; OLT, orthotopic liver transplantation; PCR, polymerase chain reaction; pos, positive.

From January 2007 onward, 10 months after retransplantation, liver enzymes were persistently elevated (maximum AST 201 U/L, ALT 279 U/L) with gradually increasing bilirubin levels (up to 100 μmol/L). Liver Doppler ultrasound was normal, as was endoscopic retrograde cholangiopancreaticography. The liver biopsy in February 2007 showed mild portal and moderate lobular hepatitis and some portal fibrosis. Infection with HBV, HDV, HCV, CMV, EBV, and herpes simplex virus type 6 was excluded. An episode of herpes zoster infection in the lumbar region was treated effectively with valaciclovir, without any effect on the liver tests.

HEV Parameters

In April 2007, anti-HEV and serum HEV RNA detection was requested. Despite the absence of anti-HEV, serum HEV RNA appeared positive. Thereafter, HEV RNA was found to be present in the liver biopsy (freeze-stored in liquid nitrogen) from February 2007. Results of additional HEV testing in serum, liver tissue, and feces are shown in Table 1. It was found that HEV RNA was absent shortly after the first liver transplant in February 1999 but became positive in the first subsequently tested serum of April 12 and remained positive thereafter. All samples were repeatedly tested and interspersed with negative control specimens, and results were reproduced. Sequence analysis of the amplified polymerase chain reaction fragment showed that the strain was a genotype 3 HEV, closely related to viruses detected in pigs and in humans in the Netherlands (Fig. 1). Interestingly, anti-HEV remained undetectable through the years, except for one serum in 2003 with a low titer of IgG. The beginning of the HEV viremia coincided with the beginning of clinical hepatitis. After retransplantation in February 2006, HEV remained present and again coincided with clinically recurrent hepatitis. HEV was also shown to be present in liver tissue (February 2007) and in feces (May 2007). The viral load peaked in 1999, and this was followed by a relatively stable level from 2000 to 2003, with a more erratic pattern and an almost 105-fold increase in the more recent samples, possibly coinciding with the enhanced immunosuppressive treatment given during this phase of the illness (Fig. 2A). In the months while this article was prepared, the immunosuppression was decreased. Subsequently, an improvement of liver tests was observed, and anti-HEV was found to appear in September 2007 (Table 1).

Because of possible transmission within the family, the husband and child were tested for the presence of anti-HEV. It was found to be absent.

Sera of the recipient of the kidney from the same donor who provided the first liver of our patient tested negative for anti-HEV and HEV RNA in the first 3

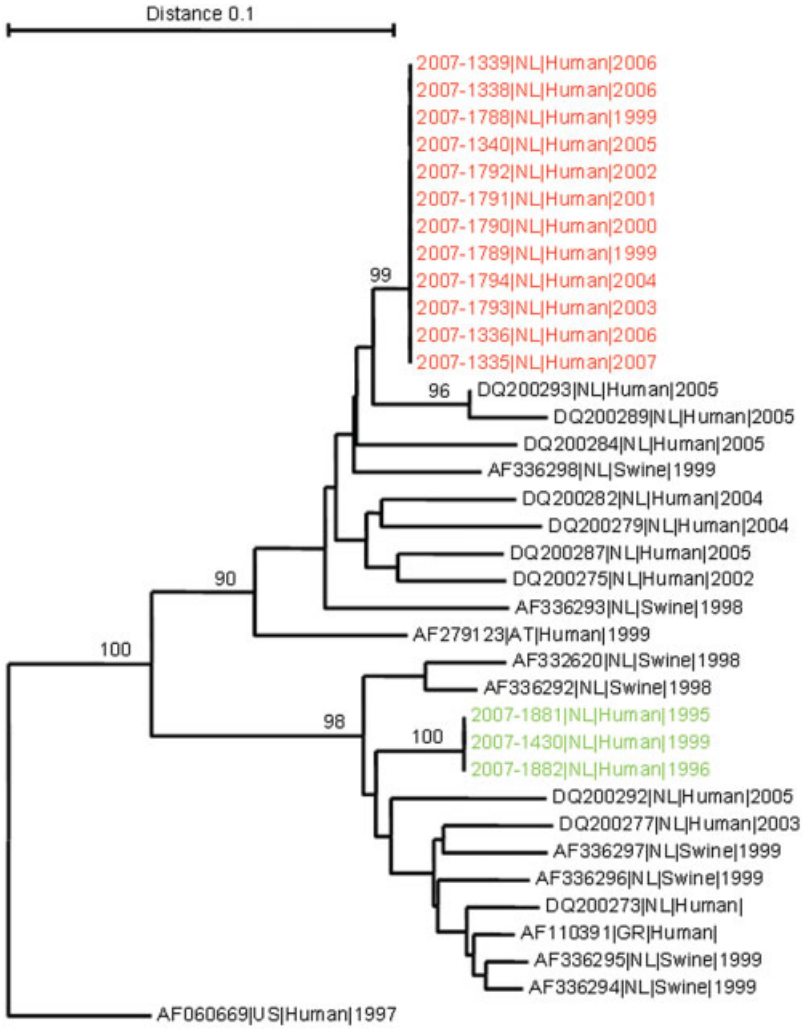

Figure 1. Phylogenetic tree based on a 148-nt fragment of the capsid gene, showing a unique strain present in all samples from cases A (red) and B (green). Closest neighbors are other genotype 3 hepatitis E virus strains that had been detected in the Netherlands in pigs or in humans with acute hepatitis.

months after renal transplantation. Sera from the organ and blood donors were not available.

Case B

Medical History

Case B, a female patient, was transplanted on October 1, 1988 for end-stage Wilson's disease at the age of 34 years. In 1993, 5 years after transplantation, liver tests and liver histology were normal. In the first half of July 1995, she and her husband visited the island of Aruba (in the Caribbean) for a vacation. Afterwards, her husband got slightly jaundiced, and elsewhere the diagnosis of acute HEV hepatitis was made. His laboratory tests on September 13, 1995, provided upon request from his general practitioner, were as follows: ALT of 336 U/L, hepatitis B surface antigen–negative, antibody to hepatitis B surface antigen–positive, antibody to hepatitis B core antigen–positive, antibody to hepatitis A virus IgM–negative, and antibody to hepatitis A virus IgG–positive. Also, his anti-HCV and EBV Monosticon tests were negative. Anti-HEV by ELISA testing was positive for both IgM and IgG. He made a full recovery. Our patient complained only of some fatigue, but liver tests appeared abnormal through September 25, 1995 with a maximum in October (AST 142 U/L, ALT 355 U/L, and bilirubin 29 μmol/L). Hepatitis B and C parameters were negative; also, anti-HEV was absent. A liver biopsy showed mild hepatitis. Liver tests never became normal afterwards. Aminotransferases remained mildly elevated (around 60-80 U/L). One year after the acute episode, anti-HEV was repeated and shown to be positive (both anti-HEV IgM and IgG). In September 2000, the patient was retransplanted because chronic hepatitis had developed into advanced disease. Pathology of the removed liver showed extensive fibrosis and moderate portal and lobular hepatitis. No signs of biliary disease or rejection were seen. Presently, she is doing well 7 years after retransplantation without signs of chronic hepatitis. The 1-year control liver biopsy was normal without signs of hepatitis.

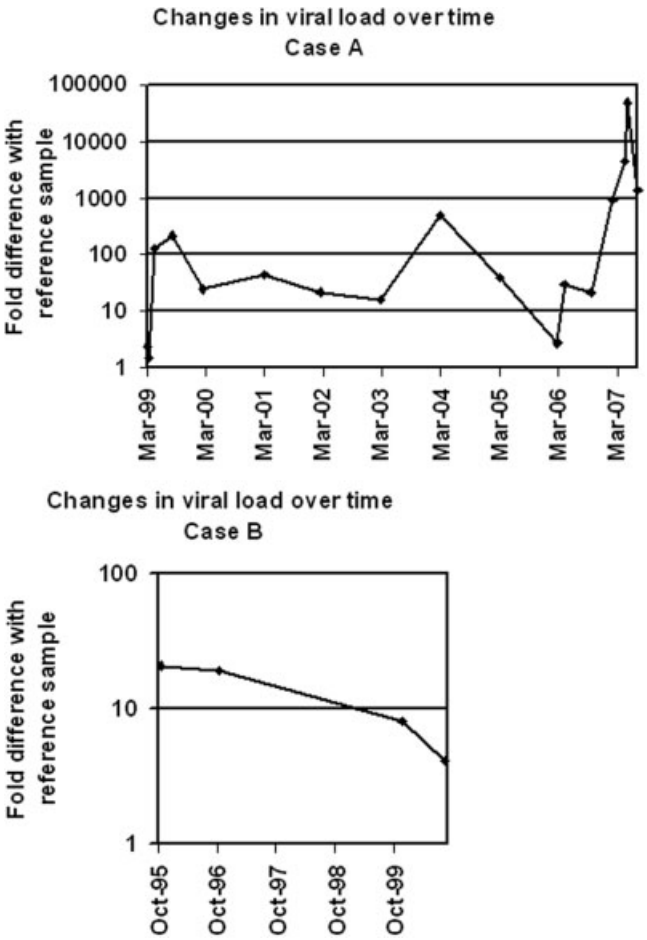

Figure 2. Changes in the viral load over time for patients (cases A and B) with chronic hepatitis E virus infection. Viral loads are expressed as described in the Patients and Methods section.

HEV Parameters

Results of HEV testing of freeze-stored sera are shown in Table 2. HEV RNA became detectable for the first time in the period in which both the patient and her husband suffered from acute hepatitis. In this early phase, we detected only a low titer of IgG with ELISA, but by blotting, both IgG and IgM antibodies were positive in the liver transplant patient. In the next 5 years, both anti-HEV IgG and IgM, in higher titers, and HEV RNA remained detectable, coinciding with clinically chronic hepatitis. The viral load gradually decreased over time (Fig. 2B). After retransplantation, however, antibodies disappeared, and HEV RNA was no longer detectable; this coincided with clinically normal aminotransferases. Sequence analysis showed the presence of a unique HEV genotype 3 strain present in all samples that yielded a product that could be sequenced (Fig. 1). This virus was clearly distinct from the virus in the first case.

DISCUSSION

We have diagnosed a chronic HEV infection in 2 liver transplant recipients. These cases are remarkable in many aspects. HEV infection, like HAV, is known to run a self-limited course with a more or less severe episode of hepatitis. In our patients, the virus, once acquired, remained present. The first patient acquired the virus shortly after liver transplantation, and presently, 8 years later, it still persists. The second patient acquired the virus 7 years after liver transplantation and cleared the infection only 5 years later after retransplantation of the liver.

HEV infection presented in both patients with the clinical picture of viral hepatitis, which was histologically confirmed. Unfortunately, the hepatitis persisted and developed gradually into cirrhosis. HEV as a cause of liver cirrhosis has not been known so far. Recently, the entity of unexplained chronic hepatitis after liver transplantation has been recognized in about 10% of patients.[16] Unidentified hepatotropic viruses have been suggested as a possible cause.[16,17] Our findings indicate that HEV might well be one of these viruses.

The main reason that HEV persisted in these 2 patients might well be the suppression of the immune system needed for prevention of graft rejection. It is remarkable that in the first patient HEV infection and HEV hepatitis recurred after retransplantation but that in the other patient this did not happen. It may be speculated that the viral load and the immune status played a role in this respect. The first patient used relatively large dosages of immunosuppression, as autoimmune disease was, in retrospect falsely, considered a possible cause of the persistent hepatitis. The second patient used less immunosuppression. By removal of the liver, during retransplantation, the major source of HEV, a hepatotropic virus, was removed. It is possible that in the second patient the immune reaction against HEV was strong enough to prevent reinfection of the newly transplanted liver graft. This correlates with the finding that the second patient developed antibodies to HEV, but the first patient did not.

From a diagnostic point of view, it is worrying to see that the diagnosis could not easily have been made, even in retrospect, by determination of antibodies to HEV. Antibodies remained absent in the first patient, except for one serum sample 4 years after acquisition of the virus; in the second patient, the ELISA result was unclear at first, although the blot was positive for both IgG and IgM. As a result, at least in future liver transplant patients, HEV RNA detection by polymerase chain reaction is warranted for diagnostic purposes. It may, however, be that the problem is present in other groups of immunosuppressed patients as well.

The second patient lost the virus after retransplantation. Remarkably, the antibody titers dropped to undetectable levels thereafter. This is in contrast to findings in nonimmunosuppressed and otherwise healthy people after acute HEV infection.[18] It follows that determination of past HEV infection might be problematic in immunosuppressed patients.

The source of the virus in both patients is not clear. The first patient most likely acquired the virus during or shortly after liver transplantation. An environmental source cannot be excluded as HEV genotype 3 is known

TABLE 2. Course of Hepatitis E Parameters in Case B

	ELISA		Blot Score		
Date (Sera)	IgG	IgM	IgG	IgM	PCR
OLT: 1-10-1988					
3-10-1994	neg	neg	neg	neg	neg
6-3-1995	neg	neg	neg	neg	neg
17-10-1995	**pos**	neg	**pos**	**pos**	**pos**
21-10-1996	**pos**	**pos**	**pos**	**pos**	**pos**
29-11-1999	**pos**	**pos**	**pos**	**pos**	**pos**
21-8-2000	**pos**	**pos**	**pos**	**pos**	**pos**
Re-OLT: 9-9-2000					
20-11-2000	**pos**	neg	**pos**	**pos**	neg
11-9-2001	neg	neg	neg	neg	neg
30-9-2003	neg	neg	neg	neg	neg
11-10-2005	neg	neg	neg	neg	neg

NOTE: First and second liver transplant dates are also listed.
Abbreviations: ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IgM, immunoglobulin M; neg, negative; OLT, orthotopic liver transplantation; PCR, polymerase chain reaction; pos, positive.

to be endemic in the Netherlands, but a parenteral source must be considered too. Blood-borne transmission has been documented in a Japanese patient who acquired the virus from transfused blood from a blood donor with HEV infection.[14] In our patients, possible sources are the liver donor and blood donors and possibly the hepatitis B hyperimmunoglobulins. The donor as the source was made unlikely as there were no signs of hepatitis in the donor and as the recipient of the kidney did not develop HEV infection.

Our second patient experienced the HEV infection in the same period as her husband. Therefore, most likely they shared the same source of the infection, or the virus was transmitted from the husband to the wife.

In developed countries such as ours, acute hepatitis E is often travel-related. However, sporadic cases are increasingly recognized,[5,15] and evidence suggests that in developed countries swine may act as a reservoir for HEV.[1,4] However, our findings suggest that immunosuppressed long-term carriers of HEV may also be a source, although HEV is considered to be not very transmissible under normal hygienic circumstances. Further studies are needed to determine if our observations are anecdotal or if HEV is a more common cause of severe chronic hepatitis.

In conclusion, chronic HEV infection may develop in immunosuppressed patients, who may then serve as long-term carriers of the virus. We hypothesize that HEV may the cause of chronic hepatitis in liver transplant recipients.

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