

# Chronic Hepatitis E Infection: Risks and Controls

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## Key Words

Hepatitis E · Hepatitis E virus · Chronic liver disease · Autochthonous hepatitis E virus infection · Zoonosis

## Abstract

Very recently, an unusual clinical presentation with an altered natural history associated with hepatitis E virus (HEV) infection has emerged in high-income industrialized nations. Although HEV infection does not develop into chronicity in general, viremia can persist for long periods of time in immunocompromised solid organ, bone marrow and stem cell transplant patients. Conceivably, the atypical clinical and virological outcomes in these cases could be related to immunosuppressive chemotherapy, resulting in sub-optimal HEV-specific immune responses. In the absence of travel to endemic regions, foodborne autochthonous HEV infection due to viral genotypes 3 and 4 has been implicated in the chronic cases. Presently, pegIFN- $\alpha$ -2a and ribavirin, the commonly used drugs to treat chronic viral hepatitis, are proving very promising in hepatitis E patients. Nevertheless, the most-awaited HEV vaccine could be protective in naïve travelers or high-risk group populations. The mechanisms of establishing chronic HEV infection and the disease severity have hitherto not been clearly understood. Therefore, a comprehensive clinical, virological and molecular study is needed to understand and control the disease.

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## Introduction

Hepatitis E is caused by hepatitis E virus (HEV) that is generally manifested by a self-limiting acute infection, and in some cases, by fulminant liver disease [1]. HEV is a non-enveloped virus, the only member of the *Hepeviridae* family, and contains a positive-sense, single-stranded RNA genome of ~7.2 kb [2]. Of the three open reading frames, ORF1 encodes a nonstructural polyprotein essential for viral RNA replication, and ORF2 codes for the viral capsid protein. ORF3 translates into a very small protein, attributed to some regulatory functions, including establishing viral infection to the host [3, 4]. However, HEV biology has so far not been completely understood, due to the lack of a robust in vivo or in vitro experimental model of infection. The viral infection may be symptomatic or asymptomatic with an overall fatality rate of about 2% worldwide [5]. In developing countries, it is primarily transmitted through contaminated water due to poor sanitation and is often associated with large epidemics [1, 5]. In endemic regions, cases of mortalities due to fulminant liver failure may also occur in about 20–30% of pregnant women or in persons with pre-existing chronic liver disease [1]. In contrast, in industrialized nations, like Japan, USA, Canada and many European countries, HEV infection occurs sporadically. The absence of travel to endemic areas and the isolation of genetically different HEV strains have supported an autochthonous origin of such sporadic cases in

North America and Europe [6]. Nevertheless, the sources and routes of indigenous HEV infections in the developed countries are still uncertain and not clearly defined.

### Chronic HEV Infection

Among the human hepatitis viruses (A, B, C, D and E), only HBV, HCV and HDV are well known to cause chronic liver diseases. HEV infection is generally acute [7–9] (table 1), and in most of the cases it is spontaneously cleared and, therefore, remains clinically silent. Acute viral hepatitis is manifested by typical symptoms, such as vomiting, myalgia, weakness, jaundice, uncolored stool and darkened urine. Serological markers of the illness include increased levels of liver transaminases, bilirubin, alkaline phosphatases and  $\gamma$ -glutamyltransferase, and in the HEV infection, detection of anti-HEV IgG/IgM antibodies as well as HEV-RNA in serum and stool. On the other hand, in the chronic course of hepatitis virus infection, there is a persistent increase in levels of liver enzymes, significant histopathological activity, including viral markers and nucleic acids. In recent years, unusual clinical presentations with severe outcomes have been encountered in association with autochthonous HEV chronic infections in North America and Europe. Recently, several cases of persistent HEV infection associated with progressive liver disease have been reported in Dutch [10, 11], German [12, 13], French [14] and Canadian [15] immunosuppressed solid organ transplant patients (table 2). Moreover, cases of viral reactivation after stem cell transplantation in leukemia patients were also reported 3 years ago [16]. All these confirmed chronic hepatitis E cases showed persistent elevations in liver enzymes, anti-HEV IgG and HEV-RNA in patients' serum as well as viral RNA in stool samples after a mean period of >12 months. So far, HEV-related liver cirrhosis has not been established but the development of cirrhosis in liver [17] and bone marrow [18] transplant recipients has been observed, too. Very recently, Kamar et al. [19] described about 66% chronic cases in HEV-infected solid organ transplant recipients and found a significant reduction in CD2+, CD3+ and CD4+ T lymphocyte counts in chronic hepatitis E patients as well as in those at risk of developing fulminant liver failure. In another study of HIV-positive Swiss patients with very low CD4+ T cell count, persistent HEV-RNA (>24 months) was detected with a delayed seroconversion [20].

Chemotherapy with immunosuppressive drugs, such as tacrolimus (FK-506 or fujimycin), is considered as the main predictive factor for the development of chronicity in HEV-

**Table 1.** Cases of autochthonous acute HEV infection

	Genotype	Zoonosis	Country	Ref. No.
Kidney transplant	3	porcine	France	[7]
Liver transplant	3	porcine	France	[8]
XIAP immunodeficiency	3	porcine	France	[8]
Lymphoblastic leukemia	3	porcine	France	[8]
Myeloblastic leukemia	4	porcine	France	[9]

**Table 2.** Cases of chronic hepatitis E in immunocompromised groups

	Geno- type	Zoonosis	Country	Ref. No.
Liver transplant	3	porcine	The Netherlands	[10, 11]
			Germany	[12]
			France	[14]
			Canada	[15]
Kidney transplant	3	porcine	Germany	[13]
Stem cell transplant	3	porcine	Germany	[16]
Bone marrow transplant	3	porcine	Canada	[18]
HIV coinfection	3	porcine	Switzerland	[19]

infected individuals [21]. It is thus, conceivable that the atypical natural history and outcomes of chronic hepatitis E could be related to immunosuppression, which might have resulted in suboptimal HEV-specific host immune responses, favoring viral persistence. Moreover, HIV-coinfected patients with an advanced stage of immunodeficiency represent another population at risk of HEV-associated chronic liver diseases [20, 22]. To sum up, impaired adaptive immune responses may be a potential reason in European cases for the establishment of chronic HEV infection. Nevertheless, the molecular mechanisms of persistent HEV infection and the disease severity in immunocompromised individuals have hitherto not been clearly understood.

### Risk Factors and Transmission Routes

Human HEV has four recognized genotypes, namely 1, 2, 3 and 4, all representing a single serotype [23]. Genotypes 1 and 2 infect only humans and primates, and have no known animal reservoir. While genotype 1 is prevalent in Asia, including the Middle East, genotype 2 is distributed in African and Latin American countries [1]. In contrast, genotypes 3 and 4 are zoonotic and primarily infect pigs

and some other mammals, in addition to humans [1]. Genotype 3 and 4 are mainly limited to Eastern Asian countries, Eastern and Western Europe and North America [1, 9, 23]. Although less pathogenic than genotypes 1 and 2, genotypes 3 and 4 have been implicated in the European locally acquired hepatitis E sporadic cases [9, 24]. Of note, human and swine HEV are genetically very close with approximately 99% sequence homology, in cases where direct zoonotic transmission is assumed [25, 26]. Swine HEV was first isolated and genetically characterized from farm pigs in the USA [27], followed by reports on many porcine isolates from some Asian and European countries. Subsequently, several descriptive studies on HEV prevalence had been carried out in cases with swine contact, including pig feces or slurry, and commercially sold liver in Japan, the USA, Canada, New Zealand, the Netherlands, Spain and the UK [28]. Since pigs represent a large reservoir of HEV in non-endemic regions, they are considered as a potential source of infection. Recently, a direct viral transmission through the consumption of contaminated pork in Japan as well as a link between eating raw pork liver sausage and the autochthonous HEV chronic infection in France has been reported [28]. Moreover, strains of HEV have been genetically detected in wild boars, deers, mongooses, rabbits and rats in different parts of the world, including Europe and the USA [28]. Several studies conducted in Europe have supported a foodborne origin of indigenous HEV (genotype 3) infection due to the consumption of gourmet figatellu and offal, including game meat of wild boar [29–32]. Fortunately, neither is genotype 1 and 2 infection in association with chronic progression reported elsewhere nor are there any data available on HEV chronic cases in immunocompetent individuals. Also, there is no information on the isolation of specific viral mutations or genetic variants related to this chronic adaptation in the immunosuppressed individuals. Interestingly, a very recent study of genotype 3 isolate from a chronic patient has revealed a recombinant viral-host genome that was infectious to swine, deer and human hepatocytes *in vitro* [33]. This finding strongly supports a cross-species adaptation of zoonotic HEV strains and their pathogenicity in humans.

## Prevention and Control

The proper and timely diagnosis of HEV infection is technically challenging. The lack of an approved algorithm, the consistency of serological tests and viral load quantification in terms of sensitivity and specificity are the limiting factors. Furthermore, serology alone may be in-

sufficient to diagnose HEV coinfection in HIV-positive patients because of delayed or failed seroconversion. Needless to say, there has been no established treatment for acute HEV infection and the resulting disease as far as its natural history is concerned. In the current situation, pegylated IFN- $\alpha$ -2a has been successfully used for treating chronic hepatitis E in transplant recipients [34]. Further, ribavirin is also shown to inhibit the viral RNA replication and induce a sustained virological response in chronically infected patients [35]. The safety and efficacy of an HEV vaccine have already been evaluated in a phase II clinical trial, showing a very good efficacy of up to 95.5% [36]. HEV infection can, therefore, be controlled with an efficient immunization program where individuals in endemic areas as well as naïve travelers from nonendemic regions could also be protected. In industrialized countries, populations at risks such as transplant recipients or people with underlying liver conditions could be vaccinated as well. In a public health care initiative, the French health authority published in its 2009 recommendations that pork liver sausages should be cooked prior to consumption. Precautions and proper care should, therefore, be taken when selecting, purchasing or hunting high-risk animals and cooking their meat. Furthermore, those employed as farmers, pig herders or veterinarians and who work with reservoir or high-risk animals as well as sewage workers must take precautionary measures to ensure adequate hygiene. Last but not the least, HEV infection-associated quantitative risk assessments would further allow to identify possible and potential transmission routes and to precisely define the strategy of viral surveillance and control.

## Conclusion

The recent trend of chronic HEV infection, at least in the immunocompromised individuals, certainly makes HEV very important, in line with other hepatitis viruses such as HBV and HCV. A further comprehensive clinical, virological and molecular study is needed to understand and control this viral paradigm shift and the disease severity.

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